FAMILIAL ADULT MYOCLONUS EPILEPSY: A clinical, neurophysiological and genetic study of a familial form of myoclonic epilepsy

by

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ABSTRACT

Progressive Myoclonic Epilepsies (PME) are characterized by progressive neurological impairment with myoclonus, seizures and dementia. In contradistinction, Familial Adult Myoclonic Epilepsy (FAME) is characterized by a benign course with rare seizures and cortical tremor. Both conditions have neurophysiological features suggestive of a cortical origin for their myoclonus.

This dissertation reports on a novel form of PME. Many of those who were affected had no or minimal progression of their illness, low seizure frequency and were cognitively intact, suggestive of non-progressive disorders linked to the FAME loci.

The majority of patients had features of cortical myoclonus, with generalized spike and wave discharges on electroencephalography, enlarged evoked potentials, enhanced C reflexes, and evidence of cortical excitability with magnetic stimulation. However, there was evidence of cerebellar dysfunction both pathologically and on imaging. With regard to similar conditions, dentatorubral pallidoluysian atrophy and Unverricht-Lundborg syndrome were excluded by linkage analysis. Similarly, linkage was not present for either the FAME 1 or FAME 2 loci.

This syndrome is both clinically and genetically novel, and has a nosology which is difficult to characterize, in which the condition appears to lie on the spectrum between FAME and PME. The dissociation between the pathological and radiological findings which suggest subcortical dysfunction, and the neurophysiological findings of cortical myoclonus is striking.

Review of the literature associated with the neurophysiology of related conditions associated with PME and FAME suggests that:

1. The assumption that generalized forms of myoclonic disorders represent multifocal forms of focal cortical discharges is an oversimplification.
2. The dissociation between initial and later components of the evoked potential is less robust than is generally supposed, and that subcortical inputs may affect later components of the evoked potential.
3. In a high proportion of cases the latency from cortical spike discharge to myoclonic jerk obtained with jerk locked averaging is incompatible with a cortical origin for the spike discharge.
4. The proposal that myoclonus is a form of long latency reflex and that myoclonus represents a reflex arising from subclinical sensory input, is unproven.

OPSOMMING

Progressiewe Miokloniese Epilepsie (PME) word gekenmerk deur progressiewe neurologiese agteruitgang met mioklonus, konvulsies en demensie. Daarenteen word Familiële Volwasse Miokloniese Epilepsie (FAME) gekenmerk deur 'n benigne verloop met ongereelde konvulsies en kortikale tremor. Beide entiteite het neurofisiologiese kenmerke suggestief van 'n kortikale oorsprong vir die mioklonus.

Hierdie manuskrip beskryf 'n nuwe vorm van PME. Baie van die aangetaste persone toon geen of min agteruitgang van die siekte oor tyd nie, met 'n lae frekwensie van konvulsies en is kognitief intak, wat suggestief is van 'n nie-progressiewe siekte gekoppel aan die FAME loci.

Die oorgrote meerderheid van pasiente het kenmerke van kortikale mioklonus gehad, met algemene spits en boog ontladings op elektroensefalografie, hoë amplitude ontlokte potensiale, versterkte C-reflekse, en tekens van kortikale eksiteerbaarheid met magnetiese stimulasie. Met neurobeelding en patologie was daar egter bewyse van serebellêre disfunksie. Soortgelyke toestande, naamlik dentatorubro-pallidoluysiese atrofie en Unverricht-Lundborg sindroom is uitgeskakel deur middel van koppelingsanalise. Koppeling met die FAME1 of FAME2 loci kon ook nie aangetoon word nie.

Die sindroom is beide klinies sowel as geneties nuut en het 'n nosologie wat moeilik gekaraktiseer kan word. Dit wil voorkom of die siekte op 'n spektrum lê tussen FAME en PME. Die dissosiasie tussen die patologiese en radiologiese bevindinge, wat suggestief is van subkortikale disfunksie, en die neurofisiologiese bevindinge van kortikale mioklonus is opmerklik.

'n Oorsig van die literatuur in verband met die neurofisiologie van toestande geassosieer met PME en FAME suggesteer die volgende:

1. Die aanname dat algemene vorme van miokloniese toestande multifokale vorme van fokale kortikale ontladings verteenwoordig, is 'n oorvereenvoudiging.
2. Die dissosiasie tussen inisiële en latere komponente van die ontlokte potensiaal is minder robuust as wat algemeen aanvaar word, en subkortikale invoer mag latere komponente van die ontlokte potensiaal beïnvloed.
3. In 'n groot proporsie van gevalle is die latensie van kortikale spits ontlading tot miokloniese ruk, verkry deur "jerk locked averaging", nie verenigbaar met met 'n kortikale oorsprong vir die spits ontlading nie.
4. Geen bewyse bestaan vir die teorie dat mioklonus 'n vorm van 'n lang latensie refleks is en dat mioklonus 'n refleks is wat ontstaan uit subkliniese sensoriese invoer nie.

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ABBREVIATIONS

AD: Autosomal Dominant
AL: Ansa lenticularis
AR: Autosomal Recessive
BAFME: Familial benign myoclonus of adult onset
BP: Bereitschaftpotential
CJD: Creutzfeldt-Jakob disease
CSF: Cerebrospinal Fluid
CT: Computerized Tomography
DCP: Dyssynergia Cerebellaris Progressiva
DDT:Dichloro-Diphenyl-Trichloroethane
DRPLA: dentatorubral pallidoluysian atrophy
EEG: Electroencephalogram
EMG: Electromyogram
EPC: Epilepsia Partialis Continua
EPSP: Excitatory Postsynaptic Potentials
ERG: Electroretinogram
FAME: Familial Adult Myoclonic Epilepsy
FCTE: Familial Cortical Tremor With Epilepsy
FCMT: Familial Cortical Myoclonic Tremor
GD: Gaucher's Disease
Gpe: Globus Pallidus, Pars Externa
Gpi: Globus Pallidus, Pars Interna
GTCS: Generalized Tonic-Clonic Seizures
HSS: Hallevorden-Spatz Syndrome
Hz: Hertz
IGE: Idiopathic Generalized Epilepsy
ISI : Interstimulus Interval
JLA: Jerk Locked Averaging
JME: Juvenile Myoclonic Epilepsy
LB: Lafora Bodies
LF: Lenticular Fasciculus
LLR: Long Latency Response:
MCD: Multiple Carboxylase Deficiencies
MEG: Magnetoencephalography

MEP: Motor Evoked Potential
MERRF: Myoclonus Elipsy And Ragged-Red Fibers
MRI: Magnetic Resonance Imaging
NB: Neuroserpin Body
NCL: Neuronal Ceroid Lipofuscinosis
NFT: Neurofibrillary Tangle
NRG: Nucleus Reticularis Gigantocellularis
NRT Nucleus Reticularis Thalami
PANK: Pantothenate Kinase
PAS: Periodic Acid-Schiff
PME: Progressive Myoclonus Epilepsy
RHS: Ramsay Hunt Syndrome
SEP: Somatosensory Evoked Potential
SNc: Substantia Nigra, Pars Compacta
SNr: Substantia Nigra, Pars Reticulate
SSPE: Subacute Sclerosing Panencephalitis
SW: Spike And Wave
VA: Ventral Anterior Thalamic Nucleus
VER: Visual Evoked Response
VL: Ventral Lateral Thalamic Nucleus
Vmp: Ventral Medial Thalamic Nucleus
VPL: Ventral Posterior Lateral Thalamic Nucleus

INTRODUCTION

Although this thesis largely concerns the investigations of a novel form of myoclonus and epilepsy, the investigations of this condition have in turn generated a number of questions. In particular, they have raised concerns about the current classification of myoclonus and the basis on which this classification rests. The disease entity itself largely falls on the spectrum between benign forms of myoclonus and more malignant conditions, such as the progressive myoclonic epilepsies (PME), and is currently termed Familial Adult Myoclonus Epilepsy type 3 (FAME 3).

Myoclonus and its causes occupy a remarkably distinctive place in the canon of neurological literature, and has featured prominently in the history of neurology. For much of the 20th century there has been controversy regarding the origin of myoclonus. Myoclonus is sometimes classified on the basis of the diseases or syndromes in which it is an obvious or striking manifestation of the illness. Alternatively, classification may take place by means of neurophysiological techniques that attempt, in general, to make a quasi-anatomical diagnosis, for example, cortical and subcortical forms of myoclonus. All classifications are imperfect, and to some extent these approaches resemble the fable of the three blind men examining the elephant and drawing various conclusions about the nature of the beast. Current classifications of myoclonus are typically based on the neurophysiology of myoclonus, but inherently also reflect the presumptive structural origin of myoclonus. On the whole, the derivation of various anatomical levels to account for the production of myoclonus from electrophysiological findings is often trivial in that it adds little to the understanding of the pathophysiology, and may represent an oversimplification. This thesis will try to demonstrate that the entity of myoclonus is highly complex, and not easily classifiable.

Regarding the disease processes which cause myoclonus, a striking feature is the lack of uniformity in the wide range of associated pathologies, which include viral encephalitides, metabolic derangements, primary and secondary epilepsies and inherited neurodegenerative diseases. Myoclonus is neither a disease process nor a syndrome, but is a phenomenon. That this phenomenon is typically associated with diffuse derangements of the central nervous system is undoubtedly correct, but the multiplicity of causes results in classifications which are intuitively unattractive.

This thesis describes a novel form of epilepsy, characterised by the presence of generalized tonic-clonic seizures (GTCS), myoclonic jerks, and associated in some individuals with progressive neurological deficit, which we have termed FAME 3[1]. Two families were identified from the Western Cape Province of South Africa, and are of mixed ancestry, predominantly resulting from intermarriage between the original inhabitants of the area, the Khoi-San, and early settlers of European origin.

FAME has autosomal dominant inheritance and often presents in early adulthood, as may PME. However, in PME, dominant inheritance is only seen in dentatorubral pallidoluysian atrophy (DRPLA[2], a single family with Kufs disease[3] and mutations in the neuroserpin gene[4]. FAME was originally described in families from Japan and is characterized by myoclonic jerks in the arms and legs, tremulous finger movements, rare GTCS and has been linked to chromosome 8q24[5;6]. Families with a clinical phenotype similar to FAME have been described from Spain in which linkage to FAME 1 was excluded, indicating genetic heterogeneity[7]. A similar condition, Autosomal Dominant Cortical Myoclonus and Epilepsy (ADCME), has features of a primary generalized seizure disorder, complex partial seizures and mental retardation in some patients, and maps to chromosome 2p11.1-q12.2[8], a locus termed FAME 2. Three other families with FAME have been linked to the same region, but did not have mental retardation or complex partial seizures, suggesting that the disorders may be allelic[9 10]. It has been proposed that FAME 1 is seen in Japanese families linked to 8q24 and FAME 2 in European families linked to 2p11.1-q12.2[10]. However, a family from the Netherlands has been described in which the loci responsible for both FAME 1 and FAME 2 were excluded[11].

The thesis outline is as follows:

1. Background
    a. Review of myoclonus, its classification and related conditions. In particular, the historical context of the development of the current classification of myoclonus is presented.
    b. Review of the various known forms of PME to illustrate the differential diagnosis of progressive illnesses presenting with myoclonus, and establishing that FAME 3 is a novel entity.
    c. Review of the anatomical structures related to the generation of some of the neurophysiological manifestations of myoclonus, in order to establish the nature of anatomical connections related to the neurophysiological investigations of myoclonus and also the pathophysiology of myoclonus.

   d. Review of the neurophysiology of myoclonus to serve as an introduction to the electrophysiological studies carried out in the group of affected individuals with FAME 3, and to illustrate the complexities of applying neurophysiological investigations in order to derive a classification of myoclonus.
2. The methodology associated with the neurophysiological investigation, neuroradiology, neuropathology, genetics and nosology of FAME 3.
3. Results of the findings in the two families of these investigations.
4. Discussion of the results with relevance to FAME 3 as a unique entity, and its relevance to the classification of myoclonus.

AIMS AND PURPOSES

The purpose of this study was to examine the following:

1. To delineate the features of a family with a novel disease resembling a form of myoclonic epilepsy.
2. To establish novelty of the disease by demonstrating lack of linkage to known loci associated with similar conditions.
3. To ascertain the neurophysiological hallmarks of this disease with regard to the features of established forms of cortical and subcortical myoclonus.
4. To review the existing literature and establish the nosology of this new syndrome within the existing categories of myoclonus.

1. OVERVIEW

1.1 HISTORICAL NOTE

In an article entitled "On convulsive tremor", William A. Hammond[12] referred to a publication by a Dr Pritchard, who in 1822[13], described, "under the name of Convulsive Tremor, an affection which, so far as I am aware, has not since been distinctly alluded to by any other author. His attention was first directed to the matter by observing that in some epileptics fits of rigor or of tremor appeared to take the place of the ordinary paroxysm"[12]. Pritchard described a patient in whom "all the muscles of the upper extremities…were constantly agitated by a convulsive movement, which was almost entirely confined to them", the legs being spared. Following blood letting and resultant syncope, " the gluteal muscles were so greatly convulsed that by their action the patient was thrown up from his seat with the motion of a man sitting on a trotting horse"[13].

Hammond himself then went on to describe a 35 year old male who would on two or three occasions during the day "be seized with severe and unrestrainable muscle tremor, involving his head and all the muscles of the trunk and arms" [12]. There was an associated feeling of anxiety and it seems not unlikely, given the paroxysmal nature of the condition, that it was a form of conversion disorder, particularly since it was subsequently noted that the first attack had begun during sexual intercourse. He was treated with potassium bromide and galvanism, the latter being able to dampen down a paroxysm which occurred during an office visit[12]. Subsequently, Hammond noted that "my opinion was, and the success of the treatment abundantly justified the view, that the condition depended upon a disorder of the cerebellum"[12].

Myoclonus has been generally accepted to have its origin with a clinical description by Friedreich[14]. He coined the term *Paramyoclonus multiplex* on the following basis: *clonus* refers to a quick movement, *myo* to muscle in order to distinguish it from an epileptic disorder, *para* indicated it was symmetrical and *multiplex* to the fact that there were multiple sites[15]. Friedreich wished to distinguish this type of involuntary movement, which he believed to originate in the spinal cord from "clonic spasm", which was thought at that time to come from the brain[15]. The myoclonic jerks affected all muscles of the body except the face and occurred at different times[14]. The frequency varied from 10-50 Hz and the movement was present at rest but accentuated with tactile or stretch stimuli and disappeared with voluntary movement and sleep[14]. There was no history of epilepsy or family history[14]. This

disorder may be described as essential myoclonus, although the lack of an effect of voluntary movement is puzzling[16].

More recently, the neurophysiological approach to myoclonus had its roots in France initially, and subsequently at the National Hospital in London, where A.M. Halliday and C.D. Marsden played a prominent role. Shibasaki in Japan and Hallett at the National Institute of Health supplemented and expanded this work, giving rise to the concepts which remain the mainstay of classification at the present time.

1.2 DEFINITIONS

Myoclonus refers to sudden, brief, shock-like involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus) arising from the central nervous system[17]. Myoclonic jerks are not associated with loss of consciousness and are frequently precipitated by stimuli such as movement, bright light or stress[18] . As has been pointed out by Symonds, voluntary movement is the most striking of the factors which exacerbate myoclonus[19]. The myoclonic jerk typically occurs at the beginning of a movement and is exaggerated by "change from one movement to another"[19]. It may be difficult to distinguish between rhythmical myoclonus and tremor[20].

The magnitude of myoclonus may vary tremendously, as may the body part involved and the rhythmicity of the movement: J.P.P. Bradshaw wrote in 1954 that the jerks are "arrhythmic and asynergic, involving portions of muscles, whole muscles or muscle groups…. the magnitude may be as small as the twitch of a fasciculation or, if the legs are affected, the patient may be thrown to the ground[21].

The diseases associated with myoclonus are heterogeneous. It is a symptom common to many syndromes in which it may appear in a variety of forms, and it is the symptom complex, particularly the associated neurological features and course of the illness which may lead to diagnosis[22].

Two broad groups emerge: the first consisting of disorders where myoclonus is the presenting and major clinical feature, with neurological deficits appearing later, and a second group in which myoclonus is a part of a progressive encephalopathy, and may be overshadowed by other neurological features[23].

Myoclonus and epilepsy may occur as part of an encephalopathy with known pathology. The pathology may be progressive, as in certain neuronal storage diseases, in which case the illness might be termed a progressive myoclonic encephalopathy. The latter includes metabolic disorders such as the GM2 and GM1 gangliosidoses, Niemann-Pick disease and Krabbe's disease, and acquired disorders such as subacute sclerosing panencephalitis (SSPE). Alternatively, the pathology may be static as after cerebral hypoxia or trauma, when the condition may be called static myoclonic encephalopathy[16].

1.3 CLASSIFICATION

Although myoclonus could be classified by pathophysiology, pharmacotherapy, or clinical phenomenology, the following classification is based on aetiology. Further classifications, predominantly physiological, are discussed in section 1.8.1.

Classification of Myoclonus (after Marsden et al.[16])

I. Physiologic myoclonus (normal subjects)
   - (a) Sleep jerks (hypnic jerks)
   - (b) Anxiety-induced
   - (c) Exercise-induced
   - (d) Hiccough
   - (e) Benign infantile myoclonus with feeding

II. Essential myoclonus (no known cause and no other gross neurologic deficit)
   - (a) Hereditary (autosomal dominant)
   - (b) Sporadic essential myoclonus
   - (c) Periodic movements of sleep (nocturnal myoclonus)

III. Epileptic myoclonus (seizures dominate and no encephalopathy, at least initially)
   - (a) Fragments of epilepsy
     - Isolated epileptic myoclonic jerks
     - Epilepsia partialis continua
     - Idiopathic stimulus-sensitive myoclonus
     - Photosensitive myoclonus
     - Myoclonic absences in petit mal
   - (b) Childhood myoclonic epilepsies
     - Benign myoclonus of infancy
     - Infantile spasms
     - Myoclonic astatic epilepsy (Lennox-Gastaut)
     - Cryptogenic myoclonus epilepsy (Aicardi)
   - (c) Juvenile myoclonic epilepsy
   - (d) Progressive myoclonic epilepsy: Baltic myoclonus (Unverricht-Lundborg)

IV. Symptomatic myoclonus (progressive or static encephalopathy dominates)
   - (a) Storage disease
     - Lafora body (LB) disease
     - Lipidoses, eg GM2 gangliosidosis, Tay-Sachs, Krabbe's
     - Ceroid-lipofuscinosis (Batten)
     - Sialidosis ("cherry-red spot")

(b) Spinocerebellar degenerations

Ramsay Hunt syndrome

Freidreich's ataxia

Ataxia telangiectasia

(c) Basal ganglia degenerations

Wilson's disease

Torsion dystonia

Hallervorden-Spatz disease

Progressive supranuclear palsy

Huntington's disease

Parkinson's disease

(d) Dementias

Creutzfeldt-Jakob disease

Alzheimer's disease

(e) Viral encephalopathies

Subacute sclerosing panencephalitis

Encephalitis lethargica

Arbo virus encephalitis

Herpes simplex encephalitis

Postinfectious encephalitis

Infantile polymyoclonus (neuroblastoma)

(f) Metabolic encephalopathies

Hepatic failure

Renal failure

Dialysis syndrome

Hyponatremia

Hypoglycemia

Infantile myoclonic encephalopathy (polymyoclonus) (± neuroblastoma)

Nonketotic hyperglycemia

Multiple carboxylase deficience

Biotin deficiency

(g) Toxic encephalopathies

Bismuth

Heavy-metal poisons

Methyl bromide

Drugs, including levodopa

(h) Physical encephalopathies

Posthypoxia (lance-Adams)

Post-traumatic

Heat stroke

Electric shock

Decompression injury

(i) Focal CNS damage

Poststroke

Postthalamotomy

Tumor

Trauma

Olivodentate lesions (palatal myoclonus)

1.4 BENIGN FORMS OF MYOCLONUS

1.4.1 ESSENTIAL MYOCLONUS

Essential myoclonus refers to a disorder of unknown aetiology in which myoclonus classically occurs as the sole neurological abnormality[17]. There is a normal life expectancy, and no seizure disorder or evidence of cerebellar dysfunction[20].

In general, the cases which have been described have been familial with an apparent autosomal dominant (AD) pattern of inheritance. The term ”esential myoclonus” is typically applied to sporadic cases. When inherited, usually as an AD trait, the condition is termed “hereditary essential myoclonus”, and synonyms include familial myoclonia, essential familial myoclonus, and benign essential myoclonus[24]. The jerks in hereditary essential myoclonus increase considerably with action and in stressful situations. They characteristically involve the proximal upper limbs and neck, and are less prominent in the face and hands[24]. Dystonia may be a feature (see below 1.4.4).

An early report was that of Pierce Clark, who in 1912, wrote that “the pathogenesis of essential myoclonus is now known to develop…either in the myoclonic’s own family or in collateral branches of the same family stock” [25]. Subsequently, in 1933 Lindemulder recorded a family with myoclonus affecting three generations, which started in the second decade and predominantly affected the face and limbs.

Daube described two families with benign hereditary myoclonus in four generations[26], however, some patients had signs of more widespread neurological involvement. In the proband, abnormal movements were first seen as he was learning to walk and feed himself. Most of the jerks occurred unpredictably on a background of voluntary movement. At age 18, the proband’s daughter developed irregular, uncontrollable jerking movements of her head and arms, and spilled drinks, wrote illegibly, and was unable to perform venipunctures. In addition, a three-year-old grandson of the proband had the disorder in the same form and severity. In the second family, jerking movements were described as early as the second year and were particularly prominent when eating or drinking. The movements were most frequent and intense in proximal muscles, affected by voluntary acitivity, and in a number of patients, they were predominantly unilateral. The older and more severely involved patients had additional symptoms of motor function impairment. These included intention tremor, unsteadiness of gait, slow alternating movements of the hands, jerky eye movements, and

speech impairment. Most of these symptoms were mild and progressed slowly with age. There was no intellectual impairment and no clinical or EEG evidence of a seizure disorder. Mahloudji[27] reported a syndrome of hereditary myoclonus of benign type, reviewing the clinical findings in 6 members of a family. The cardinal features of the disorder were myoclonus commencing in the first decade of life with a benign course, and a variable effect of voluntary movement. There were no seizures and the EEG was normal. The authors proposed the term *hereditary essential myoclonus*. Diagnostic criteria for this condition included[27]:

1. Onset of myoclonus in the first or second decade.
2. Males and females equally affected.
3. A benign course with normal lifespan, although variable severity.
4. Dominant mode of inheritance.
5. Absence of seizures, dementia, gross ataxia and other neurological deficits.
6. Normal EEG.

Fahn and Sjaastad reported on a large Norwegian family with essential myoclonus affecting 19 individuals in four generations[20]. Notable features were that one individual had dystonia and two had frequent eye blinks, which were likely to be a manifestation of blepharospasm; myoclonus was relieved to some extent by alcohol, and two individuals had complete remission of their myoclonus.

Przuntek and Muhr described an eight generation family with an AD inheritance pattern in which there were 25 affected individuals with essential myoclonus who had a striking response to alcohol [28]. The myoclonus mostly affected the neck and arms, and usually started in adulthood, with a range from 4 to 34 years. EEGs were normal in eight individuals. Seven patients had a postural tremor of the hands in addition to myoclonus.

Essential myoclonus can occur without a family history, and Bressman and Fahn described 15 patients with this entity. However, over half of these patients had either focal or segmental myoclonus, suggesting underlying cerebral pathology. The clinical findings were rather diverse, including cases of myoclonus with familial tremor, rhythmic myoclonus, (one of whom had palatal tremor, the other patient had rhythmic myoclonus of the arm, with postural tremor, and may have had cortical tremor), and four other patients with oscillating myoclonus, defined as “transient bursts of fairly regular contractions with a waxing and waning amplitude”. The authors also stated that in two of their patients, who had predominantly arrhythmic contractions, myoclonus was regular at times, implying a

continuum between rhythmic and arrhythmic myoclonus. Similarly in a review of myoclonus at the Mayo clinic, 19 out of 94 patients had essential myoclonus, of onset from 4 to 86 years, and without progression and only one patient had a family history of myoclonus[29].

1.4.2 ESSENTIAL TREMOR AND MYOCLONUS

Another area of nosological confusion is the combination of essential tremor and myoclonus, although it is by no means certain that the entity is really essential tremor. The situation is exacerbated by the difficulty in distinguishing between rhythmical myoclonus and tremor[20]. Korten et al described a family with an AD pattern of inheritance who developed essential tremor and myoclonus[30]. Seven members of the family had essential tremor, in four others there was tremor and myoclonus, and 12 had complex myoclonic jerks. The index patient had spontaneous myoclonus in the arms, abdomen and back, and had rhythmic tremor of the hands, fingers and head at a frequency varying from 3-6 Hz.

In the family with AD inherited essential myoclonus described by Przuntek and Muhr , seven patients had a postural tremor of the hands in addition to myoclonus[31]. Similarly in the Mayo Clinic review of essential myoclonus, a boy is described with tremor of the hands associated with clumsiness and the subsequent development of ataxia, and a generalized spike and wave pattern on the EEG[29].

Many patients with myoclonus and tremor are likely to have cortical tremor, a diagnosis which can be determined by standard neurophysiological characteristics of cortical myoclonus, and which is discussed in greater detail in section 2.3.

1.4.3. ALCOHOL AND ESSENTIAL MYOCLONUS

In the families reported by Przuntek and Fahn[20;28] alcohol reduced the severity of myoclonus, a feature which aids in distinguishing myoclonus from other movements such as dystonic tremor[20], although essential tremor may also respond to alcohol. A similar response to alcohol has been reported with PME[32]. Patients with hereditary essential myoclonus had rebound worsening on alcohol withdrawal.

The condition termed “dominantly inherited myoclonic dystonia with dramatic response to alcohol”, was described by Quinn and Marsden in 1984 [33]. Four families with an AD pattern of inheritance presented with childhood onset myoclonic dystonia involving the upper body and arms. A similar family described by Kurlan also showed a response to alcohol[34]. The condition has the following characteristics[35]:

1. Onset in childhood.

2. Arms and neck affected predominantly.
3. Movement disorder characterised by sudden, irregular "lightning-like" jerks.
4. Jerks were both symmetrical and asymmetrical and synchronous and asynchronous
5. Alcohol dramatically reduced the jerks (the response may be so dramatic as to be diagnostic[24]).
6. Many patients had dystonia: torticollis, retrocollis, truncal spasms, dystonic posturing of arms, writer's cramp.

1.4.4 DYSTONIA AND MYOCLONUS

Obeso et al studied the combination of myoclonus with dystonia in 14 patients[36]. In most cases the same muscle groups were involved in both movements. In all patients, voluntary muscle activity produced myoclonic jerking that was superimposed upon dystonic muscle spasms. Dystonia was most prominent in proximal muscles of the neck and shoulder, whereas myoclonus was more obvious in distal muscles. The myoclonus was irregular and usually in a segmental distribution. Electrophysiology showed sustained dystonic contractions frequently recorded concomitantly with the jerks, with no features of cortical myoclonus. The authors felt that the source of the jerks of myoclonic dystonia within the CNS was unknown, although, given that there were no features of cortical myoclonus, the jerks may have been subcortical in origin [36].

Quinn and Marsden described familial myoclonic dystonia, with normal intellect and life expectancy, and inherited in an AD fashion[24]. The topography of the movement was largely that of the upper body, with relative sparing of the face. The movements improved significantly with alcohol. The patients were similar to those with benign essential myoclonus excepting for the presence of dystonia. Kurlan has also reported a family having myoclonus or dystonia or both over three generations[34].

With regard to dystonia, of the reports described above in the section on essential myoclonus, three list features of dystonia:

1. One of the family of Mahloudji had torticollis and facial grimacing[27].
2. In the family described by Przuntek and Muhr, ten individuals had myoclonus of the neck which induced symptoms of spasmodic torticollis[31].
3. In the family described by Fahn and Sjaastad, one individual had torticollis and two probably had blepharospasm [20].

The topic was reviewed under the title of "Hereditary myoclonic dystonia, hereditary torsion dystonia and hereditary essential myoclonus: an area of confusion"[35]. The authors noted the occurrence of dystonia with many of the cases of hereditary essential myoclonus, and

emphasized that hereditary essential myoclonus may be difficult to distinguish from hereditary myoclonic dystonia[35]. Families may be characterized by myoclonus, dystonia or tremor, or a combination of all three[35].

The issue as to the cause of essential myoclonus with or without dystonia has largely been resolved by the finding of a locus on chromosome 7q21 for myoclonus-dystonia (DYT11) mapped in a North-American family with typical features of essential myoclonus associated with dystonia[37]. Subsequently, mutations in the epsilon-sarcoglycan gene were identified as causative for AD inherited myoclonus-dystonia[38]. Mutations in this gene probably account for most cases of clinically typical myoclonus-dystonia[39]. It is currently assumed that cases of essential myoclonus with essential tremor, with dramatic response to alcohol and with dystonia are all related to mutations in the epsilon-sarcoglycan gene[39].

1.4.5 OSCILLATING MYOCLONUS

This entity was first reported by Fahn in 1981[40]. Three patients had sudden bursts of oscillating movements which then faded. The movements were associated with ramp, but not ballistic movements, and involved the trunk and limbs. The EEG was normal and these patients would in other respects form part of the essential myoclonus group.

A second report described oscillatory myoclonus in two patients with perinatal anoxia[41]. The movements in the first case were described as " sudden transient bursts of myoclonic jerks…present in both arms at rest, recurring in an irregular oscillatory fashion." Posture or movement was associated with action myoclonus. The oscillations were confirmed by electromyography (EMG) which showed silent periods interrupted irregularly by bursts of alternating activity in antagonist muscles at a frequency of 3-6 Hz. The bursts lasted from 1 to 60 seconds, and the duration of individual EMG discharges was from 60 to 120 msec. The authors emphasized that this form of myoclonus was not a tremor since it was irregular, transient and had an abrupt onset[41]. The absence of features of cortical myoclonus suggested that this condition may have had a subcortical origin[42].

1.5. RAMSAY-HUNT SYNDROME

1.5.1 DESCRIPTION OF RHS

In 1914, Ramsay-Hunt described Dyssynergia Cerebellaris Progressiva (DCP), a condition of generalized intention tremor, most obvious during voluntary movement, and associated with cerebellar signs[43].

Three cases were described, none of whom had a family history. The tremor was described as coarse and irregular "atactiform shaking" on attempting any movement, and had a frequency of 3-5 Hz. The onset of the cases was 23, 28 and 40 years[43].

DCP was reported as being similar to the intention tremor of multiple sclerosis and to essential tremor[43]. Ramsay-Hunt commented "It is not improbable that some of the cases which are now grouped with the hereditary and essential tremors would show on closer examination the same progressive disturbances of the cerebellar function as to the cases which are the subject of this study"[43]. He distinguished his cases of "progressive dyssynergia" from those of hereditary tremor since his cases had a movement disorder which was "not a true tremor but a synergic disturbance which is evident only when the extremity is in action, and consists of coarse irregular tremor-like movements in which the constant, vibratory characteristics of a true tremor is almost entirely lacking"[43]. The article concluded by stating that the term 'chronic progressive cerebellar tremor' would be a reasonable appellation for the disorder described in this report[43].

Subsequently, in an article published in 1921 entitled "Dyssynergia Cerebellaris Myoclonica – Primary atrophy of the dentate system: Contribution to the pathology and symptomatology of the cerebellum", Ramsay Hunt described six cases which combined the symptomatology of his previously described DCP with myoclonus and epilepsy (Table 1)[44]. He therefore drew attention to the association of cerebellar disorders and epilepsy with myoclonus. On the basis of the neuropathology he determined that the progressive dyssynergia was due to atrophy of the efferent dentate system of the cerebellum[44].

Of the six cases, four were described as having dyssynergia cerebellaris progressiva myoclonica and a pair of affected twins were described with the same entity in association with Friedreich's ataxia[44]. However, it is unlikely that they would have been diagnosed with Friedreich's ataxia using current criteria[45]. Furthermore, as pointed out by Berkovic, although there are some similarities, the neuropathology of these cases differs from that of

Friedreich's ataxia by the presence, in most cases, of significant neuronal loss in the inferior olives and the absence of degeneration in the corticospinal tracts, and both clinical and pathological features fall within the spectrum of Myoclonus Epilepsy and Ragged-Red Fibers (MERRF)[46].

Table 1. Summary of Findings of Ramsay Hunt's cases[44]

Case	Epilepsy Onset	Myoclonus Onset	Seizures	Cerebellar signs	Family history	Cognition affected
1	17	19	3-4/year	Yes	Probably no	No
2	10	7	6/year	Yes	No	No
3	12	12	Very rare	Yes	No	Yes
4	12	13	Weekly	Mild clumsiness	No	No
5	21	? 21	Yes	Marked	Twin	Yes
6	19	?	Yes	Marked	Twin	No (?)

Case 1: This patient developed myoclonic epilepsy at age 17 years, followed by a progressive development of intention tremor with ataxia of the limbs and speech. Generalized tonic-clonic seizures occurred three to four times per year. Myoclonus was at times so severe that he occasionally fell to the ground. There was no family history.

Case 2: This patient developed myoclonic epilepsy at age 7 years with progressive ataxia involving the speech and limbs. There was no family history of a similar condition. She had approximately six generalized tonic-clonic seizures yearly. The ataxia was progressive and myoclonus was often associated with voluntary movements. There was moderate dementia present.

Case 3: A patient aged 38 who had a history of myoclonic epilepsy for 26 years without any family history of illness. Generalized tonic-clonic seizures began at the age of 12 years, followed shortly thereafter by myoclonic jerks which gradually increased in severity and frequency. There was an associated dementing illness and signs of cerebellar disturbance.

Case 4: A female patient who developed myoclonic seizures at the age of 12, followed shortly thereafter by myoclonic jerks. Subsequently her speech was involved and there was also a "slight tendency to myoclonic waves and twitching of the face." On examination there was mild ataxia in the arms.

Cases 5 & 6: These cases were those of a pair of twins reported to have Friedreich's ataxia. There was no family history.

Case 5: This patient developed generalized tonic-clonic seizures at the age of 21. Subsequently he developed myoclonic jerks and mild gait ataxia. There was an associated mild to moderate dementia. Myoclonic jerks were clearly brought out by mild voluntary movement. Speech was said to have been typically scanning and there was a marked intention tremor of both arms and ataxia in the legs. Reflexes were difficult to elicit in the upper limbs and absent in the legs, with flexor plantar reflexes. No scoliosis was present but there was a tendency to pes cavus. There was marked loss of "deep sensibility" of the legs with loss of position sense. There was also loss of sensation in the hands and fingers. Case 6: This patient's illness began at the age of 19 and was similar to that of his sibling. Marked ataxia was present and reflexes were absent.. There was no pes cavus and sensation was normal.

1.5.2 CONTROVERSIES CONCERNING THE RHS

The combination of myoclonus, with cerebellar ataxia and seizures, as described by Ramsay-Hunt in 1921, came to be known as the Ramsay-Hunt syndrome (RHS)[44].

The definition of the syndrome varies greatly. An early definition was that of Bonduelle, who in 1968 defined the condition as the association of hereditary spinocerebellar degeneration with myoclonus, and less commonly with "major or myoclonic epilepsy"[22]. According to Berkovic the clinical presentation of the syndrome has been described as that of a slowly progressive cerebellar disorder beginning between the ages of 5 to 30, followed by myoclonus with infrequent tonic-clonic seizures in many cases[47]. Some authors have regarded the condition as separate from the epilepsies, since convulsive seizures and epileptiform abnormalities on EEG have been considered to be rare[48]. In contradistinction, Roger observed that a cardinal feature of RHS was an epileptic syndrome of myoclonic seizures, with or without tonic-clonic seizures and with associated EEG changes of paroxysmal epileptiform discharges precipitated by photic stimulation[49].

Increasing confusion regarding the term in the literature led some authors to consider its continued use to be inappropriate[47]. Controversy was generated by a presentation at the 1987 American Academy meeting by Berkovic, with a report entitled "Mitochondrial encephalomyopathies: A solution to the Enigma of the Ramsay Hunt syndrome"[50]. Patients with RHS were reviewed and found to have mitochondrial disease. The authors went on to state that RHS was no longer a useful diagnostic category, and that in their experience it was completely accounted for by mitochondrial encephalomyopathies. In a subsequent review of the progressive myoclonic epilepsies, Berkovic pointed out that some patients with

PME may not have a clear diagnosis, but even in these, the use of the term RHS should be avoided, since it did not convey useful diagnostic or therapeutic information[47].

Subsequently, the debate was further defined by two opposing groups who put forward their views in the journal Movement Disorders [51] [52]. Marsden and Obeso commenced the discussion in an article entitled " The Ramsay Hunt syndrome is a useful clinical entity"[51]. They defined RHS as a triad of :

1. severe myoclonus
2. progressive ataxia
3. mild epilepsy and cognitive change.

In RHS the dominant feature was the myoclonus, with action myoclonus and stimulus-sensitive myoclonus being characteristic [51]. The authors went on to point out that a distinctive feature of RHS was a relatively infrequent occurrence of tonic-clonic seizures, which often responded well to treatment [51]. In their experience of 19 patients with the syndrome, most had fewer than one or two tonic-clonic seizures per year[51]. In addition, they distinguished RHS from PME on the basis that progressive ataxia and dementia form part of the PME spectrum, whereas in RHS dementia is not found and intellectual change, if present at all, tends to be mild[51]. Conditions which presented with RHS, and are not associated with dementia or epilepsy, included Unverricht-Lundborg Disease, later onset forms of neuronal ceroid lipofuscinosis (NCL), sialidosis, non-infantile Gaucher's disease, syndromes of dentatorubral pallidoluysian atrophy (DRPLA) and the May-White Syndrome[53]as well as coeliac disease, Whipple's disease and spino-cerebellar degenerations[51]. The point was made that movement disorders experts saw patients predominantly with myoclonus, whereas the group from the Montreal Neurological Institute saw a different spectrum of disease in which epilepsy was more obvious[51]. The utility of the RHS was in being a useful shorthand description of an easily recognized clinical syndrome with many causes[51].

In reply, the group from Montreal referred to the difficulty in separating myoclonus from ataxia, recalling that "The late Francis McNaughton (Professor of Neurology at Montreal) used to watch such patients for long periods attempting to decide whether their inability to eat with a fork was due to action myoclonus or to ataxia. It was never possible to settle this question on clinical grounds"[52]. They reported a review of 84 cases of PME seen at the Montreal Neurological Institute. Diagnoses included Lafora Body disease, Unverricht-Lundborg disease, NCL, renal failure action myoclonus syndrome and neuroaxonal dystrophy[52]. Of the remainder (fifteen cases), the majority had evidence of mitochondrial

dysfunction demonstrated either by the presence of ragged red fibers on muscle biopsy, skin biopsy or biochemically[52].

The Montreal group was of the opinion that they were able to make a diagnosis in all their cases of PME, since all patients with RHS turned out to have mitochondrial disease. However they also noted that their experience was not shared by other centers: " Why then is the Ramsay Hunt syndrome alive and well in London (and in Marseilles) whereas it has vanished in Montreal?"[52]. The possibility was raised that other neurologists had difficulties with the specificity of diagnosis of Unverricht-Lundborg disease, which the Montreal group, in collaboration with Finnish groups, had studied extensively, forming the opinion that it was a specific, genetically determined entity, characterized by prominent myoclonus, infrequent seizures and minimal dementia[52]. The implication was made that those cases of RHS without a mitochondrial cytopathy were likely to be suffering from Unverricht-Lundborg disease[52]. The Montreal group reiterated their opinion that it was possible to make a specific diagnosis in most patients with PME, and that RHS was therefore not a useful diagnostic entity[52], and that although there was likely to be a residue of difficult cases which varied from center to center, "to say that they have the Ramsay-Hunt syndrome is no advance over saying that they have PME not further diagnosed"[52]. The Montreal group concurred with the opinion of Marsden and Obeso that ascertainment bias affected the types of referrals seen, depending on whether the group saw primarily epilepsy or movement disorders.

Harding summed up the opposing positions, emphasizing that the RHS was a useful entity as long as it was seen to be a syndrome and not a disease[54]. In her opinion, there were undoubtedly cases with myoclonus, ataxia and occasional seizures without a known cause, and which were unlikely to have Unverricht-Lundborg disease[54].

In a rebuttal of the Montreal group's position, Tassinari et al published a report entitled: "Dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome): a condition unrelated to mitochondrial encephalomyopathies". This condition was also known as "Mediterranean myoclonus" to distinguish it from Baltic myoclonus[55]. In five patients the disease was inherited in an autosomal recessive (AR) pattern, and in the remainder was sporadic. The patients had action myoclonus and generalized seizures, and a mild, slowly progressive cerebellar syndrome. The mean age of onset was from 6 to 15 years, and EEG showed generalized spike-and-wave discharges with photosensitivity[55]. Muscle biopsies were normal in these patients and did not show mitochondrial abnormalities[55]. In reply, Berkovic and Andermann were of the opinion that the cases of Tassinari et al were identical to those described under the term Unverricht-Lundborg[56]. Furthermore they stated that "the use of

the term “Ramsay Hunt syndrome” for such patients was historically inaccurate and diagnostically misleading[56].

In 1990, Marsden and Harding pointed out that patients with long-standing idiopathic epilepsy and myoclonic seizures may develop ataxia after many years, perhaps related to anticonvulsant therapy[57]. They went on to discuss 30 patients with the RHS diagnosed at their institutions in Spain and the United Kingdom[57]. A clinical diagnosis was made in 12 of the patients with RHS: mitochondrial disease was thought to be probable in five, based on their clinical features or pedigree data; five patients fulfilled the diagnostic criteria for Unverricht-Lundborg disease; and two patients had celiac disease[57]. The remaining 18 patients fell into three groups[57]. Firstly, there were five patients who had the features of Unverricht-Lundborg disease, but their symptoms began too early or too late, or the course of the illness was atypical, for example, tonic-clonic seizures had not developed until after the age of 25 years[57]. Secondly, there were three patients with onset in their late teens or 20s with seizures, myoclonus, and ataxia who had normal EEGs, all of whom had normal muscle biopsy specimens[57]. Thirdly, there was an older group of patients, some with epileptic seizures, and some with parkinsonism, who appeared to have multi-system atrophy, with progressive ataxia and myoclonus, but without dementia[57]. These data suggested that, even allowing leeway in diagnostic criteria for what were already poorly defined clinical entities (Unverricht-Lundborg disease and mitochondrial encephalopathy without histochemical or ultrastructural evidence of muscle involvement), a clinical or biochemically supported diagnosis could not be made in 43% of their cases with the syndrome of Ramsay Hunt[57].

Marsden et al reiterated that the discrepancies between their findings and those of the Montreal group arose primarily because of differences in ascertainment[57]. The patients had been referred because of their group's interest in myoclonus, other movement disorders, and cerebellar ataxia, as opposed to epilepsy[57]. As noted before, tonic-clonic seizures were not a major clinical problem, and some patients did not have seizures at all[57]. When seizures did occur, they tended to be infrequent and easily controlled with anticonvulsant drugs[57]. Marsden et al emphasized that dementia is not a feature of RHS and that several disorders included in the differential diagnosis of progressive myoclonic epilepsy and studied by the Montreal group, such as Lafora body disease and NCL, would not present as RHS[57]. Finally, they expressed the opinion that the clinical and neurophysiological features of Unverricht-Lundborg syndrome were not specific, and that it could be as dangerous a clinical concept as the RHS[57]. However, time and genetic studies would prove the last statement to be incorrect[58].

Susequently the Marseilles consensus group published their findings on the classification of PME and related disorders in 1990[59]. A consensus was reached to discard the term Ramsay Hunt syndrome and to divide the patients into two broad syndromic categories, each of which demanded a specific approach to diagnosis (Figure 1) [59]. These two categories were the PMEs and the progressive myoclonic ataxias (PMAs). It was noted that a specific diagnosis could usually be made in patients with PME, whereas the converse held true for PMA.

The syndrome of PMA comprises myoclonus and progressive cerebellar ataxia with infrequent or absent epileptic seizures[59]. Known causes of PMA syndromes include spinocerebellar ataxia, mitochondrial encephalopathies, celiac disease and some early presentations of disorders typically associated with a PME syndrome such as Unverricht-Lundborg disease or the sialidoses. It was emphasized that the terms PME and PMA represented syndromes and that they overlapped[59].

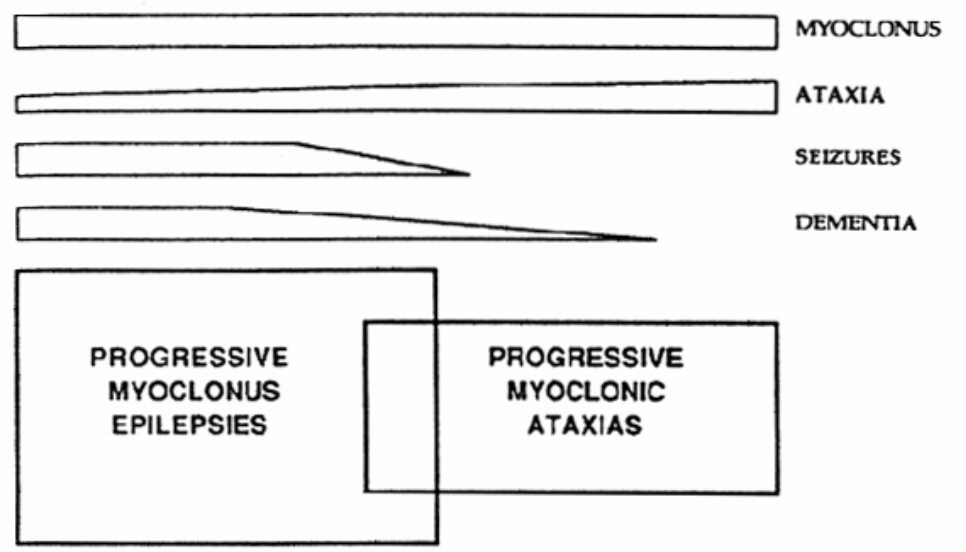

Figure 1. The relationship between PME and PMA (after Marseilles Consensus Group, 1990).

The findings of the consensus groups can be summarized as follows:

1.5.2.1 Phenomenology

In patients with moderate or severe action myoclonus, it was difficult or impossible to determine if cerebellar signs were present as well, unless the myoclonus could be controlled by drug therapy[59]. The clinical characteristics of myoclonus in all the specific causes of the

PME syndrome were very similar. Although the spectrum of severity of action myoclonus might vary in different diseases, the nature of the myoclonus would not enable a specific diagnosis to be reached. The presence of spontaneous myoclonus, although a feature of more severe disease, would not contribute to the diagnosis[59].

1.5.2.2 Special Investigations[59]

Generalized spike-wave discharges, photosensitivity, focal (especially posterior) epileptiform discharges, vertex spikes in rapid eye movement sleep, and giant somatosensory-evoked potentials (SEP) may be found in most of the disorders that cause the PME syndrome. Slowing of the background activity of the EEG occurs in all forms of PME, but is usually much more prominent and early in those diseases with diffuse neuronal damage or storage, compared with those diseases with restricted neuronal degeneration.

1.5.2.3 Specific Diseases[59]

In most parts of the world, five disease entities account for most of the cases of PME presenting to epilepsy clinics[47] [49]. These conditions are PME of Unverricht-Lundborg type, Lafora body disease, NCL, mitochondrial disorders, and the sialidoses. A different spectrum of diseases is seen in movement disorder clinics where a common additional category, particularly among older patients, is a degenerative cerebellar syndrome of unknown cause[60] [51].

1.6 PROGRESSIVE MYOCLONUS EPILEPSIES

The majority of the various disorders which comprise the PME syndrome are characterized by AR inheritance, with the major exception being disorders with mitochondrial inheritance. Rare forms of NCL, DRPLA, and the conditions known as FAME and Benign Adult Familial Myoclonus Epilepsy (BAFME) have AD inheritance. The various forms of PME are reviewed and contrasted in this section.

PME is characterized by myoclonus, tonic-clonic seizures and progressive neurologic dysfunction, particularly ataxia and dementia[47]. Myoclonus in PME is typically fairly severe and often precipitated by posture, action and sensory stimulation in a wide range of modalities[61].

The symptoms and signs in patients with primary generalized epilepsy, particularly juvenile myoclonic epilepsy, may mimic those of the PME phenotype. This is particularly true if toxicity arises from anticonvulsants, since the latter may cause ataxia, uncontrolled seizures and cognitive impairment[47].

PME also needs to be distinguished from other secondary generalized epileptic encephalopathies, such as the Lennox-Gastaut syndrome[47]. These disorders are characterized by various forms of generalized seizures, including myoclonic seizures, but frequently have a fixed neurological deficit, and the illness may progress in some cases. PME can usually be distinguished from secondary generalized epileptic encephalopathies by a history of normal development followed by a relatively rapid progression of symptoms after the illness starts.

1.6.1 UNVERRICHT-LUNDBORG DISEASE

The first form of PME to be described was that of Unverricht-Lundborg syndrome[47]. The major manifestation of the disease is either myoclonus or generalized seizures, both typically manifesting at an average age of 10 to 11 years, with a range of onset of 6 to 15 years [62]The characteristic clinical picture includes ataxia, intention tremor, dysarthria and emotional lability, with no or minimal dementia[48;62]

Unverricht initially described the condition in 1891, and in 1903 and 1912 Lundborg described 17 patients from nine families with the same disease [63] [62]he term Baltic myoclonus arose because the descriptions, first by Unverricht, and then by Lundborg, were of families from Estonia and Eastern Sweden respectively, and many cases had also been reported from Finland (Figure 2), where the incidence is estimated to exceed 1 in 20 000[64]. However, the disorder is not restricted to the Baltic region, and the term “Baltic myoclonus” has therefore fallen away. Similarly, the term "progressive myoclonus epilepsy without Lafora bodies" is no longer used[65].

Figure 2. Distribution of 127 cases of Unverricht-Lundborg disease about the Baltic sea (Figure from Eldridge, 1983).

Genton and Tassinari described a group of patients originating from the Western Mediterranean including a large number of Northern African subjects with typical features of Unverricht-Lundborg disease, with consanguinity present in 11 families[66]. The authors

reported that this condition was less severe than Baltic myoclonus, and suggested that it be called Mediterranean myoclonus. However, these conditions (Baltic and Mediterranean myoclonus) were subsequently shown to be genetically identical[58;67].

1.6.1.1 Diagnosis

Unverricht-Lundborg disease has been clearly distinguished from PME of Lafora body type[62]. The diagnosis is made on the following features:

1. Stimulus-sensitive myoclonic jerks.
2. Age at onset from 6-15 years.
3. Generalized tonic-clonic seizures.
4. Characteristic EEG.
5. Progressive course.

1.6.1.2 Inheritance

The disorder has an AR inheritance pattern [62;68]although there may be a dominant form of the condition[69]. The high prevalence in Finland, with a heterozygote frequency estimated at one in 70[64], as well as haplotype data, are compatible with a single ancestral founder mutation[70]. Lundborg's description was one of the first to detail recessive inheritance, and he published the names of the affected cases. Subsequently, consanguineous marriages appear to have been avoided in Finland, one of the earliest and largest instances of group genetic counseling[71].

1.6.1.3 Myoclonus

Myoclonus can be elicited by light, touch and other stimuli and is accentuated by voluntary movements[72]. Descriptions vary: it is described by Bonduelle as exactly "resembling that of paramyoclonus multiplex; asynergistic, asynchronous partial muscular twitching, sometimes accompanied by fasciculation, rarely producing any motor effect and sometimes affecting the whole musculature"[22]. Koskiniemi described the myoclonus developing from localised jerks to general shaking attacks sometimes leading to generalized seizures [72]. Myoclonus was reported to be most severe in the morning and jerks were said to be so severe that they caused the patient to fall to the ground or from a chair[72]. With progression of the disease, myoclonus may become more severe, arrhythmic and asynchronous[72]. The increased severity of myoclonus finally made patients unable to move unaided and rendered them bedridden and helpless towards the end of the second decade[72].

1.6.1.4 Clinical Manifestations

Koskiniemi reviewed 93 cases, and found that in addition to myoclonus, gait ataxia with frequent falls was an early symptom. All patients had cerebellar symptoms, with ataxia and intention tremor[72]. Generally, ataxia developed a few years after disease onset, although Andermann states that ataxia may be mild and progress minimally[65]. As is usual in many severe forms of myoclonus, the distinction between intention tremor and ataxia was occasionally impossible due to myoclonus[72]. After six or seven years the patients were able to walk only with support or to move in a wheelchair, and two or three years later they were confined to bed[72]. Difficulties with swallowing occurred in all patients during the final stage of the disease. Speech became dysarthric early in the course of the disease[72]. Horizontal nystagmus was found in seven of the cases examined by Koskiniemi et al[72]. Several years after the appearance of the first symptoms, spasticity was found in 28 % and brisk reflexes in 33 % [72].

Intelligence quotients ranged from 55 to 129 and some patients had an IQ over 100 even 5 to 10 years after the onset of disease[72]. However, the estimated IQ at onset of disease was 92, and this tended to deteriorate with time, with neuropsychological testing correlating well with the stage of disease [73]. Some patients developed hallucinations[72].

The average age at death was 24 years, about 14 years after the appearance of the first symptoms[72]. On the other hand, sometimes the illlness stopped progressing after many years and these patients sometimes lived for up to 20 to 30 years after the beginning of the disease[72]. Life expectancy of patients appears to be improving, probably because of better anti-epileptic drugs, and survival into adulthood is usual[47]. Patients are not uniformtly affected and a study of 19 hospitalized patients suggested that severity did not depend on duration of disease, noting that most of the patients had been affected for more than 15 years[73].

Unverricht-Lundborg disease may have had its relatively benign course altered by phenytoin so that the progression resembled that of Lafora body disease[74]. Thus, lifespan was reported to have shortened and dementia become more frequent in phenytoin treated patients[72], with average duration of survival being 14 years from onset. This report was based on 27 affected members of 15 families in the United States. Phenytoin was of no apparent benefit in all 26 patients who had taken it, and “in at least 9 patients death was associated with its administration”[74]. In contrast, “8 individuals showed marked improvement in neurological and intellectual function once valproate sodium treatment was instituted”[74]. Mean survival in the phenytoin era of 14 years[72] was contrasted with the age of the cases reported by Lundborg where five of the first six lived past the age of 50 years. Similarly,

Iivanainen also noted that patients on phenytoin appeared to do less well than on other medications [75].

1.6.1.5 Special Investigations

Until the advent of genetic testing, diagnosis was clinical, and ancillary tests served only to exclude other disorders[47], since there are no biochemical abnormalities specific to the disease[65]. EEG shows generalized slowing with spike and wave discharges and marked photosensitivity[61]. Skin biopsies have been reported to show membrane-bound vacuoles with clear contents in eccrine clear cells[76]. Identification of affected individuals through genetic testing is now available.

1.6.1.6 Pathology

In patients exposed to phenytoin, which is associated with Purkinje cells loss, a case was reported with marked change in the cerebellum with reduction in the number of Purkinje cells and degenerative changes in the remaining Purkinje cells[74] . The molecular layer had a cribriform appearance and there was a glial response noted in some areas of the inner granular layer. Koskiniemi reported diffuse Purkinje cell loss, with relative preservation of the dentate nucleus; some neuronal degeneration was noted in the medial thalamic nuclei[62]. Matthews et al reported on a case of PME without Lafora bodies and found a normal brain, excepting for almost complete Purkinje cell loss[77]. Haltia reported detailed neuropathological findings in three patients: in addition to pronounced Purkinje cell loss, there was rarefaction and chromatolysis of neurons in cerebral cortex, subpial gliosis and rarefaction of myelin. Severe neuronal loss was seen in the caudate nucleus, putamen and globus pallidus, as well as medial thalamus. In the cerebellum, there was marked loss of basket fibers, fibrillary gliosis of the molecular layer, but only slight neuronal loss and degeneration of the dentate nuclei. In the spinal cord, neurons of Clarke's column showed chromatolysis[78].

1.6.1.7 Genetics

The locus for Unverricht-Lundborg disease is at chromosome 21q22.3[67]. The gene symbol is CSTB, and the gene name is cystatin B; with EPM1 being a synonym. The gene product is Cystatin B, a cysteine protease inhibitor[79]. The genetics of the condition are remarkable in that the mutation comprises a dodecamer repeat, typically of 30-80 copies, which accounts for 90 % of known cases of Unverricht-Lundborg disease[70;80].

1.6.1.8 Epidemiology

The disorder is commonest in Finland[65], but patients have been described from Japan, Italy, France, Turkey, Sweden, the United States, and other countries[65].

1.6.1.9 Management

The drugs of choice are the antimyoclonic agents valproic acid, clonazepam, and piracetam[65]. Antiepileptic agents relatively easily control the generalized seizures, but myoclonus often proves difficult to control. Unlike most forms of epilepsy, PME is best treated by polytherapy, including the three agents mentioned above, as indicated in a study by Obeso et al of patients with post-anoxic myoclonus and the Ramsay-Hunt syndrome (some of whom may have had Unverricht-Lundborg disease)[81]. Zonisamide may be effective in the treatment of this form of progressive myoclonus epilepsy [82]. Alcohol abolishes the myoclonus briefly[32]. Treatment with *N*-acetylcysteine has resulted in improvement in seizure control and myoclonus, possibly based on its putative anti-oxidant effect [83].

1.6.2 LAFORA BODY DISEASE

In 1911 Lafora & Glueck found amyloid-like inclusions in the neurons of patients with PME, establishing the pathological hallmark of the disease which bears Lafora's name. The illness is characterized by the onset of generalized tonic-clonic seizures and/or myoclonus between the ages of 6 and 19 years[84], typically around the 14th year of life[61]. Rapid and severe mental deterioration occurs, often with psychotic symptoms[49]. Survival is short, and the mean age of death is 20 years, less than 2 to 10 years after onset[85].

1.6.2.1 Diagnosis

There is a clearly distinguishable clinical pattern from Unverricht-Lundborg disease, with the major distinctions being:

1. Later age of onset, and shorter duration of illness.
2. Focal occipital seizures in half the cases and visual impairment[86].
3. Significant and progressive cognitive impairment [47].

1.6.2.2 Inheritance

Lafora body disease follows an AR pattern of inheritance [49].

1.6.2.3 Myoclonus

At first, as with many forms of PME, the myoclonic seizures can mimic juvenile myoclonic epilepsy. The myoclonus is constant, and jerks may be massive and synchronous, usually limited to one or more muscle groups [87]. Jerks are also described as being asynchronous and asymmetrical[85]. The myoclonic jerks are not associated with loss of consciousness and are aggravated by voluntary movement. With progression, myoclonus increases in intensity and becomes quite severe and multifocal, precipitated by posture or action[84].

1.6.2.4 Clinical Manifestations

Seizures are predominantly clonic, tonic-clonic and myoclonic[49] and can be preceded by increasing myoclonus[85]. Paroxysmal visual manifestations that are epileptic in nature may be an early sign of the disease[88], and visual disturbance and blindness occur in a minority[85]. Dysarthria and cerebellar symptoms have been described frequently[85]. After a few years, there may be a rapid onset of dementia, and some cases may present with dementia [68].

A few cases of a possible adult-onset form of the disease with a more benign course have been described, with a 30 year course in one patient [89]. Although typical Lafora inclusion bodies were found in these cases, it is unclear if they represent the same disease. Of note, in Lafora body disease, inclusions are found in the neuronal perikarya, and in late-onset

Lafora body disease there are inclusions in both axons and perikarya [89;90], a similar distribution to adult polyglucosan body disease[91].

1.6.2.5 Pathophysiology

Lafora bodies have the properties of an acid mucopolysaccharide, are periodic acid-Schiff (PAS) positive, and are a polyglucosan protein complex [92]. Polyglucosans are glucose polymers, similar to glycogen, but lacking its branched structure[93]. The bodies vary in size from 1 to 30 μm in diameter, and cells may contain single or multiple bodies[23]. Deposits generally appear free in the cytoplasm of neurons[94]. The histological appearance is that of a concentric-lamellar target-like structure, with a basophilic core surrounded by a pale eosinophilic zone, containing dark radial stria [23]. At the electron microscope level, the bodies consist of filamentous and granular components, located in neuronal cell processes and perikarya [95] .

There are similarities between Lafora bodies, corpora amylacea, deposits found in type IV glycogenosis and intra-axonal bodies seen with normal ageing [91]. The bodies have been found throughout the nervous system, with dentate nucleus, substantia nigra, thalamus, and pons being the main locations, and are also seen in the retina and spinal nerves [72]. In addition, Lafora bodies are present in non-neuronal tissue, such as muscle and liver [96].

A unique biochemical pathway of glycogen metabolism appears to exist: this is made up of laforin, E3 ubiquitin ligase, and three proteins which interact with laforin. Laforin appears to bind polyglucosan accumulations and promotes their elimination[97].

1.6.2.6 Special Investigations

Skin biopsies show Lafora bodies in the eccrine ducts of sweat glands[98]. Biopsies from the axilla show bodies in the myoepithelial cells of the acini of the apocrine glands[99]. However, biopsies from apocrine glands may be a source of confusion, since apocrine glands normally contain PAS positive inclusions [100].

1.6.2.7 Pathology

LBs are an intracytoplasmic inclusion of neurons, varying in size from 1-30 μm, with a variable number of inclusions per cell. Typically on H & E staining there is a dense basophilic core and a pale periphery, with the centre staining intensely with Periodic-acid Schiff [96;101]and Alcian blue[101;102] Most other reports emphasize the presence of diffuse LBs and report moderate neuronal loss [89;102 103;104]

1.6.2.8 Genetics

The gene locus is located at chromosome 6q24, and the gene is currently termed: Epilepsy, progressive myoclonus type 2A, with the gene symbol being EPM2A. The gene product is the laforin protein, which is characterized by a carbohydrate-binding domain and a tyrosine phosphatase domain[105]. In addition, the EPM2B (also termed NHLRC1) gene has been recently identified, and encodes for the E3 ubiquitin ligase[106].

1.6.2.9 Epidemiology

Lafora body disease is a rare disorder and there are no accurate estimates of its prevalence. In a review of PME from the Montreal Neurologic Institute, an epilepsy referral centre, 12 (14.2%) of 84 patients with PME had Lafora body disease[52].

1.6.2.10 Management

Control of seizures should be attempted with antimyoclonic drugs, especially valproic acid, clonazepam, and piracetam[47].

1.6.3 CORTICAL TREMOR, FAME AND ADCME

In 1990, Ikeda et al described the entity of cortical tremor for the first time in the Western literature[107]. They reported two patients who had rare seizures and who had developed fine tremor in the 4th and 7th decades.

1.6.3.1 Diagnosis

Since 1990, a number of similar conditions have been described from Japan, typically characterized by a benign clinical course, with rare seizures, normal cerebellar function, absence of dementia and and associated with tremor[108]. The tremor can be demonstrated to be of cortical origin, and represents a manifestation of cortical reflex myoclonus.

These conditions include:

1. "Cortical tremor" (reported by Ikeda in 1990[107])
2. "Benign adult familial myoclonus epilepsy (BAFME)" (reported by Kuwano in 1996 [109])
3. "Familial cortical myoclonic tremor" (reported by Terada in 1997[108])
4. "Familial cortical tremor with epilepsy" (FCTE) (reported by Okuma in 1997) [110]
5. "Familial benign myoclonus epilepsy of adult onset" (reported by Okino in 1997[111])
6. "Familial adult myoclonic epilepsy (FAME)" (reported by Plaster in 1999)

In addition, similar conditions have been described in European families, namely ADCME with complex partial and generalized seizures and Familial Cortical Tremor, Epilepsy and Mental Retardation[8;112].

1.6.3.2 Inheritance

In Ikeda's report, one of the patients had six siblings, of whom two had a similar tremor, indicating a possible AD condition[107]. Terada et al described three pedigrees with AD inheritance[108] and Okuma reported on a further Japanese family in which five members in three generations had a similar condition, and three further families in which the disorder was present in two successive generations[110]. Kuwano reported five families, with age of onset between 18 and 50 years with AD inheritance[109]. Plaster et al reported that AD inheritance was a criterion for FAME, and that penetrance was unusually high[5].

1.6.3.3 Myoclonus and Cortical Tremor

Wilkins et al had previously published on a group of patients in an article entitled 'Primary generalised epileptic myoclonus: a frequent manifestation of minipolymyoclonus of central origin"[113]. However, since the distribution and latency of the recorded premovement discharge, Ikeda et al coined the term "cortical tremor" although the movement resembled

polyminimyoclonus. The tremor was fine and shivering-like, brought out by outstretched posture and accentuated by action[107]

In Okino's report of 1997, rare seizures occurred, usually preceded by a worsening of myoclonic movements. Examination showed "fine myoclonus in the distal portion of the upper limbs"in one patient, whose 81 year old mother was reported to have "marked generalized myoclonus" after a seizure[111]. Okuma described "tremulous shivering-like movements" with posture-holding[110].

1.6.3.4 Clinical Manifestations

Table 2 reporting radiological findings and Table 3 reporting results of linkage analysis are found on page 52 and 53 respectively. Table 16 concerning progression of disease and Table 18 concerning clinical features are available on page 206 and 212 respectively.

Ikeda's initial report described two patients who had rare seizures and who had developed fine tremor in the 4th and 7th decades. Seizures occurred twice in the older patient and the younger one had "several seizures every 1 to 2 years, especially when tired or tense". The tremor generalized prior to the seizure in both cases. There were no cerebellar signs in either patient. In one of the patients, "the involuntary movement was so severe that intensive medication was required to prevent generalized convulsion (sic)"[107].

In familial benign myoclonus epilepsy of adult onset, three families with onset of illness between the third and fifth decades were reported[111]. The illness was characterised by jerks in arms and eyelids, which were exacerbated by movement. There was no dementia, cerebellar ataxia or other characteristic signs of PME. However, one 64 year old patient had slowly progressive generalized myoclonus, and had suffered seizures several times over the two decades prior to admission. At admission, he was mildly drowsy with generalized myoclonus.

BAFME has also been associated with night-blindness and abnormalities on electroretinography. Manabe reported a family in which a 34-year-old proband developed night-blindness at the age of 13 and tremulous finger movements three years later[114]. On examination the only abnormal finding was that of fine tremor in the fingers and myoclonus in the arms and legs at rest. In particular, the reflexes were normal and there was no dementia present. MRI scan was normal. The proband's mother had myoclonus of the arms and legs when tired from the age of 30, and generalized seizures from age 33. The proband's sister had myoclonus in the arms and legs, and fine tremulous movements in the fingers[114].

In 1997, there was a report by Terada et al, originating from the same group which had originally coined the term “cortical tremor”, and now termed “Familial Cortical Myoclonic Tremor”[108]. The patients had ‘tremulous involuntary movements’ which were rhythmic and seen in both the upper and lower limbs, and were exacerbated by posture and action. They had been previously diagnosed as having familial essential tremor. In six patients from three families, tremor commenced at a mean of 37 years and gradually progressed. Three patients had episodes of loss of consciousness, but these were extremely rare, “on one to three occasions throughout the clinical course”. One patient had akinesia, rigidity and gait disturbance with a limited response to dopamine replacement, but otherwise the neurological examination was normal. Terada et al proposed the following criteria for the condition[108].

1. AD inheritance.
2. Adult onset.
3. Slowly progressive, but mild clinical course.
4. Relatively rhythmic small jerks predominantly involving the distal limbs, markedly enhanced during movement.
5. Infrequent attacks of loss of consciousness.
6. No other neruological findings (no dementia or ataxia).
7. Electrophysiology of :
   7.1. Generalized EEG spikes, with photoparoxysmal response.
   7.2. Giant SEPs.
   7.3. Enhanced C-reflex.
   7.4. Cortical spikes on jerk locked averaging (JLA).
   7.5. Preservation of normal bereitschaftpotential (BP).

Okuma described “Familial cortical tremor with epilepsy” in which the clinical features were “tremulous, shivering-like movements” and rare seizures[110]. On standing the proband had rhythmic oscillations of the legs resembling orthostatic tremor. He had a seizure three decades previously at the age of 25. All of the four other members of the family who were described had a normal neurological examination with fine tremor of the fingers with posture holding. CT and MRI of the brain were normal in the proband and his daughter. Seizure onset occurred in the proband’s mother at 32 years, and in his daughter at 20, and in his son at age 32.

In a second report by Okuma et al, three additional families with seven affected patients were described[115]. The proband had a seizure at the age of 20 and had tremulous finger movements from that time. At the age of 39, she was on anticonvulsants which controlled

the seizures, and when these were stopped myoclonus reappeared. The tremor was not progressive and there was no evidence of corticospinal or cerebellar dysfunction.

The entity of FAME was reported by Uyama in 1996[116]. There were four families, with 27 affected members presenting over three generations with high penetrance. The following characteristics were noted [5]:

1. Adult onset at a mean age of 37.5 years.
2. The course was benign, without associated ataxia or dementia.
3. The condition had been only reported in Japan.
4. The clinical features of FAME were myoclonic jerks in the arms and legs, tremulous finger movements and rare generalized tonic-clonic seizures (GTCS).
5. Myoclonic jerks could be precipitated by fatigue, insomnia and photic stimuli.
6. The EEG showed generalized spikes and polyspikes.

In 1999, the FAME locus was mapped to chromosome 8q24[5] by Plaster et al. BAFME was mapped to the same locus, termed the FAME 1 locus (8q23.3-q24.11) by Mikami et al. who used microsatellite markers to demonstrate a maximum multipoint LOD score of 5.42 in the interval between the markers D8S555 and D8S1779[6]. The authors of the latter report pointed out the following characteristics:

1. Autosomal dominant inheritance, tremulous finger movements and myoclonus of extremities.
2. Infrequent epileptic seizures.
3. EEG showed polyspike and wave with marked photosensitivity.
4. Features of cortical myoclonus were present, including enlarged SEPs, enhanced C reflexes and positive spikes preceding myoclonus.
5. Benign nonprogressive course without cerebellar ataxia and dementia[6].

Mikami et al described a family with three affected generations and 17 affected patients[6]. The onset of tremulous movements in fingers or myoclonus of the extremities typically occurred at an average age of 30.5 years (range 18-45 years). In half the patients myoclonus involved both arms and legs, and was restricted to the arms in the remainder. Seizures occurred infrequently, often less than four times throughout the lifespan of the patient. Two of the 17 patients did not have generalised seizures. No evidence of cerebellar ataxia of dementia was seen over an observation period of more than a decade. CT demonstrated mild atrophy of the cerebral cortex in three patients.

Subsequently, a four-generation family with FAME was reported from Spain: ten living and three deceased family members had “involuntary rhythmic movements of the extremities”, the mean age of onset being 41 years[7]. The movements were described as myoclonic, rather than tremulous. Eight of the 13 had generalized tonic-seizures, the mean age of onset being 44.6 years. EEG showed polyspike and wave discharges without photosensitivity, and electrophysiological findings were compatible with cortical myoclonus[7].

Van Rootselaar described a family from the Netherlands with FCTE[117]. There were 13 definite affected patients, and three probably affected. The proband had finger twitching, tremor, and trembling of his legs, worsened by stress and after waking. He had a kinesogenic tremor with superimposed myoclonus in his fingers and toes. He had rare seizures. Linkage was negative for the FAME 1 and 2 loci[118].

A European family was described by Elia et al. with cortical tremor, epilepsy and mental retardation, although mental retardation was present in only one individual[112]. The family had a six generation pedigree with seven affected individuals and appears to have been transmitted only through the female line, suggesting a mitochondrial disorder. Two individuals in the first generation only had finger tremor. One patient had no seizures, and seizure onset was age five in two patients, and age 18 in another. Seizures were well controlled by Phenobarbital in two patients. MRI scan showed mildly enlarged subarachnoid space and lateral ventricles in two patients, and was normal in a third.

In 2001, Guerrini et al described a family from Tuscany of 11 individuals over five generations characterized by similarities to FAME but also having complex partial seizures[8]. The condition had linkage to chromosome 2p11.1-q12.2, and linkage to the locus for FAME was excluded. This condition was termed ADCME[8]. The features of the condition were:

1. Onset in adulthood. The age of onset of myoclonus range from 12 - 50 years, with a mean of 23 years and typically slightly preceded or commenced at the same time as the first GTCS.
2. The course of the illness was not progressive.
3. Distal, semi-continuous, rhythmic myoclonus resembling tremor of variable ampitude. Myoclonus of the hands was present at rest, but exacerbated by maintenance of posture. There were also isolated multifocal jerks of the arms proximally and intermittent myoclonus of eyelids.
4. Of the eight family members, two had only one or two isolated GTCS, and three had seizures in remission on treatment, in two for 20 years. One had treatment resistant

GTCS, two had intractable complex partial seizures, and one had complex partial seizures that responded to treatment.

5. Three patients had mild to moderate mental retardation and one borderline intellectual functioning, and in the remaining three patients intelligence was below average.
6. EEG abnormalities included features of primary generalized epilepsy as well as frontotemporal or focal temporal spike discharges.

Electrophysiological testing was compatible with myoclonus of cortical origin. MRI imaging was normal. This family had two phenotypes: a core syndrome of rhythmic myoclonus and GTCS, and a more severe phenotype associated with complex partial seizures. It was proposed that this could have been the consequence of a gene causing widespread cortical hyperexcitability, but particularly involving the frontotemporal regions[8].

Two further Italian families were described with linkage to 2p11.1-q12.2[9]. These families had cortical tremor, and seizures were present in 40 % of one family and 60 % of the other, but were rare (one to five attacks) in those affected. There was no dementia present, and neurological examination was normal apart from the presence of tremor. This locus has been termed the FAME 2 locus.

Subsequently, Striano et al reported a new BAFME pedigree, with possible linkage to the FAME 2 locus, since lod scores only reached 1.55[10]. Seven with the condition had cortical tremor and GTCS was present in six. MRI of the brain was normal in three patients. The authors proposed that the condition was found worldwide, but genetically heterogenous, with Japanese families linked to the FAME 1 locus and European ones to the FAME 2 locus[10]. Similarly, Okuma and Mizuno pointed out that FAME, BAFME and familial cortical tremor were likely to be one entity[119].

FAME associated with migraine has been described in a five generation family from Turkey in which myoclonus started in the third or fourth decades[120]. Generalised seizures were extremely uncommon, the only feature of note on examination was postural tremor of the hands, and both myoclonus and migraine were decreased by valproic acid[120].

1.6.3.5 Pathophysiology

Since BAFME responds to sodium valproate and diazepam, and since GABA receptors are the site of action of these drugs, linkage studies of the DNA polymorphisms of the GABA receptors, GABARβ1, GABARβ3 and GABARα6 were performed. However, the gene for

BAFME was not linked to a gene for the GABA receptors[109]. Lack of neurodegeneration in FAME may suggest that the disorder is one of membrane excitability[5].

1.6.3.6 Special Investigations

Neuroradiological findings are summed up in Table 2. Predominanly, both CT and MRI are normal in a wide range of reports. Mild cerebellar and cerebral atrophy have been noted relatively infrequently.

Table 2. Neuroradiological findings in FAME and related families.

	CT	MRI
Ikeda, 1990	Periventricular lucency Moderate cerebral atrophy in patient aged 75.	
Okino, 1997		Infarction in cerebellar hemisphere (patient 1). Normal (patient 3). Multiple lacunar infarctions (patient 4).
Okuma, 1997	Normal (2)	Normal
Okuma, 1998	Normal	Normal
Plaster, 1999	Normal	Normal
Elia, 1998		Mild enlarged subarachnoid space and lateral ventricles in two. Normal in one.
Mikami, 1999	Mild atrophy in three	
Guerrini, 2001		Normal (six)
Labauge, 2002		Normal (five)
Van Rootselaar, 2002		Slight cerebellar atrophy (two) Normal (two)
De Falco, 2003		Normal (nine)
Van Rootselaar, 2004	Atrophy, particularly cerebellum	
Manabe, 2002		Normal
Striano, 2004		Normal
Saka, 2000		Normal
Guerrini, 2001		Normal (six)

The EEG shows generalized spike and wave discharges[108;111]. and photosensitivity is often present[108;109;115]. Recordings suggested origin of the movement in the sensorimotor area, possibly in hyperexcitable motor cortex[107] and results of electrophysiological testing appear to be uniformly compatible with cortical reflex myoclonus[107;108;111;115]. Electrophysiological features of the European family with mental retardation were similar to those found in the families reported from Japan, including photosensitivity on EEG[112].

1.6.3.7 Pathology

In the Japanese literature, normal findings were reported in three patients with myoclonus and epilepsy, some of whom had "myoclonic tremor" ([121]cited in [110]).

Van Rootselaar reported on a case of FCTE in which there was extensive mineralization of vessel walls and neurons in the globus pallidus. The cerebellum showed Purkinje cell loss with Bergmann gliosis, atrophy of the molecular layer and abnormal Purkinje cell morphology. Gliosis of the cerebellar white matter and cell loss and gliosis of the dentate nucleus were present[122].

1.6.3.8 Genetics

Linkage analysis of known studies is presented in Table 3.

Table 3. Linkage analysis in FAME and related families.

Reference	Origin	2p11.1-q12.2 FAME 2	8q24 FAME 1
Plaster, 1999	Japan		+
Mikami, 1999	Japan		+
Guerrini, 2001	Tuscany	+	-
De Falco, 2003	Naples	+	-
Labauge, 2002	Southern Spain		-
Van Rootselaar 2002; Bouwer, 2002	Netherlands	-	-
Striano, 2004	Italy	+ (Lod score 1.55)	-

1.6.3.9 Management

Myoclonus, including finger tremor, and seizures were effectively treated with a combination of clonazepam and valproic acid[108;115].

1.6.4 HEREDITARY DENTATORUBROPALLIDOLUYSIAN ATROPHY

1.6.4.1 Diagnosis

Systemic degenerations of the extrapyramidal nuclei have been classified by Jellinger into 4 groups[123]:

1. Pure pallidal atrophy (PA), with lesions found only in the efferent pallidal system.
2. Pure pallidoluysian atrophy (PLA).
3. Pallidal degeneration with involvement of the striatum or Substantia Nigra (PLNA).
4. Combinations of the first 3 types with other "cerebrospinal degenerations" such as pallidoluysiodentate atrophy (PLDA).

Myoclonic epilepsy has not been associated with PA, PLA or PLNA, but is described in the group of PLDA.

There are two early reports of pathological system degenerations of the pallido-Luysian and dentato-rubral pathways:

1. In 1946 Titica and Van Bogaert described a patient with progressive dementia and "hemiballismus", described as " involuntary contorting movements of the left arm and grimacing", associated with visual loss[124]. His older sister had cataracts, marked intention tremor, and progressive ataxia.
2. Smith described a patient with dysarthria, choreoathetosis and cerebellar signs[125]. Autopsy showed changes predominantly in the cerebellofugal and extrapyramidal systems with marked neuronal loss in the dentate nuclei, loss of Purkinje cells, and marked demyelination of the subthalamic nuclei and the globus pallidus.

Although two cases of familial PME from Japan were described in 1965, with pathology involving the brainstem and cerebellum [126] , the condition known as DRPLA, and characterized by AD inheritance, was first described in Japan in 1977. There were four cases from three separate Japanese families with AD myoclonic epilepsy, with pathological findings of degeneration of the dentate nuclei, superior cerebellar peduncles, and the pallido-luysian system ([127] cited in [128]). DRPLA was first described in the Western literature in 1978 by Takahata[129].

1.10.2 Clinical Manifestations

In 1982, Naito described five different families with myoclonus, epilepsy, ataxia, dementia and choreoathetosis, all of whom had degeneration of the dentatorubral and pallidoluysian systems[2]. He noted that this was a new neurologic disease, "hereditary dentatorubral-pallidoluysian atrophy", with the following unique features[2]:

(1) A PME syndrome with or without cerebellar ataxia or choreathetosis or both.

(2) Pathological findings of dentatorubral-pallidoluysian atrophy.
(3) AD heredity.

Iizuka et al expanded the clinical phenotype, and distinguished two clinical types of DRPLA (1984) in addition to PME[128]:

(1) Ataxo-choreoathetoid type: ataxia was prominent in the ataxo-choreoathetoid type in the early stages of the illness, and choreoathetoid movements more prominent with disease progression. Disturbances of external ocular momements were commonly observed[128].
(2) Pseudo-Huntington type: Choreic movenents and dementia were always predominant, and ataxia was mild or latent throughout the course.

The disorder has been most commonly reported from Japan, but cases have been described in Europe[130]. Age of onset varies from childhood to late adulthood. The differential diagnosis includes Huntington's disease, Parkinson's disease, mitochondrial encephalopathies and cerebellar ataxias[131]. Myoclonus, epilepsy and cerebellar features, which include ataxia, postural and intention tremor, are characteristic of DRPLA[130]. Hyperkinetic involuntary movements and rigidity may be related to involvement of the pallidofugal system, and may be difficult to distinguish from Huntington disease, possibly since they may mask the cerebellar signs[130].

In general, patients with disease of early onset have a more rapid progression and manifest as PME, whereas those presenting later have cerebellar ataxia, choreoathetosis and dementia, although there are exceptions to this in families of non-Japanese descent[2 132].

1.6.4.3 Inheritance

DRPLA is inherited as an autosomal dominant disorder, and in common with many triplet codon repeat disorders, there is a correlation between repeat number and age of onset of the illlness[133] and anticipation is present[129].

1.6.4.4 Special Investigations

MRI may demonstrate atrophy of the cerebellum and brainstem, correlating with the size of the trincucleotide CAG repeat expansion [134]. T-2 weighted high intensity signal change is also in the white matter and brainstem[135].

1.6.4.5 Neuropathology

There is neuronal loss in the cortex, thalamus and chromatolytic changes in the neurons of the pons, locus ceruleus, hypoglossal and dorsal vagal nuclei. In the cerebellum, the dentate nuclei showed neuronal loss and chromatolytic changes, and reduction in the number of Purkinje cells[129]. Some patients also showed neuronal loss in the globus pallidus

and gliosis of the subthalamic nucleus[129;129]. Patients may have severe degeneration of the dentate and axonal loss in the superior cerebellar peduncle[2;136].

1.6.4.6 Genetics

The gene locus for DRPLA is located at chromosome 12p13.31 and the gene codes for a protein termed atrophin 1. DRPLA is due to expansion of an unstable trinucleotide (CAG) repeat[137]. In the Japanese population the number of repeats is highly polymorphic with a distinct, bimodal distribution of normal and expanded alleles[133]. In normal individuals allele sizes vary between 7 and 23 copies, whereas patients with DRPLA have expansions in the range of 49 to 75 repeats[138].

1.6.4.7 Epidemiology

DRPLA is described worldwide, although is commonest in Japan, where the incidence is 0.2-0.7 per 100 000 [139;140].

1.6.5 NEURONAL CEROID LIPOFUSCINOSES

NCL consists of a group of genetically determined neurodegenerative disorders characterized by the accumulation of abnormal amounts of fluorescent lipopigments, which include lipofuscin and ceroid, within neuronal perikarya[141;142].

The disorder was initially classified as a form of amaurotic familial idiocy due to the presence of visual loss and dementia. The histological accompaniment of amaurotic familial idiocy was widespread distention of neurons by lipid material. With time, infantile amaurotic familial idiocy (Tay-Sachs disease) was separated from late infantile/juvenile amaurotic familial idiocy (NCL). The adult variant of NCL was recognized in 1925.

There are four clinical and genetic subtypes [143]

1. The infantile type does not present as a PME syndrome[47].

2. The late infantile form (Janský-Bielschowsky disease) is an AR disorder that starts between the ages of 2 and 4 years with a wide range of seizure types including atypical absence, atonic and tonic-clonic seizures[68]. Shortly after the onset of seizures, ataxia, dementia and stimulus-sensitive myoclonic seizures develop, with myoclonus being a prominent feature, including "myoclonic status epilepticus" [143142]. The subsequent course is rapid and is characterized by resistant epilepsy, spasticity and blindness [142 143]. Death typically occurs between 6 to 9 years[142 144].

3. The juvenile type (Spielmeyer-Vogt-Sjögren Disease), more commonly known as Batten's disease[145], develops between the age of 4 and 10 years. As with most forms of NCL, visual failure is usually the first symptom, and subsequently seizures, dysarthria and dementia develop, often with severe rigidity[143]. A wide variety of seizures types are seen, including myoclonic, tonic-clonic and absence seizures [49]. Optic atrophy, macular degeneration and attenuation of retinal vessels may occur [47]. Life expectancy ranges between 5 and 13 years [143].

4. The adult form (Kuf's Disease) is uncommon and more clinically heterogeneous [144]. The onset is typically about the age of 30 years but may range from adolescence[141] until the 5th decade[146]. It can present as a PME, although cases may also present with a picture of dementia and extrapyramidal or cerebellar disturbance[143]. A case of progressive cerebellar ataxia, associated with atrophy and fasciculations, without cognitive impairment and commencing at the age of 43 has also been described[147]. Blindness is notably absent, and the optic fundi are normal, although retinal storage of lipofuscin can occur[148]. The clinical course from onset to death is approximately 15 years [141] .

1.6.5.1 Diagnosis

Diagnosis presently requires the demonstration of characteristic inclusions by electron microscopy, typically of both skin and muscle[142].

1.6.5.2 Inheritance

The disorder has AR inheritance. However, one family with adult onset and AD inheritance has been described: 11 members of a four generation family from New Jersey of English origin with PME developed a disorder in their 4th decade characterized by dementia, nystagmus, myoclonus, and associated generalized tonic-clonic seizures. Progressive cerebellar ataxia was present, and the average duration of illness was 7 years[3].

The genetics of the various forms of NCL demonstrates that they are heterogeneous disorders with common pathologic and clinical features (Table 5).

1.6.5.3 Myoclonus

In the AD form of NCL, presenting as PME, myoclonus was associated with tremor and voluntary movement increased the severity of myoclonus and could elicit massive myoclonias[3]. In the juvenile form of NCL, myoclonus is described as fragmental, segmental and massive[49]. In Kuf's disease it is described as "elementary or complex, of variable extent, and occurs in irregular paroxysms, sometimes synchronous in all affected muscles, resulting in universal myoclonic discharges"[22].

1.6.5.4 Pathophysiology

Widespread accumulation of autofluorescent lipopigment inclusions in various organs is a characteristic feature. The inclusions, which under the electron microscope appear as fingerprint profiles, or as curvilinear and granulomatous bodies, may not always be detected or correctly interpreted, leading to missed diagnoses[149]. Early investigators were struck by the widespread nature of abnormal neurons, and Zeman et al stated "in our collective material there was no type of neuron,nor any topographical region consistently exempt from lipopigment accumulation" [143]. However, the most severe nerve cell loss occurs in the cerebellar cortex.

The curvilinear profiles, which are comprised of lamellae showing alternate light and dark lines, are contained in a membrane-bound cytosome, as are fingerprint profiles[142]. The lipopigment accumulates at a much earlier age than lipofuscin of aging, and differs from it in that it predominantly contains ceroid. Pronounced and selective neuronal vulnerability and total loss of small pigment-laden stellate cells, a local circuit neuron, has been demonstrated in the cortex of patients with juvenile neuronal ceroid lipofuscinosis[150].

1.6.5.5 Special Investigations

Assay of urinary sediment dolichols, which are lipid intermediates in the biosynthesis of glycoproteins, shows levels that are ten times higher than controls, and are particularly elevated in the infantile and late infantile forms [151]. Findings of special investigations are outlined in Table 4.

The clinical suspicion of NCL may be supported by electrophysiologic studies with the late infantile and juvenile types having characteristic findings on the EEG, electroretinography and VEP examination[47].

Table 4 Histological and Immunochemical Diagnosis (After Pearlman and Naidu, 2004)

	CLN1	*CLN2*	*CNL5*	*CNL3*	*CNL4*
Tissue	Skin	Skin	Skin	Skin	Skin
Diagnosis	Rectal	Rectal	Rectal	Rectal	Rectal
Electron Micrograph	Conjunctiva	Conjunctiva	Conjunctiva	Conjunctiva	Muscle
Inclusions	Granular	Curvilinear	Curvilinear	Fingerprint/ Curvilinear	Fingerprint/ Granular
Macular degeneration	+	+	+	+	-
EEG-isoelectric	1.5-2 years	-	-	-	-
Visual evoked potential	-	+++	+++	-	-
MRI-brain atrophy	++	+	+	+	+
Hypointensity,thalamus, and basal ganglia T2-weighted images	+	+	+	-	-

Diagnosis requires the demonstration of characteristic inclusions by electron microscopy. These can be found most simply in eccrine secretory cells, as well as in neurons, appendix, skeletal muscle and rectal mucosa[142;148;148]. The inclusions take various forms with curvilinear profiles being characteristic of a late infantile NCL, and fingerprint profiles being usual in the juvenile and adult forms, although a number of variations occur[142]. In Kuf's disease there is restricted, rather than generalized, neuronal involvement. The electron-microscopic evaluation of the skin may miss inclusions, and rectal biopsy has a higher rate of diagnostic success, although it is not commonly studied[145].

1.6.5.6 Neuropathology

In the dominant form of NCL, neurons from brainstem, frontal cortex, thalamus and cerebellum showed extensive PAS positive granule accumulation with neuronal loss in the substantia nigra. There was severe loss of Purkinje cells in the cerebellum and diffuse demyelination of the cerebellar and cerebral hemispheric white matter[3;3]. In infantile NCL, cortical neuronal loss and astrogliosis are seen, with a reduction in the density of white matter fibres. The basal ganglia showed similar changes, and there was variable Purkinje cell loss in the cerebellum with the dentate nucleus showing a large number of lipid flakes in degenerated neurons[152]. In a case of Kuf's disease, severe neuronal dropout was observed thoughout the cortex, with remaining neurons loaded with ceroid- lipofuscin granules. In the basal ganglia, basal ganglia, and the cerebellum had Purkinje cell loss and all neurons in the dentate were distended with ceroid- lipofuscin[148]. In a case with onset at age 49, widespread distention of neurons with lipofuscin was noted in the cortex, basal ganglia and spinal cord, with widespread Purkinje cell loss and neuronal loss in the dentate, without evident neuronal loss in the cerebral cortex[146]

1.6.5.7 Genetics

Loci for the various forms of NCL are outlined in Table 5.

Table 5 Genetic Information of NCL Variants (after Schiffman, 2004 and Gardiner, 2002)

Variant	Gene Name	Gene Product	Chromosome
Infantile	*CLN1*	Palmitoyl protein thioesterase	1p32
Late infantile	*CLN2*	Tripeptidyl peptidase	11p15
Late infantile Finnish variant	*CLN5*	"Battenin"	13q21.1-q32
Late infantile variant	*CLN6*		
Juvenile	*CLN3*	Endosomal/lysosomal transmembrane protein	16p12
Adult	*CLN4*		

1.6.5.8 Epidemiology

The NCL group of disorders appears to be panethnic, with a special predilection for the infantile subtype in Finland. The frequency is reported to be as high as 1:12,000 to 1:25,000 live births[153], and in Finland the infantile form alone has an incidence of 1:13,000 live births.

1.6.6 GM2 GANGLIOSIDOSES

Tay-Sachs disease, the prototype of the lysosomal sphingolipid storage disorders, is a hereditary disorder involving the accumulation of a ganglioside, GM2. The enzymatic defect in Tay-Sachs disease is a deficiency of the lysosomal enzyme beta-hexosaminidase A (HEX A or GM2 gangliosidase)[154], which is responsible for the cleavage of a terminal N-acetylgalactosamine from the GM2 ganglioside.

1.6.6.1 Diagnosis

Diagnosis is on clinical grounds with confirmation by biochemical analysis of beta-hexosaminidase A in serum, leucocytes and skin.

1.6.6.2 Inheritance

All of the variant forms of GM2 gangliosidosis are inherited as an AR trait.

1.6.6.3 Myoclonus

Watson and Denny-Brown described three families with familial amaurotic familial idiocy, in which myoclonus was present with movement or sudden stimuli[155]. In addition, seizures were precipitated by passive movement, sound and light in one case. In the third case a sudden passive movement would result in violent, clonic contractions of the muscle at first confined to the joint moved, but spreading rapidly if passive stretch was repeated. Sudden loud sounds or light flashes led to symmetrical clonic flexion movements of both upper and lower limbs and if this was repeated at a particular rate, the clonic response became self-sustained and resulted in a generalized seizures.

1.6.6.4 Clinical manifestations

Infantile onset

The infantile onset form is characterized by an excessive startle response. As the disease progresses, motor development slows and the children are unable to learn to sit, with associated axial hypotonia, increased tone, hyperreflexia and macular cherry-red spots[156]. During the second year of life, macrocephaly becomes apparent, presumably caused by intraneuronal storage of gangliosides and other lipids, and concomitantly, seizures may develop which can be induced by auditory stimuli. Myoclonus is characteristic of the initial stages [22]. Between the second and third years of age the children become severely cognitively impaired, decerebrate, blind, and unable to respond to most stimuli.

Late-onset.

The late-onset (juvenile/adult) variant of GM2 gangliosidosis, and has an indolent clinical presentation. Although this variant has been called the "adult-onset variant," the illness usually begins in adolescence. Early gross motor development is normal, although affected individuals are are often considered clumsy and awkward as children. An intention tremor, frequently seen in the first decade, may be the first indication of a neurologic problem. Dysarthria also develops early, and difficulties in school may also be apparent. Myoclonus or seizures may be prominent early symptoms [22;68]. Dementia, ataxia, spasticity and dystonia present later[68;156]. During adolescence, proximal muscle weakness begins with fasciculations and atrophy that has an appearance of juvenile-onset spinal muscular atrophy[157]. Development of a broad-based ataxic gait usually follows, making walking even more difficult. Patients have may present in adulthood with depression, visual hallucinations, paranoid delusions and catatonic states[158 159].

1.6.6.4 Special Investigations

Enzyme analysis remains the most effective means of diagnosing patients with GM2 gangliosidosis. Although neuroradiological studies may be normal at first, the CT head scans in children with GM2 gangliosidosis eventually show low density in the basal ganglia and white matter, and increased signal intensity on T2-weighted MRI [160]. Late-onset forms of GM2 gangliosidosis have prominent cerebellar atrophy, especially of the vermis, but a normal-appearing cerebral cortex on CT or MRI scans, despite cognitive decline and psychosis[158].

Initially, the EEG in Tay-Sachs disease will frequently show slowing, but when seizures develop multifocal spikes may appear. Watson and Denny-Brown's case showed generalized synchronous and asynchronous bilateral spike and slow wave activity on a generally slow background with periodic bursts of slow waves[155].

Electron microscopic analysis of skin, conjunctiva, and rectal mucosa biopsies frequently shows storage of membranous cytoplasmic bodies or other electron-dense storage material within nerve cells and myelinated and unmyelinated axons[161]. Neuropathological findings characteristically are ballooning of neurons, with massive intralysosomal accumulations of lipophilic membranous bodies.

1.6.6.5 Neuropathology

A child with seizures and myoclonus came to autopsy, where all neurons were seen to be distended with lipid granules; there was extensive degeneration of cerebral cortex, and involvement of basal ganglia including globus pallidus, putamen and thalamus. In the

cerebellum, there was diffuse atrophy, with a virtually absent granular cell layer, marked reduction in Purkinje cells, and widespread gliosis[162].

1.6.6.6 Epidemiology

Tay-Sachs disease is inherited as an AR disorder. People of Eastern or Central European Jewish ancestry have a predilection for this disease, but other populations, specifically French-Canadians, also have a higher than average incidence of the disease. The carrier frequency is estimated to be 1 in 31 in the Jewish population and 1 in 277 in non-Jewish populations[163].

1.6.6.7 Management

Valproic acid appears to be the most efficacious anticonvulsant, and clonazepam and other benzodiazepines may prove effective in controlling severe irritability and psychiatric symptoms[159].

1.6.7 SIALIDOSIS

The sialidoses are the least common of the major forms of PME[68]. The term "sialidosis" refers to lysosomal enzyme defects arising from a deficiency of neuraminidase (sialidase), the enzyme which cleaves the terminal sialyl linkages of several oligosaccharides and glycoproteins[164]. Deficiency of the enzyme results in intralysosomal storage of glycoproteins in neuronal cells[165]. Sialidoses have also been referred to as mucolipidosis I, since the first patients described with this enzyme abnormality shared features of both the mucopolysaccharidoses and the sphingolipidoses [165]. Subsequently a separate group of patients, the cherry-red spot-myoclonus syndrome, was described. These patients presented in adolescence and adulthood, and are now referred to as sialidosis type I [166 167].

1.6.7.1 Diagnosis

The disorder is characterized by:

1. Visual loss.
2. A cherry-red spot on fundoscopy.
3. Myoclonus, often associated with simultaneous polyspike and wave discharge on EEG.
4. No mental deterioration.

1.6.7.2 Inheritance

The various forms of sialidosis are inherited in an AR manner [164].

1.6.7.3 Myoclonus

Stimulation, movement, or emotion usually induces the myoclonus [166]. As the disease progresses, the myoclonus may interfere with walking and sitting, and become so severe that it results in impaired bulbar function [47], particularly since the myoclonus is resistant to therapy[49]. Generalized seizures in two patients have been noted to be the climax of a series of myoclonic jerks [166].

1.6.7.4 Clinical Manifestations

The primary neuraminidase deficiencies can be divided into two groups [164].

Sialidosis-type I (primary neuraminidase deficiency without dysmorphism):

The illness begins in adolescence (range 8-29 years) and patients usually have normal growth, physical appearance, and intellect[168]. This form is associated with the myoclonus-cherry-red spot phenotype, with severe myoclonus, progressive visual failure, tonic-clonic seizures and ataxia[68;169]. Lens opacities and a mild peripheral neuropathy may occur [68].

Sialidosis-type II:

Congenital, infantile and juvenile types occur, with mental retardation being the predominant feature of the first two types [169]. Patients are more severely affected than in type I, with early onset of a progressive mucopolysaccharidosis-like phenotype, with short stature, bony abnormalities, lens opacities, hearing loss and visceromegaly[164;169]. This condition occurs predominantly in Japan[68]. In addition, during adolescence most patients develop macular cherry-red spots associated with progressive decline in visual acuity. This is associated with myoclonus and ataxia, tonic-clonic seizures, as well as dementia [68].

Andermann described four members of three sibships from Quebec, who developed a tremor of the fingers, progressing to severe action and spontaneous myoclonus in the late teens and associated with clonic seizures[170]. Renal failure developed rapidly three to four years after the onset of neurologic symptoms in three patients; in the fourth, it preceded the neurologic syndrome. Assays of leukocyte alpha-neuraminidase revealed almost complete absence of activity.

1.6.7.5 Pathophysiology

A deficiency of neuraminidase results in excessive amounts of urinary and tissue concentrations of compounds containing N-acetylneuraminic acid.

1.6.7.6 Special Investigations

The presence of cherry-red spots in the macular region of the fundus and a downhill clinical course may make the sialidoses difficult to distinguish from Tay-Sachs disease or other lysosomal storage disorders.

X-rays may show dysostosis multiplex, and vacuolated lymphocytes and bone marrow foam cells may be seen[169]. Analysis of the oligosaccharides in urine distinguish sialidoses from other disorders of oligosaccharide metabolism, such as mannosidosis, fucosidosis or aspartylglycosaminuria.

1.6.7.7 Pathology

Allegranza reported a case characterized by myoclonus and GTCS, with features of cortical myoclonus[171]. PAS positive material stained virtually the entire neuronal population of the brain and spinal cord. In the olivary nuclei and dentate nucleus it formed an homogenous mass, being finely granular in other neurons. The cerebral white matter was preserved. There was moderate neuronal loss in the substantia nigra, and there was loss of Purkinje cells with rarefaction of the granular layer. In the spinal cord, the dorsal column nuclei showed severe neuronal loss.

1.6.7.8 Genetics

Sialidoses arise from mutations in the neuraminidase gene[172].

1.6.7.9 Management

The myoclonus is poorly controlled by medication.

1.6.8 MITOCHONDRIAL DISEASE

The identification of mitochondrial diseases, and particularly MERRF, as a cause of PME[68] also led to a major controversy as to the causes and usefulness of the Ramsay-Hunt syndrome (discussed in section 1.5.) MERRF is historically unique in two senses: it was the first disease in which maternal inheritance was clearly demonstrated, indicating a defect of mitochondrial DNA, and it was also the first disorder in which a molecular defect was associated with epilepsy[173].

1.6.8.1 Diagnosis

The place of mitochondrial disorders as a cause of the PME syndrome was highlighted in a review of patients from the Montreal Neurological Institute by Berkovic[46]. Eighty-four cases of PME in 53 sibships were studied. Thirteen patients had MERRF comprising one family with multiple affected members and seven sporadic cases. Myoclonus was usually the first symptom. Myoclonus and ataxia were the central features in 11 cases, these patients having all previously been diagnosed as having RHS. Clinical evidence of myopathy was usually absent or mild, but was sometimes prominent. Less frequent features included optic atrophy, hearing loss, neuropathy, pes cavus, short stature, endocrine abnormalities and subcutaneous cervical lipomas.

1.6.8.2 Inheritance

The disorder is maternally inherited.

1.6.8.3 Clinical Manifestations

Onset is usually in childhood, although adult onset is not uncommon, with the mean age being 21 years (range 5-42 years)[174]. Myoclonus and ataxia are constant features of MERFF, and tonic-clonic seizures are usual, with other features including short stature, hearing loss, optic atrophy, neuropathy, and migraine[175 176-178].

The prognosis of the disorder is variable, and mildly affected cases may not progress [173]. Although dementia may occur, and significant neurological deficits such as cortical blindness are described, MERRF usually has a relatively long course and only mild behavioural and cognitive deficits [174]. The disease may vary in its extent in particular families, and otherwise asymptomatic older relatives may, for example, only have hearing loss[173].

It is possible that some reports of PME associated with Friedreich's ataxia represent cases of MERRF. Prominent amongst these are the twins originally reported by Ramsay-Hunt, who had myoclonus, ataxia, absent reflexes, pes cavus and loss of sensation in the legs (see Section 1.5.1). Similarly, a report by Ziegler et al entitled Myoclonic Epilepsia Partialis

Continua and Friedreich Ataxia describes a patient who had myoclonus, generalized seizures and spike and wave discharges on EEG[179].

Similarly, the May-White Syndrome is a familial disorder with variable penetrance which causes PME associated with deafness and ataxia [53;180], and has been associated with a mitochondrial myopathy[68].

1.6.8.4 Special Investigations

Lactate levels in serum or CSF may be elevated[68], and skeletal muscle classically shows ragged-red fibers. However, the latter are not a reliable marker and are not invariably found in affected members of well-studied families[173].

1.6.8.5 Pathology

Baraitser reported on a 74 year old patient with a history of myoclonus, ataxia and deafness[180]. The basal ganglia and brainstem were normal, apart from some gliosis of the inferior olive; there were foci of laminar necrosis in the pericallosal gyrus and loss of the pyramidal cells in Ammon's horn. In the cerebellum, there was neuronal loss in the dentate nucleus, reduction in white matter volume and mild reduction in Purkinje cells. There was moderate pallor of the gracile tract in the spinal cord.

Skre reported on a family with myoclonic epilepsy and dementia, associated with peripheral neuropathy and external ophthalmoplegia. There was diffuse atrophy of the cerebral cortex[181]. There was diffuse atrophy of the cerebral cortex, with demyelination of white matter, sponginess of the thalamus and minor changes in the striatum. In the brainstem, there was degeneration of the pontine and red nuclei. The cerebellum showed loss of Purkinje cells, myelin loss in the white matter and some atrophy of the dentate nucleus. In the spinal cord, there was marked atrophy of the dorsal columns, with atrophy of anterior horn cells and Clarke's columns. Berkovic reported findings from three cases of MERRF: the cortex was normal, but the brainstem showed diffuse gliosis, and neuronal loss in the red nucleus and inferior olive[46]. In the cerebellum, there was mild loss of Purkinje cells, considerable loss of neurons in the dentate nucleus and astrocytic gliosis throughout the white matter, densely around the dentate nucleus. In the spinal cord, there was pallor of the dorsal columns.

1.6.8.6 Genetics

Molecular defects include the A8344G mutation of the $tRNA^{Lys}$ gene of mitochondrial DNA [182]. This mutation is also sometimes a cause of Leigh's syndrome. Two other mutations associated with MERRF are also in the $tRNA^{Lys}$ gene (T8356C and G8363A)[138]. The gene

symbol is MTTK (previously MERRF). Mutations associated with myoclonic seizures are also found in the $tRNA^{Leu}$ gene, which is usually linked with mitochondrial encephalopathy, lactic acidosis and strokes[183].

1.6.9 NEUROSERPIN MUTATIONS

The protein neuroserpin has recently been found to be involved in the pathogenesis of a novel form of PME[4]. Two families have been described, one from New York[184], and one from Indiana[185].

1.6.9.1 Diagnosis

The pathological hallmark is an eosinophilic inclusion body found in neurons, termed the neuroserpin body (NB). Neuroserpin is a member of a large family of serine protease inhibitors.

Berkovic has also reported on five cases of atypical inclusion body PME, a condition which may be similar to that described due to neuroserpin mutations[186 187].

1.6.9.2 Inheritance

Inheritance follows an AD pattern. In the report of Takao et al, the proband's mother presented at age 25 with PME and died at age 37 years, and his brother was also affected with PME[185]. A paternal uncle and sibling of a paternal grandmother died of epilepsy with psychosis and pathologically confirmed Alzheimer disease respectively. The pedigree of this family consisted of 46 members over 7 generations.

1.6.9.3 Clinical Manifestations

The proband of the Indiana family had generalized seizures followed by action myoclonus, associated with a decline in work performance and memory[185]. Various seizure types were noted, including myoclonic, complex partial and tonic-clonic, often refractory to medical treatment, with several episodes of status epilepticus.

On examination, dysarthria and nystagmus were present, with hyperreflexia, except for absent ankle reflexes and distal sensory loss. Myoclonus was noted in the extremities.

Severe dementia developed by age 38, five years before death.

As noted in Takao's report, the proband's mother had PME, and the proband had action myoclonus, and generalized seizures at night[185]. The seizures subsequently worsened and included myoclonic and complex partial seizures. Subsequently, he developed nystagmus, dysarthria, cognitive decline, hyperreflexia and a sensorimotor neuropathy.

The individuals with the S49P mutation (New York family) presented at a later age, around the fifth decade, and developed dementia[4;184], whereas members from both the Indiana and Oregon families, who have the S52R mutation, developed PME associated with dementia[188 4].

1.6.9.4 Pathophysiology

Neuroserpin is a serine protease inhibitor mainly expressed in the central nervous system, and is a regulatory element of extracellular proteolytic events, inhibiting the activity of a tissue plasminogen activator. Mutations are associated with polymerization of the protein.

1.6.9.5 Special Investigations

The proband of the Indiana family's EEG showed frequent spike and wave complexes. Nerve conduction studies demonstrated a distal axonopathy. MRI showed mild cerebellar atrophy at the age of 35.

1.6.9.6 Pathology

The most striking finding is the presence of NBs in neuronal perikarya and neuropil within the gray matter of cortex and spinal cord, with striking cortical pathology as well as involvement of subcortical nuclei [185].

There was moderate neuronal loss in the cerebral cortex with numerous NBs. The basal ganglia showed mild neuronal loss and gliosis associated with NBs. In the brainstem, there was neuronal loss in the substantia nigra and locus ceruleus and in the cerebellum, moderate loss of Purkinje cells, and mild gliosis of the cerebellar white matter. Gliosis was also noted in the dentate nucleus, although the cerebellar cortex and dentate were virtually free of NBs. NBs were seen in the spinal cord, in Clarke's nucleus, the posterior columns and anterior horn cells. Takao et al. commented that the distribution of NBs involved practically all cortical layers of both association and projection cortices as well as multiple subcortical neuronal populations, making a specific clinicopathologic correlation relevant to the myoclonus difficult, with relative sparing of cerebellar cortex and dentate nucleus.

1.6.9.7 Genetics

Three families have been reported. Mutations cause either a proline for serine substitution at residue 49 or an arginine for serine substitution at codon 52 in exon 2.

1.6.10 HALLERVORDEN-SPATZ SYNDROME (HSS)

HSS is a rare cause of PME [68;189]. Myoclonus is generally uncommon in HSS and other similar conditions which are associated with axonal spheroids and excessive pigment in the basal ganglia[190].

HSS typically starts in childhood and adolescence and manifests with choreathetosis, dystonia, rigidity, bulbar dysfunction, and dementia, although onset may occasionally be in adulthood[190]. The Hallervorden-Spatz eponym has unpleasant connotations due to Hallevorden's involvement in euthanasia programs conducted in Nazi Germany, and suggestions have been made that the term "Panthothenate kinase associated neurodegeneration" replace HSS[191]. However,mutations of the PANK-2 gene are not invariably found, indicating both genetic heterogeneity as well as nosological difficulties in using the term PANK-2 to replace HSP, and the term "neurodegeneration with brain iron accumulation type 1" has been proposed for this subgroup[192].

1.6.10.1 Diagnosis

Obligate features (from Swaiman[193]):

1. Onset during the first two decades of life.
2. Progression of signs and symptoms.
3. Evidence of extrapyramidal dysfunction, including one or more of the following: Dystonia, rigidity, and choreoathetosis.

Corroborative features[193]:

1. Corticospinal tract involvement.
2. Progressive intellectual impairment.
3. Retinitis pigmentosa or optic atrophy.
4. Positive family history consistent with AR inheritance.
5. Hypodense areas on MRI involving the basal ganglia, particularly the substantia nigra (most obvious in children during the first decade of life).
6. Abnormal cytosomes in circulating lymphocytes or sea-blue histiocytes in bone marrow[194].

1.6.10.2 Inheritance

The range of clinical presentations, and the fact that PANK-2 mutations are not always found, suggests that there are several conditions that are either genetically distinct or

represent allelic variants. When familial, the condition appears to be inherited as an AR condition, with consanguinity present in some instances.

1.6.10.3 Clinical manifestations

Clinical manifestations of HSS vary, and the clinical course varies between rapid progression to death over 2 years to a more protracted one[193].

In a review, Dooling and E.P. Richardson summarized the clinical features and postmortem examinations of 64 individuals with possible HSS[195]. Both clinical and pathological features were required in order to make the diagnosis, and they identified three groups of patients. Their group III patients are of interest with respect to the differential diagnosis of PME, since they were defined as having pathological changes similar to the typical cases but clinically had a wide range of presentations including childhood mental retardation, alcoholism and "senility", as well as cases manifesting with myoclonus, ataxia, tremor, seizures, and spasticity. Gilman and Barret reported the case of a girl who died at age 17 years, with a 9 year history of progressive cerebellar signs, hyperreflexia and focal myoclonus of the right arm and seizures. Autopsy showed rusty discolouration of the globus pallidus[190].

The adult type is rare, presenting typically with a problem of a movement disorder, the nature of which may be more varied than in the early-onset types. At times athetosis, chorea, and myoclonus may predominate; nevertheless, dystonia is the most frequently associated movement disorder. Megalencephaly, mental retardation and dopa responsive Parkinsonism with HSS[196] have been described, although there is typically a poor response to levodopa[192]. Atypical presentations associated with PANK mutations will usually have palilalia, dysarthria, perseverative behaviour and dystonia with progressive dementia and freezing similar to that seen in Parkinson's disease[197].

1.6.10.4 Pathophysiology

Pantothenate kinase is a regulatory enzyme in the pathway leading to synthesis of coenzyme A; its product reacts with cysteine. PANK2 mutations lead to loss of function and accumulation of cysteine, an iron chelator. Excess cysteine may react with accumulated iron, leading to oxidative stress and neurodegeneration.

In the normal brain, iron is increased in the globus pallidus, SNc and SNr, red nucleus, and cerebellar dentate nucleus. In HSS there is increased iron content in the globus pallidus and SNr, with the rust-brown pigmentation of these regions being a striking neuropathologic feature. The iron granules are located in large astrocytes, microglial cells, and neurons. There are asymmetric partially destructive lesions of the globus pallidus, especially the GPi.

Spheroids, which are large round structures containing pigment granules and surrounded by glia, are presumed to represent swollen axons. In HSS, they exist in large numbers in white and gray matter, as well as the subthalamic nucleus, pallidum and substantia nigra, an appearance suggestive of neuroaxonal dystrophy[193].

Other pathological features associated with Hallervorden-Spatz syndrome include neurofibrillary tangles (NFT) and Lewy bodies in a case associated with myoclonus. Lewy bodies are seen in the substantia nigra, substantia innominata, dorsal nucleus of vagus, and locus ceruleus and showed immunostaining with α-synuclein[198 199].

1.6.10.5 Special Investigations

MRI studies demonstrate hypodensity in the basal ganglia, most pronounced in the globus pallidus due to the paramagnetic effect of iron and associated T2 shortening[200]. HSS patients often manifest an area of higher signal intensity in the central or anteromedial part of the globus pallidus, termed the "eye of the tiger" [200], which correlates strongly with the presence of a PANK2 mutation[197].

1.6.10.6 Neuropathology

In a case reported by Yakovlev in 1942 (with pes cavus and maternal inheritance raising the possibility of a mitochondrial disorder) as a “case of myoclonus epilepsy with atrophy of brainstem and Hallervorden-Spatz type of pathologic change in the pallidum, substantia nigra and dentate nucleus[189]. There was marked atrophy of the globus pallidus, status marmoratus of the putamen and iron pigement in the pallidum, substantia nigra and dentate nuclei, and widespread atrophy in the cerebellum with Purkinje cell loss and atrophy and gliosis of the dentate nucleus; in the brainstem there was atrophy of the olive and pallor of the medial lemniscus, spinocerebellar fibers and nuclei and tracts of Goll.

1.6.10.7 Genetics

PANK2 mutations are associated with all cases of classic HSS and one third of cases with atypical disease[197].

1.6.11 JUVENILE NEUROAXONAL DYSTROPHY

Neuroaxonal dystrophy, typically a disease of infancy or childhood and may rarely present in late childhood or adolescence as a PME[68]. Additional clinical features include dementia, ataxia, chorea, and lower motor neuron involvement[201;202]

Two familial cases of neuroaxonal dystrophy with PME were reported by Scheithauer, who distinguished them from HSS since there was no iron deposition in the globus pallidus or substantia nigra [203]. Dorfman et al described two brothers with PME associated with cerebellar ataxia and cognitive decline that commenced in the second decade[201]. The age of onset and rate of progression would favour HSS, but pathology was typical of neuroaxonal dystrophy. These cases may represent a transitional state between the two conditions, and the authors therefore proposed the term juvenile neuroaxonal dystrophy to illustrate this.

Infantile neuroaxonal dystrophy includes a broad category of patients with variable clinical presentations. The onset of illness is usually at the end of the first or beginning of the second year of life. Infantile neuroaxonal dystrophy and HSS may be variants of neuroaxonal dystrophy, since similar pathological findings are found in the two conditions[201]. However, HSS usually starts later, and progresses more slowly, and the presence of iron containing pigment in the basal ganglia is uncommon in neuroaxonal dystrophy[201].

1.6.11.1 Diagnosis

The neuropathological hallmark of this disease is the presence of spheroids, which are dystrophic axonal swellings found in great abundance throughout the nervous system of affected individuals.

1.6.11.2 Myoclonus

The two patients of Dorfman et al developed myoclonic jerks of the upper body, particularly in the morning. In one, myoclonus became more severe and was associated with generalized tonic-clonic and absence seizures. The myoclonus could be precipitated by any muscle activity and was associated with a progressive dementing illness and ataxia. Myoclonus in the other patient was described as being a severe action type of myoclonus, which interfered with any purposeful movement and was sometimes so violent that he would be thrown to the ground[201].

1.6.11.3 Clinical Manifestations

Infantile neuroaxonal dystrophy is characterized by delayed milestones and subsequently combinations of pyramidal tract signs, dystonia, rigidity with dementia and seizures, lower motor neuron involvement, and early visual disturbances.

1.6.11.4 Pathophysiology

Similar spheroids to those of neuroaxonal dystrophy are also found in HSS. Although seen in other diseases, including ataxia-telangiectasia and Tay-Sachs disease, spheroids are particularly numerous in infantile neuroaxonal dystrophy and HSS and may reflect the primary pathophysiological process. However, in HSS the dystrophic axonal swellings are largely confined to the basal ganglia, whereas they are widespread in neuroaxonal dystrophy[201]. However there are transitional cases in which intermediate clinical and neuropathological features are found[201]. Cerebellar atrophy and degeneration of the posterior columns, pyramidal tracts, spinocerebellar tracts and optic pathways are also noted [190].

1.6.11.5 Special Investigations

Infantile neuroaxonal dystrophy is characterized by typical spheroids in cortical or peripheral (skin and conjunctival) biopsies. In the cases of Dorfman et al, the EEG showed a slowed background, with frequent occipital spikes, rhythmic delta and a photoparoxysmal response. The amplitudes of evoked potentials were increased in size, suggesting that myoclonus may have been of cortical origin[201].

1.6.11.6 Neuropathology

Scheithauer reported on the case of two siblings with neuroaxonal dystrophy[203]. They developed myoclonus associated with other seizure types, associated with ataxia and dementia. Dystrophic swellings were noted throughout the cortex, and dense spheroid accumulation in the external globus pallidus and thalamus, and to a lesser extent in the caudate nucleus, and putamen. Similarly, there was dense spheroid accumulation in substantia nigra and red nucleus and the dentate nucleus. There was marked cerebellar atrophy, with virtually complete Purkinje cell loss and gliosis of the entire cerebellum, including the white matter.

Wakabayashi reported a case with a spastic tetraparesis, who developed myoclonus and dementia and GTCS[198]. Pigmented, iron positive granules were found scattered throughout the neuropil and round blood vessels. Numerous axonal spheroids were present throughout the nervous system. There was virtually complete absence of cerebral, neostriatal and globus pallidus neurons. Similarly, there was moderate loss of Purkinje cells and granule

cells and prominent axonal spheroids in the dentate nucleus. There was marked neuronal dropout in the substantia nigra.

1.6.12 COELIAC DISEASE

An extensive clinical and pathological review of 16 cases of coeliac disease from Birmingham reported the presence of dementia, peripheral neuropathy and spinal cord dysfunction [204]. In addition, many patients had ataxia, in some of whom there was also position sense loss[204].

1.6.12.1 Clinical Manifestations

The first report of myoclonus associated with coeliac disease was that of Finelli et al in 1980 [205]. They described a 56 year old man who developed generalized ataxia with nystagmus. Despite a gluten free diet, his condition deteriorated and he developed rhythmic tremor of the eyelids, chin and palate.

Bhatia et al reported four patients with progressive myoclonic ataxia associated with coeliac disease [206].

1.6.12.2 Myoclonus

Bhatia et al's cases had action myoclonus, stimulus sensitive myoclonus and two had seizures[206].

1.6.12.3 Special Investigations

Electrophysiology appears typical of cortical myoclonus[206].

1.6.12.4 Neuropathology

In Finelli's case, at autopsy there was marked cerebellar atrophy with loss of neurons in the dentate nucleus and marked Purkinje cell loss[205].

In Bhatia et al's report, autopsy of one patient revealed atrophy of the cerebellar hemispheres [206]. Histology of the cerebral cortex was normal, as were the basal ganglia and thalamus. There was marked loss of Purkinje cells in the cerebellum with marked Bergmann astrocytosis. There was astrocytosis of the internal granular cell layer and of the dentate nucleus, and olives with mild neuronal loss in the latter.

In a case of celiac disease, associated with GTCS and ataxia, in the cerebellum there was neuronal atrophy in the dentate nucleus and astrocytic hypertrophy, with focal Purkinje cell loss throughout the cerebellar cortex. Neuronal atrophy with perivascular cuffing with lymphocytes was seen in the olivary nuclei[204].

1.6.13 BIOTIN DEFICIENCY

1.6.13.1 Diagnosis

This is a form of myoclonus characterized by biotin deficiency

1.6.13.2 Myoclonus

Low amplitude spontaneous and action-induced multifocal myoclonus.

1.6.13.3 Clinical Manifestations

Bressman and Fahn described a female patient who had some unsteadiness of her trunk as an adolescent and in her third decade became aware of jerking movements of the trunk as well as increasing deafness and difficulty walking [207]. A year later seizures developed and subsequently she developed a sustained right hemiparesis after a right focal seizure. On examination, she had saccadic pursuit, slowed saccades and sensori-neural hearing loss. There was marked limb and gait ataxia and myoclonus present.

1.6.13.4 Special Investigations

Biotin levels.

1.6.13.5 Pathophysiology

This disorder probably falls in a group of biotin-responsive multiple carboxylase deficiencies (MCD). Late onset or juvenile MCD typically appears in the first months of life and clinical features include skin rash, ataxia and hearing loss [208]. The likely cause of the disorder is a deficiency of Biotinidase.

1.6.13..6 Management

Patient responded to biotin supplements

1.6.14 GAUCHER DISEASE (GD)

The condition of non-infantile, neuronopathic Gaucher's Disease is characterized by the features of PME.

GD is a lysosomal storage disorder resulting from deficient activity of glucocerebrosidase and the accumulation of its substrate, glucocerebroside, made up of a long chain amino alcohol (sphingosine), a long chain fatty acid and a molecule of glucose [209]. The storage material occurs primarily in cells of the macrophage-monocyte system, resulting in a multisystem disease with progressive visceromegaly and gradual replacement of the marrow with distinctive lipid-laden macrophages, the Gaucher cells[210].

There are three subtypes, with types 2 and 3 having neurologic involvement. Type 2 disease progresses rapidly, resulting in death in early childhood [209] and is characterised by bulbar palsy, hepatosplenomegaly, spasticity and seizures [211].

Type 3 disease (the juvenile form) has been subclassified into types 3a and 3b. Patients with type 3a disease have progressive neurologic deterioration, often with recurrent myoclonic and generalized tonic-clonic seizures and moderate hepatosplenomegaly[210]. Neurological signs include horizontal supranuclear gaze palsy, dementia, spasticity and ataxia [209]. Type 3b is characterized by significant hepatosplenomegaly and supranuclear gaze palsies, the latter being the sole neurological sign [209]. A family in which two siblings with slowly progressive, late onset myoclonus, intention tremor and gaze palsies has been described[211]. PME as a result of Gaucher's disease has been described in an adult, commencing at the age of 17[212].

1.6.14.1 Diagnosis

Diagnosis is confirmed by markedly reduced ß-glucosidase activity towards the substrate, glucosylceramide.

1.6.14.2 Myoclonus

Myoclonus is described as being progressive, refractory to medication and stimulus sensitive[211]. Typically, jerks begin in the limbs and become progressively more stimulus sensitive, reacting to noise or touch. Negative myoclonus may also be observed. Both myoclonic and generalized seizures may occur.

1.6.14.3 Clinical Manifestations

Progressive neurological deterioration, with frequent myoclonic seizures and hepatosplenomegaly.

1.6.14.4 Special Investigations

EEG may show spike and wave discharges, either multifocal or diffuse [212] [213;214]SEPs may be significantly increased in amplitude in patients with type 3 Gaucher disease [215].

1.6.14.5 Pathophysiology

In type 3 GD there is neuronal loss in cortical and subcortical structures [209], and Gaucher cells may be present in brain parenchyma [214].

1.6.14.6 Neuropathology

Verghese reported on a case with onset of Gaucher disease in the second year of life, with stimulus sensitive myoclonus and normal EEG. Cerebral cortex was normal, as were the basal ganglia and brainstem, excepting for Alzheimer type 2 astrocytes in the SN, and the inferior olivary nucleus. There was marked loss of neurons in the cerebellar dentate nucleus with many of the residual neurons showing pyknosis and nuclear condensation. The fiber loss was selective to the dentatorubrothalamic pathway with loss of fibers in the superior cerebellar peduncle but not in the cerebellar white matter or the other peduncles[210]. Conradi reported on a young child with severe myoclonus and spike and wave activity on EEG[214]. The cerebral cortex and white matter showed focal alterations consisting of intra-parenchymal and perivascular accumulation of Gaucher's cells. The dorsal tegmentum, pons and medulla showed Gaucher's cells and astrocytosis and astrogliosis around capillaries to varying degrees[214]. There was a slight loss of Purkinje cells and the granular cell layer was affected by a focal, severe loss of granule and Golgi cells, as well as astrogliosis and intra-parenchymal Gaucher's cells[214]. The dentate nucleus showed a severe loss of neurons with astrocytosis and astrogliosis.

Winkelman described two siblings with Gaucher disease, one of whom had myoclonus which worsened prior to a seizure[211]. Cerebral cortex and brainstem were normal, although collections of Gaucher cells were widely disseminated in the basal ganglia and subcortical white matter[211]. . Relatively diffuse involvement of the brainstem was present, with neuronophagia and nests of microglia. The inferior olive showed diffuse astrogliosis, and there was severe disease of the dentate, fastigial, and emboliform nuclei, with preservation of the Purkinje cell and granule cell layer[211].

1.6.14.7 Genetics

Mutations in the glucocerebrosidase gene include point mutations, insertions and substitutions[209].

1.6.15 ANGELMAN SYNDROME

An example of myoclonus associated with tremulous activity is that of Angelman syndrome. Patients display rapid jerking resulting in a coarse distal tremor, with associated electrophysiological features of cortical myoclonus[216].

1.6.15.1 Diagnosis

Angelman syndrome is a condition of severe mental retardation with characteristic facies, seizures and a “puppetlike” motor pattern, consisting of ataxic gait, jerky limb movements and tremulousness[216].

1.6.15.2 Inheritance

Paternal deletion of chromosome 15q11-13 is associated with 60 % of cases[217].

1.6.15.3 Myoclonus

Patients studied by long-term video-EEG and EMG monitoring demonstrated very rapid jerking of variable amplitude. Myoclonus was brought out by voluntary movement and also occurred at rest in prolonged runs. Muscle bursts typically started in the face or hand and then spread, with recruitment of muscles in a rostrocaudal sequence. Myoclonus was associated with rhythmic 5 to 10 Hz sinusoidal or sharp activity (Figure 3), seen in the contralateral hemisphere or bilaterally, but EEG activity was not time-locked to the myoclonus.

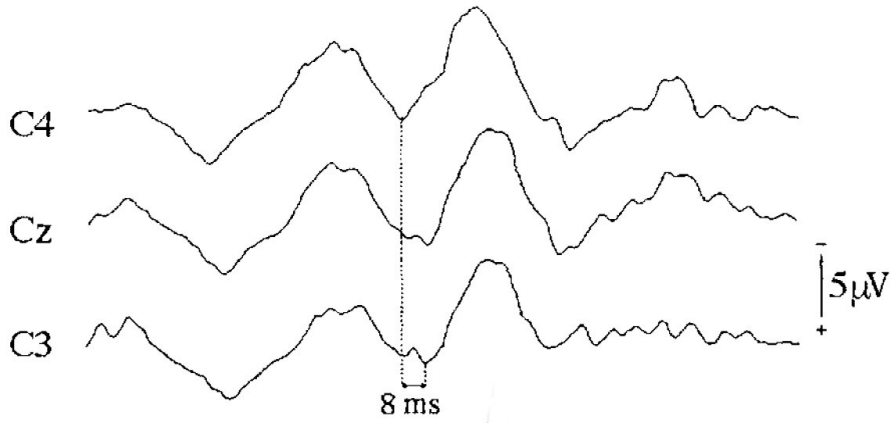

Figure 3. Rhythmic sinusoidal activity (from Guerrini et al., 1996).

1.6.15.4 Clinical Manifestations

Manifestations include severe mental retardation, microcephaly, inappropriate laughter, and seizures.

1.6.15.5 Pathophysiology

The majority of patients have a deletion of chromosome 15q11-13[217]. This is associated with a deletion of $GABA_A$ receptor genes ($\beta 3$, $\alpha 5$, $\gamma 3$). However, myoclonus is expressed similarly in patients without deletions [216].

1.6.15.6 Special Investigations

SEPs were not enlarged and the C-reflexes were not present[216].. However, JLA demonstrated a premyoclonus transient[216].

1.6.16 RETT SYNDROME

Rett syndrome is associated with dementia, and occurs in female children. There is a characteristic pattern with specific stages. Although development initially occurs normally, it ceases to advance around the age of one year. Thereafter, regression occurs, with development of dementia 1.5 years after the start of the illness.

1.6.16.1 Diagnosis

The condition is characterized by dementia, with associated features of autism, seizures, acquired microcephaly and truncal ataxia. The majority of patients tend to become bradykinetic. Myoclonus occurs in about half of patients older than 4 years.

1.6.16.2 Myoclonus

In a study by Guerrini, nine out of ten patients had myoclonus[218]. The myoclonus was multifocal and varied greatly in severity, occurred at rest, and was enhanced by voluntary movement. Bilateral or generalized myoclonus was not recorded.

1.6.16.3 Special Investigations

EEG showed slow background activity, with a 4-6 Hz rhythmic sinusoidal pattern typical of Rett syndrome. Myoclonus was only occasionally time-locked with spike discharges. However, all nine patients with myoclonus had a reproducible premyoclonic spike recorded by JLA.

SEPs showed a significant increase in the amplitudes of the N20-P30 and P30-N35 complexes. The C reflex was reported as being hyperexcitable in all patients[218]. .

1.6.16.4 Genetics

In 5 of 21 sporadic patients with Rett syndrome, Amir et al identified three de novo missense mutations in the gene encoding methyl-CpG-binding protein-2[219].

1.7. ANATOMY OF MYOCLONUS

1.7.1 ANATOMY OF THE BASAL GANGLIA

The functional unit of the striatum is made up of the caudate nucleus and putamen, separated from each other by the fibers of the internal capsule. The putamen and globus pallidus (GP) form the lentiform nucleus. The GP is divided into external and internal segments, the GPe and GPi respectively.

Basal ganglia output comprises three different components (Figure 4):

(1) A dorsal division, the lenticular fasciculus.

(2) A middle division, the fasciculus subthalamicus, which projects through the internal capsule to the subthalamic nucleus.

(3) A ventral division, the ansa lenticularis[220].

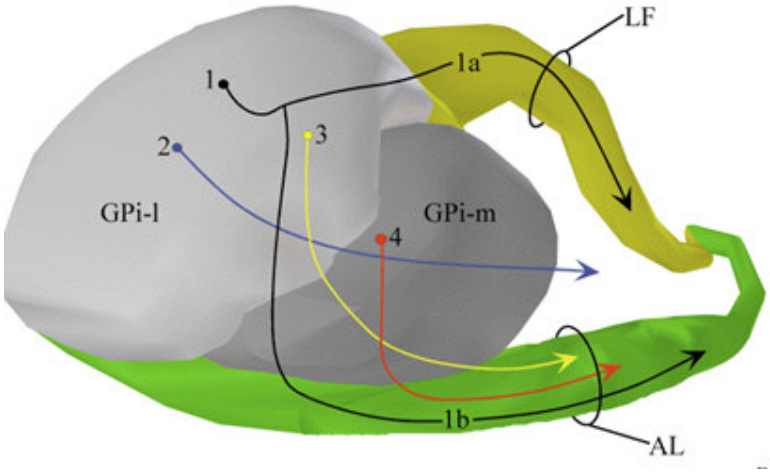

Figure 4. Projections of the GPi via the LF (lenticular fasciculus)and AL (ansa lenticularis) (Figure from Parent and Parent, 2004[220]).

The dorsal lenticular fasciculus fibers cross through the internal capsule and then sweeps caudally to reach the ansa lenticularis in Forel's field H. In so doing, they merge into field H2 of Forel;which is the area along the course of the lenticular fasciculus where the fibers of the fasciculus merge with the dorsal aspect of the subthalamic nucleus and the ventral aspect of the zona incerta (Figure 5). The ansa lenticularis courses ventromedially around the posterior limb of the internal capsule and then enters Forel's field H. Ultimately, the ansa lenticularis and lenticular fasciculus merge to form the thalamic fasciculus (Forel's field H1) located dorsal to the zona incerta.

In addition, Forel's Field H contains dentatothalamic and rubrothalamic fibers which merge with pallidofugal fibers. This region is therefore also called the prerubral field or the tegmental field.

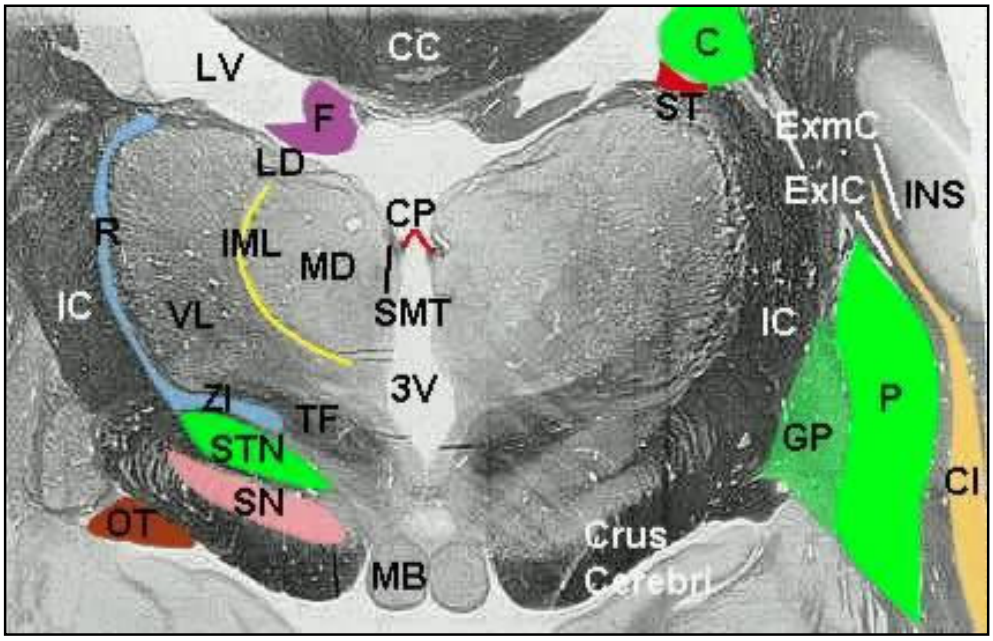

Figure 5. Anatomy of the subthalamic region (from Loyola University Medical Education Network [221])

1.7.2 ANATOMY OF THE SUBTHALAMIC REGION

The subthalamus is located between the H2 field of Forel and the internal capsule, and consists largely of the upward continuation of the tegmentum of the midbrain. It is found ventrolaterally to the thalamus, and separates the thalamus from the internal capsule. Caudally, the red nucleus and substantia nigra extend upwards into the subthalamic region, and the floor of the third ventricle lies medial. The zona incerta lies between Forel's fields H2 inferiorly and Field H1 medially.

1.7.3 ANATOMY OF THE CEREBELLUM AND CEREBELLAR OUTPUTS

The major efferent pathway of the dentate, emboliform and globose nuclei is through the hilum of the dentate and then to the brainstem via the superior cerebellar peduncle.

1.7.4 ANATOMY OF THE SUBSTANTIA NIGRA

The substantia nigra has two divisions, the pars reticulata (SNr) and pars compacta (SNc). The SNc has dopaminergic projections to the striatum, and the SNr serves as an outflow nucleus for the basal ganglia.

1.7.5 ANATOMY OF THE THALAMUS, AND THALAMIC CONNECTIONS:

The divisions of the thalamus are derived from the distribution of its major afferent systems. The ventral thalamus is divided into ventral anterior (VA), principal ventral medial (VMp), ventral lateral (VL), and ventral posterior lateral (VPL) thalamic nuclei. The VA has two components, magno- and parvocellular, termed the VAmc and VA respectively[222].

The VL and VPL nuclei are each subdivided into anterior and posterior subnuclei, termed VLa and VLp, and VPLa and VPLp (Figure 6)[223]. VL is also divided into the ventro-oralis anterior and posterior of Hassler (Voa and Vop) [224], noting that VLa is probably equivalent to Voa and Vop[223].

Olszewski gives a broadly similar breakdown, excepting that VL is divided into pars oralis (VLo), pars caudalis (VLc), pars medialis (VLm), pars postrema (VLps), and area X (Figure 6). VPL is divided into oral and caudal subnuclei, VPLo and VPLc. (VPLo, VLc, VLps and area X were termed VLp by Jones)[223].

According to the model grouping proposed by Morel, the ventral thalamus is grouped into two divisions [225] . Anteriorly, the schema is largely unchanged, comprising the VA, VL and VM nuclei. VA has a magnocellular subdivision (VAmc), VL is again divided into anterior and posterior components, but VLp is further subdivided into dorsal (VLpd), ventral (VLpv) and paralamellar (VLpv). However, the ventral posterior nucleus (VP) is divided into three main nuclei: the traditional ventral posterior lateral (VPL), ventral posterior medial (VPM) and ventral posterior inferior (VPI). VPL nucleus is divided into a pars oralis and caudalis.

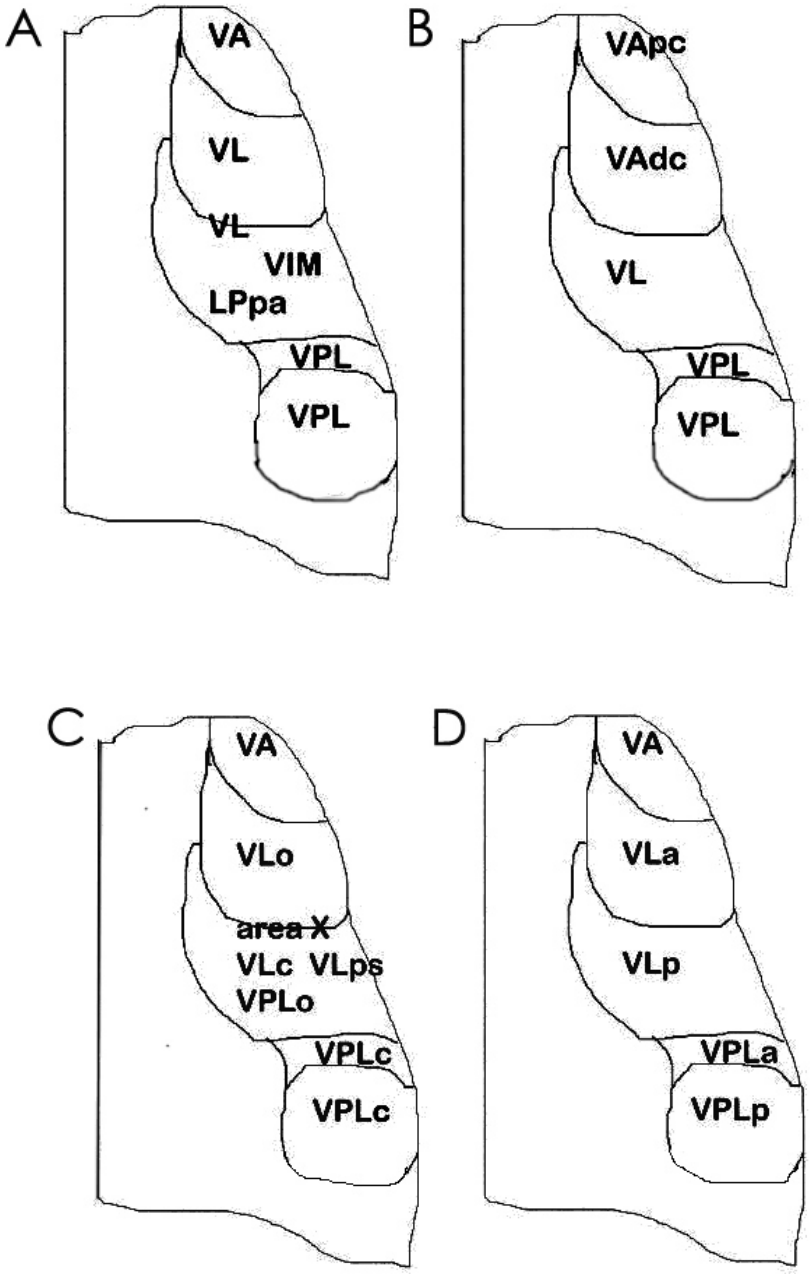

Figure 6. Comparison of monkey motor thalamus: nomenclature of Walker (A), Ilinksy (B), Olszewski (C) and Jones (D). (data derived from table 1, Macchi and Jones, 1987).

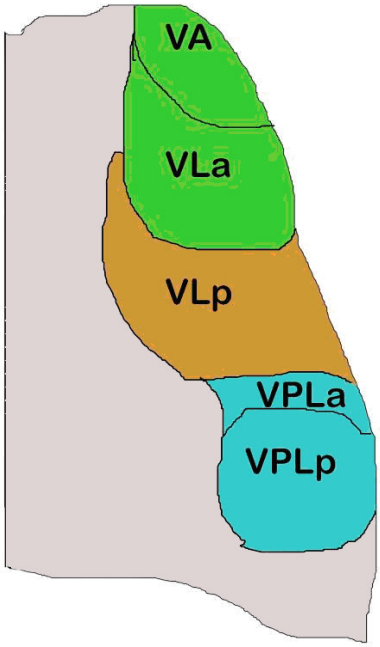

Figure 7. Input to Motor Thalamus: green is pallidal input, brown is cerebellar input and blue is lemniscal input[223].

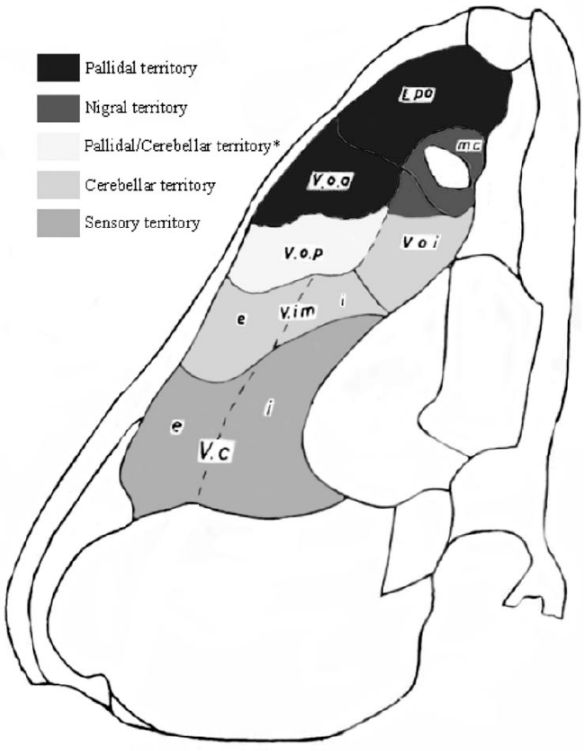

Figure 8. Connections of the thalamus (from Hamani et al., 2006).

1.7.5.1 Input to Thalamus (Figures 6,7,8 and Table 6)

Table 6. Connections of the thalamus (taken from Hamani et al.[222]

TABLE 2. Correlation between afferent projections to the motor thalamus and the thalamic nuclei described according to nomenclatures[a]

	Jones and Hirai and Jones	Ilinsky and Kultas-Ilinsky	Hassler
Nigral territory	VAmc	Vamc	Lpomc
	VMp	VM (part of the nucleus)	Voi (anterior part)
	VA (small part of the nucleus)		
Pallidal territory	VA (most of the nucleus)	VApc	Lpo
	VLa	VAdc	Voa
			Vop[b]
Cerebellar territory	VLp	VL	Voi (posterior part) Vop[a]
			Vim

[a] VAmc, ventral anterior nucleus magnocellular; Lpomc, lateropolaris magnocellularis; VMp, principal ventral medial; VM, ventral medial nucleus; Voi, ventro-oralis, internus; VA, ventral anterior nucleus; VApc, ventral anterior nucleus parvicellular; Lpo, lateropolaris; VLa, ventral lateral nucleus posterior; VAdc, ventral anterior nucleus densicellular; Voa, ventro-oralis anterior; Vop, ventro-oralis posterior; VLp, ventral lateral poaterior nucleus; VL, ventral lateral nucleus; Vim, ventrointermedius.
[b] Vop is represented twice because there is no consensus whether it is part of the pallidal or cerebellar territory of the motor thalamus (see text for details).

1.7.5.1.1 Substantia Nigra: the substantia nigra projects to VAmc and VA[223].

1.7.5.1.2 Basal Ganglia: According to the scheme of Jones, basal ganglia output is to the VA and VLa (this corresponds to Voa, Vop and Lpo of Hassler)[223]. In the scheme of Olszewski, basal ganglia projections are to VLo and most of VA[222].

1.7.5.1.3 Cerebellum: The major cerebellar input is to VLp. In the scheme of Olszewski, the input from the cerebellum is to VLc, VLps, area X and VPLo, noting that these nuclei and VLp correspond to one another[223]. In Hassler's scheme, Vop receives cerebellar inputs; and there is no consensus as to whether Vop lies in cerebellar or pallidal territory [222]. The Vim nucleus, a common site of functional surgery, is included in VLp.

1.7.5.1.4 Sensory: According to Jones; the VPL is a sensory nucleus, with the VPLa receiving deep lemniscal afferents, and the VPLp superficial sensory lemniscal fibers (Figure 9). In Olszewski's schema, VPLc is the region which receives lemniscal fibers, containing muscle reflex afferents[226]. Spinothalamic fibers project only to ventral VPLo,

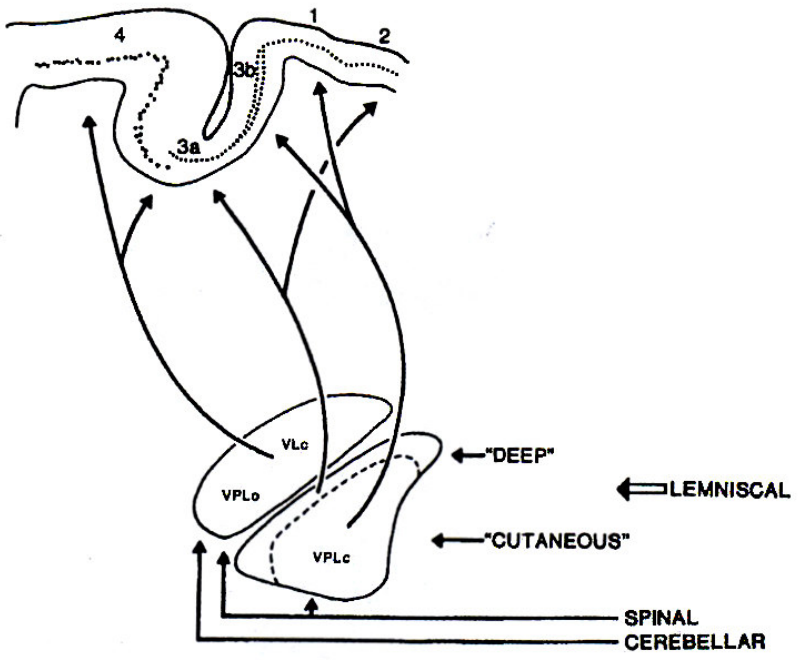

Figure 9. Diagram indicating thalamic lemniscal input from VPLc to cortical areas 3a, 3b, 1 and 2. Terminology of Olszewski (Figure from Jones, 1983[226]).

1.7.5.2 Thalamic Output:

1.7.5.2.1 Substantia Nigra: The region of thalamus that receives afferents from the substantia nigra projects to the SMA.

1.7.5.1.2 Basal Ganglia: VA and VLa innervate the SMA and preSMA; however, primary motor cortex and prefrontal motor cortex are also supplied from pallidal territory.

1.7.5.1.3 Cerebellum: VLc and VPLo both project to area 4, suggesting they form a common cerebellar relay nucleus [226]. The thalamic regions receiving cerebellar input also supply the preSMA, the SMA and the premotor cortex.

1.7.5.1.4 Sensory: According to Jones, the caudal division of ventral posterior lateral nucleus (VPLc) and its trigeminal counterpart (VPM) projects to sensory cortex[226]. Group 1 afferents from muscle receptors project to VPLc; and these appear to project to area 3a, and to a lesser degree, area 2 (Figure 9) [226]. The cutaneous core of VPLc projects only to areas 3b and 1 and does not project to motor cortex. (Discussed further in Section 1.8.13).

1.7.6 ANATOMY OF SENSORY CORTEX

Area 3a is characterized by a zone of attenuated layer IV granule cells intervening between the thick granularity of area 3b and the giant pyramidal cells of area 4[226]. (Discussed further in Section 4.13).

1.8 PHYSIOLOGY OF MYOCLONUS

This chapter reviews in detail the relationship of myoclonus to epilepsy and the physiology of myoclonus, both cortical and subcortical, including animal studies.

In view of their importance to the diagnosis of cortical myoclonus, detailed overviews are included of the SEP, JLA, long latency reflexes and excitability cycles. Particularly after the advent of JLA, myoclonus was classified into cortical and reticular reflex forms. If myoclonus was associated with a brief EMG discharge, had a premyoclonus spike on JLA, enlarged SEP and easily elicited C reflex it would be termed cortical myoclonus. With regard to localization of myoclonus, cortical myoclonus was imputed to be of cortical origin and reticular reflex myoclonus considered to arise in the brainstem reticular formation.

However, as Dawson pointed out as early as 1946, "the disturbances in the EEG in myoclonic epilepsy are so large and so widespread that it seems highly unlikely that of cortex or basal structures, pyramidal or other efferent systems, any one will be active in isolation"[227]. Hallett also noted that although most cases of myoclonus with brief EMG discharges reported in the literature apparently fitted the cortical or reticular formation mechanism, or both, many cases did not [228].

It is perhaps unnecessary to comment on the integral relationship between the subcortical structures and the cortex, in particular thalamo-cortical interactions. However, the question as to whether myoclonus is predominantly cortical in origin or is significantly influenced by subcortical structures is a key feature of this thesis, and hence the question needs to be explored in some detail. The notion that myoclonus may be of subcortical origin is not new: Van Bougaaart noted that "this generalization of synchronous slow waves, followed by generalization of spikes, allows the hypotheses that cortical instability is primarily determined by instability in some subcortical mechanism with diffuse effect, responsible for the slow waves"[229]. Subsequently, Watson and Denny-Brown described a case of myoclonus in a patient with lipid storage disease, and neuronal damage in the thalamus and dentate nuclei, and concluded that "instability in the diffuse neuronal subcortical system is an essential part of an epileptic process of generalized myoclonic seizures" [230].

As will be seen in the discussion of the nosology of myoclonus, there are a number of dificulties that arise when trying to classify myoclonus, and this becomes exaggerated when attempting to dissect out the underlying pathophysiology, particularly with regard to separating cortical from subcortical causes. Obvious (but not trivial) examples of this include

Hallett et al's observation that in some patients with Epilepsia Partialis Continua (EPC), where myoclonus virtually by definition should arise from motor cortex, pathological examination of the cortex may reveal a normal appearance[231]. In patients with PME, the pathology is frequently not cortical, but can be found elsewhere, such as the cerebellum [60].

A neat summation of the viewpoint that myoclonus is *not* of cortical origin is that of Halliday, writing in 1980 " Myoclonic epilepsy appears to reflect a disordered function of this system (the medullary reticular formation), associated with an abnormal epileptic discharge in the medullary reticular formation. The enhanced cortical evoked potentials and the associated disorders of the background rhythm of the EEG are no doubt a secondary result of this disordered function, and appear to be mediated by the ascending fibres relaying in the midline thalamic nuclei (nucelus reticularis thalami) which in turn modulate SEP amplitude at the level of VPL and VPM" [232].

Similarly, Chauvel in his review of seizures of frontal lobe origin, commented that "Recent issues in motor system physiology place the primary motor cortex in a key position inside a large ensemble of related cortical areas, interconnected with feedback loops, of efferent projecting thalamic, cerebellar and brainstem structures, of efferent projecting pathways to subcortical nuclei (as relays of internal loops), and to the spinal cord through more or less direct interneuronal networks. Whether a circumscribed pathology, unique or multiple, produces disturbances of a system as a whole or disconnects part of it, thus leading to a functionally autonomous subsystem, it most likely underlies the distinctive features of the clinical patterns. Such complexity prompts us to consider that, facing each individual case of apparently typical 'cortical myoclonus', no a priori statement about a primary role of the motor cortex can be put forward before having obtained convincing electrical-clinical correlations. Alternative possibilities of subcortical pacemakers, as well as cooperative cortico-subcortical mechanism, cannot be easily ruled out. The same is obviously true for the reverse situation, i.e. demonstrating the non-cortical origin of myoclonus" [233].

1.8.1 NOSOLOGY OF MYOCLONUS

Largely because myoclonus is the result of disturbances on many levels of the nervous system, it tends to defy classification and attempts to classify myoclonus tend to be oversimplistic, as exemplified by statements such as this one: "When the alteration occurs predominantly at cerebral levels they are called seizures; when motoneurons are involved fasciculations result; and when the stratum of origin is interneuronal in brainstem or spinal cord, the term is myoclonus" [234]. A crucial question concerns the existence of a myoclonus centre, a concept which first held sway with the publication of Hodskins and Yakovlev's paper on myoclonus in 1930, where the majority of patients had pathological evidence of neuronal loss in the dentate nucleus of the cerebellum [235]. Since then, the pendulum has swung back again, and although today the concept of a myoclonus centre might be risible, it is nevertheless true that the current literature usually implies or explicitly states that myoclonus is of cortical origin. In effect, the myoclonus centre has moved from the cerebellum to the cortex. Of course, it may be that myoclonus results from abnormal conditions arising diffusely within a neural network, rather than the dysfunction of a single specific structure [236].

Pathological classifications

Hodskins and Yakovlev proposed a pathological classification [235]:

1. Myoclonus associated with epilepsy involved the dentate system, midbrain and basal ganglia.
2. Myoclonus not associated with epilepsy involved only the dentate system.

In 1950 van Bogaert proposed a classification according to the site of presumptive pathologic involvemen [229]:

1. Cortical: Jacksonian epilepsy or epilepsia partialis continua (EPC)
2. Central gray substance: Unverricht-Lundborg disease.
3. Bulbo-ponto-cerebellar formation: palatal myoclonus, paramyoclonus, or dyssnergia myoclonus cerebellaris of Ramsay-Hunt.

Phenomenonological classification

Denny-Brown proposed dividing myoclonus into four groups, and was the first (1956) to note the presence of stimulus sensitive myoclonus in a classification of PME [237].

1. Spontaneous epileptic myoclonus (in patients with idiopathic epilepsy).
2. Stimulus-sensitive myoclonus (in patients with familial myoclonic epilepsy, lipidoses or Lafora body disease).
3. Palatal myoclonus.

4. Bulbar myoclonus, which varied from rhythmical myoclonus to isolated twitches, and was exemplified by patients with Creutzfeld-Jakob disease.

Similarly to Denny-Brown, Bonduelle classified myoclonus into epileptic and brainstem types:[22]

1. Epileptic: bilateral, synchronous and synergistic, best seen in the myoclonus associated with childhood absence.

2. Brainstem myoclonias: the appearance of this myoclonus was either simple or complex, rhythmic or arrhythmic, and asynchronous. This myoclonus was believed to involve the extrapyramidal system, including the corpus striatum, the subthalamic nucleus, substantia nigra, red nucleus, dentate nucleus and inferior olive.

Bonduelle observed that "no single specific lesion can be accepted as the cause of the myoclonic syndrome and that modern thought has abandoned the idea of a 'myoclonic centre' in the brainstem " [22].

Another approach to the phenomena associated with myoclonus was that of Rothwell [238]:

1. Sponaneous myoclonus: myoclonus occurring at rest
2. Action myoclonus: myoclonus present during attempted voluntary movement
3. Reflex myoclonus: myoclonus triggered by sensory stimuli.

Physiological classifications

In his review of 1967 [239], Halliday divided myoclonus into three groups, using an approach that extrapolated from the results of neurophysiological tests to give rise to anatomical localization, an approach which continues to be used up until the present:

1. Pyramidal.
2. Extrapyramidal.
3. Segmental.

The first group, pyramidal, was characterized by myoclonus of brief duration which followed a cortical discharge by a fixed time period. The cortical discharge could be focal or diffuse, but typically involved the contralateral motor area. This condition was associated with enhanced cortical potentials and myoclonic jerks had a fixed temporal relationship to peripheral stimuli [239].

The second group, extrapyramidal, was characterized by the absence of a cortical discharge, with a less tight connection between the timing of cortical potentials and EMG bursts. The cortical potentials could occur at the same time as the myoclonic jerk or subsequently to it, and the myoclonic jerk was of longer duration. Examples of this group were SSPE and Creutzfeldt-Jakob disease (CJD) [239].

In an important advance, Shibasaki subsequently described the technique of back-averaging and divided groups of myoclonus into pyramidal or non-pyramidal based on the presence or absence of a cortical discharge occurring prior to the myoclonus [240].

Shibasaki has also classified myoclonus into two groups according to whether they were stimulus sensitive or not [241]. However, if the purpose of classifications is to distinguish conditions from one another, this distinction is not particularly useful, since virtually all myoclonus, particularly if related to PME or cortical lesions, falls into a stimulus sensitive category, a point made by Shibasaki in a subsequent monograph [242]. The non-stimulus sensitive myoclonias (CJD, SSPE, spinal myoclonus) are typically identified by their own unique clinical and historical characteristics, and the myoclonus associated with these conditions is often distinctive, all of these features being more striking than their lack of stimulus sensitivity.

Anatomical classifications

The most recent classification is anatomical, and divides myoclonus into cortical and subcortical and overlaps with Halliday's extrapyramidal-pyramidal dichotomy [242] (Table 7).

Examples of cortical myoclonus include disorders associated with PME, as well as JME (juvenile myoclonic epilepsy), post-anoxic myoclonus, Alzheimer's disease, CJD, metabolic encephalopathies, olivoponto cerebellar atrophy, cortical-basal ganglionic degeneration and Rett syndrome.

Table 7. Distinguishing features between cortical, subcortical and spinal myoclonus. (derived from Shibasaki, 2000)

	Cortical	Subcortical	Spinal
Movement	Shock-like	Less shock-like	Can be shock-like
Condition	Posture, movement	Rest	Rest
Rhythmicity	Irregular, but often appears rhythmic	Tends to be periodic	Periodic or rhythmic
Stimulus sensitivity	Highly sensitive	Not sensitive	Can be sensitive

Subcortical myoclonus includes essential myoclonus, periodic myoclonus, dystonic myoclonus, reticular reflex myoclonus, startle syndrome, and palatal tremor.

1.8.2 DEFINITIONS OF TYPES OF MYOCLONUS

In a natural succession to the previous classifications, a greater concentration on neurophysiological testing gave rise to a more specific classification of myoclonus. This consisted of:

- Myoclonus with its origin in the brainstem, termed reticular reflex myoclonus [243].
- Myoclonus with neurophysiological features suggestive of a cortical origin, termed cortical reflex myoclonus [228;244].

However, as Hallett et al noted in their paper on cortical reflex myoclonus, "although most cases of myoclonus with brief EMG discharges reported in the literature apparently fit the cortical or reticular formation mechanism, or both, many cases do not" [228]. In a similar vein, referring to patients with pyramidal myoclonus, Halliday has commented: "The fact that jerks depending on cortical spike discharges occur in these patients does not necessarily mean that all their jerks are determined in this way. The cortical spikes occur on a background of raised excitability, and there is no reason to suppose that this is confined to the neurons or afferent pathways. Indeed, such excitability changes are only likely to be at all localized in the relatively unusual cases of epilepsia partialis continuans associated with a Rolandic focus" [239].

Focal reflex myoclonus

This term was first used by Sutton and Mayer in 1974 in a patient with hemiplegia associated with myoclonus, in whom there were focal jerks preceded by a cortical spike [245].

Reticular reflex myoclonus[243]:

This is characterized by the following features:

1. The myoclonic jerk is generalized.
2. Jerks can be triggered by peripheral sensory stimuli.
3. Cortical EEG correlate is not time-locked to the EMG event.
4. Muscles are activated up the brainstem and down the spinal cord [238].
5. The EMG correlate is a brief burst lasting 10-30 msec [16].

Cortical reflex myoclonus[228]

This condition has been defined as[238]:

1. A focal, sensitive area, commonly on the hand and forearm, stimulation of which evokes the myoclonic jerk.
2. Focal muscle jerk limited to a few muscles in the same part of the body.

3. Short burst of EMG activity (10-30 msec).
4. Muscles are activated in sequence passing down the brainstem and spinal cord.
5. Enlarged SEP frequently present.
6. If spontaneous or action myoclonus is present, a cortical EEG correlate is present, time-locked to the event.
7. Latency of the SEP is about half the latency of the reflex muscle jerk: for example in the upper limb, SEP latency is 18-25 msec, and that of the reflex jerk is 36-50 msec.

Cortical Myoclonus

An important question revolves around the issue of whether the term cortical myoclonus is similar to or synonymous with cortical reflex myoclonus. Currently it would generally be accepted that cortical reflex myoclonus, with its emphasis on a focal stimulus-sensitive area, is a subset of a larger group of cortical myoclonus [242]. As Shibasaki wrote, "most myoclonic jerks of cortical origin are stimulus sensitive, being elicited by stimuli of a single or multiple modalities, and and thus called 'reflex myoclonus"[242].

However, it is uncertain whether the clinical phenomena of *focal* myoclonus and *generalized* forms of myoclonus are underpinned by the same underlying pathophysiological processes. The term used initially was cortical reflex myoclonus and had been introduced by Chadwick and Hallett to describe the myoclonus in patients who had a cerebral anoxic event[228;244]. This corresponded to the syndrome of Lance and Adams[246], in which, typically following a cerebral hypoxic event, in which myoclonus could be seen associated with voluntary movement[246].

Features of the syndrome of cortical myoclonus included:

1. Enhanced SEPs.
2. Enhanced Long latency reflexes.
3. Myoclonus was evoked by stretch.
4. Cortical events could be triggered by myoclonus[228].

Hallett subsequently described cortical reflex myoclonus[247] as a "fragment of focal or partial epilepsy. Each myoclonic jerk typically involves only a few adjacent muscles for example, only an antagonist pair." The difficulty with reconciling cortical reflex myoclonus as being a generalized condition, *as initially described* in the patients with cerebral anoxia[228], with the concept that cortical reflex myoclonus is focal (a fragment of epilepsy), is apparent. The answer may lie in Hallett's proposal that most myoclonus is neither focal nor generalized, but multifocal: "Many or all muscles in the body can be affected by different jerks, so that the myoclonus is 'multifocal' " [247].

Obeso, Rothwell and Marsden expanded the concept of cortical reflex myoclonus in their article entitled “The Spectrum of Cortical Myoclonus: from focal reflex jerks to spontaneous motor epilepsy“[60]. Citing Dawson’s case of cortical reflex myoclonus[248], the case of EPC described by Kugelberg[249], and their previous reports on reticular reflex myoclonus and cortical reflex myoclonus[228], they concluded that there was “evidence of muscle jerking arising in the motor cortex”[60]. In particular, they noted that jerk locked averaging “went a long way to clarify the mystery of the relationship of the EEG to myoclonic jerks. Many previous observers had found it difficult to interpret the significance of the presence or absence of spike discharges in the EEG, and their time relation to myoclonic twitches. It was not until it was possible to establish whether such EEG spikes were time-locked to the muscle jerks, or whether any other form of EEG abnormality could be averaged in relation to muscle twitches, that the true significance of cortical discharge in relation to myoclonus could be appreciated”[60].

Cortical myoclonus was believed to arise from the cortex based on the following observations: “ (1) spike discharges in the routine EEG preceding the muscle EMG bursts responsible for the myoclonus, as in many cases of typical epilepsia partialis continua; (2) the discovery of an EEG potential preceding the EMG bursts responsible for the myoclonus by the technique of back-averaging; (3) the provocation of myoclonus by external stimuli, which also caused abnormal cerebral evoked potentials recorded from the surface of the scalp over the sensorimotor cortex or elsewhere”[60].

However, it is not clear from this discussion whether all or only some of these three features are necessary for a diagnosis of cortical myoclonus, and the authors themselves performed back averaging in less than half of their cases. This article is notable, since for the first time it introduced the entity termed cortical myoclonus to describe a group of conditions which were not always clearly associated with well defined cortical lesions or with cortical reflex myoclonus. Of their eleven cases, three had focal myoclonus and were stimulus sensitive (touch and pinprick), one had focal myoclonus and was not stimulus sensitive, and two others had multifocal myoclonus and had touch or pinprick induced myoclonus. The diagnoses included probable multi-system atrophy (two), Ramsay-Hunt syndrome (three), posttraumatic myoclonus (one), early onset cerebellar ataxia with retained reflexes (one), EPC (one), possible corticobasal degeneration (one) and unknown (two). Of the eleven cases, seven had clinical and CT evidence of cerebellar damage, although the conclusion remained that "all these patients described appear to have myoclonus as a result of abnormal electrical discharges arising from the cerebral cortex"[60].

Shibasaki and Obeso independently proposed that spontaneous myoclonus is not spontaneous at all, but is triggered by subclinical stimuli [60;250], an idea first put forward by Watson and Denny-Brown in 1955: "since some small natural movement of the patient often precipitated myoclonic jerks in the part that was moved, it is clearly possible that "spontaneity" of appearance was related to the variable pattern of stimulus inherent in the milieu of the living organism"[230]. However, at least one report would suggest that this is not the case, since experimentally a distinction may be made between spontaneous and induced myoclonus (the frontal cortical areas are activated with peripheral stimulation, but this is not seen in spontaneous myoclonus[251]).

Subequently, in their review of myoclonus in the Handbook of Clinical Neurology, Hallett, Marsden and Fahn[231] proposed a phenomenonological classification based on the distribution of myoclonus (focal, multifocal or generalized) and the source of the "responsible electrical discharge" (cortical, brainstem, spinal).

Focal myoclonus included cortical myoclonus, and the term was characterized by jerks limited to a few muscles, sometimes induced by modality specific stimuli. Associated electrophysiological features included [231] :

1. Brief EMG burst (30-60 msec).
2. Myoclonus time-locked to a cortical event, typically a focal positive-negative transient over sensorimotor cortex contralateral to the jerk.
3. The transient preceded the jerks by about 20 msec.
4. Giant SEP.
5. C-reflexes.
6. Muscles activated in a sequence passing down the brainstem and spinal cord.

Multifocal myoclonus was described as "while each jerk is focal, multiple sites in the body might be affected by different jerks." *Generalized* myoclonus was described as "each jerk affects much of the body". Multifocal and generalized myoclonus could occur in the same patient, had similar etiologies and were considered synonymous with "epileptic myoclonus". The causes of epileptic myoclonus were largely the group of diseases associated with PME. The four subtypes of epileptic myoclonus included cortical myoclonus, reticular myoclonus, combined cortical and reticular myoclonus, and primary generalized epileptic myoclonus (section 1.8.9).

Cortical myoclonus was described as being identical to focal myoclonus excepting that it was multifocal, and that, as opposed to a focal region of cortex being hyperexcitable, in multifocal

myoclonus there was “generalized cortical excitability”[231]. The neurophysiological findings were identical to focal myoclonus.

To recap, the myoclonus of PME was defined as a subtype of epileptic myoclonus and was associated with cortical myoclonus. In the development of these descriptions and classifications it appears that a well-defined entity, stimulus induced focal myoclonus, had become the basis for conceptualizing virtually all forms of myoclonus, other than reticular reflex myoclonus, CJD or SSPE. The primary reason for this appears to be that cortical reflex myoclonus and other forms of myoclonus of cerebral origin shared abnormalities on neurophysiological testing. Since the neurophysiology was similar, cortical reflex myoclonus was termed focal cortical myoclonus, and other forms of myoclonus were viewed as multifocal cortical myoclonus. This would be illustrated by a patient with EPC having the same mechanism of myoclonus as a patient with PME. Indeed, Marsden accepted cases of PME and post-anoxic myoclonus as being cortical reflex myoclonus, saying that cortical reflex myoclonus occurred in “progressive myoclonic encephalopathies and in a number of other diffuse degenerative disease”[16]. In contradistinction, authors such as Halliday have drawn a distinction between “focalized myoclonus, i.e., between the type of jerking seen in epilepsia partialis continua, which clearly has a constant primary focal distribution (even if it may spread from the focus by a jacksonian march)” and “the generalized diffuse myoclonus that is so characteristic of many of the progressive myoclonic epileptic patients”[252]. Historically, the underpinning for the notion of myoclonus arising from the cortex may have rested on Marsden’s report of 1973 entitled “Is the human stretch reflex cortical rather than spinal“ in which he proposed that myoclonus was the result of hyperactive stretch reflexes which involved the cortex[253]. The derivation of the terms cortical reflex myoclonus and reticular reflex myoclonus follow directly from this proposal, their names reflecting the importance that Marsden’s group attached to their findings from working on the human stretch reflex.

It needs to be emphasized that the current literature universally accepts cortical myoclonus as being defined by electrophysiological criteria that are identical with those which Hallett, Marsden and Fahn originally used to define focal cortical myoclonus[231]. What is less clear is whether most forms of PME truly represent “multifocal cortical reflex myoclonus”.

1.8.3 MYOCLONUS AND EPILEPSY

Myoclonus is often considered to be a fragment of epilepsy, and as a part of the approach to the physiological classification of myoclonus, it is perhaps easiest to begin with defining focal and generalized epilepsies. Focal motor seizures are jerks of part of the body, related to a discharge in a corresponding area of motor cortex. Recurrent jerks are known as EPC. In a process termed secondary generalization, the focal cortical discharge may spread, resulting in a secondarily generalized seizure.

In contradistinction, primary generalized epilepsies are likely to be genetic in origin, and current understanding is that the generalized spike and wave activity which is the hallmark of such epilepsies is due to abnormal discharges arising from thalamo-cortical connections [254]. Typical clinical manifestations of generalized epilepsies include myoclonus, absence seizures and generalized tonic-clonic seizures. The EEG in these cases shows spike and wave discharges, typically with symmetrical involvement of both hemispheres, but not infrequently asymmetrical. Myoclonus in primary generalized epilepsy is typically symmetrical, but may be frequently asymmetrical or focal.

In addition, there is a group of epileptic conditions termed secondarily generalized epilepsies, a prominent example being the Lennox Gastaut syndrome. These disorders have EEG features of generalized spike and wave, but are characterized by progression and cognitive decline, features which overlap with the disorders associated with PME. Similarly to the question of the origin of generalized myoclonic jerks in PME, it is unclear if the epileptic discharges in the secondarily generalized epilepsies are multifocal (arising from multiple discrete focal areas of abnormality) or are generalized, arising from thalamo-cortical interactions, as occurs in primary generalized or idiopathic epilepsies. Given that absence seizures are the basis of the model for thalamo-cortical interactions that characterize primary generalized epilepsy, it is salient to point out that 2-3 Hz spike and wave discharges as seen in absence seizures are also described in secondary generalized encephalopathies[255].

With regard to myoclonus and primary generalized epilepsies, in the case of absence seizures, Gibbs et al observed that patients often had associated "motor movements of a clonic sort" [256]. Subsequently, Jasper reported that when clonic movements occurred in absence seizures, the latency between the spike and wave discharge and the movement was variable, raising the possibility of autonomous subcortical centers being responsible[257]. Tassinari noted that in patients with myoclonic absence the EEG showed a wave of positive polarity, the amplitude of which correlated with the myoclonic jerks. Each positive transient

was followed by a single jerk with a constant latency, ranging from 15-40 msec for more proximal muscles and 50-70 msec for more distal muscles [258]. Hallett et al, referring to these cases of myoclonic absence, raised the possibility that the spike and wave discharge time-locked to the jerk "might be due to a brainstem discharge diffusely activating cortex to provoke a cortically determined generalized myoclonus"[228].

There appears to be some overlap in the neurophysiology of patients with primary generalized seizures disorders and PME. Thus, in JME, a form of primary generalized epilepsy which is characterized by myoclonus and generalized seizures, the amplitudes of the SEP are significantly higher than in patients with other forms of idiopathic generalized epilepsy[259]. Enlarged SEPs are held to be a feature of cortical myoclonus, and similarly, JLA of myoclonus in JME showed a positive-negative EEG transient[260], as may be seen in cortical myoclonus. The myoclonus in JME was related to bursts of polyspikes, not spike and wave activity, and the JLA transient also resembled a burst of polyspikes [260]. The authors proposed that "a wide cortical area is responsible for the PSW discharges, but that myoclonic events arise when PS (polyspike) frequency approaches that of central motor rhythm, and when paroxysmal activity reaches a critical threshold at which it activates the motor cortex"[260]. An additional area of overlap between PME and the idiopathic generalized epilepsies is photosensitivity on EEG, which may be blocked by apomorphine in both conditions[261].

Although these findings would suggest diffuse cortical excitability is associated with the myoclonus in JME, paradoxically in patients with IGE and absence seizures, when magnetic stimulation of the cortex time locked to spike-wave discharges is used, the resulting motor evoked potential (MEP) is reduced in amplitude, and threshold to stimulation is elevated, implying decreased cortical excitability[262]. Other reports have found reported enhanced visual evoked responses during spike-wave discharges, particularly in fronto-central regions [263]. Experiments in primates showed a reduction in VEP amplitude during spike and wave activity, although there was a similar gradient to humans, in that there was enhancement of the response frontally as compared with occipital response [263].

With regard to similarities between cortical reflex myoclonus and epilepsy, there is a single case report of two sisters who had both JME and reflex writing epileptic jerks[264]. However, although the myoclonic jerks in these patients might arise on the basis of peripheral sensory stimulation (as in cortical reflex myoclonus), other mechanisms related to higher order cognitive processing are also potentially implicated, given that the reflex seizures worsened with tasks of greater semantic difficulty or phonetic complexity.

1.8.4 FUNDAMENTAL PATTERNS OF MYOCLONUS: ANIMAL STUDIES

Although the induction of myolconus has been widely studied in animals, it should be noted that the use of agents known to precipitate myoclonus, and to a lesser degree lesion experiments, are both unlikely to correspond to the situation where a chronic neurodegenerative condition results in myoclonus.

Noting that enlarged evoked responses are a hallmark of cortical myoclonus, if visual, auditory or touch stimuli are applied to an animal which has been given the GABA antagonist Metrazol, large cortical evoked potentials will occur. Additionally, high voltage symmetrical spike and wave activity, sometimes developing into 3 Hz spike and wave, the typical frequency of absence seizures, is seen[265]. Myoclonus and generalized seizures may develop, depending on the frequency of photic stimulation used[265]. Catechol (1,2 - dihydroxybenzene) administration results in enhanced responses from thalamic sensory relay nuclei and cortex, and once the cortical response reaches threshold amplitude, myoclonus can result[266].

Similarly, jerks induced by chlorolose may be evoked by light touch and are associated with a discharge in the motor cortex [267], followed by a burst in the pyramidal tract [268]. These jerks are abolished by ablation of the motor area, and temporarily also by transient carotid occlusion [268], suggesting that cortex is implicated in the development of myoclonus[252]. However, subcortical pathways appear also to be utilized since although cortical ablations markedly reduced visual evoked responses and myoclonus in cats given Metrazol [265;269], both myoclonus and generalized spike and wave activity, albeit of prolonged latency, could still be elicited[265]. The motor cortex is therefore not indispensable for the generation of myoclonus, although it does affect the threshold required to generate myoclonus[239].

Early investigators proposed that there were two systems resulting in myoclonus[239;265]:

1. A pathway giving rise to a short latency, low threshold response, ascending in the lemniscal system to the primary cortical sensory areas, resulting in a large evoked response. Subsequently, the discharge travelled from motor cortex via the corticospinal tract.
2. A pathways resulting in a longer latency, higher threshold response which depends on subcortical pathways and could persist despite ablation of both the sensory and motor areas. It is likely that the second mechanism was mediated via the thalamic reticular nuclei[270]. In decorticate animals this response arose from the reticular formation of the brainstem [267;271].

However, the two systems are not discrete and may interact, as exemplified by myoclonus initiated in the motor cortex that may descend either in the corticospinal system or by the non-somatopically organized corticoreticulospinal route[252]. Similarly, catechol may not only produce a stimulus induced corticospinal reflex and increase the cortical evoked response, but may also result in a spino-bulbo-spinal reflex, the origin of which is probably the nucleus reticularis gigantocellularis (NRG)[272]. In addition, both chloralose and pentylenetetrazol activate cortical and subcortical mechanisms, and their use will give rise to myoclonus which persists even if the corticospinal tracts have been lesioned at the level of the medulla, indicative of the involvement of non-pyramidal pathways in the generation of myoclonus[252]. Similarly, decorticate and decerebrate cats may develop generalized myoclonus in response to peripheral stimulation under chloralose anaesthesia[271].

More precise localization of the origin of myoclonus to the reticular formation can be demonstrated experimentally. Infusions of urea result in irregular spikes seen in the brainstem reticular formation, particularly in the medullary reticular formation in the NRG[273]. This results in stimulus sensitive myoclonus which becomes more generalized until finally a tonic-clonic convulsion occurs[273]. Dichloro-Diphenyl-Trichloroethane (DDT)-induced myoclonus has a similar origin[274]. When DDT is injected into the NRG, myoclonus develops and is then followed by unilateral spikes, stimulus sensitive myoclonus and periodic runs of EEG spikes. Two hours after injection, when the cortical EEG had became normal, myoclonus persisted. DDT was also able to produce generalized myoclonus from injections in the cerebellar nuclei, inferior olive and red nucleus, but not the ventral thalamus[274]. This model appears robust, since cobalt injected into the medulla gives similar findings of myoclonus and irregular bilateral spike and wave on EEG [275].

In primates, Denny Brown demonstrated that stimulus-sensitive myoclonus developed a month after ablation of the postcentral or precentral cortex, and worsened after removal of the cerebellum[276]. In baboons, myoclonus may be induced by ablation of the cerebellar vermis[277]. The myoclonus involved proximal muscles, was brief, bilateral, symmetric and synchronous, and resembled an exaggerated startle response. It was of late onset and was both light-sensitive and spontaneous, and could be elicited by passive movements or touch if the animal was awake[278].

1.8.5 MYOCLONUS AND SUBCORTICAL LESIONS

Given that myoclonus may be divided into subcortical and cortical forms, this section reviews the literature concerning subcortical lesions and myoclonus.

Lance & Adams (1963) pointed out that myoclonus had been observed in anencephalic infants, indicating that cortex in humans is not required for the generation of myoclonus.

Thalamic Lesions

Following hypoxia, in rats with myoclonus, extensive neuropathological changes are noted in the region of the Nucleus Reticularis Thalami (NRT) [279]. Injection of $GABA_A$ antagonists into the NRT in rodent models produced spontaneous, rhythmic myoclonus ipsilateral to the side of the injection, whereas $GABA_B$ antagonists failed to show similar results. JLA showed a central/frontal negative potential in these cases[279]. Long latencies, of greater than 100 msec, were noted between the EEG and EMG responses suggesting that "extrapyramidal, rather than pyramidal, systems are involved in the myoclonus triggered through the NRT"[236].

Matsumoto et al postulated that disruption of $GABA_A$ receptor function in the NRT triggered myoclonus through a circuit involving the cortex[279]. Since there are no direct efferents from the NRT to the cortex and there was a delay between the injection and the onset of movements, other thalamic relays are probably involved, with progressive recruitment of cortical neurons resulting in myoclonus[279].

In humans, thalamic lesions comprising extensive neuronal loss and gliosis are reported in post-hypoxic patients with myoclonus[280].

With regard to specific regions of the thalamus, and their involvement in the production of myoclonus, Hassler noted that single stimuli in the Voa nucleus produced jerks in the contralateral limb. He observed further that "stereotaxic coagulation of Vop produced a good effect in myoclonic syndromes"[281]. However, Fahn reported on a case of cortical myoclonus following cardiac arrest in whom bilateral thalamotomies failed to control myoclonus [282]. Lance and Adams viewed intention or action myoclonus induced by hypoxia, not as pure cortical myoclonus, but rather resulting from "synchronous and repetitive firing of thalamocortical neurons"[246].

Milhorat described the effect of medial thalamectomies in monkeys, which was likely to have involved the intralaminar nuclei, and resulted in the development of myoclonus, both

spontaneous and elicited by pentylenetetrazol[283]. This was associated with the development of ipsilateral paroxysmal bursts of spikes. Recurrent stimuli resulted in the development of focal seizures.

Munchau et al described a patient with an infarction in the right posterolateral thalamus, who developed severe postural and kinetic tremor, with dystonic posturing and myoclonic jerks[284]. Using paired-pulse transcranial magnetic stimulation, they demonstrated a reduction of cortico-cortical inhibition, and proposed that this was due to damage to the loop connecting basal ganglia with thalamus and cortex or as a result of abnormal input to the reticular nucleus of thalamus. Similarly, in a patient with a lesion of the dorsomedian and intralaminar thalamic nuclei, the normal short latency afferent inhibition induced by a peripheral stimulation was attenuated, resulting in a larger evoked response to magnetic stimulation[285]. This would suggest that thalamic lesions result in a loss of the normal thalamic enhancement of cortical inhibitory networks.

In a patient with PME and photic myoclonus as a result of MERRF, regional cerebral blood flow was measured by positron emission tomography at rest and during myoclonus provoked by photic stimulation. During photic stimulation, there was significantly increased activity in the thalami, occipital cortex, supplementary motor cortex and right primary motor cortex[286]. When myoclonus was present, there was significant increased activity in the SMA, as opposed to when absent, and the authors proposed a thalamic focus for photic myoclonus in MERRF, with projection to precentral motor cortex by thalamo-cortical connections.

Globus Pallidus

Ono et al reported a patient with myoclonus due to manganese toxicity with high intensity signals in the globus pallidus. There were no features of cortical myoclonus neurophysiologically and the duration of the EMG burst associated with myoclonus was 100-500 msec[287], a feature of extrapyramidal myoclonus.

Caudate

In rodents, injections into the caudate using $GABA_A$ antagonists (picrotoxin) or $GABA_A$ channel blockers resulted in myoclonus, which typically progressed to focal seizures[288]. Injections in the GP, thalamus and cortex failed to evoke myoclonus. However, in order to evoke myoclonus, the cannula had to pass through sensorimotor cortex, and it appeared that this combination of a caudate lesion and damage to cortex was necessary for myoclonus to develop [288]. However, spikes were seen initially in the caudate nucleus and subsequently in cortex[288].

Similarly, patients with Huntington disease with stimulus sensitive myoclonus have been described, in whom generalized and multifocal myoclonus were found[289]. Neuropathology of a single case showed marked neuronal loss and gliosis in the caudate nucleus, with atrophy and gliosis in the globus pallidus and putamen. The cerebral cortex and cerebellum appeared normal. Mild astrocytosis was present in the thalamus, subthalamic nucleus and red nucleus. In another case, there was generalized cortical atrophy, marked neuronal loss and gliosis in the caudate and anterior putamen and lesser involvement of the thalamus, with minimal changes in the red nucleus, subthalamic nucleus and dentate nuclei.

In these cases, the EMG duration of myoclonus was short, late responses were detected after median nerve stimulation and back-averaging showed a positive-negative wave preceding the myoclonus by 20 msec, all features of cortical myoclonus (Figure 10)[289]. Myoclonus could be induced by flash, magnetic stimulation and peripheral nerve stimulation, and magnetic stimulation resulted in repetitive myoclonus. The SEPs were not enlarged, although there was a widespread positive wave corresponding to P30-N40. The first burst of myoclonus induced by peripheral nerve stimulation occurred at 40 msec, a relatively short latency, given that cortical reflex myoclonus has a latency of about 50 msec[289]. The authors comment that the "short latency of reflex myoclonus in HD is unusual for classic cortical reflex myoclonus, and might support a subcortical site of origin. Although there are two crucial differences between the myoclonus in HD and typical cortical reflex myoclonus, several observations in the present patients point towards a cortical origin for their myoclonus. The presence of spike and wave discharges on the EEG and a backaveraged cortical potential preceding the myoclonus is characteristic of a cortical origin. Cortical hyperexcitability is also suggested by the repetitive responses to magnetic brain stimulation, and by the repetitive cortical potentials that followed peripheral nerve or flash stimuli"[289]. The authors postulated that the repetitive reflex jerks (Figure 11) might be related to abnormal thalamocortical influences due to striatal degeneration.

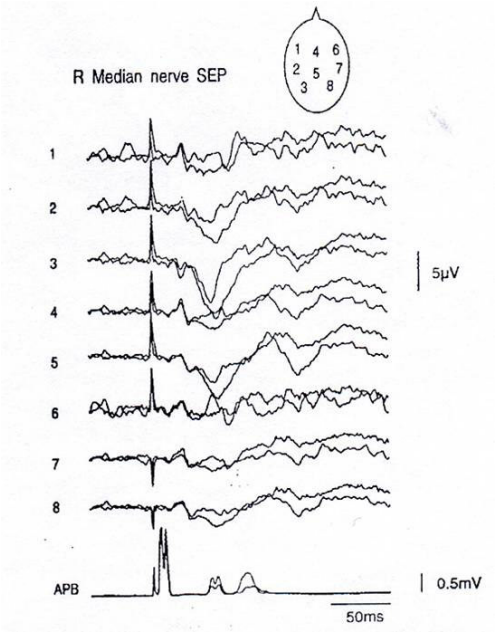

Figure 10. JLA demonstrating a cortical potential in a case of Huntington disease. The potential occurrs prior to the myoclonic spike by 18 msec; repetitive cortical waves followed and were time locked to the repetitive myoclonus (taken from Case 3 of Thompson et al., 1994a).

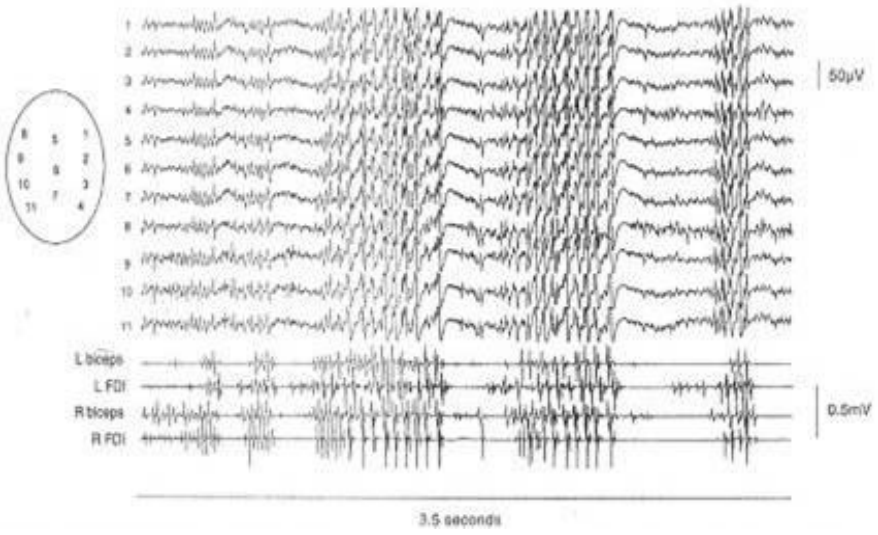

Figure 11. Simultaneous recording of EEG and EMG during action myoclonus in patient with Huntington disease. Bursts of myoclonus are associated with repetitive spike and wave EEG discharges (from Thompson et al., 1994a).

Similarly, in corticobasal degeneration, a condition characterized pathologically by neuronal degeneration in the cortex, basal ganglia and thalamus, stimulus sensitive myoclonus was described in two cases, in which the myoclonus was characterised by trains of repetitive,

synchronous discharges, often accompanied by repetitive long latency responses. The SEPs showed reduced N20-P25 responses, but C reflexes were present, JLA revealed a small positive potential and myoclonus duration was 20-40 msec, compatible with cortical myoclonus[290].

1.8.6 MYOCLONUS AND CORTICAL LESIONS

Since myoclonus may be divided into cortical and subcortical forms, this section reviews literature reporting on pure cortical lesions associated with myoclonus (Table 8). The classical example of cortical myoclonus is that arising from a focal cortical lesion. However, cortical myoclonus may exist without associated structural change in the cortex[253], and somewhat unexpectedly, lesions are not necessarily located in motor cortex.

Table 8. Case reports of myoclonus associated with cortical lesions.

REFERENCE	SEIZURE TYPE	CORTICAL REGION	STIMULUS	STRUCTURAL ABNORMALITY
Dawson, 1947b	Focal myoclonus	3 cm anterior to central sulcus	Tendon reflex Pressure	None
Forster, 1949	Focal Motor Reflex Epilepsy	Precentral gyrus	Touch	Post-central
Kugelberg, 1954	Focal Motor Focal myoclonus	Precentral gyrus	Leg movement Tendon jerk Electrical stimulation	Precentral gyrus (presumed)
Cowan, 1986	EPC	Parietal		Parietal Cortex
Vignal, 1988	Reflex Epilepsy	Parietal Rolandic	Touch	(MRI normal)
Volkmann, 1998	EPC	Parietal		None
Ashby, 1999	Focal myoclonus	Motor cortex		

On an experimental basis, Chauvel induced a chronic epileptogenic focus in primates, resulting in periods of EPC and Jacksonian type seizures[291]. Weak peripheral stimuli produced an evoked biphasic positive negative potential over the primary motor area, but stronger stimuli resulted in the superimposition of a large amplitude (1-2 mV) potential, resembling an epileptic spike.

With regard to individual case reports, in 1947 Dawson described focal myoclonus in a patient, and was the first patient to be described with giant evoked potentials, and who subsequently came to autopsy, where no lesion could be demonstrated, although neurophysiological testing had suggested that the myoclonus originated from anterior to the motor strip[248].

Subsequently, in 1949 Forster reported a case of a patient with a vascular naevus of the Rolandic fissure, associated with atrophy of the post-central gyrus, associated with focal motor seizures and reflex epilepsy which was induced by touch to the left shoulder. Tapping the shoulder also produced a large evoked potential over the right vertex centrally. The precentral gyrus was found to be excitable based on its response to direct electrical stimulation, and the excitable region lay directly in front of the area producing the enlarged evoked potentials [292].

Kugelberg and Widen described a case of EPC with focal myoclonus with a spike focus in the central head regions. Each spike was followed by a discharge 27-34 msec later in the tibialis anterior muscle[249]. Spikes were spontaneous or could be induced by passive or active motion of the leg, tendon jerk, or electrical stimulation. Electrical stimulation of the tibial nerve resulted in a cortical spike with a latency of 30 msec. A small region of cortical hyperexcitability was identified by direct cortical recording localized to the medial surface of the precentral gyrus, and spike potentials were noted to phase reverse 0.5-1 mm below the cortical surface and disappear a few mm deeper. Myoclonus ceased following corticectomy.

Vignal [293] reported on a case of reflex partial seizures characterized by the patient being able to provoke a seizure by pseudorhythmic tapping over his chest, in the same region where he experienced a sensory aura prior to his spontaneous seizures. MRI and standard scalp SEPs were normal. Peripheral stimulation resulted in rhythmic polyspikes over the central region and vertex, followed by widespread flattening of the EEG, associated with tonic contraction of the left arm, flexion of the body, contraction of the left leg and then the right side. Depth electrodes showed that tapping induced slow waves with brief overlapping rapid discharges in the parietal sensory cortex and rolandic motor cortex.

Volkmann et al. reported on a patient with EPC. SEPs were not enlarged, and MRI was normal, although previously one hemisphere was swollen, suggestive of Rasmussen's encephalitis[294]. Using magnetoencephalography (MEG) and source localization of dipoles, interictal spikes were localized to the inferior parietal lobule, which was concordant with PET

data. JLA of MEG waveforms showed a single deflection with a latency of 31 msec, which could be localized to the anterior border of the region giving rise to interictal spikes.

Ashby reported a case of a patient with celiac disease with focal myoclonus, evoked by action or sensory stimuli[295]. MRI showed areas of increased signal in the white matter. At electrocorticography, bursts of high frequency (25-30 Hz) spikes were recorded from motor cortex associated with myoclonic jerks. With more severe myoclonus the bursts of spikes evolved into electographic seizures. SEPs showed an initial response over the sensory cortex, followed by a large potential in the leg area of the motor cortex. With JLA, the latency from the first major deflection to myoclonus was 35 msec. Stimulation over the cortex resulted in a series of myoclonic jerks, and it was concluded that both myoclonus and the giant evoked potential arose from motor cortex. At electrocorticography the multiple spike bursts were found to be electropositive, indicating that neurons were depolarized at the level of the cell body.

1.8.7 RETICULAR REFLEX MYOCLONUS

Reticular reflex myoclonus refers to myoclonus of brainstem origin, believed to originate in the reticular system, but as with cortical myoclonus, this form of myoclonus may also arise as a result of peripheral stimulation.

However, the characteristic features of the entity of reticular reflex myoclonus are rather unclear, since only a few patients have been described[296]. There appears to be a spectrum from reticular reflex myoclonus to cortical reflex myoclonus: on one extreme there are cases of generalized myoclonus of brainstem origin without any of the usual manifestations of cortical reflex myoclonus (normal SEP, normal EEG, no C reflex, brief EMG duration of myoclonus), and on the other, there are cases which appear to overlap with cortical myoclonus since the EEG is abnormal and a C reflex is present.

The definition of reticular reflex myoclonus includes[297]:

1. Generalized myoclonus.
2. Absence of JLA related spike.
3. Evidence of caudo-rostral spread of the discharge from the brainstem.

Generalized myoclonus is typically defined as synchronous jerks of the whole body, although reports of reticular reflex myoclonus have shown that jerks display a gradient of onset, depending on the distance of affected muscle groups from brainstem centres[297]. Hallett et al, referring to generalized myoclonus, stated that it involved "jerks affecting much, if not all, of the body musculature; effective stimuli anywhere in the body would produce a similar jerk"[228].

Although it is a rare phenomenon[296], the causes of reticular reflex myoclonus are the same as the causes of cortical reflex myoclonus, which appears to far more common[247]. In reticular reflex myoclonus, the myoclonus can be spontaneous or induced by action and sensory stimulation, and the stimulus is often modality specific, as is seen in cortical myoclonus[231]. Hallett et al proposed that the pattern of muscle activation, which was widespread with flexor and proximal muscle group predominance, was consistent with an origin in the polysynaptic reticular formation and the reticulospinal tract [231].
Reticular reflex myoclonus has often been associated with the spino-bulbo-spinal reflex described by Shimamura[298], who showed that stimulation of the dorsal root afferents resulted in an impulse which subsequently relayed in the caudal medulla, and then re-entered the

cord. Ascending pathways conducted signals rapidly, whereas descending fibers had relatively slower conduction times.

The majority of patients with brainstem myoclonus probably have their myoclonus mediated through a system similar to that involved in the startle response. A typical startle reaction consists of a generalized flexion response, although activity can also be recorded in extensor muscles[296]. The latency of the response is relatively long and variable, and the pattern of muscle recruitment is typically that of sternocleidomastoid activation initially followed by other cranial muscles (Figure 12) [299] [296]. Startle reflexes are believed to commence in the caudal brainstem and spread rostrally and caudally. As with the spino-bulbo-spinal reflex, the spinal efferent conduction velocity is at a relatively low speed [300]. Distal responses are delayed compared with proximal ones, suggesting there is a preferential activation of axial and proximal muscles [296]. However, the orbicularis oculi often appears to be activated *before* the sternocleidomastoid, a feature which is incompatible with rostro-caudal activation of brainstem structures. This phenomenon may represent a blink response followed by a startle response[300].

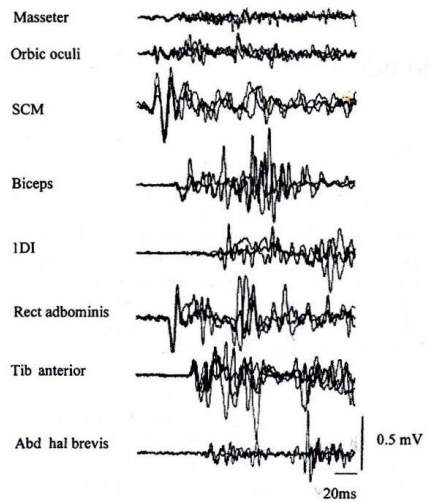

Figure 12. Three superimposed trials of an abnormal startle response elicited by taps to the head in a patient with hyperekplexia. EMG activity is seen first in sternocleidomastoid, and then in orbicularis oculi, masseter, trunk and limb muscles. From Brown et al., 1991d.

Chadwick and co-workers were the first group to describe patients in whom stimuli resulted in generalized, predominantly proximal myoclonic jerks[244]. The EEG showed spike-wave activity, but the SEPs were normal, and there was no spike prior to myoclonus. The myoclonus appeared to propagate upwards from the brainstem[244]. Hallett and colleagues subsequently described a 55 year-old man who developed spontaneous and stimulus sensitive myoclonus after cardiorespiratory arrest, and proposed the term “Reticular Reflex

Myoclonus"[243]. However, this patient was atypica, since that the conduction time of the efferent stimulus was very rapid[296]. Myoclonus was present at rest, and was made worse by attempted voluntary and passive movement[243]. On EMG, the duration of the jerks varied from 10-30 msec (although jerks of brief duration are more typically a feature of cortical myoclonus, see page 99)[243]. The EEG showed very frequent spikes, usually but not always associated with the myoclonic jerks[243]. The EEG abnormalities suggest there was cortical involvement, as might be expected following diffuse cerebral anoxia, which seems credible, given the history of cardiac arrest.

The EEG spikes were not time-locked to the EMG discharges and data on the relationship between the EEG and myoclonus had to be derived from series of single trials[243]. (Shibasaki has commented that variable latency seems characteristic of reticular reflex myoclonus, and that averaging of responses is less useful than examining individual responses [241]). The SEP was not enlarged, but a C reflex was present[243]. Myoclonic jerks could be precipitated by a variety of sensory stimuli[243]. Spontaneous jerks of the lower cranial nerve musculature (sternocleidomastoid and trapezius) usually preceded the cortical spike, whereas those of the upper cranial nerve musculature (orbicularis oris and masseter) followed the spike (see Figure 13)[243].

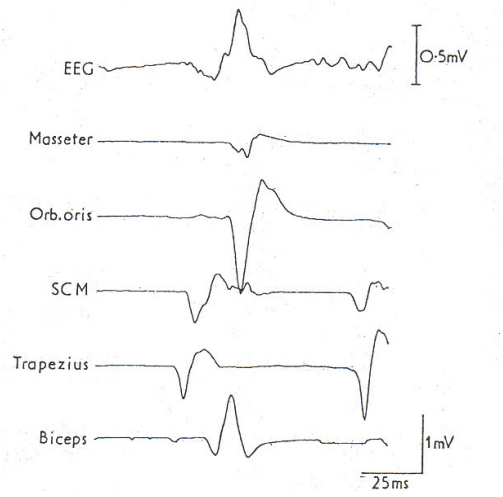

Figure 13. Figure showing a spontaneous myoclonic jerk in a case of reticular reflex myoclonus. There is activation of cranial nerves in a caudal-rostral direction. From Hallett et al, 1977.

The authors derived central conduction times based on the latencies of the jerks and peripheral conduction times[243]. From this they deduced that activation of cranial nerves was upward and arose in the medulla[243]. As Rothwell noted, the critical factor that suggested a brainstem origin was the order of muscle activation: the sternocleidomastoid initially, followed by orbicularis oris 7 msec later, and then the masseter 9 msec after that[296]. As

opposed to the findings in the spino-bulbo-spinal reflex of Shimamura, afferent cord conduction time was long (14 msec), whereas efferent cord conduction time was short (2 msec)[243]. However, the derived latencies and conclusions appear unlikely to be correct. The 7th nerve nucleus was activated 10 msec after the trapezius, and the 5th nerve nucleus 19 msec after trapezius. The authors state "Thus the signal producing the myoclonus seemed to travel (rather slowly) up the brain stem"[243]. However, the signal took 10 msec from the cervical cord to the 7th nerve nucleus (the authors appear to have wrongly assumed that the nucleus for sternocleidomastoid was in the brainstem, the correct location extending from the lower medulla to the upper cervical spinal cord), but then took 9 msec to travel from the 5th to the 7th nucleus, although both nuclei are located in the pons. The difference in afferent and efferent conduction times in the cord, of 14msec and 2 msec respectively seems unlikely to be correct., since a latency of 2 msec is equivalent to a velocity of 250 m/sec. In the case quoted by Rothwell[244], the latencies of the afferent and efferent cord conduction were similar. These differences prompted Rothwell et al to surmise that there might be more than one form of reticular reflex myoclonus[238].

Hallett et al's case, although termed reticular reflex myoclonus, had at at least three features suggestive of cortical involvement, namely the presence of a C reflex, the brief EMG discharges, and frequent cortical spikes[243]. Similarly, Brown reported a case of a 65 year old man who developed features of both cortical and reticular reflex myoclonus after cerebral anoxia. Myoclonus was both spontaneous and generalized after somaesthetic and auditory stimulation, and multifocal action myoclonus was present during voluntary movements[297]. The EEG showed frequent generalized polyspikes, often associated with myoclonus. The EMG bursts were of 25-100 msec duration; and with JLA there was a positive-negative spike maximal over the vertex and contralateral hand area, with a latency between the positive spike and myoclonus of 10 msec[297]. Cortical SEPs were not enlarged. EMG activity was first noted in sternocleidomas toid and later in more rostral cranial nerves. In addition, the R1 component of the blink reflex was delayed, suggesting brainstem dysfunction[297].

More typical cases include that of a patient with generalized jerks in response to tendon tap and electrical nerve stimulation described by Rothwell[238]. The SEPs were of normal size, and the jerks began in the brainstem and spread rostrally and caudally[238]. Similarly, Shibasaki described a patient with generalized myoclonus of brainstem origin, associated with a midbrain infarct and in whom the myoclonus was induced by stimuli such as sound or tapping (Figure 14)[301]. Somatosensory evoked potentials showed a small, long duration potential at C3 obtained at 31.8 msec. There was no sponaneous myoclonus, and the C reflex and EEG were normal. Afferent conduction velocity was rapid, whereas efferent

conduction was slow, as in the spino-bulbo-spinal reflex[298]. However, midbrain lesions should typically not affect centers involved in the startle reflex, nor the reticular formation that has previously been implicated in experimental animals in brainstem myoclonus (see Section 1.8.4).

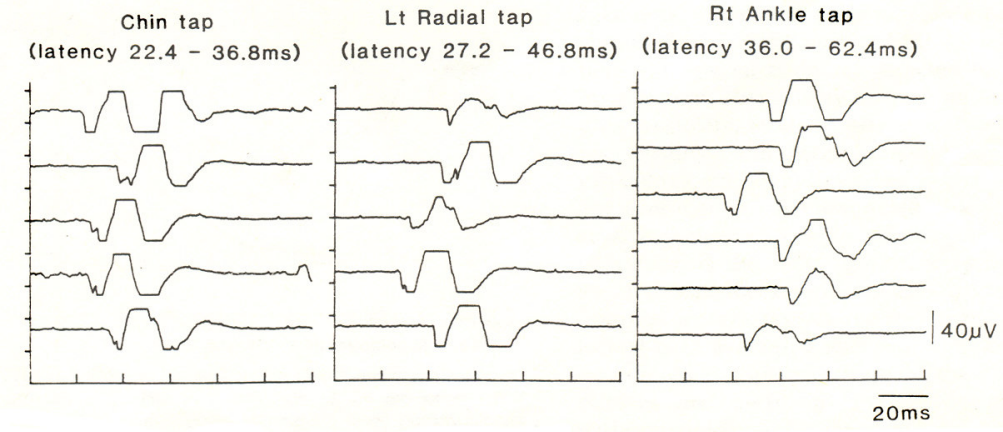

Figure 14. Myoclonus recorded over the biceps in response to stimuli at the chin, forearm and ankle in a case of generalized myoclonus associated with a brainstem infarction. Five traces recorded from each site. Note the variable latencies of response. Figure from Shibasaki, 1988.

A similar case was described by Oguro et al. in a patient with post-hypoxic myoclonus and CT scan evidence of diffuse subcortical change. Myoclonus could be elicited by auditory stimuli and taps to the body. There were no EEG spikes or potentials noted with JLA, and N20 wave of the SEP was prolonged and of low amplitude. Myoclonus was generalized and symmetrical and presumed to be of brainstem origin, with efferent conduction of 14 msec for the spinal cord[302].

A clear illustration of a borderline case between reticular reflex and cortical myoclonus was described in the Japanese literature. A patient with persistent generalized myoclonus was found to have a brainstem lesion on MRI associated with herpes encephalitis. The EEG was slowed, and SEPs were enlarged and C reflexes were enhanced[303]. The converse situation was described by Shibasaki in a patient with CJD in whom photic stimulation resulted in large amplitude evoked responses diffusely. However, SEPs were not enhanced and C reflexes were absent, illustrative of a dissociation between a reduction in cortical inhibition and the production of enlarged SEPs.

Given that the startle response and presumably reticular reflex myoclonus are of brainstem origin, an interesting observation has been made that startle seizures (typically tonic motor seizures triggered by auditory or somatosensory stimuli) have been shown by depth

electrodes to commence in the motor cortex or supplementary motor area[233]. These seizures are typically seen in children with extensive hemispheric injury, usually of an ischaemic nature. Frequently, there appears to be a sensory stimulus which triggers the motor attack, this stimulus sometimes being localized to a limb[233]. Epileptiform discharges are known to arise in the reticular formation of the lower brainstem and may influence sensory input to the cortex [304]. Similarly, it is possible that myoclonus of brainstem origin may arise from reflex jerks arising in the somatosensory cortex, which may trigger responses in the reticular formation mediated via the spino-bulbo-spinal reflex arc [271;272]. Noting that both generalized myoclonus as well as spike and wave discharges on EEG may arise from the brainstem reticular formation, Halliday stressed that the medullary reticular formation ascends to the midline thalamic nuclei, and may modulate afferent inpulses in the specific nuclei[232]. In animal experiments, stimulation of the intralaminar thalamic nuclei enhanced the EMG response to a corticospinal volley, although this response may survive ablation of motor cortex, suggesting that the enhancement results from a projection to spinal motor neurons rather than cortex [305].

1.8.8 CORTICAL REFLEX MYOCLONUS AND CORTICAL MYOCLONUS

Synchronous frontal polyspike discharges and associated myoclonic jerks were first recorded in 1938 in a patient with PME [306]. Subseqently, in 1946, Dawson reported on the relationship between EEG spikes and myoclonus in two patients who had a buildup of generalized, irregular, myoclonic jerks over one to two hours which culminated in a generalized seizure[227]. These cases would probably correspond to the current definition of cortical reflex myoclonus, since eliciting tendon jerks resulted in myoclonus. In these patients, the interictal EEG showed mild diffuse slowing with single or multiple epileptogenic spikes. During episodes of myoclonic jerking, bursts of spikes were seen on the EEG at frequencies of 8-13 Hz. As is shown in Figure 15, the longer the EEG discharge, the more prolonged were the myoclonic jerks.

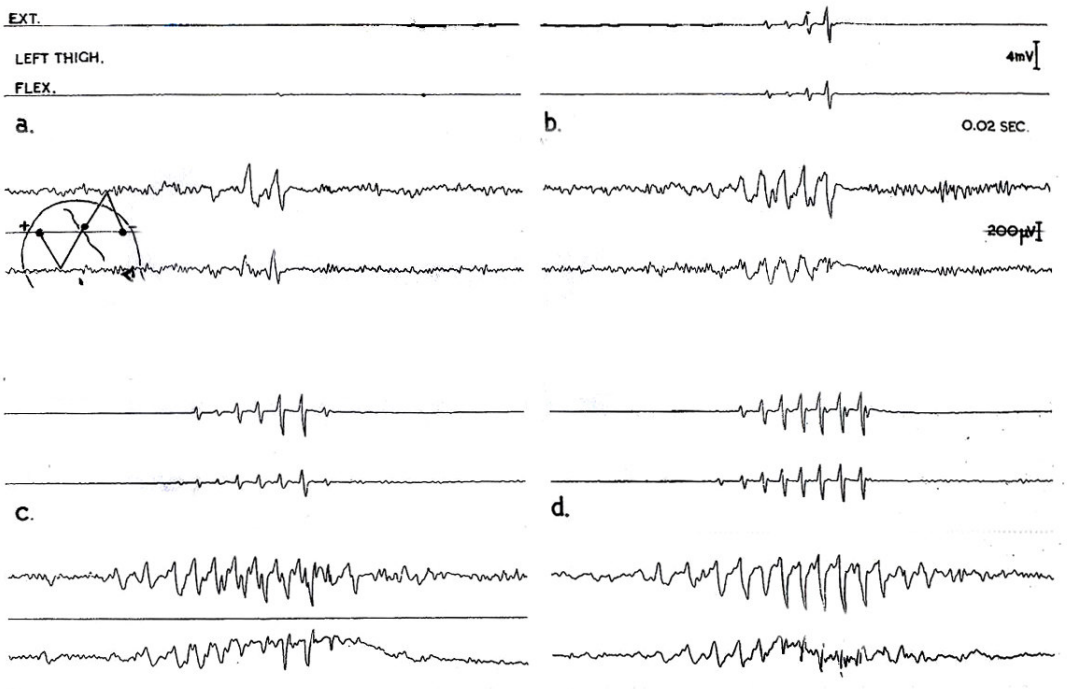

Figure 15. Example of cortical reflex myoclonus. Four recordings (marked a,b,c,d) of simultaneously recorded EMG (top two traces) and EEG (bottom two traces) (from Dawson, 1946).

In addition, eliciting the knee reflex resulted in a myoclonic jerk 80-180 msec later (Figure 16). There was no EEG correlate at this stage, which was in the initial period before the seizure.

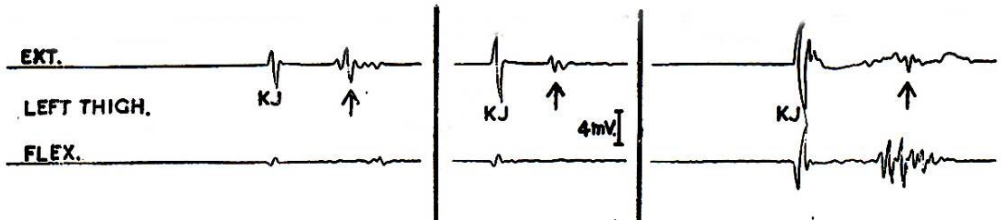

Figure 16. Case of cortical reflex myoclonus. A myoclonic jerk (arrow) is elicited by the knee jerk, indicated by KJ. The figure shows three examples, recording from extensor ("EXT") and flexor ("FLEX") muscle groups (from Dawson, 1946).

At a later stage, prior to the onset of the seizure, a tendon tap or sudden noise would induce a generalized myoclonic jerk (Figure 17). This was associated with a group of "spike potentials" on EEG. These were seen 130-150 msec after the jerk, and were larger over the hemisphere contralateral to the site of stimulation.

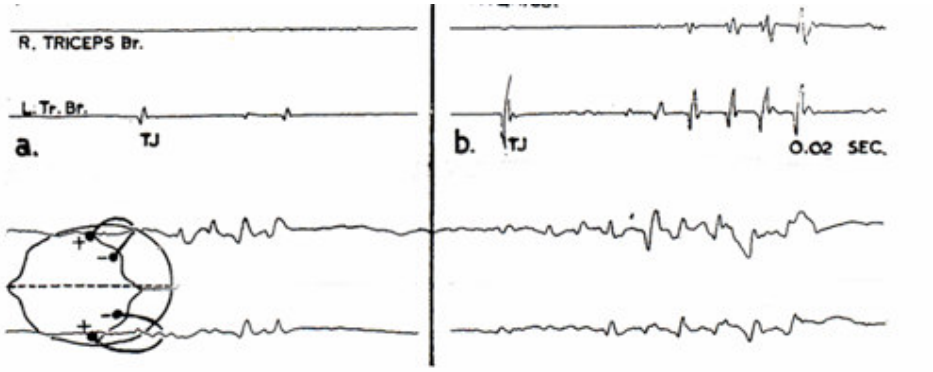

Figure 17. Case of cortical reflex myoclonus. Two examples of a tendon tap (indicated in the figure as TJ) eliciting EEG activity and a generalized myoclonic jerk. (from Dawson, 1946).

The entity of Cortical Reflex Myoclonus was described by Hallett et al[243] although Sutton and Mayer had previously described a similar condition in a report entitled Focal Reflex Myoclonus[245]. All three cases were likely to be post anoxic in nature, and therefore had features of Lance-Adams syndrome [246]. All had generalized tonic-clonic seizures and all had myoclonus which was precipitated by voluntary movement, and by various modalities (Table 9). One patient also had myoclonus evoked by touch, and of the three patients described in Hallett et al's original paper, probably only this patient would currently be defined as having cortical reflex myoclonus [238;307].

The myoclonus often resulted in an irregular, coarse, distal tremor on action, as noted previously by Chadwick [244]. EEG showed generalized bursts of irregular spike and wave and polyspike and wave activity in Case 1, a few small sharp waves intermittently in Case 2, and irregular diffuse slow wave activity with occasional sharp waves in Case 3.

Table 9. Clinical characteristics of patients with cortical myoclonus; from Hallett et al, 1979.

	Age	Event	Myoclonus at rest	Myoclonus Action	Myoclonus Passive movements	Myoclonus Discrete sensory stimuli
1	47	Severe Head Injury	-	+	+	-
2	37	Cerebral Anoxia	-	+	+	-
3	79	Syncope	-	+		-

The myoclonic jerks lasted 10-30 msec. As opposed to reticular reflex myoclonus, myoclonus appeared to travel in a purely rostro-caudal direction down the brainstem and spinal cord (Figure 18). However, as can be seen from the figure, given the difficulty of establishing the precise latency of onset, determining the order of activation of muscles is difficult.

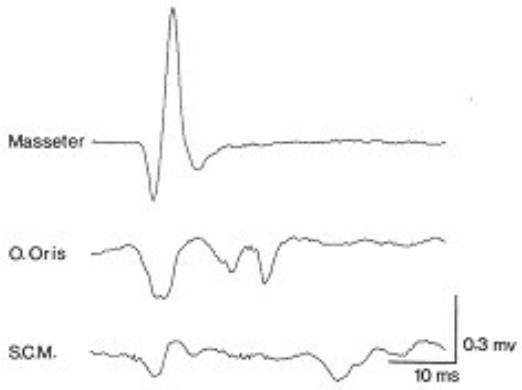

Figure 18. Case of cortical myoclonus: following a tap to the jaw "the monosynaptic reflex (jaw jerk) is following by the myoclonic response in orbicularis oris and sternocleidomastoid" (from Hallett et al. 1979).

All three patients had enlarged SEPs, of maximal amplitude over the contralateral hand area. Deuschl found subsequenlty that early SEP components (N20/P25/N33) were normal in the Lance-Adams syndrome [307], and Fahn has described a similar case of post-anoxic myoclonus with generalized spike and wave on the EEG, and abnormal poorly formed SEPs[282].

Jerk-locked averaging showed a single positive wave of highest amplitude at the hand areas of both hemispheres. There were long-latency responses at 40 msec, and the EEG response to stretch was a series of repetitive negative transients in the contralateral hemisphere over the hand area.

Hallett et al contrasted their description of cortical reflex myoclonus with three uncommon forms of myoclonus, namely ballistic-overflow myoclonus, segmental myoclonus, and myoclonus of SSPE, and drew the following conclusions:

1. They termed the condition cortical reflex myoclonus: defined as "myoclonus in which a brief EMG burst, synchronous in agonist and antagonist muscles, causes the involuntary muscle jerk and is time-locked to a cortical event"[228].
2. Cortical reflex myoclonus was focal or multifocal, and similar jerks were seen in "epilepsia partialis continua or focal epilepsy", and arose from a focal cortical discharge activating a focal muscle contraction[228].
3. Cortical reflex myoclonus might arise from hyperactivity of a component of the long-latency stretch reflex.

Other than cerebral anoxia, typical cortical reflex myoclonus has also been described in the following conditions[308].

1. RHS (Obeso, 1985, Deuschl 1987).
2. Spino-cerebellar degeneration (Obeso 1985)
3. Olivopontocerebellar atrophy and multiple system atrophy (Obeso 1985; Chen 1992; Rodriguez 1994).
4. Cerebral anoxia (Hallett 1979 Deuschl 1987).)
5. Metabolic degenerations such as NCL, Sialidoses and the cherry red spot myoclonus syndrome(Shibasaki 1985; Deuschl 1987).
6. Alzheimer's disease (Ugawa 1991).
7. Mitochondrial disease (So 1989;Deuschl 1991, Mima 1997).

1.8.9 PRIMARY GENERALIZED EPILEPTIC MYOCLONUS

Noting that primary generalized epilepsies refer to idiopathic epilepsies, classically associated with a normal neurological examination, and with a generalized spike and wave pattern on EEG, Wilkins et al. described primary generalized epileptic myoclonus[113;309]. They examined eleven patients with myoclonus and "chronic epileptic/myoclonic disorders". Patients were selected on the basis of the similarity of their JLA data. Six patients had Lennox-Gastaut syndrome, two had Alzheimer's disease, and there were single cases of PME, "degenerative disease" and typical petit mal.

Clinically, the patients had minipolymyoclonus and generalized, synchronized, whole body jerks, which were stated to resemble those of reticular reflex myoclonus. However, myoclonus was sometimes restricted to individual muscles but was seen often in antagonist pairs or other muscles of the same limb. Bilateral synchronous discharges were frequently found. EMG bursts were between 10 and 50 msec in duration and were often recorded in rapid sequential patterns causing tremulousness. EEG showed absent alpha and diffuse theta in nine patients; the majority had atypical or typical spike and wave discharges.

In seven patients, JLA showed a frontal or frontocentral negative cerebral potential, of 100-250 msec duration, and commencing 5-500 msec before the jerk. In the other four cases the jerk was preceded by a shorter duration potential of 30-100 msec, which was time-locked to between 40 and 60 msec before onset of EMG. In one patient with Lennox-Gastaut syndrome, JLA showed an 8 Hz bifrontal rhythmn (Figure 19).

As opposed to other studies, this group of patients were singular in that no clear JLA associated spike was detected, but instead a diffuse frontal negativity. The authors suggested that the pathophysiological process was the same as that of primary generalized epilepsy, since they felt their patients all had the latter condition, although this group of patients would not currently be considered to have primary generalized epilepsy, excepting for the one case of typical petit mal. Guerrini has pointed out that this condition is perhaps incorrectly named since many of the patients would currently be viewed as having generalized symptomatic, non-genetic epilepsies[8].

The authors speculated on subcortical and cortical interactions in the genesis of the JLA-associated frontal negativity, but noted that "the cortical event always precedes the myoclonus", indicating they believed that the frontal negativity caused the myoclonus. However, unlike cortical reflex myoclonus, there was "loose coupling between EMG and

EEG events"[113]. Bilateral simultaneous EMG bursts also distinguished this condition from multifocal cortical myoclonus. Barrett has suggested that a possible mechanism for the multiple small twitches seen was "individual small areas of motor cortex become hyperexcitable and generated multiple small spikes leading to tremulous activity in distal muscles"[310], although this is the same mechanism proposed for multifocal cortical myoclonus put forward by Hallett, Marsden and Fahn (Section 1.8.2)[231].

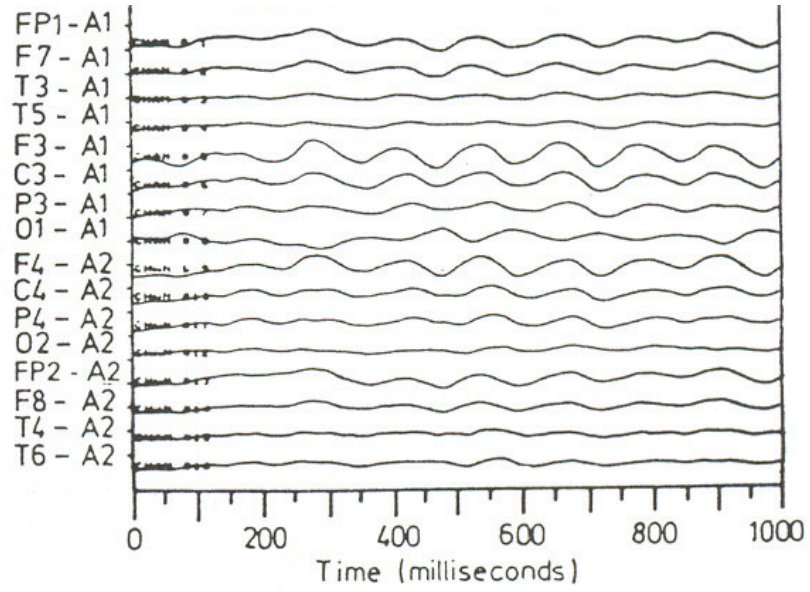

Figure 19. JLA demonstrating an 8 Hz bifrontal rhythmn in primary generalized epileptic myoclonus.[113]

1.8.10 PHYSIOLOGY OF CORTICAL TREMOR

The group of conditions discussed in section 2.3 (Cortical tremor, FAME and ADCME) are frequently characterized by tremulous movements, termed cortical tremor. The consensus statement of the Movement Disorders society [311] defines cortical tremor as a specific form of rhythmic myoclonus, consisting of:

1. High frequency, irregular tremor-like postural and kinetic myoclonus almost indistinguishable from high-frequency postural tremor.
2. Synchronous, short, high-frequency jerks (7-18 Hz) on EMG

In 1993, Toro et al from the Human Motor Control section of the NIH reported on the detailed physiology of a number of patients who had cortical tremor. They described ten patients, three of whom had postural tremor, seven had action myoclonus, of whom two had sensory reflex myoclonus. Of the five remaining patients with action myoclonus, the underlying etiologies were Lafora body disease, postonoxic myoclonus, PME and Baltic myoclonus in two. JLA showed a positive-negative transient in seven patients and a more complex series of wavelets in three others, with a latency from the peak of the positive cortical discharge to myoclonus of 22 ± 11msec. The five patients with action-induced myoclonus had giant SEPs and C-reflexes. All patients had abnormal rhythmic bursting seen on EMG during voluntary contraction, usually with synchronous activity in the agonist and antagonist muscles. The authors proposed that the abnormality lay in the motor cortex and that descending corticospinal volleys resulted in the rhythmic EMG pattern. They also noted that cortical neurons firing in excessive synchrony may lead to the sensori-motor cortex oscillating between activation and inhibition[312].

Ikeda reported two patients who appeared clinically to have essential tremor, but electrophysiologically were characterised by the features of cortical reflex myoclonus (clinical features are discussed in Section 2.3)[107]. The patients had rare seizures and 'fine shivering-like twitching' in the fingers and hands which were worsened by posture holding or movement of the hands. Surface EMG at rest showed irregular discharges involving muscles of the arms in either a synchronous or asynchronous fashion. EMG bursts were typically of 50 msec duration. With regard to SEPs, the amplitudes of the P25 and N33 responses were both significantly elevated. C-reflexes were enhanced, and JLA demonstrated a positive-negative biphasic EEG discharge (Figure 20).

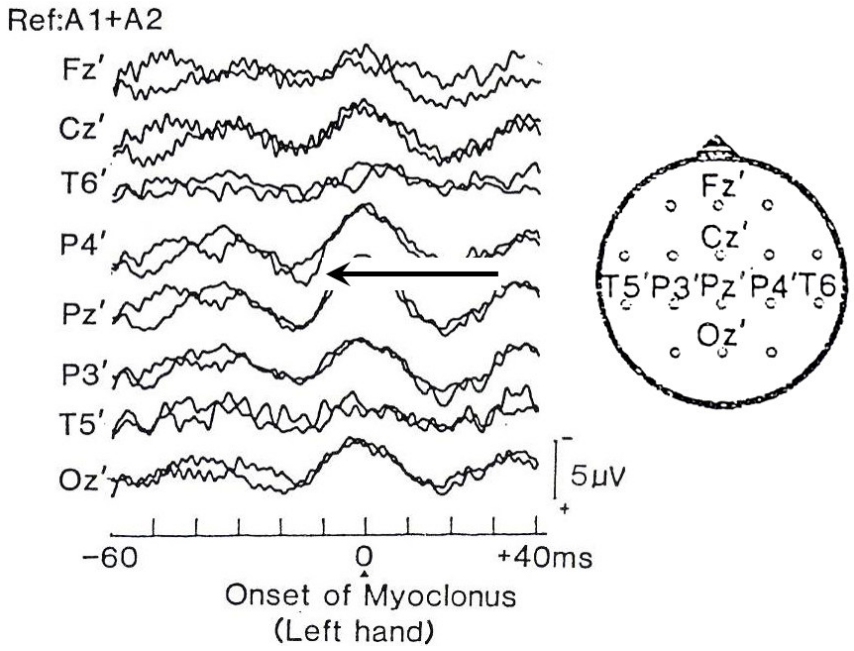

Figure 20. JLA in a patient with cortical tremor showing that the positive peak is maximal at the right sensorimotor area (arrow), and precedes the myoclonus by a latency of 15.4 msec (two superimposed sets) (from Ikeda et al., 1980).

EEG showed occasional generalised poly-spike and wave complexes and generalised intermittent slow activity in one patient and a slow background and generalised intermittent 4-6 Hz slow activity without distinct epileptiform discharges in the other. The authors noted that this involuntary movement resembled polyminimyoclonus as originally reported by Spiro[313] and subsequently by Wilkins et al[309]. They proposed that small areas of motor cortex were hyper-excitable and generated numerous small spikes in a multifocal manner, thereby causing frequent low amplitude twitches in the hands. There was a degree of rhythmicity on posturing and on voluntary muscle contraction resembling tremor, and the condition was therefore termed cortical tremor[107].

Terada in 1997 reported on familial cortical myoclonic tremor as a form of cortical reflex myoclonus[108]. The authors considered that their cases had the same condition as that reported by Ikeda. Neurophysiologic testing demonstrated that there was an arrhythmic 8-10 Hz discharge involving the arms, sometimes synchronous and sometimes not. The EEG showed generalised spike and wave discharges in four patients and photoparoxysmal responses in all of these. SEPs demonstrated N20 responses within normal limits in all patients, and abnormally enlarged subsequent components in all except for one. C-responses were elicited, both ipsi- and contralaterally in all patients. JLA demonstrated a positive-negative biphasic spike prior to myoclonus in three patients (Figure 21), maximal at

the central region contralateral to the side of EMG recording. The latency from the positive EEG spike to the EMG discharge was approximately 30msec[108].

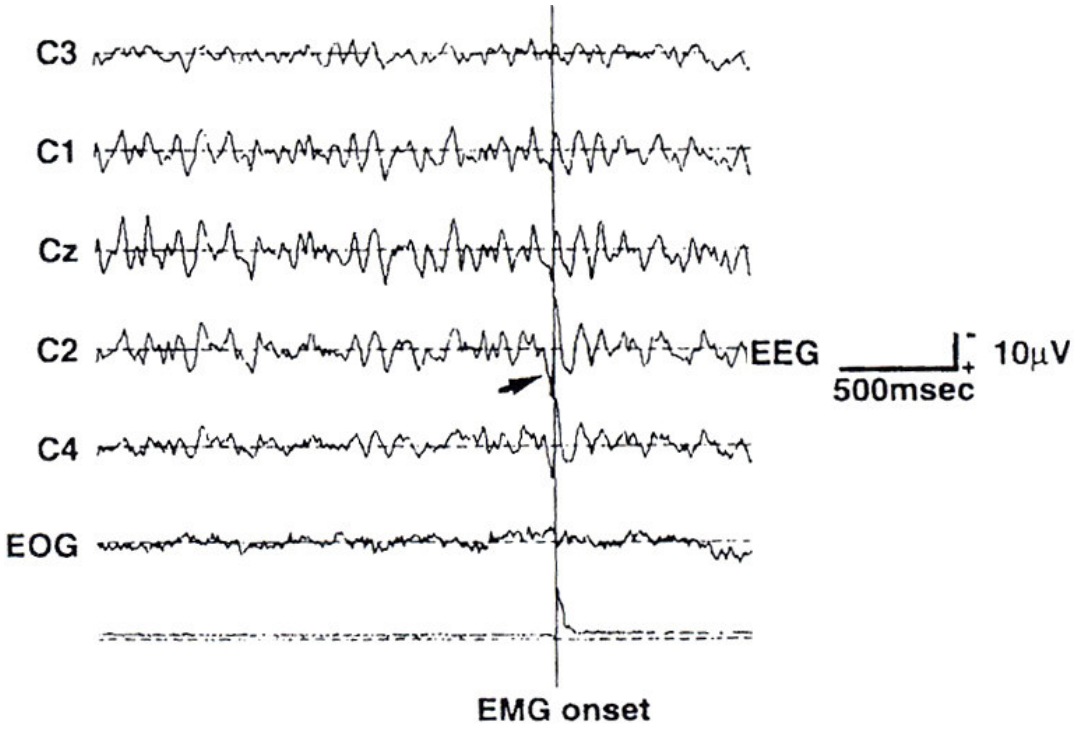

Figure 21. JLA in a case of cortical tremor shows a positive-negative biphasic spike maximal at the right central area (arrow), preceding EMG onset in the first doral interosseous muscle by about 30 msec (fromTerada et al., 1997)

Okino et al described four patients with familial benign myoclonus epilepsy of adult onset, characterized by myoclonus and rare seizures, in which the EEG showed frequent generalized polyspikes[111]. Surface EMG showed synchronous bursts occurring irregularly. Evoked potential studies showed a normal N20, but enlarged P25 and N33 in two patients. One patient had normal sized evoked potential responses and one had borderline increased responses. Long-loop C reflexes were easily obtained, with latencies ranging from 32 to 45 msec. JLA demonstrated a positive-negative EEG potential in two of 4 patients, with a latency of 23 msec. In two patients the myoclonus was “too fine and rare to obtain a trigger burst”.

Okuma et al published two reports on familial cortical tremor with epilepsy. The first report concerned a family with an autosomal dominant condition comprising rare seizures and postural tremulous movements of the fingers[110]. The proband also developed arrhythmic oscillations in the legs on standing, resembling orthostatic tremor. EEG showed a slight excess of theta activity with both multifocal spikes and spike and polyspike and wave discharges in the proband, a photoparoxysmal response with mild excess theta in a second

patient, and focal sharp waves and generalised spike and wave complexes in a third Surface EMG showed rhythmic bursts at a frequency of 7-9 Hz of 10-50 msec duration in the forearm flexors and extensors, and similar bursts were recorded in the legs when the patient stood. In these two patients SEPs were enlarged in both and C-reflexes were obtained in one[110]. JLA demonstrated a positive spike with a latency of 16 msec prior to myoclonus recorded from the forearm extensor muscles and 18 msec prior to myoclonus in the quadriceps myoclonus.

The second report concerned three families with seven affected members [115]. The proband had an EEG which showed spike and polyspike and wave complexes and a photoparoxysmal response. Surface EMG showed rhythmic bursts of 10-50 msec duration at a frequency of 8-10 Hz in forearm flexors and extensors. SEPs demonstrated giant potentials and C-reflexes were present. JLA demonstrated a positive spike with a latency of 15 msec preceding myoclonus in extensor muscles of the forearm. The three other patients examined had identical neurophysiology of enlarged N20-P25 and P25-N33 components of the SEP, C-reflexes and spike and polyspike discharges on EEG. Two of the four patients had a photoparoxysmal response[115].

Uyama reported in abstract form on 27 affected patients with FAME, with electrophysiological features of cortical myoclonus[116]; Subsequently, Plaster and Uyama reported on linkage to the FAME 1 locus[5]. EEG showed generalised spikes or multiple spikes and slow waves on EEG and there was photosensitivity in 67% of patients. Studies of evoked potentials and C reflexes were compatible with cortical reflex myoclonus[5].

In the report by Mikami of 17 affected patients from a single family with BAFME, the EEG was abnormal in all patients and most patients had generalised polyspike and wave complexes[6]. The P25 and N33 components of the SEP were enlarged in all patients. JLA demonstrated a positive spike preceding myoclonus in four patients and C-reflexes were recorded in all patients.

A five generation family with autosomal dominant inheritance was described from Turkey in which myoclonus started in the third or fourth decades, associated with migraine[120]. EEG showed generalised spike and multiple spike and wave complexes. Photic stimulation could provoke myoclonic jerks and resulted in a photoparoxysmal response on EEG.
Two Italian families were described with BAFME with linkage to the FAME 2 locus[9]. These families had cortical tremor, and rare seizures in about half the patients. The EEG was normal in six, and showed spike and wave activity in ten, with a photoparoxysmal response

in eight of these. JLA showed a positive-negative premyoclonic spike or a “more complex series of wavelets” (Figure 22). Ten patients showed giant SEPs, and in the remaining five, SEPs were normal. C reflexes were observed in all but one patient.

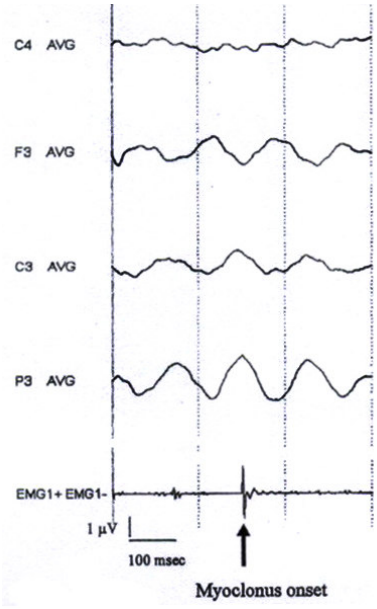

Figure 22. Patient with BAFME, in whom JLA showed “a series of waves with a premyoclonic positive-negative potential” (from de Falco et al., 2003).

Labauge et al reported on a family with FAME, with features of cortical myoclonus[7]. Surface EMG showed rhythmic 10-13 Hz bursts. The P25-N33 waves of the SEP were enlarged, but reached a value of 8.5 μV in three of five patients (a figure of 8.5 μV is usually considered to represent the upper limit of normal for these responses[250]) . C reflexes were present in all patients, and JLA demonstrated a biphasic positive-negative discharge.

Similarly, Striano et al reported an additional family with BAFME[10]. Of five patients examined, all had abnormal EEGs, with a photoparoxysmal response in two. Giant SEPs were present in three, and all had a C reflex JLA showed a positive-negative spike or series of wavelets related to myoclonus.

In a further family with BAFME, associated with night blindness, the SEP showed a marked increase in the P25 and N33 components, and C-reflexes were enhanced. JLA demonstrated a positive spike, or a series of wavelets, preceding the myoclonus by 20 msec, which arose from the centro-parietal region[114].

Van Rooteselaar reported a Dutch family with FCTE with 13 affected members[117]. The cortical tremor was irregular with a frequency of 10-16 Hz. JLA could either not be done, or

showed no cortical potentials. SEPs showed P25-N33 amplitudes that were within normal limits (3.8-6.5μV) in three of five patients, the remaining two having enlarged responses. C reflexes were obtained in four of five patients. EEG was only done in five patients, of whom two had normal recordings.

Elia reported on three patients from a family with possible mitochondrial inheritance pattern where the predominant clinical features were postural and action tremor, seizures, and mental retardation in one patient. EEG revealed spikes over the posterior regions of both hemispheres and diffuse sharp waves in one patient, a 7Hz background with diffuse spike and wave complexes and posterior spikes in another, a slow background with diffuse slow waves or spike and wave complexes in the third patient, and rare spikes mostly over the left posterior regions in the fourth patient. IPS resulted in photoparoxysmal activity in all patients. Surface EMG demonstrated prominently synchronous contractions of agonist and antagonist muscles at a frequency of 8-10 Hz. SEPs showed giant P25-N40 waves and C-reflexes were enhanced. JLA (Figure 23) demonstrated a positive wave immediately prior to the myoclonic jerk.

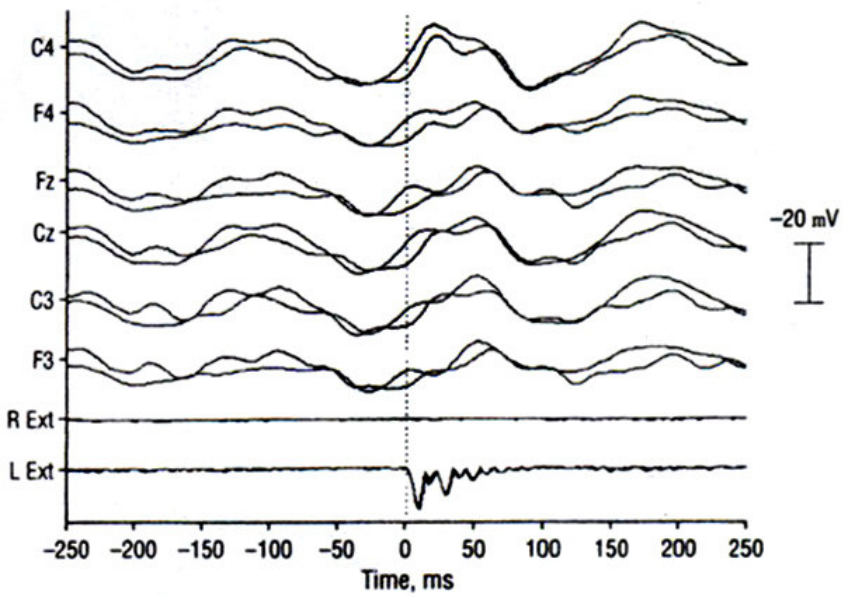

Figure 23. JLA in a patient with familial cortical tremor and mental retardation reportedly showing "a positive deflection preceding the electromyographic burst of 27 msec" (from Elia, 1998).

Guerrini et al reported on a family with seizures and myoclonus, termed Autosomal Dominant Cortical Myoclonus with Epilepsy (ADCME) [8]. The interictal EEG showed a normal background; six of seven patients had focal temporal or frontotemporal spikes or spike and wave discharges, and photic stimulation resulted in a photoparoxysmal response.

EMG showed synchronous agonist and antagonist contraction at a mean frequency of 12 Hz. The amplitude of the N20 response was normal, but there was a significant increase in the N20-N30 amplitudes and the P30-N35 amplitudes, and flash VEP showed a significant increase in the amplitude of the greatest positive peak. All patients had C reflexes, with a contralateral response after 8 msec. Back-averaging generated a series of waves, with a similar frequency to the myoclonus (Figure 24). The largest response was a positive-negative biphasic transient, and the positive peak occurred 21 msec before the EMG of wrist extensors. However, as the authors pointed out: "as both myoclonus-related EMG and EEG activities were rhythmic, it was difficult to establish with absolute certainty from back-averages which of the various waves time-locked to the EMG discharge bore the most fixed temporal relationship to the EMG trigger"[8].

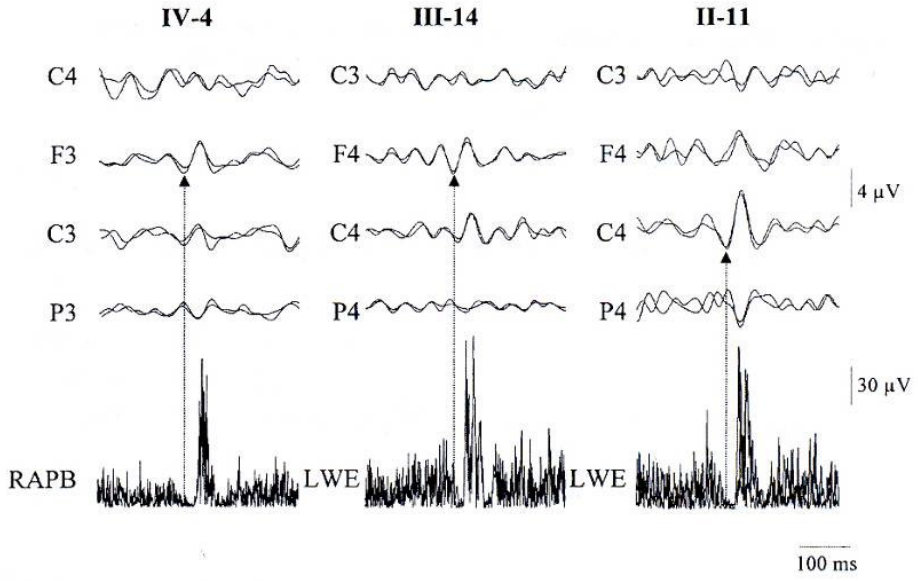

Figure 24. JLA in three patients with ADCME[8]. Arrows indicate the peaks from where the latencies were measured (common average reference). RAPD= right abductor pollicis brevis; LWE= left wrist extensor (from Guerrini et al., 2001.

Frequency analysis demonstrated significant peaks in coherence between EEG and EMG over the contralateral rolandic area in five of seven patients studied, with the frequency of coherence ranging from 8-25 Hz (Figure 25). Phase spectra showed that EEG activity preceded EMG activity, although the EMG lag (8-15 msec) was shorter than that seen with back-averaging and was brief for even the fastest cortical pathways.

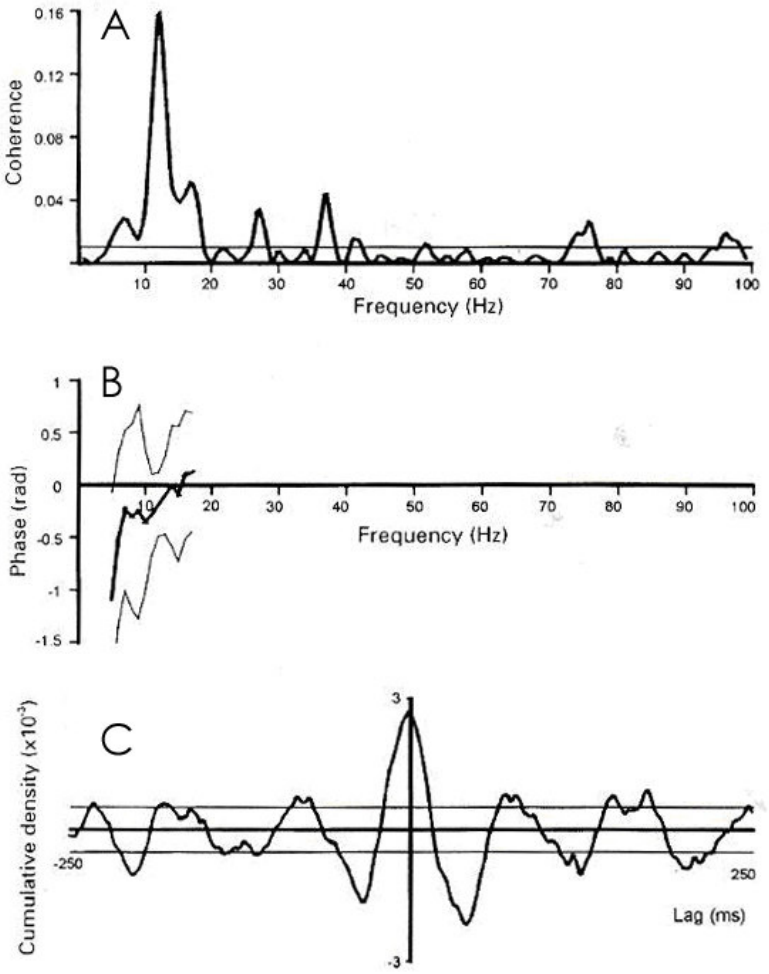

Figure 25. Frequency analysis in a patient from Guerrini et al.'s report of ADCME (2001). The thin lines in A, B & C indicate 95 % confidence limits. A shows coherence between the EMG of the wrist extensor and the F4-C4 EEG. B shows the phase spectrum with linear phase coherence at the frequencies where there is strong coherence. C shows cumulant density estimates (equivalent to the cross-correlation between signals).

Regarding reports in which JLA showed a series of waves, it should be noted that oscillatory activity in the motor areas of the human cortex is prominent in the primary sensorimotor area where activities of 10 and 20 Hz are seen[314]. This rhythm may be a basic feature of motor cortex function and may explain the facilitation of EEG-EMG events in the 20 Hz range. In patients with cortical tremor, there have been a number of reports of activity of similar frequency associated with myoclonus. Ugawa reported on four patients, two with benign familial myoclonus epilepsy, one with tuberculous meningitis and a patient with negative myoclonus secondary to hepatic encephalopathy. In the patients with positive myoclonus, JLA showed a 20 Hz EEG rhythm preceding the myoclonus, and in the patient with negative myoclonus (Figure 26), silent period averaging showed a 16 Hz EEG oscillation over the

contralateral motor cortex[315]. Toro et al. also reported that JLA showed a positive-negative transient in seven patients and a more complex series of wavelets in three others in their initial report on cortical myoclonus[312].

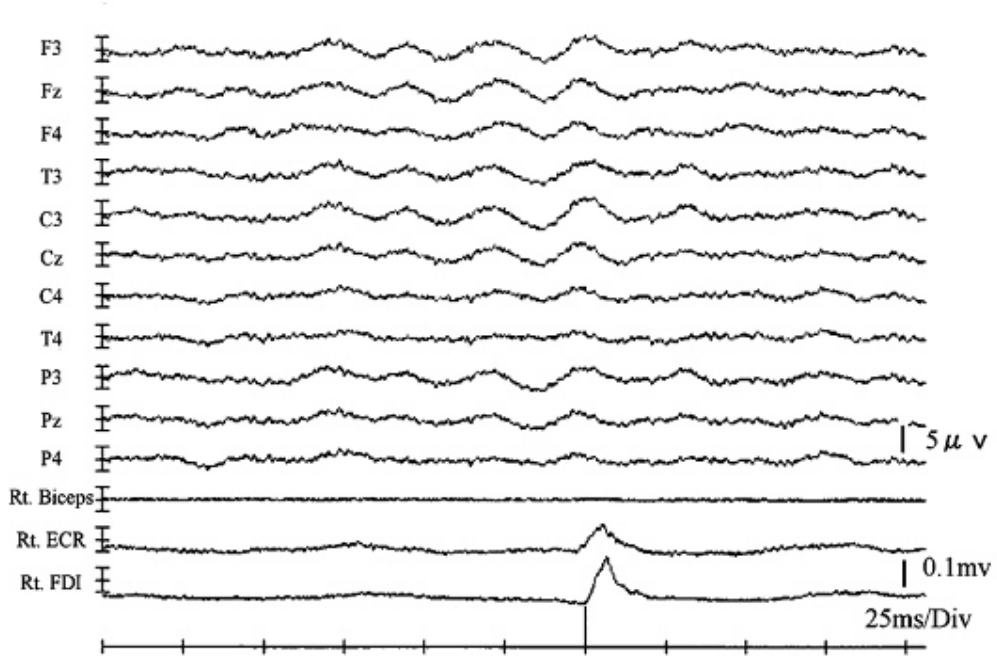

Figure 26. JLA from report of Ugawa(2003); 489 trials averaged showing 20 Hz oscillatory activity, maximal at the C3 electrode.

Similarly, sinusoidal cortical discharges associated with JLA have been reported in an HIV positive patient who presented with action myoclonus of the left leg. CT showed white matter lesions of the right internal capsule and left temporal lobe, and likely diagnoses were either HIV encephalopathy or PML[316]. Although SEP amplitudes were not enlarged, the EEG showed bursts of polyspike and wave acitivity of high frequency (40-55 Hz) over the sensorimotor cortex. JLA demonstrated a high amplitude positive-negative-positive complex of maximal amplitude over the vertex (Figure 27).

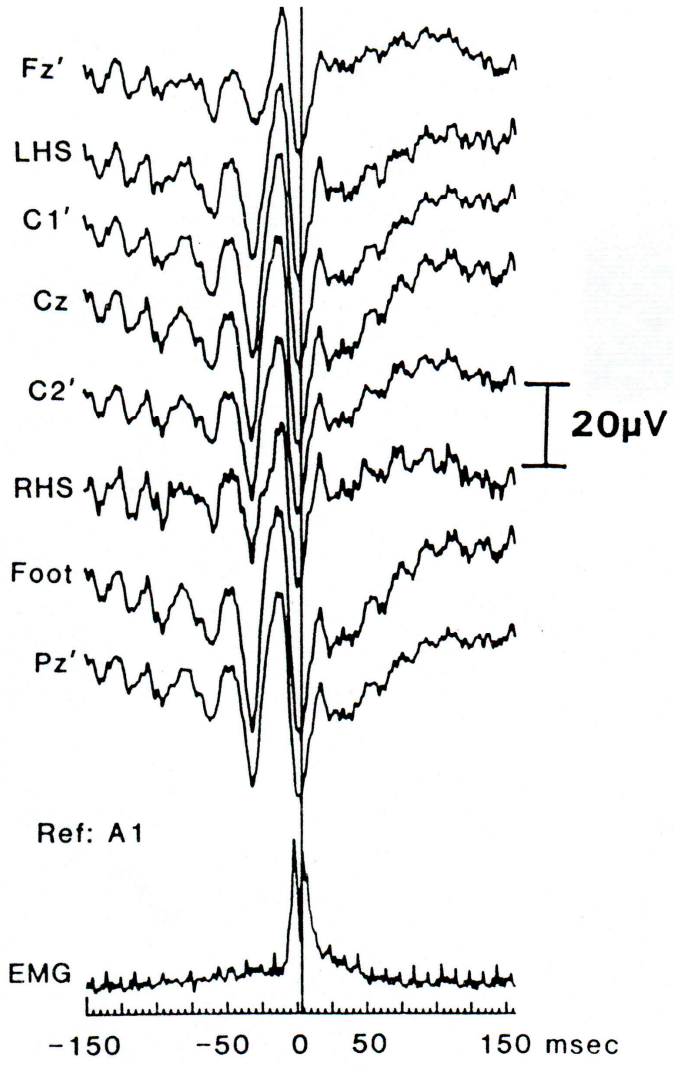

Figure 27. JLA showing a high amplitude positive-negative-positive complex of maximal amplitude over the vertex (from Kapoor et al., 1991).

Rhythmic myoclonus has also been reported in an HIV positive patient presenting with ataxia, associated with multiple areas of signal abnormality in the white matter[317]. EMG recordings showed that the movements were of 50 msec duration and had a frequency of 10 Hz. EEG showed a slow background with intermittent runs of high amplitude activity in the alpha range in the frontocentral and vertex regions. JLA resulted in "a complex shape that included multiple waves due to the rhythmic recurrence of the jerks and EEG waves". A positive peak preceded the jerks by 12-18 msec. Autoregressive spectral analysis determined that there was coherence between rhythmic EEG discharges and EMG bursts, with a peak at a frequency of 10.8 Hz[317]. The authors proposed that since rhythmic activity was visible on EEG, and significant coherence was demonstrable, the oscillations were generated by large, synchronous discharges of hyperexcitable cortical neurons[317].

Rhythmic 25 or 50 Hz cortical and muscle discharges have been described in cortical myoclonus. Myoclonus was first induced and then often occurred in series of bursts (Figure 28-A). The EEG correlate was often a rhythmic series of giant positive spike and slow negative wave complexes[318]. The intervals between spikes and bursts of myoclonus were similar, being about 20 msec. On back-averaging, frequency histograms of the cortical spike to EMG burst were derived from the individual jerk-locked events (not averaged); the majority of the histograms demonstrating the existence of more than one peak (Figure 28-B).

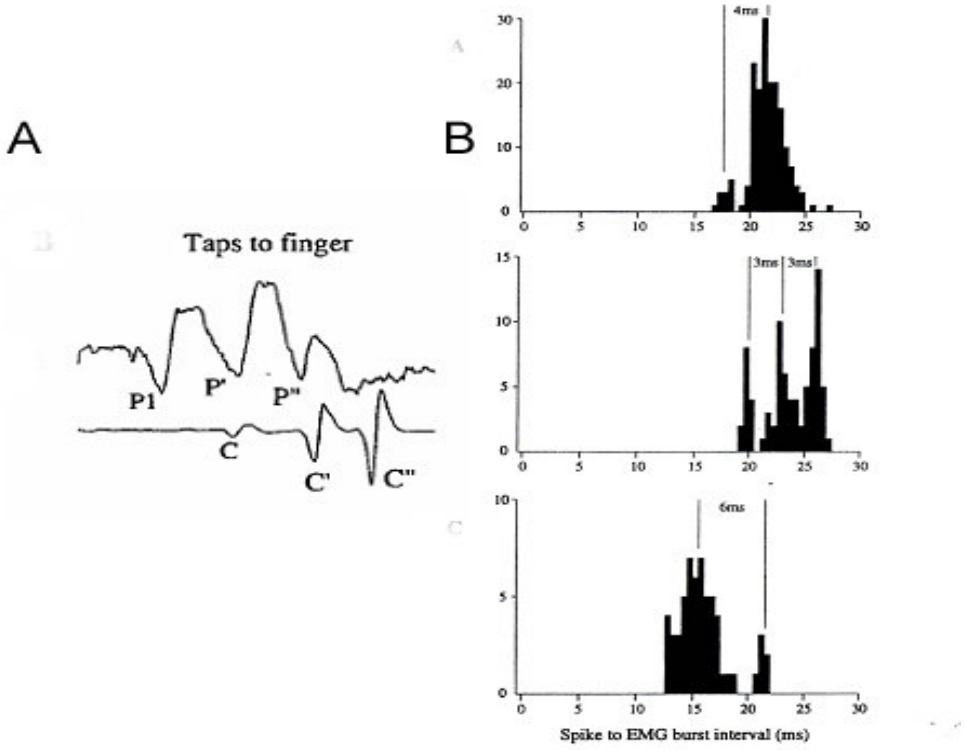

Figure 28. A shows recurrent cortical potentials (P1, P',P'')) followed by myoclonus (C, C', C''), B shows histograms of the interval between EEG spike and muscle response (C reflex). the top graph demonstrating two peaks, the middle three peaks, and the bottom graph shows the spike to EMG intervals during voluntary action. From Brown and Marsden, 1986.

In PME, patients have been shown to have low voltage 20 Hz arrhythmic EEG activity coupled to myoclonic jerks of a similar frequency, possibly related to a loss of cortical inhibition and therefore increasing entrainment of neurons[319]. Figure 29 shows the results from a patient with PME and shows rhythmic EEG activity at 20 Hz, associated with muscle jerks in the right ECR. The next trace shows another PME patient with rhythmic EEG activity at 20 Hz coupled to muscle jerks of the right ECR at rest.

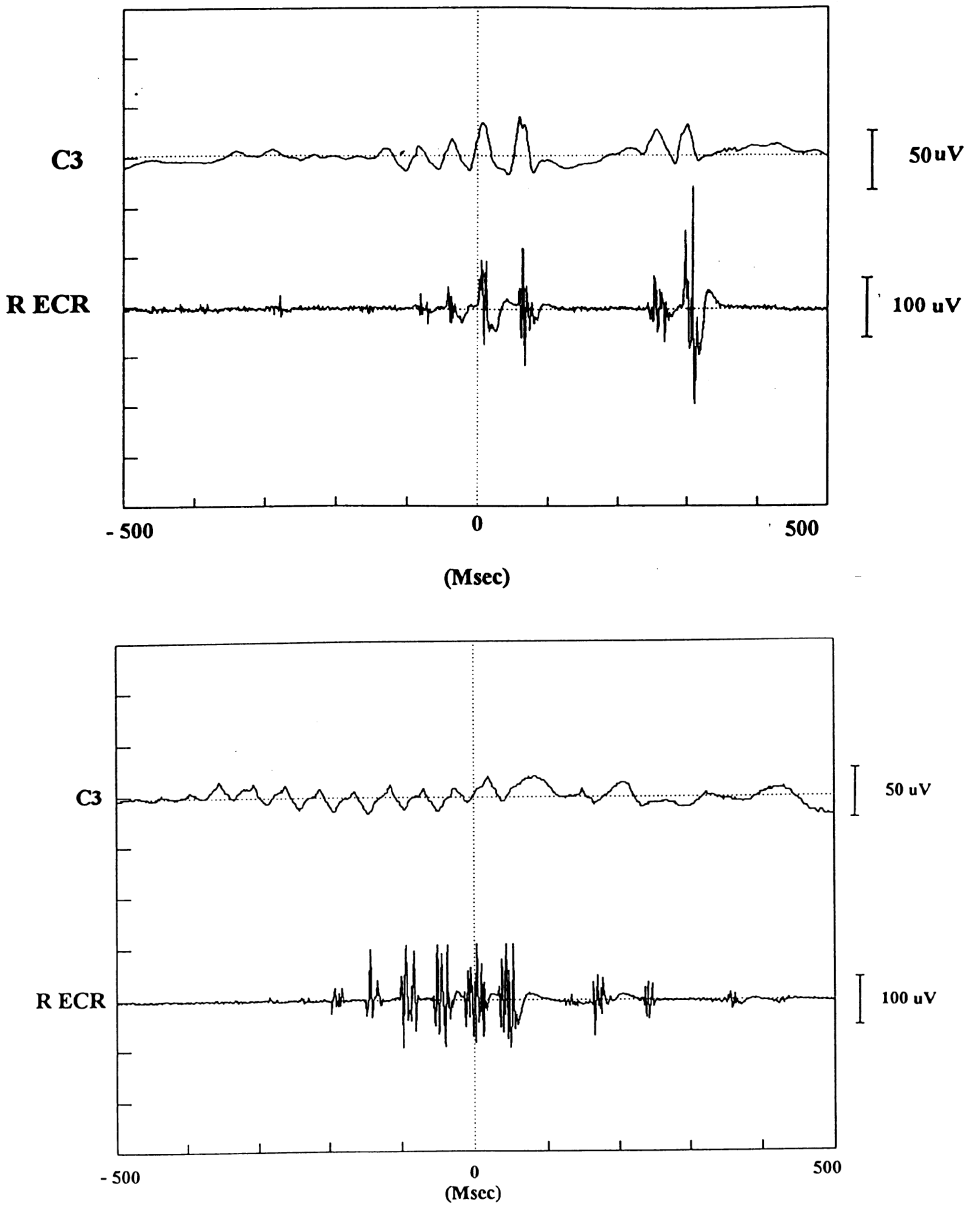

Figure 29. 20 Hz rhythmic EEG activity associated with myoclonus at rest. The recording is a polygraphic one comprising EEG and EMG.

1.8.11 LONG LATENCY REFLEXES AND C REFLEXES

This section concerns transcortical reflexes, of importance since the current division of myoclonus into cortical and reticular reflex myoclonus is based on the concept that myoclonus is due to an enhanced transcortical reflex, and that cortical myoclonus has a long latency reflex as an integral feature. Inherent in the concept of long latency reflexes, is that the physiological responses interconnecting sensory input to motor output must relate to the potential ability of the motor cortex to adjust its output in response to changing peripheral sensory input[320]. The somatosensory system needs to be tightly linked with the motor system for the generation of discrete, coordinated movements such as hand-mouth coordination and fine tactile discrimination[321].

As opposed to the monosynaptic stretch reflex which occurs at rest, stretching a muscle which is actively contracting will result in a long latency stretch reflex[322], and it has been suggested that this may represent a transcortical servo loop which acts to control motor output during movement [323]. In normal subjects, peripheral nerve stimulation facilitates subsequent motor evoked potentials at latencies which are compatible with a peripheral input reaching sensory cortex followed by cortical motor discharge, supportive evidence for the existence of long latency reflexes[324].

The terminology used is somewhat confusing: responses to electrical stimuli or joint displacements are termed M1 or E1, and correspond to the tendon reflex; this is also known as the long latency response 1 (LLR 1). The long latency component at a latency of 40 msec is usually also termed a C reflex, which is synonomous with M2 or LLR II[325]. A later component is termed M3 (LLR III), and typically has a latency of about 90 msec[326]. Typically in PME and similar conditions, a C reflex may be identified, with latencies ranging from 31 to 58 msec[241], often associated with an enlarged SEP and other features of cortical myoclonus[327].

Cortical reflexes were studied by Evarts in monkeys[328], by noting responses in motor and sensory cortices during a task in which a sudden force displaced a limb. Typically, sensory cortex neurons discharged at 10 msec, and pyramidal neurons 4 msec later. There were EMG responses in muscle at 12 msec, compatible with a monosynaptic stretch reflex, and a second phase was seen at 30-40 msec and a third at 80 msec. Evarts believed that the second phase was not a pure reflex, but that there was a learnt component, and that motor set was also involved, both features of voluntary movement[328], a finding confirmed by

others[326], although the subject of controversy[325]. In a primate model of EPC and secondarily generalized seizures induced by subpial injections of alumina cream, Chauvel described succesive bursts in the injured hemisphere after peripheral stimulation stimulation[329].

1. The first corresponded to the monosynaptic reflex;
2. The second component had a latency of 40 msec (termed E1).
3. A third response had a latency of 80 msec, and duration of 70-90 msec (termed E2).

Direct cortical stimulation in the region of the focus (hindlimb area) resulted in two EMG bursts, the first with a latency of 12 msec and the second with a latency of 40-50 msec. Chauvel et al suggested that the E1 and E2 reflexes were transcortical in nature and that the E1 reflex was analagous to a long-loop reflex. Furthermore, they postulated that transcortical reflexes could trigger short myoclonic jerks and maintain longer seizures, stating that "the neuronal organization of the mammalian motor cortex is indeed such that a cell receiving afferent impulses of muscular origin projects in turn to the very same muscle from which these impulses originate"[329].

In humans, Marsden et al. suggested that there were different pathways for the tendon reflex and the stretch reflex, having noted that responses to stretch and other stimuli in muscles occurred at about twice the latency as was seen in tendon jerks, and proposed that they arose from a transcortical stretch reflex pathway[253]. They also examined a patient in whom stretch of the thumb resulted in a myoclonic jerk of the whole arm, with a latency of 50 msec. Marsden subsequently demonstrated that posterior column lesions could abolish late respones, noting that the posterior column was physiologically an appropriate pathway for the rapid transfer of spindle information to the cortex[330]. In patients with DRPLA, in whom SEPs are not enlarged, but have prolonged latencies, the amplitude of the LLR 2 was significantly smaller than controls, possibly related to degeneration of the medial lemniscus, with consequent reduction in cortical input[331]. Similarly, lesions of the cortex itself could also abolish the servo response to displacement of the thumb; the initial component at around 40 msec was frequently lost, often with persistence of later components, for example, at 55 msec, or in the case of a patient with a lesion of the sensory cortex, at 75 msec[332]. As a result of these findings, Marsden's group theorized that cortical myoclonus was the result of exaggerated long loop reflexes, perhaps triggered by poorly discernible peripheral stimuli[60;247]. However, the experimental setup for determing long latency reflexes was hampered by mechanical problems such as the inability of torque motors to generate discrete stimuli (rather producing stimuli lasting 100 msec or more), and that mechanical stimuli activate not only muscle stretch receptors but also multiple sensory receptors [326] .

Moreover, there are other theories to account for the presence of long latency reflexes being distinct from the tendon reflex. These include dispersed spindle afferent volleys and mediation of the stretch reflex by slowly conducting afferents such as group II secondary spindle afferents[322]. Similarly, with regard to the finding of abolition of long latency reflexes by lesions, the long latency pathway may involve slowly conducting polysynaptic spinal routes which are subject to descending influence from supraspinal structures, and removal of a hypothetical facilitatory influence on this pathway could explain the absence of long latency responses in the patients[322]. In addition, the relationship between the responses that Marsden et al obtained from muscle stretch and the C reflex seen in cortical myoclonus is unclear. These responses arise from different stimuli, stretch and electrical stimulation of peripheral nerve respectively, and electrical stimulation of the peripheral nerve does not usually elicit a tendon reflex. Despite these caveats, there is likely to be involvement of long-loop pathways involving the motor cortex for distal hand and fingers muscles[333]. However, this has not been shown to be the case for proximal muscles in the arm, and Chen has reported that for proximal muscles, the estimated central delay is too short for a transcortical reflex[334]. Additionally, in the legs, long latency responses do not appear to be analogous to those demonstrated in the human hand[325].

With regard to the original hypothesis of long latency reflexes being intimately involved in a servo loop linking motor and sensory responses, long latency components appear to be inadequate in the production of an effective control of limb position, and it seems unlikely that long latency reflexes form part of an error-feedback system to restore the position of a limb after its displacement[326]. An additional difficulty is that although afferents to the motor cortex may be involved in cortical reflexes, the nature of the afferents (whether direct or mediated through the sensory cortex) is unclear. Marsden wrote in 1973 that “such a transcortical stretch reflex derives its recent plausibility from the discovery that impulses from muscle stretch receptors (muscle spindles) have a rapid pathway to the cerebral cortex. First found in lower mammals, this pathway has been traced in the baboon to a cortical area in the depths of the central sulcus, immediately next door to the motor area”. However, the existence of a short latency input, if any, to the motor cortex is uncertain (see discussion, Section 1.8.13). The situation may be summed up in this quote by Butler,: “a preoccupation in the literature with long-loop reflexes has, in our opinion, placed excessive emphasis on the shortest latency input. Most skilled movements are pre-programmed and it is more likely that sensory input is used to detail the progress of a movement and its outcome, rather than to provide input to allow the cortex to respond to perturbations”[335].

Concerning the more specific role of these reflexes and myoclonus, subsequent to Marsden's reports on long latency reflexes, he and Hallett published their paper on cortical reflex myoclonus (Section 1.8.8) reporting that in normal subjects, the long-latency responses to stretch started at about 40 msec and lasted till about 90 msec (Figure 30). In addition, they reported that long latency responses often appeared to be composed of two parts, termed A and B. The early A response began 40 msec after the onset of muscle stretch, whereas the B component had a latency of 50-60 msec.

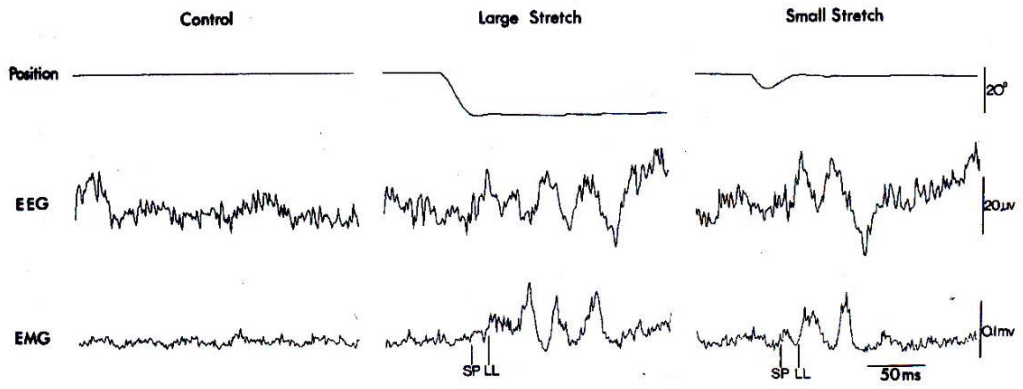

Figure 30. EEG and EMG responses to stretch of the thumb. SP indicates the spinal monosynaptic reflex and LL indicates the onset of the long latency reflex" Figure from Hallett et al., 1979.

Although a feature of cortical reflex myoclonus, remarkably, given the presumptive cortical origin of long latency reflexes, Shibasaki reports that these reflexes may also be enhanced in reticular reflex myoclonus, although the latter is ascribed to brainstem dysfunction[242].

1.8.12 CORTICAL EXCITABILITY

A critical question regarding the pathophysiology of myoclonus is whether the cerebral cortex is abnormally disinhibited and therefore, hyperexcitable. In certain cases, where the cortex has less inhibition than normal, peripheral stimuli may lead directly to myoclonus, or recurrent peripheral stimulation may be required in order to bring cortex to a threshold above which myoclonus will occur. As Adrian and Moruzzi put it "to cause movement the cortex must be stimulated many times at short intervals in order to build up the requisite degree of facilitation. This is a process which takes place in the cortex itself and is associated with a progressive increase in the size of the potential wave following each shock" [268].

Early examples of this phenomenon included Dawson's case in whom it was noted that myoclonus could gradually increase over days and culminate in a generalized seizure[227]. With reference to this patient, Hallliday noted the "frequent occurrence of recruitment in the muscle jerks, suggesting that the train of cortical spikes, which had a frequency of about 8-13 per sec, had to build up to a state of excitability in the intervening pathways by repetitive firing"[252]. In an analogous fashion, Dawson observed that, following a series of tendon taps, initial stimuli produced focal jerks without apparent EEG change, while subsequent stimuli produced generalized EEG spikes and generalized myoclonus [227]. Similarly, Watson and Denny Brown, in a patient with PME due to lipidosis, recognized a sustained afterdischarge resulting from stimulation in various modalities at a favourable rhythm and duration of stimulus[336]. With repetition of a stimulus at a favourable rate, there was a spread of cortical discharge and the evoked slow wave was detected in an area larger than that of evoked spikes. Likewise, in a patient with infantile hemiplegia and stimulus sensitive myoclonus studied by Fullerton and Giblin, myoclonus showed recruitment as determined by an increase in amplitude when stimuli were given at a frequency of 1 Hz[239].

The effects of peripheral stimulation allow inferences to be drawn regarding the potentially different states of cortical excitability. Similarly, the determination of excitability cyles, in which stimuli may be given in pairs, and the interval between stimuli varied is a useful experimental technique in assessing cortical excitation. Shibasaki has proposed that demonstration of enhanced excitability following a single stimulus is evidence for cortical involvement in producing reflex myoclonus[242]. An increase in the degree of cortical excitability may account for successive SEP peaks and C reflexes seen after a single stimulus, a phenomenon described in a number of reports in patients with PME [228;318]), and corticobasal degeneration [289].

With regard to excitability cycles, in Dawson's initial study of the normal SEP in man, he found that the amplitude of the response to the second of a set of paired stimuli could be facilitated by as much as 50 to 70 % during the facilitatory period lasted from 60 to 100 msec and again from 120 and 160 msec, with a period of depression from 10 to 30 msec (Table 10)[248]. The response of the second stimulus is believed to correlate with the level of cortical excitability[241]. Sutton and Mayer found mild facilitation with interstimulus intervals (ISI) from 32 to 63 msec, and again from 130 to 250 msec (Table 10)[245].

Table 10. Results of experiments of excitability cyles in patients with myoclonus.

	Enhancement (ISI)	Attenuation (ISI)
Dawson, 1947b	60 –100	10 - 30; 120 -160
Sutton & Mayer, 1974	32 - 63; 130 - 250	
Seyal, 1991	40 – 200	<40; 300 - 500

Seyal described two patients with cortical reflex myoclonus, with giant SEPs and C-reflexes: in one, seizures could be brought on by movement; in the other, taps over the hand resulted in spikes in the opposite centroparietal region and rhythmic myoclonus could be induced by stimulation of the foot[337]. At ISIs of less than 40 msec, the SEP amplitudes following the second stimulus were decreased compared to those following the first stimulus; whereas at ISIs of 40-200 msec, the SEP amplitudes were increased; a second period of attenuation occurred at ISIs of 300-500 msec (Table 10)[337]. The excitability cycle of the C-reflex paralleled that of the SEPs. These excitability cycles are abnormal, since in normal individuals no enhancement of SEPs occurs until an ISI of 200 msec[338].

Shibasaki used a different technique: using stimuli at varying intervals after myoclonic discharges, he was able to obtain a cortical excitability curve by comparing the amplitude of the evoked potential following myoclonus with that obtained irrespective of myoclonus[339]. There was enhancement of the N33 evoked response and the C reflex for 20 msec after the myoclonus[339]. When a pair of shocks was used to elicit the SEP in a patient with PME, giant SEP and C reflexes were observed to be enhanced with ISI of 35 msec but attenuated at an interval of 65 msec[250]. Ugawa examined cortical excitability by studying the recovery function of the SEP, which was investigated by the paired stimulation technique in which paired stimuli are given at various time invervals. The SEP obtained by the second stimulus

was obtained by subtracting the SEP evoked by the first stimulus from the result of the paired stimulus[340]. . At short interstimulus intervals, in patients with Alzheimer's disease with myoclonus, galactosialidosis, and in PME (not specified), the SEP- recovery curve was abnormal, suggestive of cortical excitability being present. There was a dissociation between the SEP amplitude and the SEP-function, since some patients had an abnormal SEP-recovery curve, although their SEPs were not enlarged, and vice versa[340].

Using JLA, Brown et al demonstrated interhemispheric and transcallosal spread of myoclonic activity in patients with myoclonus who developed bilateral jerks even when only one limb was stimulated, and proposed that this represented abnormal excitation of cortex which might be relevant to the development of seizures in these patients[341]. Subsequently, it was shown that patients with multifocal myoclonus have lower cortico-cortico inhibition and transcallosal inhibition in the event that they have bilateral or generalized jerks compared to the group which does not have generalized jerks [342].

Cortical excitability may also assessed by use of magnetic stimulation. Reutens et al demonstrated increased cortical excitability in idiopathic generalised epilepsy[343;344]. In two of three patients with PME (MERRF and Unverricht-Lundborg), with peripheral stimulation, motor evoked potentials were facilitated at ISIs between20 and 60 msec, suggesting that cortex was abnormally excitable[345]. Similarly, in a patient with focal myoclonus associated with celiac disease, the threshold to magnetic stimulation was reduced over the affected hemisphere[295].

In a group of patients with DRPLA, peripheral nerve stimulation preceding magnetic stimulation facilitated motor evoked potentials in some patients, although somewhat paradoxically, these patients had SEPs which were not enlarged, and had prolonged latencies, with a reduction in long latency responses. The authors proposed that this dissociation was the result of activation of different populations of cortical pyramidal neurons[331]. In patients with ADCME, the resting motor threshold intensity was significantly reduced (even though patients were on antiepileptic drug treatment), and the post MEP silent period during rhythmic EMG bursting was markedly shortened compared with controls, both findings suggesting loss of cortical inhibition[8].

In Unverricht-Lundborg disease Silen et al. have shown that patients have reduced cortical inhibition, as demonstrated by lack of the normal rebound response (stimuli normally elicited a small transient decrease, followed by a strong increase ("rebound") of the 20 Hz component of the mu rhythm following peripheral stimulation) [346].

Similary, in cases of Unverricht-Lundborg disease with myoclonus but no seizures, the responses of the primary somatosensory cortex, as determined by the size of evoked potentials, were only slightly enhanced or were normal, and no ipsilateral responses were seen, whereas in those patients with seizures, SEPs were enlarged. This suggests that in the group of patients without seizures the motor cortex was less excitable and had less disturbed transcallosal conduction[347]. The same authors also used MEG to examine the cortical drive on spinal motor neurones in Unverricht-Lundborg disease, and demonstrated enhanced cortex-muscle coherence during isometric contraction, as compared to normal subjects[348]. The authors suggested that abnormal coherence may be due to reduced inhibition in motor cortex or altered cerebello-thalamo cortical output. However, Karhu reported that cortical inhibition in Unverricht-Lundborg disease was normal, as studied by the response of the neuromagnetic somatosensory evoked field to a paired stimulus paradigm of median and ulnar nerves and by altering the ISI[349].

Hanajima used a paired-pulse magnetic stimulation technique to study cortico-cortical inhibition of the motor cortex: normal results are inhibition at short intervals and facilitation at long intervals[350]. Patients with PME had reduced inhibition at short intervals, perhaps associated with an alteration in the excitability of cortical inhibitory interneurons. Similarly, normal inhibition was lost in patients with lesions affecting either the basal ganglia or their connections with motor cortex, whereas patients with lesions in the sensory cortex or thalamus had normal findings. Using magnetic stimulation over the hand areas of the cortex, one being the conditioning stimulus, and the other the test stimulus, Hanajima demonstrated facilitation at early ISIs of 4-6 msec, with no late inhibition, whereas normally there is late inhibition at ISIs of 8-20 msec and no facilitation, the findings being suggestive of impaired cortical inhibition in affected patients[351].

1.8.13 NORMAL SEP

Electrical stimulation of peripheral nerves activates a large number of large diameter fibers, predominantly cutaneous afferents of Group I and II in type[352]. Group I and II afferents are derived from cutaneous receptors, muscle spindles (primary and secondary endings), Golgi tendon organs and joint capsule receptors. However, there is controversy over the degree to which cortical SEPs are the result of stimulation of Group II cutaneous and/or joint afferents, or to Group I and II muscle afferents[353].

The afferents for the SEP are conducted along the dorsal columns, medial lemnisci and the caudal division of the ventral posterior lateral nucleus of the thalamus (discussed in greater detail in Section 3.5.2)[354,226;232]. With regard to the role of thalamic nuclei in the evoked potential, in man lesions of the VPL encroaching on VPM reduced the evoked potential, whereas lesions of VL had no effect, suggesting that the evoked potential is mediated through the VPL and VPM nuclei, and not VL[355]. Stimulation peripherally results in responses at latencies of 7-20 msec in N ventralis posterior, depending on the region of the body stimulated[356].

In patients with cortical reflex myoclonus the short latency between stimulus and response suggested that the cortical event arose synchronously with or shortly after the afferent volley's arrival at the cortex [248]. This would necessitate a direct sensory input to motor cortex, termed a short latency afferent, or rapid projection from sensory to motor cortex. However, the nature of the peripheral projections to motor and sensory cortices is complex. In cats, there are direct short latency cutaneous and muscle afferents projections to the motor cortex via the VPL nucleus [357]. In primates, short latency somatosensory afferents projecting to area 4 have been recorded[226;358]; with area 4 receiving input from cutaneous and deep receptors, but most area 4 neurons are predominatly responsive to joint movement or deep pressure[359 358].

Moreover, somatosensory projections to area 4 of motor cortex are sparse compared with those to area 3b of sensory cortex. Although SEPs have been recorded in area 4 of motor cortex in cats and monkeys[360], removal of the hand area of somatosensory cortex abolishes the SEP, indicating that the motor component of the SEP is likely to be trivial or non-existent[361]. However, Goldring found smaller and later potentials than those recorded from somatosensory cortex, suggesting that potentials from motor cortex could contribute to the P25-N35 component of the SEP in some cases, although it is unclear whether these could be derived from sensory cortex or not[362].

Although the motor cortex appears likely to receive short latency input from deep forelimb afferents, it is unclear how this occurs. Posterior column input appears to be involved, since cervical cord lesions result in lack of responsiveness of area 4 neurons to peripheral stimuli[363]. However, the posterior columns project to VPLc, and there is no anatomic evidence of a projection from VPLc to motor cortex[364]. On the contrary, group I muscle and muscle spindle afferents pass via the posterior columns through the shell of VPLc and project to area 3a [365] and cutaneous afferents project via the central core of VPLc to areas 3b and 1[226]. VPLc and its subcomponent, VPm, project to areas 3a, 3b, 1, and 2 (Figure 9)[226]. Group I and II afferent projections likely reach area 3b prior to reaching area 1[361]. Area 3b projects posteriorly to areas 1 and 2, and anteriorly to area 3a. Area 3a, which receives Group I afferents and projects to area 1, resembles a zone of attenuated layer IV granule cells intervening between the pyramidal cells of area 4 and the thick granular cell layer of area 3b, and is therefore an overlap zone, functionally sensory rather than motor cortex [226;366].

Only area 2 of somatosensory cortex projects forward to area 4[226]. However, cooling of this region does not reduce the responses of motor cortex to passive joint movement[363;365], indicating that the origin of short latency inputs to motor cortex is unlikely to be transmitted via area 2.

An alternative pathway of short latency inputs to motor cortex would involve VPLo, which receives cerebellar inputs and projects to motor cortex [364]. However, the role of this nucleus in cortical projections of afferent input from muscle and joints is unclear, since it does not receive a projection from the dorsal columns [367]. Furthermore, when compared to VPLo neurons in the cerebellar thalamus, VPLc neurons fire at shorter latency, have more discrete and lower threshold sensory fields and have fields which resemble those of motor cortex, making it more likely that VPLc neurons are likely to be responsible for the short latency input [335]. There may be overlap between terminations of the medial lemniscus and cerebellum at the VPLo and VPLc border, but this is controversial [367]. Different populations of neurons in this boundary zone have been identified which project to either motor or sensory cortex [359].

It remains unclear how short-latency lemniscal inputs reach motor cortex, and if they do so via VPLo [367 226]. The cerebellum can also supply sensory input to the motor cortex, and cerebellar thalamic neurons have sensory fields, although the response is weaker than that seen in VPLc [335]. However, cerebellar sensory information is likely to contribute only to later

motor cortical responses to peripheral stimuli since sensory input to limb perturbation arrives in the cerebellar thalamic nuclei 16 msec after responses in VPL to the same stimulus [335]. Furthermore, many cerebellar thalamic neurons fire too late for a monosynaptic connection from the interpositus nuclei to provide the source for the short latency input. For example, interpositus neurons respond with latencies of 20-40 msec[368], whereas neurons in cerebellar thalamus respond at latencies of 48 msec [335]. Only the earliest firing cells in the cerebellum could contribute to the short latency motor cortical response, which has a latency of 20-50 msec following displacement of a limb[328].

With regard to the neurophysiology of the evoked potential at cellular level, activation of mammalian somatosensory cortex generates a surface positive-negative sequence, the sum of slow postsynaptic potentials, often termed the primary evoked response[369]. The primary positivity is believed to represent depolarization of pyramidal cell bodies and proximal apical dendrites, whereas the primary negativity is believed to reflect later depolarization of distal apical dendrites [360;370]. Pyramidal cells perpendicular to the cortex therefore give rise to a dipole with opposite polarities at the surface of the cortex and lower cortical levels; this being termed a radial dipole. In contrast, a tangential dipole consists of neurons in the wall of a sulcus, resulting in a potential field of opposite polarities on either side of the sulcus. Such a dipole is detectable by MEG, which allows for a determination of the direction of the intracellular current flow, that is, the site of depolarization in the apical dendrites of large pyramidal cells[242].

Dawson had initially recorded a positive-negative deflection, corresponding to the primary evoked response [371]. Subsequently, cortical recordings by Giblin showed a similar positive-negative response (Figure 31) and it was concluded that mammalian and human responses were similar, with respect to the polarity and relationship of the primary positivity and negativity[372]. Giblin described an initial positivity, P25, largest in the region medial to where N20 was recorded, and the conclusion was that P25 was the primary positivity of somatosensory cortex [361]. However, Broughton noted the polarities of the primary response were inverted in man compared to the usual mammalian responses, since the major initial response was N20/P20, followed by P30/N30, and proposed that in man the primary cortical SEP generator could be located deep in the posterior wall of the central sulcus[373].

In the normal SEP, the primary triphasic complex is believed to represent the cortical response to the afferent volley [374]. Waves have been labelled as follows:
N20: First cortical negative wave at 20 msec, also termed N1
P25: Following positive potential at 25-32 msec, also termed P1

N30: Subsequent negative potential at 33-40 msec, also termed N2[374]

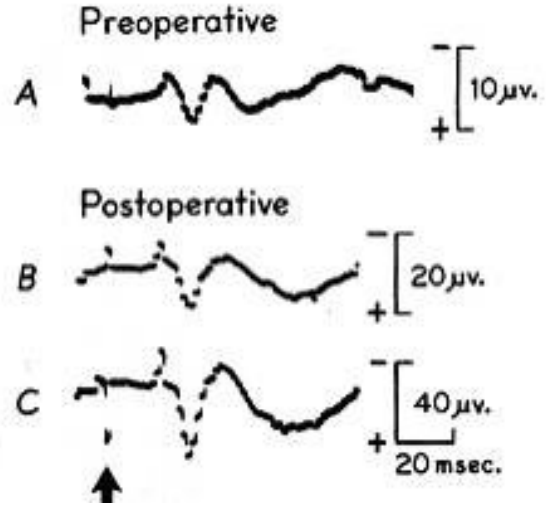

Figure 31. These responses show SEPs: A and B are scalp recordings; C was recorded from the cortical surface of the postcentral gyrus (from Giblin, 1964).

However, the origin of the normal human SEP is somewhat controversial. With reference to Figure 32, based on Allison's work (1991) it seems likely that the typical waveforms seen in human cortex are:

P20-N30: corresponding to the hand area of motor cortex; location 1 (Figure 32-C), recorded from motor cortex and frontal scalp.

P25-N35: corresponding to the medial portion of hand area of somatosensory cortex near the central sulcus, but also recorded at smaller amplitudes from the motor cortex near the central sulcus: location 2 (Figure 32-C).

N20-P30: largest in the lateral portion of the hand area of somatosensory cortex and adjacent parietal cortex: location 3 (Figure 32-C).

These potentials appear to be generated in somatosensory cortex in area 3b and 1, and not elsewhere[361]. Depth probe recordings have recorded the largest P20-N30 potential at one to two cm beneath the cortical surface[360], which is compatible with the major axis of a dipole generator sited in area 3b [361]. Similarly, MEG recordings have shown a tangential source 2-3 cm beneath the scalp in the region of the somatosensory cortex [375;376]. Recordings of both MEGs and SEPs confirm that they are produced by a single tangential generator; the direction of intracellular current flow detected in magnetic recordings being consistent with initial depolarizion of neurons in somatosensory cortex, but not motor cortex [361]: MEG demonstrates that area 3b is the major contributor to the 20 msec and 30 msec potentials.

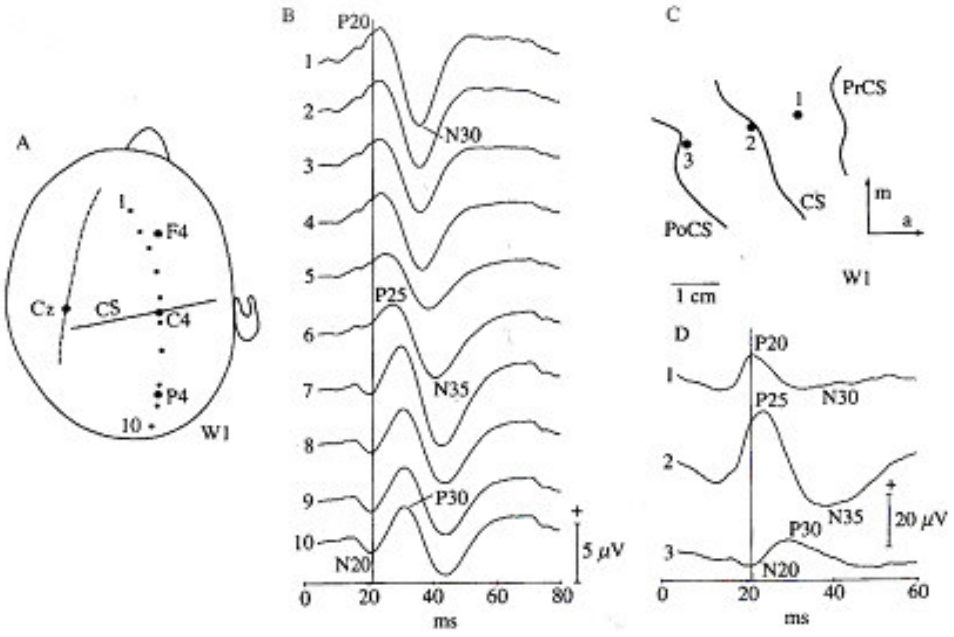

Figure 32. A shows position of the electrodes over the scalp (oblique view). B shows the SEPs recorded from the electrodes in A (note the polarities are reversed compared with usual conventions). C shows the cortical surface of the hemisphere, where CS is the central sulcus. D shows SEPs recorded from the cortical surface (from Allison, 1991)

1.8.14 PATHOLOGICALLY ENLARGED SEPS

A central tenet of the current classification of myoclonus into cortical and subcortical types is that in cortical myoclonus the SEPs are enlarged. However, particularly given that subcortical structures are involved pathologically, it is important to try and establish the basis for our understanding of enlarged evoked potentials as being of cortical origin. Summed excitatory postsynaptic potentials (EPSPs) give rise to the P1-N2 wave either due to abnormal afferent inputs, or because of a primary disorder of cortical inhibitory interneurons or a secondary failure of inhibition from other subcortical structures[374]. As Dawson wrote in 1947: "If in fact the initial wave in the response to stimulation in the myoclonic subject… is associated with the arrival of the afferent volley at the cortex and not with any subsequent cortical activity, as is suggested by the short latency and polarity of the response, then the cause of the great difference in size between the responses in the healthy and the myoclonic subjects must be sought below the cortex, possibly at the level of the thalamus" [248].

Halliday observed that "in a sense it is to the phenomenon of myoclonus that we owe the discovery of the somatosensory evoked response in the human cortex"[239]. Having demonstrated that peripheral electrical stimulation in a patient with myoclonus brought about changes in cortical potentials, Dawson went on to describe SEPs in normal individuals[371]. A few months later, Dawson noted that SEPs could be enlarged some five to ten times in focal myoclonus, the first example of the intimate relationship of myoclonus with abnormal SEPs [248]. The subject had a complaint that when he put weight on his toes, his foot began to shake and seizures occurred preceded by altered sensation of the left arm. Generalized myoclonic jerks were elicited by evoking tendon reflexes and active or passive movements. During myoclonic jerks the EEG showed groups of polyspikes (fast focal sinusoidal discharge) occurring every few seconds..

Features of the SEPs associated with myoclonus include:

- Focal limb myoclonus is associated with unilaterally enlarged SEPs[374]. In this case the myoclonus is usually a combination of cortical reflex myoclonus and spontaneous myoclonus, worsened by action[374]. This form of focal myoclonus is typically limited to an abnormality of a small cortical area.
- Bilaterally enlarged SEPs are seen with multifocal or generalized myoclonus [374]. Myoclonus is typically worsened by action, but spontaneous and cortical reflex myoclonus are often present. Reflex jerks may be present on stimulation, as may generalized myoclonus. The pathophysiology is that of a generalized encephalopathy, or due to loss of inhibition, frequently associated with cerebellar disease [374].

However, patients may have enlarged SEPs without myoclonus; [252] [374]. and conversely, myoclonus is not necessarily associated with enlarged SEPs[230;239;374;377]. Myoclonus may only be present if the SEP reaches a particular amplitude [239], and large SEPs may be present only when actual jerking is taking place in focal myoclonus[374].

There is experimental evidence for subcortical activity being expressed as an evoked potential, and as early as 1964, Giblin recorded a negative potential at a latency of 17 msec, and concluded that "since this negative wave precedes the positive wave of the primary, it can only be due to presynaptic potentials in thalamocortical projection fibres" [372]. Subsequently, a diffuse negativity at N18 was noted to persist despite thalamic or suprathalamic lesions which aborted N20 and later potentials [378], and was therefore interpreted as being of thalamic or brainstem origin. However, animal recordings have shown that evoked potentials recorded in VPL appear at the cortical surface as a *positive* inflection on the rising phase of the primary positive wave; this early potential having a subcortical source since it increases in amplitude at increasing depth from cortical surface, as opposed to the primary positive-negative complex which inverts in polarity in deep cortical layers [373].

An autopsied case with an absent N19 was shown to have diffuse cortical atrophy with normal thalamus and thalamocortical radiation, suggesting that potentials with latencies of 19 msec and later are of cortical origin [379]. Direct recordings from the Vop nucleus of the thalamus showed that the latencies of thalamic potentials were shorter than N20, "consistent with a cortical origin for N20"[379].

In recordings made during stereotactic thalamotomy, carried out under local anaesthesia, the nucleus ventro-caudalis, which lies in the sensory territory of thalamus, was found to have the clearest responses to stimulation, and its response was invariably related to the initial negative response of the cortical SEP, which occurred 1-2 msec later (Figure 33). It was concluded that this cortical response represented the afferent volley of the thalamo-cortical fibres[380]. Similarly, Pagni reported a cortical positive wave at 15-20 msec, about 2 msec later than the thalamic response [381].

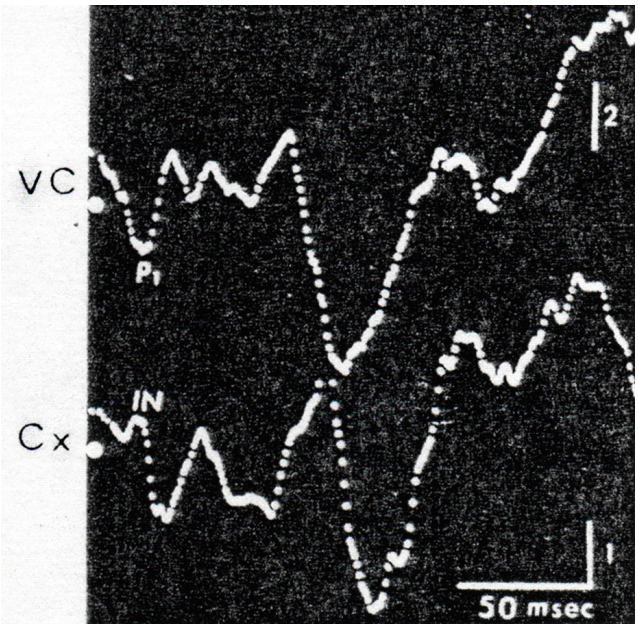

Figure 33. Recordings during stereotactic thalamotomy; SEP recorded simultaneously with the thalamic recording; electrical stimuli consisted of 0.1 msec rectangular pulses at random intervals from 1-1.5 seconds, usually over median nerve. VC nucleus of thalamus showed clearest responses to stimulation: a single positive deflection, at a latency of 12.2 msec to onset and 17.5 msec to peak (P1), related to the initial negative response (IN) of the cortical SEP (Cx), which occurred 1-2 msec later (from Fukushima, 1976).

Cortical responses as a result of activation of subcortical structures, as exemplified by the SEP, are not unique to thalamo-cortical interactions. Further examples of subcortical structures giving rise to evoked potentials include the subthalamic nucleus and the lateral geniculate body:

1. Stimulation of the subthalamic nucleus results in both positive and negative potentials at latencies of 19 and 23 msec respectively at the medial-posterior frontal regions on EEG. The more prolonged latency is believed to be related to stimulation of the premotor cortex [382].
2. When recording the VEP, flash stimulation in the primate produces a broadly frontal negative response, N25. In the lateral geniculate body, early current sinks in the parvocellular lamina 3 and magnocellular lamina 2 generate the initial part of N25, and the peak and later parts of this wave arise from depolarization of cells in lamina 6 [383].

A critical point in the argument that myoclonus is of cortical origin is the apparent dissociation between the amplitude of the N1 response, which is of normal amplitude [250;377;384;385] and the subsequent P1 and N2 responses which are enlarged. Although there is uncertainty as to whether the waves seen in giant SEPs are analogous to those seen in

normal SEPs, the latency and distribution of the first negative cortical response is equivalent to the N20 of normal individuals [238;250;377;385;386].

Although giant evoked potentials are typically recorded from sites corresponding to somatosensory cortex, their origin may be more widespread, or they may arise from other cortical areas or represent abnormal input from subcortical structures. However, since the N1/N20 response classically represents the thalamic afferent volley[357;387], it is assumed that the abnormal enlarged responses of PME and similar conditions are not related to thalamic or other forms of abnormal input, but that the cortical area from which the evoked potentials are recorded is itself abnormal.

However, the N1 response in cases of PME is not always of normal size. Shibasaki initially reported that the amplitude of the N1 and P19 were within normal limits or slightly larger than normal [250;384], and Rothwell reported a slight increase in size in two patients[377], noting that "some patients have an enhanced N1 response in the SEP, which may indicate that the afferent volley reaching the cortex is enlarged"[238]. Jones reported a case with an enhanced, asymmetrical N20 response, and commented that " it is puzzling that the majority of studies should find little evidence for enhancement of N20, since this component is widely believed to be generated at suprathalamic level, but recent experience suggests that N20 may be affected more often than previously thought"[304]. The use of MEG has demonstrated an enlarged N20m in patients with Lafora body disease, Familial Cortical Myoclonic Tremor [388], and in Unverricht-Lundborg disease[349] potentially indicating that the 'subcortical structures may also play some role in the pathogenesis of myoclonus' [388]. Similarly, N1 amplitudes are enhanced in CBD, more so in the hemisphere not associated with myoclonus[308], although not always [334]. However, in another study of patients with Unverricht-Lundborg disease using MEG, the amplitudes of cortical evoked responses at 20 msecs were not larger than controls[389], and Mima found normal sized N1 responses in patients with MERRF and a second case of Familial Cortical Myoclonic Tremor[388].

To an extent, as much as there is controversy as to the size of the N20 response, it is equally uncertain whether the subsequent enlarged responses are due purely to cortical activity, or whether they are affected by subcortical input. There may be subsequent processing of the input seen at N1 or the later arrival of an enlarged slower conducting afferent input, which is then responsible for the development of the enlarged P1 [238].

The fundamental basis of the origin of the N20 is unknown and it is reported both as being generated by postsynaptic potentials of pyramidal neurons of area 3b of somatosensory

cortex[390], as well as being due to “presynaptic activity originating from the primary sensory cortex”[384]. An evoked potential is a summation of a number of complex cortical events, many of which are poorly understood: “the possibilities for addition and subtraction of action currents for so many derivations make it clear that a single physiological unit of which the gross evoked potential is the integral must be a constantly changing will-of-the-wisp. This is not to say that an evoked potential is not a function of the numbers and rates of discharge of single cells, but rather that the function is a difficult one to solve precisely, especially when different members of the population may be simultaneously active in different ways”[370].

However, animal models of evoked potentials have been described. A study of local cortical micro-circuits in rodents using current source density analysis allowed three phases to be discerned in the primary evoked field potential (Figure 34): in the first phase, thalamic afferents depolarize layer III and V pyramidal cells [391]. A second phase was determined largely by *intracortical* projections, and in the third phase, spikes were generated in layer V pyramidal cells, presumed to be excited by thalamo-cortical input (sink f in Figure 34). This finding suggests that, at least in rodents, a detailed analysis of the components of the evoked response indicates that thalamic afferents play a role in determining the cortical evoked response in most or all of the components of the evoked potential that are noted to be enlarged in cortical myoclonus. It should be emphasized that there are considerable similarities between humans, primates, cats and rodents, certainly with regard to the primary response, which corresponds to the N20/P20 component in humans [392].

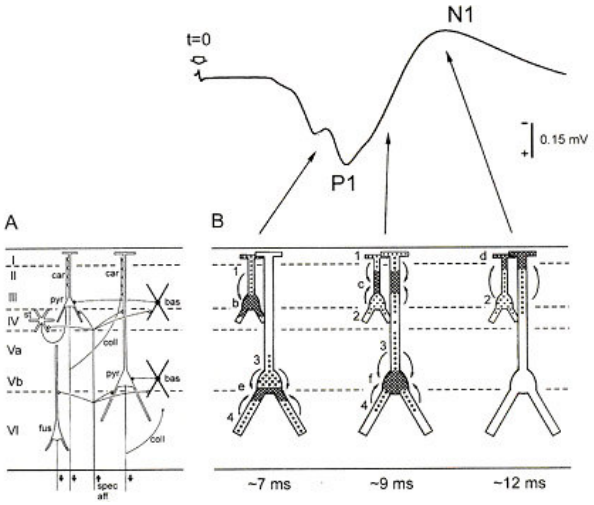

Figure 34. Note: N1 in this figure does not correspond to human N1, but corresponds to human P1. A: Depicting termination of specific thalamo-cortical afferents (spec aff) in the border of layers Vb/VI and layers IIIb-IV. B: Sequence of sink-source configuration, depicted in two pyramidal cells with cell bodies in layers III and V. Sinks (net inward current) are hatched and sources (net outward current) are dotted.

It is pertinent to note that although only 5% to 20% of the excitatory synapses onto layer 4 neurons in the cortex are thalamocortical, since these connections are more powerful than intracortical connections, a small number of thalamocortical axons may dominate the activity of cortical layer 4 cells during sensory inflow[393]; in addition, layer 4 networks may amplify the thalamocortical input [394].

One indication that the process underpinning evoked potentials in humans is more complex than it would appear at first sight is that in patients with myoclonus the amplitudes of the positive and negative waves vary independently [239], suggesting that neuronal populations in cortex are behaving differently. Thalamotomies in humans involving VL and part of VPL reduced evoked responses at latencies of 19.2 and 24.3 msec suggesting that "the two wave forms are related, both being reduced by the same thalamic lesion"[355]. Evidence supporting Rothwell's hypothesis that subsequent processing takes place after arrival of the afferent volley is potentially seen in Unverricht-Lundborg disease, where the N1 response is significantly delayed[349].

1.8.15 LOCALIZATION OF THE SEP

This section reviews current understanding of the localization of the giant evoked potentials associated with myoclonus. In the setting of an abnormally disinhibited cerebral cortex, giant potentials may not necessarily arise by the same mechanisms as the evoked potential in a normal subject.

Dawson observed that evoked responses were largest over the hemisphere contralateral to the site of stimulation and were topographic, in the sense that the potentials corresponded to the arm or leg area of the cortex. These potentials were thought to arise from central or post-central cerebral cortex[371]. However, SEPs may be widespread, and not limited to somatosensory cortex, as seen in patients with PME, sialidosis and uraemia, where giant SEPs can be widespread, involving the central, parietal and frontal regions, [384].

In part related to the belief that the generator of the SEP and the C reflex were identical (see page 163, Rothwell et al. proposed that giant SEPs could be considered to represent an abnormal synchronous discharge of *motor* cortex pyramidal tract neurons which could activate the spinal motoneurons via a monosynaptic fast conducting pathway [377]. Moroever, they also noted that the postcentral cortex could give rise to pyramidal tract neurons. Similarly, Obeso et al suggested that "the giant SEP might represent the discharge of those cortical neurons responsible for activating the anterior horn cells innervating the jerking muscles" [374], although given that there is no clinical evidence of impaired cortical motor function such as weakness or incoordination, the source of the SEP is unlikely to be in the motor cortex[374].

In Dawson's case, the source of the abnormal evoked potential was recorded 3 cm anterior to the central sulcus [248], and in a case of Rothwell's was found to lie in the sensory cortex by electrocorticography [377]. These cases suggest that the giant SEP reflects abnormal cortical function outside of the motor area, with involvement of regions such as the supplementary motor area or the somatosensory cortex [377]. A further example of this potential mechanism is seen in patients with multisystem atrophy with photic reflex and action myoclonus where photic stimulation induces a normal VEP, followed by a discharge which phase reverses between temperofrontal and prerolandic electrodes [395]. Brain mapping of giant SEPs suggested neuronal sources in the rolandic (sensorimotor) region, and it was proposed that following a normal occipital potential, the excitatory volley projected to premotor cortex [395]. In a more complex case of cortical reflex myoclonus, electrocorticography showed bursts of spikes associated with myoclonic bursts, with the source of spikes corresponding to the leg

area of motor cortex[295]. This region was resected, with improvement in myoclonus. The earliest SEPs were recorded over sensory cortex, but the giant SEP was recorded from motor cortex, about 3 msec after the sensory cortex SEP. Stimulation of sensory cortex did not result in myoclonic jerks, whereas stimulation of the motor cortex did result in myoclonus[295].

Certainly, the majority of cases appear to have abnormal EPs arising from sensory cortex, for example, in Cowan's case of EPC, a large parietal cortex excision including the region responsible for generation of the giant SEPs resulted in abolition of reflex myoclonus[386]. Obeso suggested that in cases where the abnormal SEP was localized posterior to the central sulcus, the motor cortex could be physiologically normal, and driven by abnormal inputs from sensory cortex [60]. An example of this mechanism would be the case of cortical reflex myoclonus described by Rosen, in whom myoclonus could be evoked by touch, vibration and stretch, presumed to be due to a zone of increased excitability in the left sensori-motor regionit was postulated that an initial positive wave at a latency of 20 msec represented abnormal excitation of area 3a (the primary projection area for muscle spindle afferents), followed by abnormal excitation 20 msec later of a larger area involving the motor cortex[396].

With the use of MEG, it can be shown that the the equivalent current dipole of the somatosensory evoked magnetic fields (N20m) is localized in the posterior bank of the central sulcus, probably area 3b [242]. Largely, MEG in patients with myoclonus has complemented previously documented findings for the giant SEP and the normal evoked potential.

1.8.16 LOCALIZATION & LATENCY OF THE JLA SPIKE

A cardinal feature of cortical myoclonus is the presence of a spike detemined by JLA. The modern approach to the classification of myoclonus was initiated by Shibasaki in 1975 when he described the technique of back averaging[240].

In Shibasaki's initial report there were two cases (lipidosis and idiopathic RHS) in whom clear spikes could be demonstrated with JLA. The spikes were biphasic, of positive-negative polarity and preceded myoclonic jerks in the upper limb by 10-17 msec (Figure 35)[240]. JLA was therefore able to establish that myoclonus was closely related to an EEG spike, as opposed to routine EMG-EEG recordings where this association was usually not evident. Shibasaki, with reference to Halliday's classification of myoclonus into pyramidal and extrapyramidal, thought that the spike demonstrated by JLA corresponded to the pyramidal group, whereas those without a spike were of the extrapyramidal type[240]. As noted previously (page 101), JLA allowed a number of cases to be termed cortical myoclonus or cortical reflex myoclonus[60].

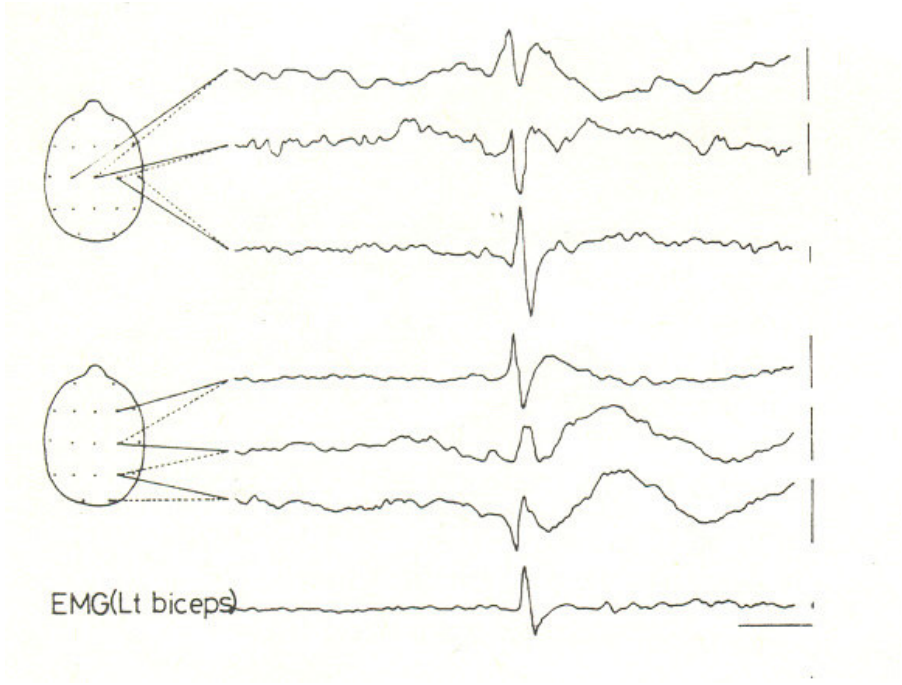

Figure 35. Averaged recording of case of RHS, showing a focus of the spike posterior to the right central region, related to myoclonus of the left biceps. Calibration: 10μV for amplitude and 100 msec for time (from Shibasaki and Kuroiwa, 1975). Upward deflection indicates negativity.

In subsequent papers, in 1978 and 1985, Shibasaki looked at larger groups of patients with myoclonus, and found similar results[250;385]. JLA showed positive-negative "sharp potentials"

related to myoclonic discharges in patients with PME. The second phase of the biphasic potential of negative polarity was termed the “spike potential”. The latency from the onset (the preceding positive peak) to a myoclonic discharge in the arm varied from 7 to 15 msec[385]. The onset was defined as commencing at the preceding positive peak (Figure 35 and 36).

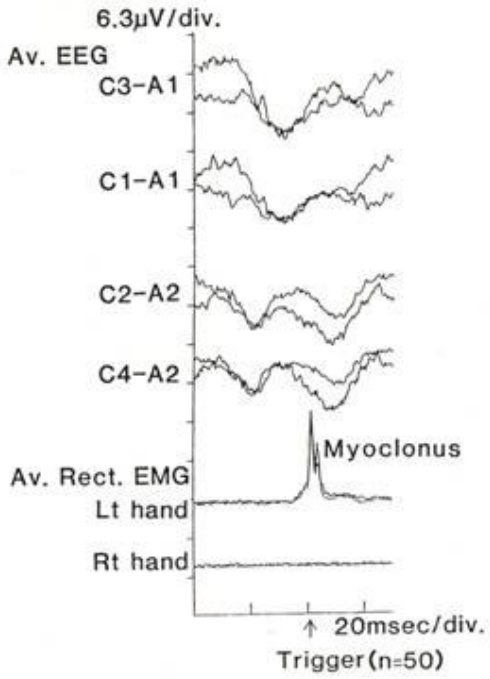

Figure 36. Averaged recording in a case of PME showing a spike at the right central electrodes, related to myoclonus of the left hand (from Shibasaki et al., 1988)).

The decision to use the positive peak relates to the work of Lance and Adams in patients with hypoxic myoclonus, since they reported that “measurement of the latency between cortical spike and muscle potential must take the positive cortical deflection as its starting point, for this would represent the time at which a descending volley might be initiated in the pyramidal tract”[246]. Lance and Adams noted that work in animals had shown that stimulation of the specific relay nuclei of the thalamus resulted in a cortical discharge, initially positive and subsequently of negative polarity. A descending discharge could be recorded in the corticospinal tract, and commenced “at the same time as the early positive component of the cerebral complex”[397].

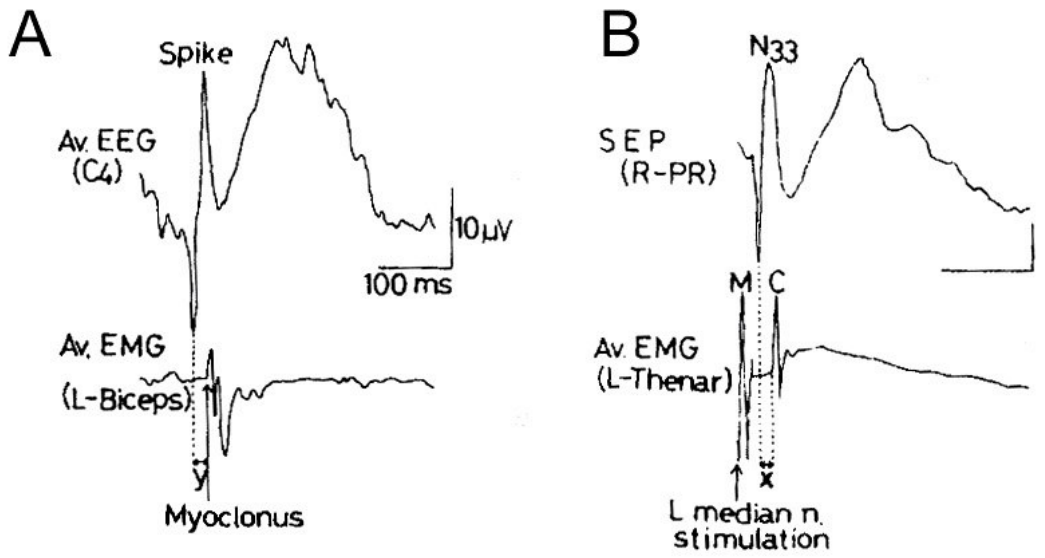

Figure 37. A: JLA showing cortical spike with latency of 12 msec from spike to onset of myoclonus (interval y). B: SEP showing enlarged N33 response. Time interval from P25 (early positive peak) to C reflex is 14 msec (interval x). Figure from Shibasaki, 1978.

Given that peripheral stimulation resulted in giant evoked potentials and a subsequent myoclonic jerk (C reflex), and that JLA is dependant on recording from myoclonus, it is perhaps not suprising that a possible relationship between the spike seen with JLA and giant evoked potentials was proposed (examples are seen in Figure 37 and Figure 38 [307;385]. Not only were the wave forms of the myoclonus-related spike and the N33 of the SEP similar, but also the latency from the JLA associated spike potential to myoclonus was similar to that from the N33 wave of the SEP to the C reflex[385]. Further evidence for a relationship between the giant evoked potential and the JLA spike was that the N33 component of the SEP phase reversed at the area corresponding to the contralateral precentral hand area, as did the JLA recorded EEG spike, although the SEP was more widely distributed[250]. Obeso et al noted that the potential seen with JLA and SEPs shared "the same morphology, topography, and time relation to the myoclonic jerking"[374]. The proposal was made that the myoclonus related spike and giant SEP which precede spontaneous myoclonus and reflex-evoked myoclonus respectively were directly related[250]. Shibasaki concluded that the “myoclonus-related spike and the giant SEP seen in those cases of “cortical reflex myoclonus” have common physiological mechanisms, although they may not be identical “[327], and proposed that the myoclonus was of cortical origin[385].

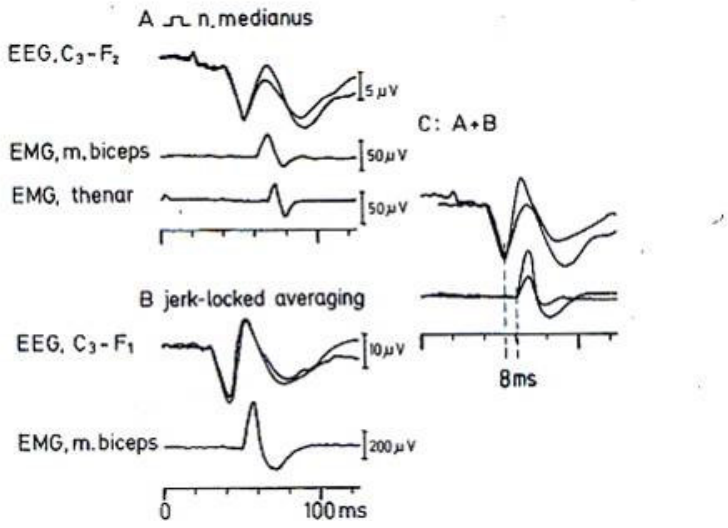

Figure 38. Patient with Lance-Adams syndrome. A shows SEP and C reflexes. B shows JLA with spike and myoclonic jerks. C shows the two traces superimposed. Figure from Deusch et al., 1987.

However, it appears unlikely that the giant SEP of reflex-evoked myoclonus and the cortical spike determined by JLA are indeed similar. As previously noted (page 153), the giant SEP and myoclonus are often dissociated, with giant SEPs not present in all patients with cortical reflex myoclonus, and some patients having giant SEPs without myoclonus[250;374].

Furthermore, the frontal and parietal distributions of SEPs and premyoclonus spikes in patients with cortical reflex myoclonus also differ[251]. A dissociation may be detected between the SEP and the myoclonic jerk, in that anti-myclonic drugs can reduce the frequency and severity of jerks, whereas the amplitude of the SEP is unaffected or even increased[337;377]. Similarly, in patients with focal myoclonus taking 5-hydroxytryptophan, there was a dissociation between SEP size and C-reflexes, since the latter disappeared on treatment, whereas SEPs did not[337].

A further problem with the application of JLA to determine the nature of the myoclonic discharge lies in establishing the latency from the premyoclonus spike to the onset of myoclonus. The JLA spike is believed to arise from the motor cortex in cortical myoclonus on the basis of a latency of aproximately 20 msec, which is similar to that obtained from direct stimulation of human motor cortex, where the latency from electrical stimulation of the cortex to motor response is about 22 msec[238] (Figure 39), or the latency obtained by transcranial magnetic stimulation, which varies from 23.5 msec[334] to 22.6 msec [308]. Mean latencies of 19.8 msec and 21.3 msec for contracted and uncontracted for thenar muscles

were obtained by Day.[398] with the latency from time of cortical stimulation to response in the thumb being 19.2 msec [399].

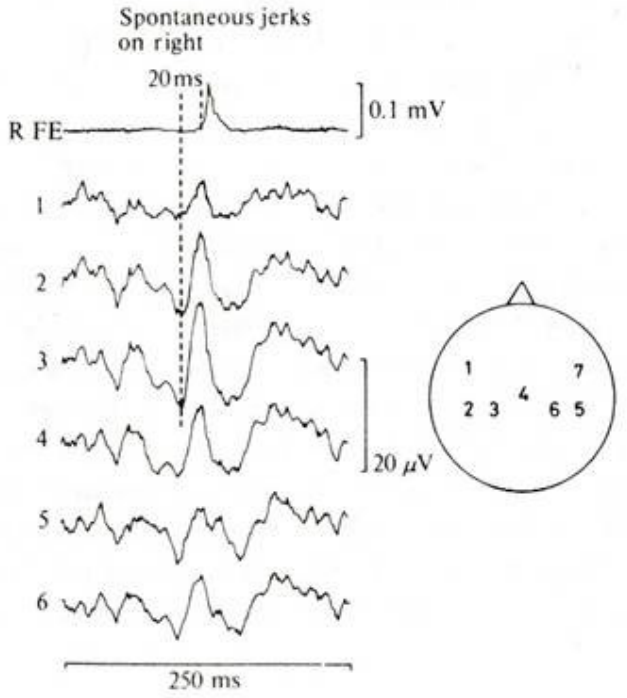

Figure 39. Example of JLA, where a positive wave is reported to precede the jerk by 20 msec (from Obeso, 1985).

Shibasaki, who described JLA in relation to myoclonus, found that the positive peak of the spike preceded the onset of myoclonus with latencies ranging from 10-17 msec, 7-15 msec and 6-22 msec in his three initial reports [240;241;385]. In the first of these, he proposed that these short latencies were indicative of "a deep origin for both the cortical paroxysmal activity and the myoclonic jerk", since the conduction of impulses from the motor cortex to a muscle of the contralateral arm was known to take approximately 25 msec"[240]. Since then there have been many reports demonstrating a lack of consistent correlation between cortical spikes and muscle jerks, or discrepancies in the expected latency differences. A summary of the results from JLA in a number of articles is presented in Table 11. In ADCME, Guerrini et al. found that analysis of phase spectra showed that EEG activity preceded EMG activity, although the EMG lag (8-15 msec) was shorter than that seen with back-averaging and was brief for even the fastest cortical pathways. When Brown et al drew up frequency histograms in rhythmic myoclonus of the cortical spike to EMG burst, they noted several different peaks (Figure 28): one of these peaks had a latency of only 17 msec and was 5 msec shorter than the conduction time to FDI measured by magnetic stimulation

of the motor cortex in that patient; the authors comment “thus the descending motor volley must, in some trials, have left the cortex 5 msec or so before the peak positivity of the giant spike”[318].

Furthermore, the configuration of the spike is rather variable (Figures 35, 36 & 39), and determining the latency from the spike to onset of myoclonus may be difficult (Figures 36 & 39). In addition, problems with JLA including the arbitrary nature of the trigger level and that high-frequency myoclonus may prevent analyses[400]. Shibasaki also noted ‘jerk-locked averaging might be associated with a considerable time jitter between the actual onset of myoclonic EMG discharge and the trigger pulse which was obtained from that EMG, resulting in a poorly synchronized averaging, whereas SEP is consistently time-locked to the stimulus onset”[401].

Noting that the MEP latency is inversely proportional to the amplitude, and that experiments using magnetic stimulation of the cortex would therefore tend to overestimate the speed of cortico-muscular conduction[402], Cantello et al used magnetic stimulation to evoke a potential of the same amplitude as the spontaneous myoclonic discharge, and found a corticomuscular conduction time of 23 msec[403]. The interval between the initial positive wave and myoclonus obtained with JLA ranged from 13.3 to 16.3 msec, and the authors inferred that the origin of the abnormal potential was therefore subcortical [403].

With regard to the origin of the JLA associated spike, it should first be noted that direct recordings have been obtained in patients with myoclonus. In a patient with anoxic induced myoclonus, spontaneous myoclonus was preceded by a cortical spike with a latency compatible with discharge down the corticospinal tract. Recordings from the VL nucleus showed that discharges *followed* the cortical spike and were simultaneous with the muscle jerks. Peripheral stimuli led to a motor cortical response, with or without myoclonus, without an associated VL response, and stereotaxic lesions of VL had no effect on myoclonus[404]. However, VL lies in the cerebellar territory of the thalamus, and it is unlikely that short latency afferents project via this nucleus to sensorimotor cortex (see discussion page 149). Two cases of Unverricht-Lundborg syndrome have been studied with depth electrodes in the sensorimotor cortex, GPi, VL and VPL nuclei of thalamus, internal capsule and red nucleus. Myoclonus always followed a cortical spike recorded from sensorimotor cortex contralateral to the myoclonus, with a fixed latency[381]. Stimulation of the VP nucleus of thalamus (the principal sensory nucleus, comprising the VPL and VPm[405]) evoked a bilateral myoclonic jerk, “mediated through the sensorimotor cortex” [381].

Similarly, Tassinari studied two cases of Unverricht-Lundborg syndrome with depth electrodes in the sensorimotor cortex, GPi, VL and centromedian nuclei of thalamus, and red nucleus. He reported that spike discharges in the thalamus occurred independently of paroxysmal activity in the cortex, and action myoclonus was not necessarily associated with ventrolateral thalamic nucleus discharges[406]. As can be seen in Figure 40 reporting Tassinari's findings, action myoclonus was associated with spike discharges in the ventrolateral thalamic nuclei and red nucleus, and possibly in the motor cortex.

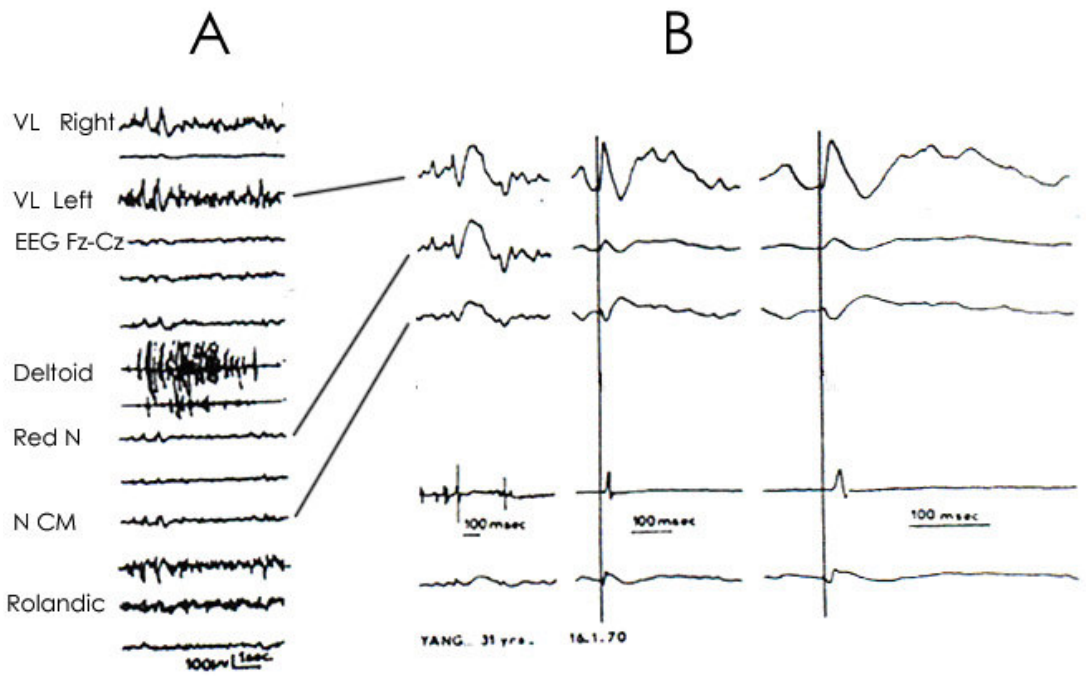

Figure 40. Surface EEG Enlarged sections of that seen on the left: paroxysmal activity noted in the first three channels "doubtful activity was observed in the left rolandic cortex". Figure redrawn from Tassinari, 1998

Table 11. Results of JLA from various sources

Reference	Conditions	Wave type	Location	Muscle	Peak used for latency	Latency (msec)
Shibasaki, 1988	Cortical reflex or cortical	Positive Negative	Corresponding to muscle from where recorded			6 to 22
Obeso, 1985	Case 8 (Hallett 79)	Positive Negative	Sensorimotor cortex		Positive	17
	Case 9 focal myoclonus	Positive Negative	Widespread		Positive	22
	Case 11	Positive Negative	Sensorimotor cortex		Positive	20
	Case 10 EPC	Negative	Midline Rolandic	Quadriceps		30
Guerit, 1994	Focal myoclonus	Positive Negative				53
Guerit, 1994	Focal myoclonus	Positive Negative			Negative	27
Terao, 1997	Focal myoclonus	Positive Negative		Tibialis Anterior	Positive	24.4
Uesaka, 1996	EPC	Positive Negative		ECR	Positive	31.6
				ECR	Negative	15.8
				ECR	Positive	9.6
				ECR	Negative	25.5
Ochi[407]	EPC			Wrist extensor	Positive	20.0
Volmann, 1998 (MEG)	EPC	Single deflection	Inferior Parietal	Flex Dig Sup	N/A	31 (normal TMS time of 17.2 msec in 11 year old)
Rothwell, 1984						17-22
Tobimatsu, 1985	Sialidosis			Thenar	Positive	23.8-31.1
Tobimatsu, 1985	Sialidosis			EDC	Positive	16.8
Brunt, 1985	Sialidosis			APB	Positive	14
	Sialidosis			EDC	Positive	8

Table 11 continued. Results of JLA from various sources

Reference	Conditions	Wave type	Location	Muscle	Peak used for latency	Latency (msec)
Deuschl, 1987	NCL			Thenar	Positive	17
Shibasaki, 1975	Lipidosis	Positive Negative	Central	Extensor Indicis		17
				Brachio-radialis		10
Deuschl, 1987	PME			Thenar	Positive	16
	PME			Thenar	Positive	16
	PME			Thenar	Positive	15
	PME			Thenar	Positive	17
Shibasaki, 1978	PME	Positive Negative		Dorsal Interossei	Positive	12
				Biceps	Positive	7
				FCU	Positive	14
				Brachiorad	Positive	15
				Extensor Indicis	Positive	10
				FCU	Positive	13
				Biceps	Positive	9-12
				Brachiorad	Positive	9
				Biceps	Positive	8-12
				Deltoid	Positive	7-14
Shibasaki, 1986	PME				Positive	6-22
Brunt, 1985	PME			APB	Positive	13
	PME			APB	Positive	15.8
Mima, 1988	PME	Positive		ECR	Negative	14.3
	PME	Positive		ECR	Negative	14.3
	FAME	Positive		ECR	Negative	14.3

Table 11 continued. Results of JLA from various sources

Reference	Conditions	Wave type	Location	Muscle	Peak used for latency	Latency (msec)
Uesaka, 1996	Familial myoclonic epilepsy (4 cases)	Present		FDI		16.2
Elia, 1998	Familial cortical myoclonus	Positive	Fronto-centro midline		Positive	25-30
Ikeda, 1990	Cortical Tremor			Extensor indicis		15.4
Ikeda, 1990	Cortical Tremor			Extensor indicis		20.8
				FDI		24.0
Shibasaki, 1975	RHS	Positive Negative	Little posterior to central region	biceps	?Negative	13
				FCU	?Negative	13
Deuschl, 1987	RHS			Thenar	Negative	19
Obeso, 1985	RHS	Positive Negative	Sensorimotor cortex		Positive	20
Kunesch, 1991	RHS					80
Deuschl, 1991	MERRF			Present		
Brown, 1996	PMA (coeliac)			Forearm extensor	Positive	15
Brown, 1999	Coeliac disease			ADM		27
	PMA			F Ext		14
Wilkins, 1984	Alzheimer's disease	Negative	Contralateral central area			20 to 40
Mima, 1988	Alzheimer's disease					28
Panzica, 2001	JME	Positive Negative	Frontal	Deltoid	Positive	10.25

Table 11 continued. Results of JLA from various sources

Reference	Conditions	Wave type	Location	Muscle	Peak used for latency	Latency (msec)
Mima, 1988	LGS	Negative (standard JLA)	Contralateral central area (standard JLA)			65 (standard JLA and MEG)
Deuschl, 1987	Lance Adams			Thenar	Positive	20
	Lance Adams			Biceps	Positive	8
	Lance Adams			Biceps	Positive	9
	Lance Adams			Biceps	Positive	10
	Lance Adams			Biceps	Positive	9
Brunt, 1985	Lance Adams			APB	Positive	13.2
Uesaka, 1996	Lance Adams	Present				
Mima, 1988	CBD			DIO	Positive	15
Brunt, 1985	CBD	Small Positive F3-C3		APB	Positive	18

2 METHODS

2.1 IDENTIFICATION OF AFFECTED CASES

The proband of family A (A-III-8) was identified from a search for patients with idiopathic generalized epilepsies (IGE) (Figure 41), and that for family B (B-IV-3) was referred with epilepsy from a psychiatric ward at Tygerberg hospital (Figure 42). Participants were examined and underwent MRI and routine neurophysiological investigations including EEG, visual evoked potentials (VEP) and somatosensory evoked potentials (SEP) and nerve conduction studies. In addition, jerk locked averaging was performed, and the response to magnetic stimulation was determined. Pathology of the fixed brain of subject A-III-9 was obtained.

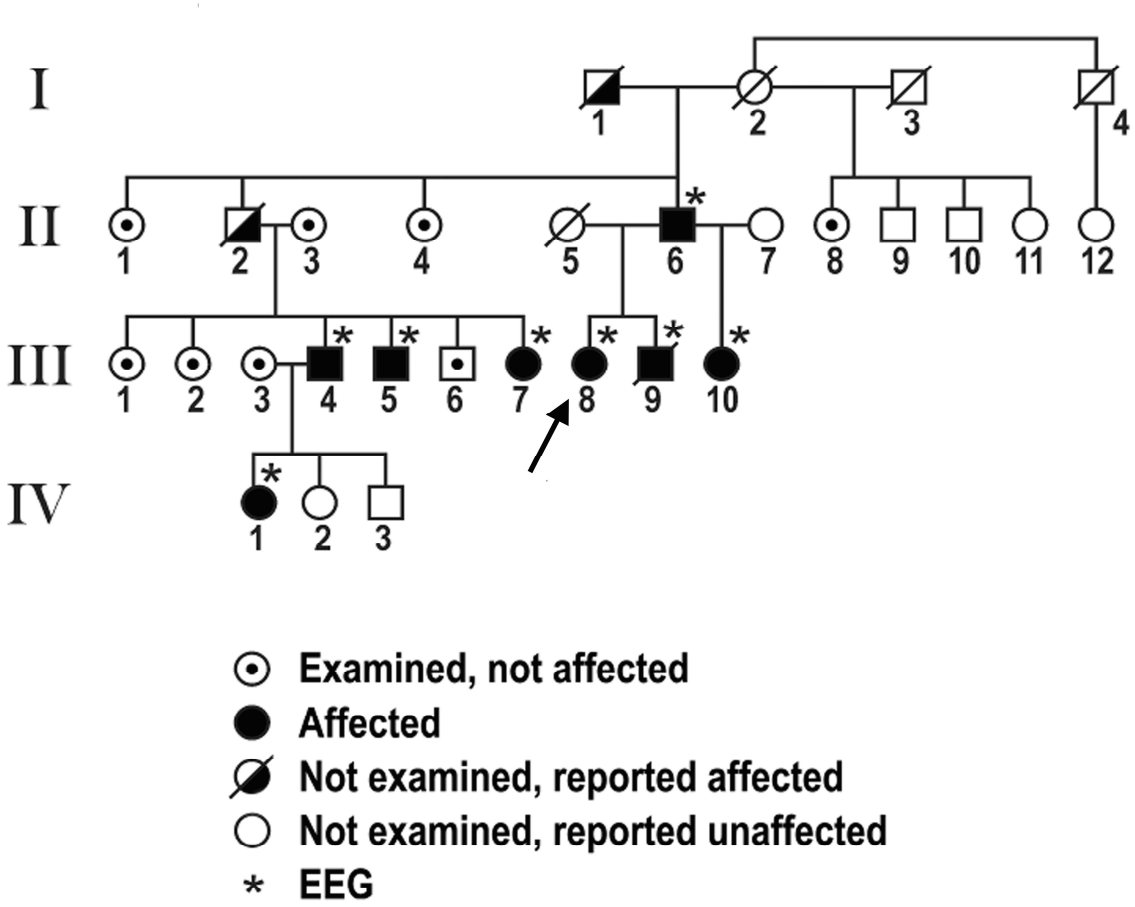

Figure 41. Family tree for Family A.

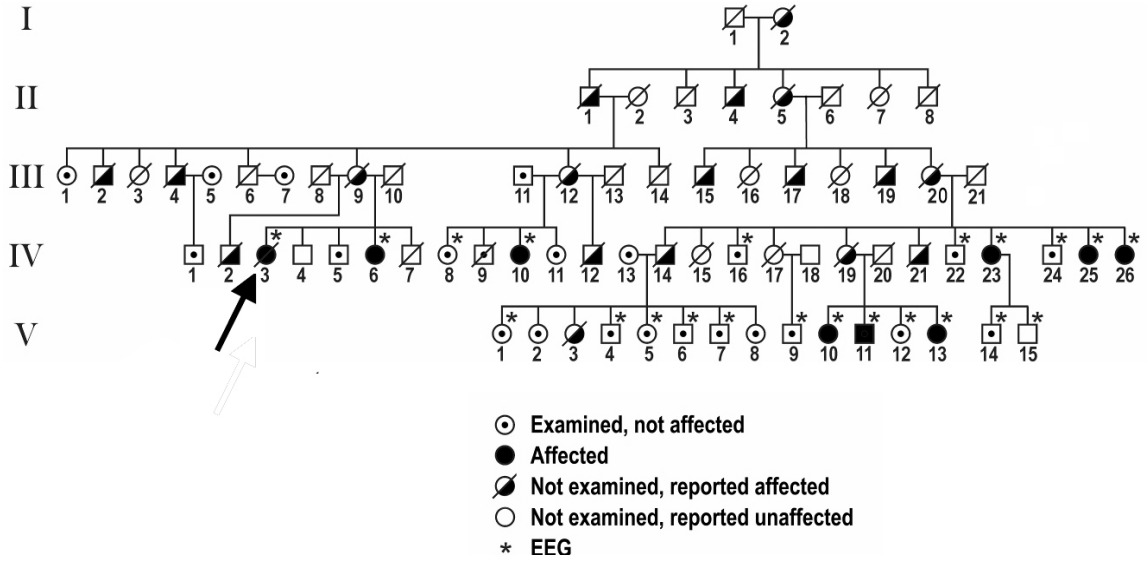

Figure 42. Family tree for Family B.

2.2 NEUROPHYSIOLOGY

Ethical approval was obtained from the University of Stellenbosch for neurophysiological investigations.

2.2.1 EEG

EEGs were obtained after the application of electrodes and conducting jelly, using the International 10-20 system.

2.2.2 NERVE CONDUCTION STUDIES

Standard techniques were used[408], and peroneal and tibial motor responses and sural sensory responses were recorded. Duration of myoclonus and synchronicity of discharges was also recorded.

2.2.3 EVOKED POTENTIALS

For SEPs, the median nerve at the wrist was stimulated, and upper limb SEPs were recorded at the contralateral scalp (C3' and C4': 2 cm posterior to C3 and C4 on the international 10-20 system). Stimulation rate was 3 Hz, with a duration of 0.2 msec. Digital averaging was performed using 200 rectified samples; the filters were set at a high cut of 500 Hz, and a low cut of 10 Hz. The latencies of the N20, P25 and N33 peaks, and the interpeak amplitudes of N20-P25 and P25-N33 were recorded, as were the N20 amplitudes. Averaging was typically performed three times to ensure reproducibility. For VEPs, responses were measured using checkerboard pattern-reversal stimuli. The stimulation frequency was 2 Hz, with filters set to a high cut of 50 Hz and low cut of 20 Hz. Digital averaging was performed using 100 rectified samples.

2.2.4 C REFLEXES.

Long-loop reflexes were obtained by stimulation of the median nerve while recording over the thenar muscle, with EMG monitoring to ensure that the muscle was relaxed.

2.2.5 JERK-LOCKED AVERAGING.

Jerk-locked averaging was performed on a Neuropack electromyograph (Nihon Koden, Japan). EEG recordings were obtained from the $C4^{I}$-Cz derivation with filter settings of 50

Hz and 0.05 Hz for high and low cut. EMG filter settings were 3 KHz and 5 Hz for high and low cut. Some patients had additional derivations recorded, such as C4-Fz. Recordings were obtained from the thenar eminence, a site where regular myoclonic jerks occurred, and where jerks could be obtained regularly and reliably at rest. Jerks occurred frequently but were well defined. Movement artefact did not present problems since the jerks were of low amplitude.

2.2.6 MAGNETIC STIMULATION

For magnetic stimulation surface EMG was recorded from the right abductor pollicis brevis muscle (Figure 43). The study was performed at rest, silence being monitored on the EMG. A Magstim 200 stimulator (The Magstim Company, Dyfed, United Kingdom) was used with a double circular 7 cm coil. Based on handedness, the dominant cortex was stimulated in the region of the hand area. The threshold for motor stimulation was determined from a trial of 10, being the minimum percentage of the stimulator output required to produce a response in half the trials, at a sensitivity of 200 μV/div.

The trigger input socket of the Magstim was synchronized to the electromyograph, the trigger mode of which was set to random. Paired stimuli were administered to the median nerve, with a stimulus interval of 8 msec, with the duration of the first and second stimuli being 0.5 msec[345]. The strength of the stimulus was maintained at a point which was subthreshold for evoking a compound muscle action potential (CMAP). MEPs were recorded with filter settings of 3 KHz and 2 Hz for the high and low cut. The delay to the time of triggering the Magstim varied from 10 msec through to 70 msec in increments of 10, with the delay being measured from the first of the 2 paired stimuli. For each time period, 8 shocks were administered, and between shocks the MEP amplitude was measured from onset to peak. At each stimulus interval from 10 to 70 msec, two runs were done, one at 20% above threshold (termed low level stimulus), and one at maximum power (termed high level stimulus), this being defined as that power which was determined to give the maximum MEP. Three participants were examined and compared with a control group of 28 subjects. Three additional subjects were excluded since responses could only be obtained at maximum power.

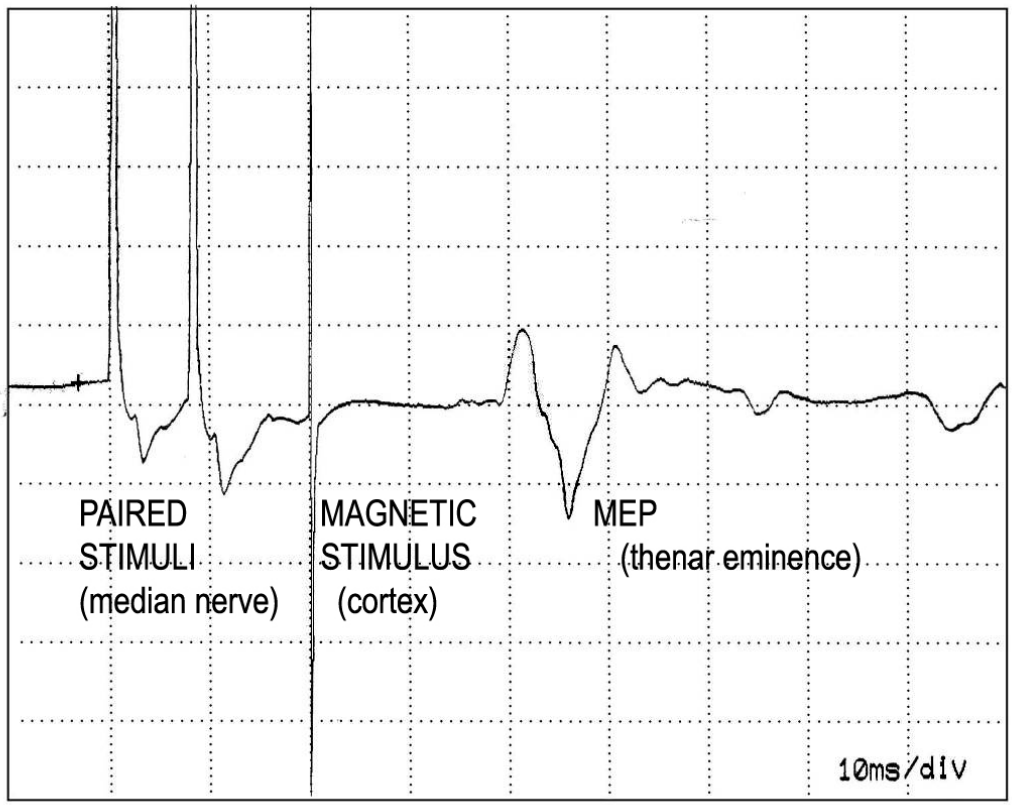

Figure 43. To illustrate the method of magnetic stimulation. Paired stimuli were given peripherally. These serve to trigger a magnetic stimulus, in this example with a delay of 20 msec, and this results in an evoked potential.

2.3 MAGNETIC RESONANCE IMAGING

MRI was obtained in 10 subjects, using standard sagittal and axial T1, axial T2/Proton Density and coronal T2, and in more recent studies, FLAIR sequences.

2.4 PATHOLOGY

Patient A-III-9 was reported to have died at night following a seizure. The precise cause of death is unknown. Post mortem was obtained approximately 14 hours after death, limited to the brain.

2.5 GENOTYPING AND LINKAGE ANALYSIS

Ethical approval was obtained from the University of Stellenbosch for extraction and analysis of DNA.

Eight blood samples were collected from Family A, including II-3, 4, 6, III-4, 5, 7, 8, 10, and 19 blood samples from Family B, including III-1, 11, IV-3, 5, 6, 8, 9, 10, 11, 16, 23, 24, 25, 26, V-9, 10, 12, 13, 14. Genomic DNA was extracted from peripheral blood leukocytes by a standard phenol extraction method. Three microsatellite markers (D21S2040, D21S1912, and D21S1959) from the *EPM1* locus (chromosome 21q22.3)[409] were studied, as was a CAG repeat in the *DRPLA* gene (chromosome 12p13.31)[137], and seven microsatellite markers (D8S1784, D8S1830, D8S1779, D8S547, D8S1694, D8S342, and D8S1826) across the *FAME1* locus (chromosome 8q23.3-q24.1), and ten microsatellite markers (D2S139, D2S2180, D2S1387, D2S2333, D2S2161, D2S388, D2S2216, D2S2264, D2S135, and D2S1897) from the *FAME2* locus (chromosome 2p11.1-q12.2). The markers on *FAME1* and *FAME2* loci were selected from those listed on the genetic map at the Marshfield Medical Clinical Website (http://research.marshfieldclinic.org/ genetics/home/index.asp). The microsatellite markers were amplified by PCR with one primer pair for each microsatellite marker. PCR products were separated by electrophoresis on a CEQ 8000 Genetic Analysis System and analyzed with Fragment Analysis software (Beckman Coulter, CA) per the manufacturer's instructions. The MLINK program was used to run the two-point linkage analysis with the following model: autosomal dominant inheritance, frequency of the dominant allele of the causative gene being 0.0001, and penetrance being 0.9.

3. RESULTS

3.1 CLINICAL CHARACTERISTICS

Two families were identified from the Western Cape province of South Africa, an area also known by its Afrikaans name of the "Swartland" –black land, due to the appearance of the dark vegetation of the region. The affected families are of mixed ancestry, predominantly representing intermarriage between the Khoisan and early settlers of Caucasian origin. The disease is likely to have originated in a common ancestor in the two families in the Namaqualand area of the Northern Cape. It is then postulated that migration in a southerly direction took place to the small towns of the Swartland where the participants were identified (Figure 44). The proband of family A was identified in Moorreesburg, a small town whose existence is largely related to the activities of the wheat farms in the area. All the affected members of family A still live in Moorreesburg. The proband of family B lives in Atlantis, a city established in the latter days of apartheid with the purpose of establishing a city for people of mixed ancestry on the principal of separate development. The proband's cousin lives on a farm two kilometres from Moorreesburg, and the proband's mother's extended family lived and died on farms in the Moorressburg area.

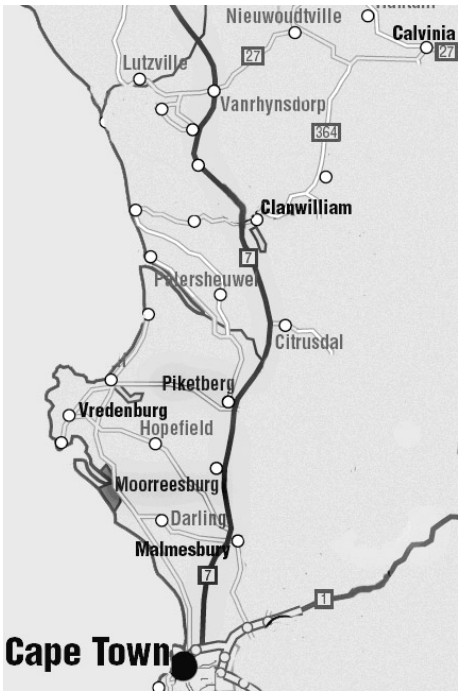

Figure 44. Map showing the towns of the Swartland region mentioned in the text. Calvinia is present in the top right of the figure.

Four generations were reported to have been affected in family B: a granddaughter aged 74 at the time of interview reported that her grandmother had tremor and fits, and had largely been bed-bound although able to walk. The grandmother had lived in Calvinia, and was probably born between 1870 and 1880. Calvinia is 330 kilometres from Moorreessburg. Many participants were uncertain of their birth dates, of where they grew up and of the whereabouts of close family members. Marked alcohol abuse, frequent movement from one farm to another and impoverished social circumstances with minimal education were the rule, features probably related to the conditions of farm workers in the area, rather than a reaction to disease. Although a common ancestor could not be identified, the rarity of the disorder and the geographical proximity of the families makes it highly likely that they are related. A high mortality of older generations due to homicide and other causes and the lack of birth records has made the task of linking the two families more difficult.

During the study, seventeen affected individuals were identified, with the oldest affected at the age of 31 (B-IV-3), and the youngest at 13 years (A-IV-1), with a median age of onset of 20 years. The core syndrome of the illness consisted of GTCS and myoclonus.
Myoclonus comprised both positive and negative myoclonus of the whole body, predominantly involving the upper limbs and trunk, as well as tremulousness of the hands, brought out by maintenance of outstretched limb posture. Although myoclonic jerks were observed in the legs these were considerably less than in the arms. Blepharospasm was also noted, but no other jerks of the face were seen. Additional features, such as nystagmus, abnormal pursuit, dysarthria and hyperreflexia were observed (Table 12). Eleven participants had combinations of truncal and limb ataxia. Eleven participants had either hyperreflexia, an extensor plantar response, or both. Two participants (B-IV-25 and B-V-10) were observed to have prominent, high amplitude positive and negative myoclonus resulting in occasional falls, in both of whom myoclonus responded to valproate and clonazepam. Seven participants reported runs of myoclonus prior to a generalized tonic-clonic seizure. In four participants myoclonus was either very slight or absent, although tremor was present in all except B-V-11, whose status was determined by generalized spike discharges on EEG.

Patient A-III-9 died following a seizure at the age of 31, B-IV-3 died at the age of 39, and B-V-10 died at the age of 35 years. The disorder may affect life expectancy for the usual reasons seen in poorly controlled epilepsy. It is unclear whether, in addition, as a result primarily of an associated neurodegenerative process, there is increased mortality. It appears that similarly to Unverricht-Lundborg disease, this condition may have been

worsened by phenytoin[74]. Certainly, in all participants in whom reasonable compliance occurred and response could be assessed (six patients), there was considerable improvement on valproate.

A number of participants were noted at the time of presentation to have cognitive impairment. The father of the proband of family A, who was severely disabled, answered questions slowly and with difficulty, and had an MMSE of 16. In addition, patient B-V-10 was severely demented, patient B-IV-26 had an MMSE of 9, although she also had a history of severe alcohol abuse and had callosal agenesis, and her two affected sisters had MMSE scores of 15 and 16.

Some participants also had considerable neurological disability at the time of presentation, or were observed to have a decline in function during the course of the study. The proband of family B, who developed the disease relatively late at the age of 31, felt that the illness was progressive, and led to impaired functioning at home, to the extent that she was no longer able to care for herself. She died eight years after onset of her illness. Patient B-IV-23 was noted to become forgetful and developed dysarthria. Patient B-V-10 was noted to be demented and ataxic at the time of her initial presentation at the age of 29, and both conditions deteriorated over the next five years. Patient A-II-6 had prominent dysarthria, ataxia and cognitive impairment when initially assessed at the age of 46, and reported progression of his condition, particularly truncal ataxia. His nephew, A-III-5, was noted to have a clear decline in coordination with gait ataxia.

Many participants also reported that their affected parents were neurologically impaired and died young: B-III-9 and B-III-12 were reported to have been affected in their early thirties and died in their late thirties. B-III-9 had visual hallucinations, complained of strange smells, and was admitted to a mental institution. B-IV-19 died at the age of 45 following a seizure, had frequent seizures, unsteadiness of gait and confusion at times. Patient B-II-1 had tremor, many seizures, and drowned after he ran into a farm dam following a seizure. Patient B-III-21 had seizures every 2-3 weeks and walked as though she were intoxicated.

Table 12. Clinical features of Families A and B (+ Present /- Absent/nd not done)

Patient	Onset	MMSE	Seizure Frequency	Nystagmus	Dysarthria	Ataxia	Hyperreflexia/ Babinski
A-II-6	22	16	Rare	—	+	+	+
A-III-4	20	28	Rare	—	—	+	—
A-III-5	18	9	2-3/month	—	—	+	—
A-III-7	14	nd	1/month	+	+	—	+
A-III-8	18	27	2/month	—	—	+	—
A-III-9	20	nd	1/month	—	+	+	+
A-III-10	23	26	Rare	+	—	+	+
A-IV-1	13	30	None	—	—	—	—
B-IV-3	31	nd	Seldom	—	—	—	—
B-IV-6	20	28	2-3/month	—	—	+	+
B-IV-10	25	nd	2-3/month	—	—	+	+
B-IV-23	17	15	1-2/year	—	+	+	+
B-IV-25	19	16	Rare	—	—	+	+
B-IV-26	30	9	Rare	—	—	—	+
B-V-10	25	Unable	Very frequent	+	+	+	+
B-V-13	19	18	Rare	—	—	—	+

3.2 NEUROPHYSIOLOGY

Results of investigations are presented in Table 13.

3.2.1 EEG (Details of individual recordings in Table 19, Appendix 2)

Patients A-III-5, A-IV-1, B-V-11, and B-V-13 only underwent EEG studies. 16 participants had a total of 26 recordings. All of the participants had at least one abnormal study, except for one (A-III-7), who did not have an EEG. In family A, seven participants had either an abnormal background or intermittent bursts of slow activity (theta and delta bursts). Four participants had polyspike and wave activity (PSW), and the remainder had clear epileptogenic activity (independent focal spikes (1), single burst of PSW (1), and left frontal spike (1). In family B, seven participants had an abnormal background or intermittent bursts of slowing. Two had a normal background (both with recurrent bursts of PSW). Six participants had abundant PSW activity and one had brief frontal spike discharges.

One patient (B-V-13) had no spike or PSW discharges (total of 3 EEGs), but had a markedly abnormal background.

Patient B-V-11, with no history of myoclonus or epilepsy, had a normal EEG on one occasion, and a second EEG that showed a single burst of polyspike and wave. Subsequent long term recordings showed abundant generalized spike and wave activity.

With regard to photic responses, one patient, B-IV-25, had a photoparoxysmal response associated with clinical myoclonus, although three other subsequent EEGs did not show this response. Another patient, B-V-10, had jerks associated with photic stimulation, and the study was terminated. Two further EEGs in this patient did not show a photoparoxysmal response.

Unaffected family members: Individual B-V-9 had right temporal spikes and right temporal delta, a normal neurological examination, and seizures which were controlled with phenytoin, and was classified as unaffected. Ten unaffected family members had 16 EEGs, which were normal, as indicated in Figures 41 and 42.

Table 13. Results of investigations in Family A and Family B (• Present /o Absent/nd not done)

Patient	Abnormal EEG	Photic response	Enlarged SEP	Abnormal C response	Symmetrical myoclonus	JLA spikes
A-II-6	•	o	•	•	Rare	_
A-III-4	•	o	•	•	nd	nd
A-III-5	•	o			nd	nd
A-III-7	•	o			nd	nd
A-III-8	•	o		•	At times	+
A-III-9	•	o		•	At times	+
A-III-10	•	o			No	+
A-IV-1	•	o			nd	nd
B-IV-3	•	o	o	•	Variable	+
B-IV-6	•	o		•	nd	+
B-IV-10*	•	o	•	•	Frequent	+
B-IV-23	•	o	•	•	At times	+
B-IV-25**	•	•	•	•	At times	nd
B-IV-26	•	o	•	•	No	nd
B-V-10	•	o	•	•	No	nd
B-V-11	•	o			nd	nd
B-V-13	•	o	•		nd	nd

*: Photoparoxysmal response with associated clinical myoclonias
**: Had jerks associated with IPS, but study was terminated

3.2.2 NERVE CONDUCTION STUDIES (Details of recordings in Table 20, Appendix 2)

11 participants had nerve conduction studies: in nine, the sural, peroneal and tibial latencies, amplitudes and velocities were normal, and in two, only the sural was examined and was normal.

Myoclonic jerks were examined in nine participants, and the duration of the EMG discharge was less than 50 msec in all (Table 21, Appendix 2).

Synchronicity was recorded in eight participants, and showed variable results (Table 21, Appendix 2), and Figures 65 and 66, Appendix 2.

3.2.3 EVOKED POTENTIALS (Details of evoked potentials in a control group in Appendix 1)

With regard to evoked potentials, of eleven participants examined, eight had enlarged SEPs (N20-P25 > 8.6 μV; P25-N33 >8.4 μV[250]) (Table 14); average values for our laboratory were 3.7 μV and 2.6 μV respectively, Table 22, Appendix 2). The latencies of SEPs were normal. VEPs were normal in amplitude and latency. An example of an enlarged evoked potential is shown in Figure 45.

Table 14. Amplitudes of evoked potentials, measured in μV. Successive recordings separated by a /.

Patient	Amplitude N20	Amplitude N20-P25	Amplitude P25-N33
A-II-6	1.1 /1.1 /1.56 /1.32	8.5 /3.7	19.5 /7.3
A-III-4	1.8 /1/ 0.9	12.5/9.7/7.4	25.4 /22.7/ 15.3
A-III-8	10.4	6.3 /8.0/ 6.2	13.6/14.1/12.6
A-III-10	1.0 /0.8		
B-IV-3	0.4 /0.8/ 0.5	2.3 /1.4/ 1.7	2.9/3.6/4.6
B-IV-10	0.9	8.5	11.5
B-IV-23	0.7 /2.5	9.5 /10.8	18.0 /18.3
B-IV-25		7.8 /9.2/ 9.0/ 8.9	14.7 /14.2
B-IV-26	3 /3.7/ 3	9.4 /10.4/ 10.5	10.4/8.7/ 9.2
B-V-10	3.7/ 3.5	14.5/ 13.5	30/ 31.3
B-V-13	4.5	15.7/ 14.9	14.2/ 15.7

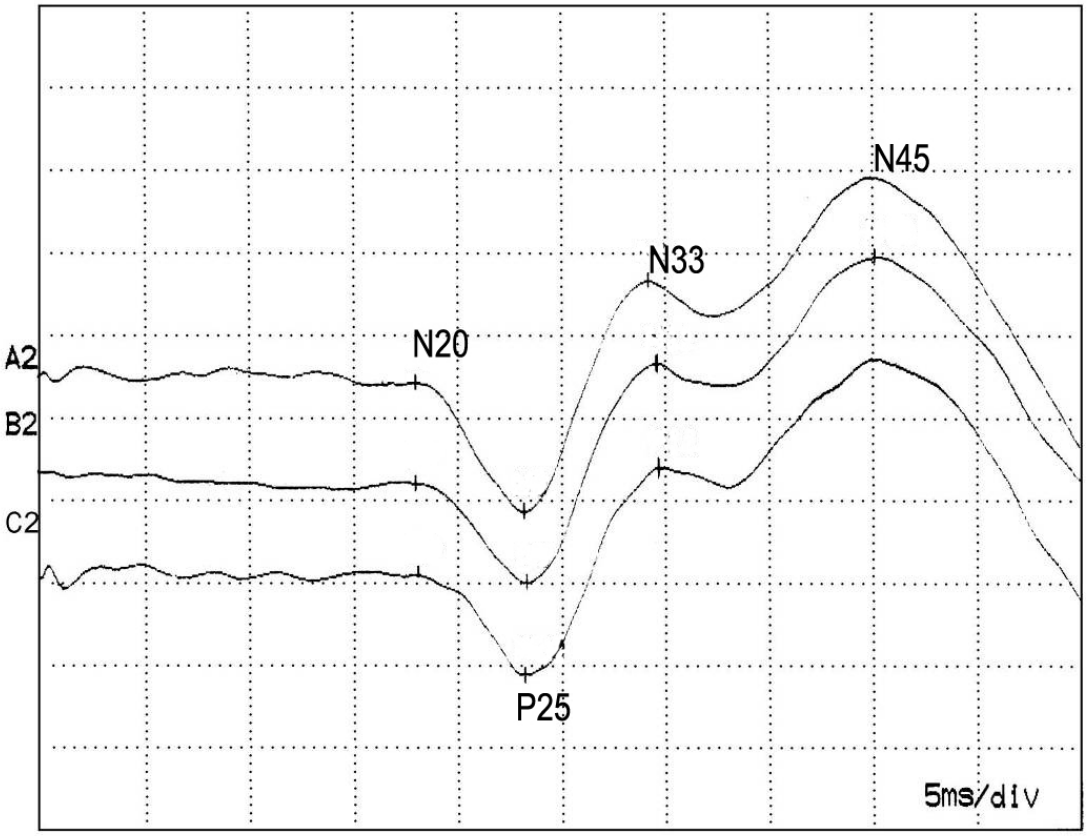

Figure 45. Enlarged SEP (Median nerve stimulation, patient A-III-8); vertical axis 5µV.

3.2.4 LATE RESPONSES

11 participants were examined for late responses by stimulation of the median nerve. At low stimulation currents late responses were easily evoked and replicated, with latencies of between 36.2 to 46.6 msec. Examples of late potentials are shown in Figures 46 and 47. (Further details may be found in Table 23, Appendix 2).

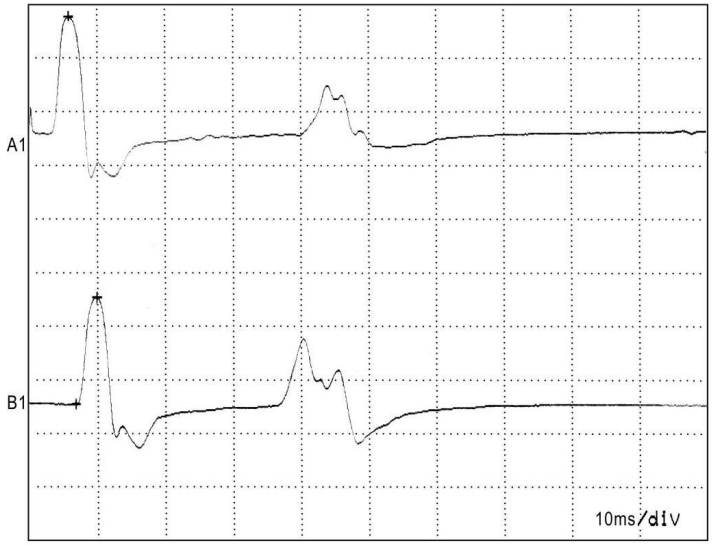

Figure 46. Late response in patient B-IV-3 (distal and proximal median nerve stimulation; horizontal time base of 10 msec/division).

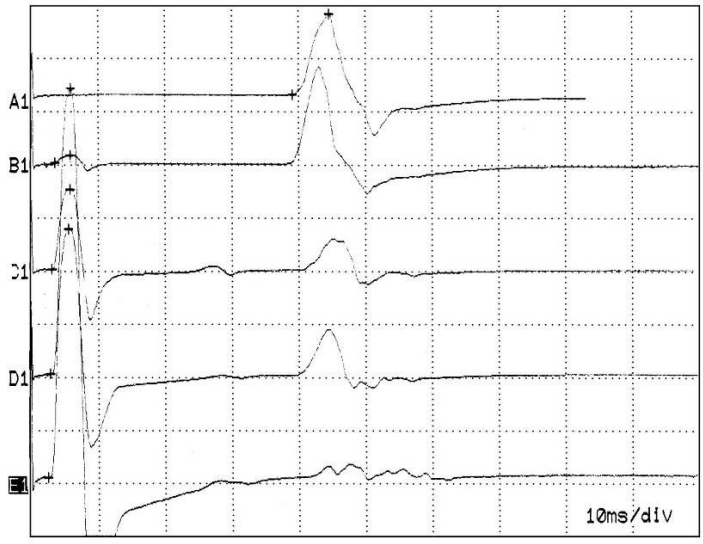

Figure 47. Late response in patient A-III-8 C. (Series of stimuli at increasing current strength, compound muscle action potential at left of figure; horizontal time base of 10 msec/division)

3.2.5 JERK-LOCKED AVERAGING.

In the majority of participants studied, jerk-locked averaging showed a 8-10 Hz frequency spindle time locked to the jerk (Figure 48). Similar examples from other participants are shown in Figures 49, 50 and 54. Recording from the right upper limb showed that this activity phase reversed at C3-P3, with some waves exhibiting electronegative phase-reversal at C3 on parasagittal and coronal montages and the C3-P3 derivation being relatively isoelectric (Figures 51 - 53).

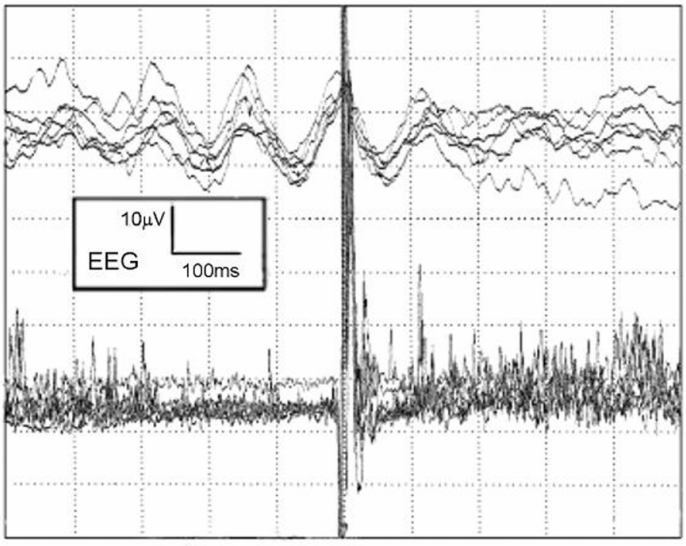

Figure 48. Jerk locked averaging. Seven superimposed averages from patient B-IV-23, each of 100 averages. Vertical division of 10µV/division. Horizontal division of 100 msec/division.

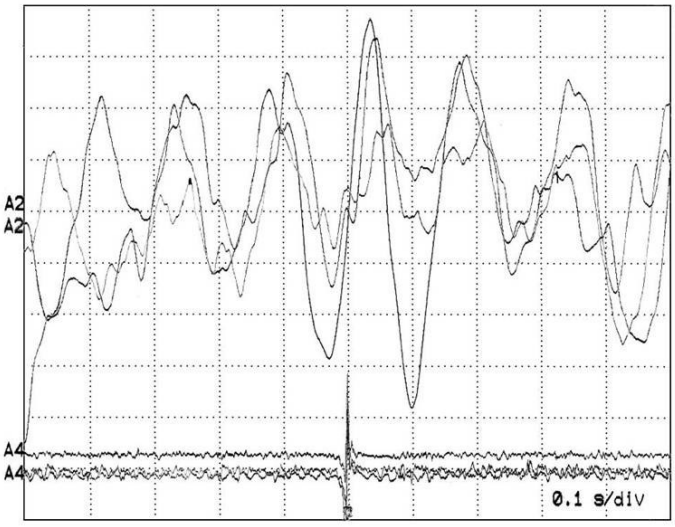

Figure 49. Jerk locked averaging. Three superimposed averages from patient A-III-10.

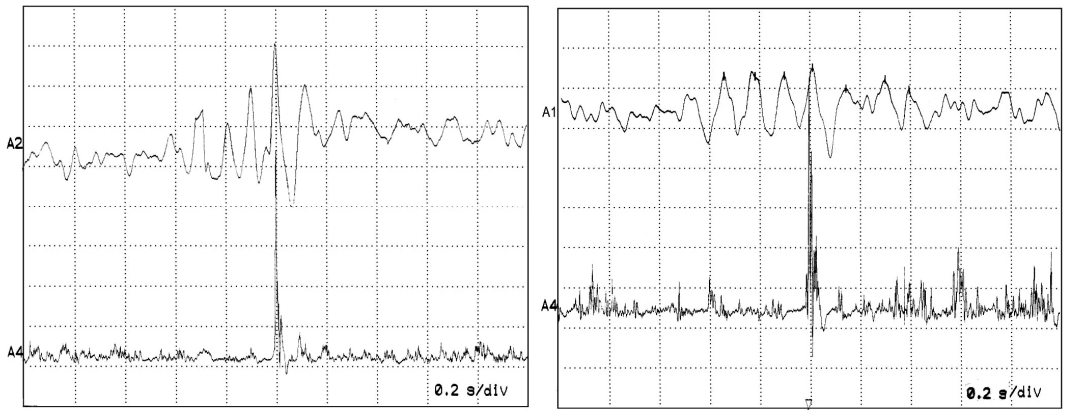

Figure 50. JLA in patient B-IV-10 : averaged records showing group of waves associated with myoclonic jerks. Horizontal division of 200 msec/division.

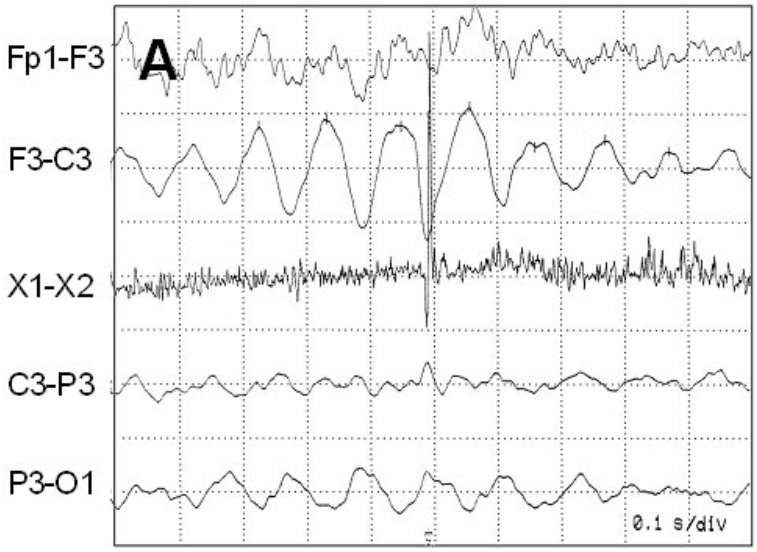

Figure 51. A: Bipolar parasagittal montage. JLA from patient A-III-8, recording from right thenar eminence. Electrodes labeled according to the International 10-20 system. EMG record corresponds to X1-X2. Vertical division of 5 μV/division. Horizontal division of 100 msec/division.

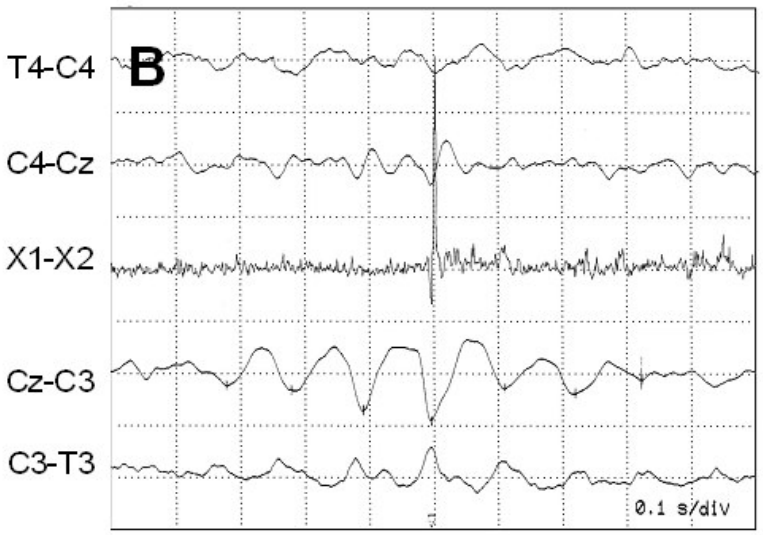

Figure 52. B: Coronal montage JLA from patient A-III-8, recording from right thenar eminence. Electrodes labeled according to the International 10-20 system. EMG record corresponds to X1-X2. Vertical division of 5 µV/division. Horizontal division of 100 msec/division.

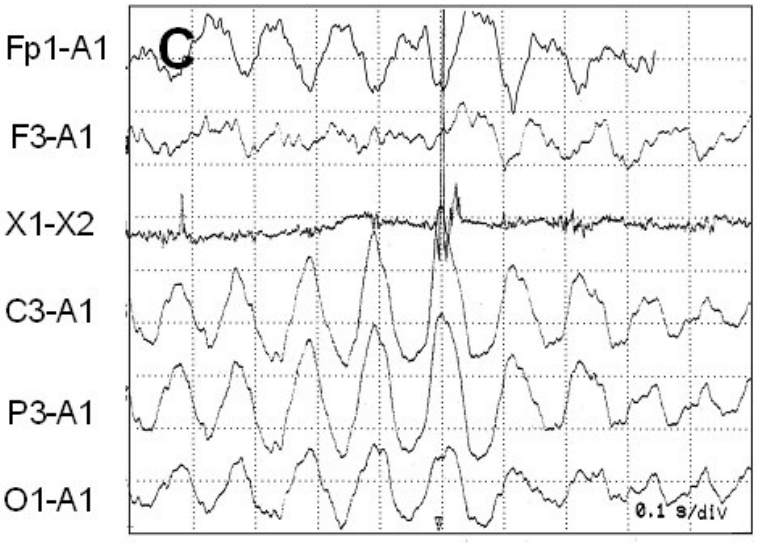

Figure 53. C: Referential montage to ipsilateral ear. JLA from patient A-III-8, recording from right thenar eminence. Electrodes labeled according to the International 10-20 system. EMG record corresponds to X1-X2. Vertical division of 5 µV/division. Horizontal division of 100 msec/division.

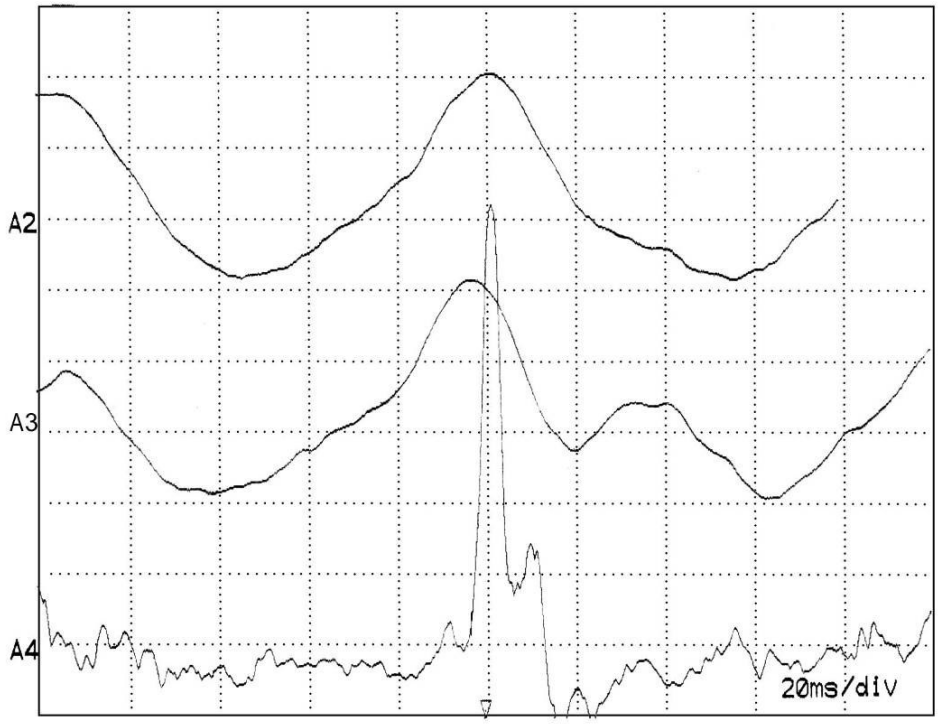

Figure 54. Jerk locked averaging from patient B-IV-3, recording from right thenar eminence. Horizontal division of 20 msec/division.

3.2.6 MAGNETIC STIMULATION.

For magnetic stimulation, a comparison was performed between three participants and 28 controls, recruited from staff and medical students. Using the package Statsgraphics (Manugistics, Inc), men and women in the control group overall showed no significant differences, although at individual duration times, there were significant differences; therefore the male controls were removed from subsequent analyses used to examine differences between the ten female controls and the three female participants. Repeated Measures ANOVA for low level stimuli and high level stimuli showed effects for group and duration and the group x duration interaction which were highly significant.

Statistical analysis of the results of the magnetic stimulation findings is found in Appendix 2. Individual results of the magnetic stimulation in participants and controls for low and high level stimuli are available in Appendix 3.

3.3 PATHOLOGY

Patient A-III-8: biopsies of the axillary apocrine glands and palmar eccrine glands did not show any abnormal storage material or evidence of neuronal ceroid lipofuscinosis on routine histology or electron microscopy. A muscle biopsy was normal.

Patient A-III-9: Examination of brain: macroscopically, the gyral pattern was within normal limits and there was no cerebral atrophy. Sections showed normal sized ventricles, a well-defined cortical ribbon and unremarkable central grey matter. The substantia nigra and the locus ceruleus appeared well pigmented, and the mamillary bodies and red nuclei appeared normal. The brainstem structures did not appear atrophic and there was no evidence of cerebellar atrophy, involving either the lateral lobes or vermis. Regarding histology, the brain was extensively sampled in an attempt to assess the presence of neuronal loss and gliosis. The most obvious changes were seen in the sections of the cerebellum where there was focal Purkinje cell loss, with early Bergman gliosis and the presence of torpedoes (especially evident in silver stains) (Figures 55 and 58). In addition, the dentate nucleus showed patchy neuronal loss and neuronal atrophy, with occasional "ghost cells" and neurons with large eosinophilic, hyaline cytoplasmic inclusions (Figures 56 and 57). The hilus showed some myelin pallor and scattered microglial clusters were noted in the middle cerebellar peduncle. The superior cerebellar peduncles appeared atrophic. The olives showed mild neuronal loss and some evidence of astrocytosis on glial fibrillary acid protein stain.

Sections of the basal ganglia show mild neuronal loss and astrocytic gliosis in the external segment of the pallidum, while there was probable atrophy of large striatal neurones and lipofuscin accumulation. The subthalamic nucleus showed no obvious neuronal loss, but a single microglial cluster was noted. The substantia nigra was normal. Sections of the neocortex from many areas show no obvious neuronal loss and normal lamination appeared to be maintained. The centrum semiovale showed some pallor of myelin staining.

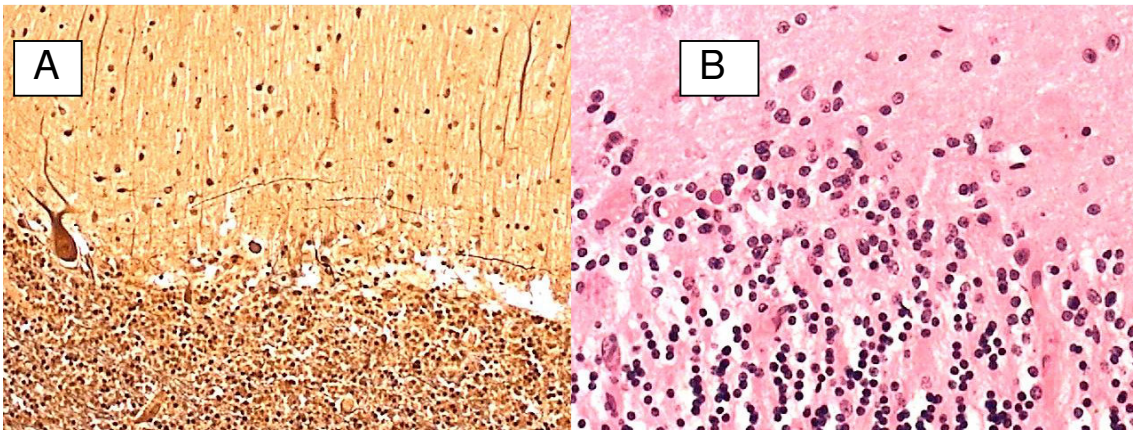

Figure 55. Cerebellar cortex. A. **showing loss of Purkinje cells (Palmgren silver stain x 100);** B. **Early Bergmann Gliosis (hematoxylin and eosin staining x 100).**

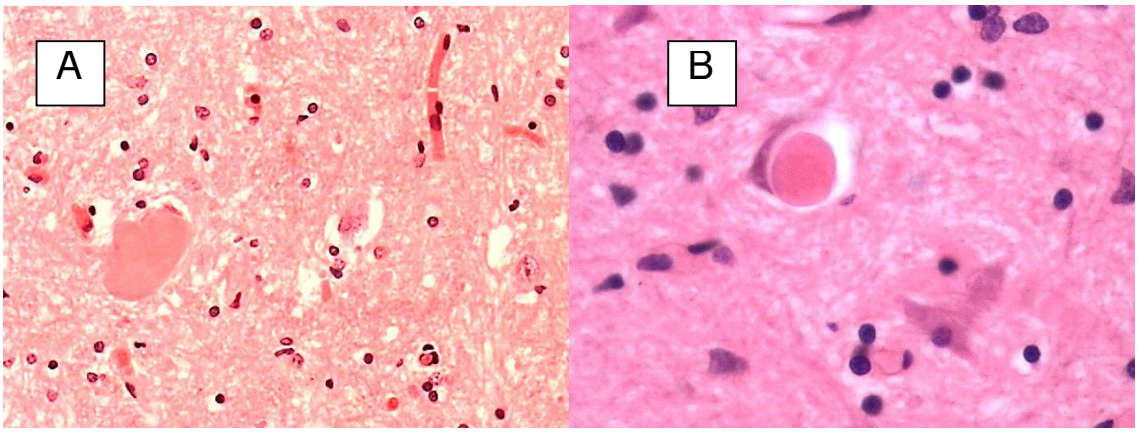

Figure 56. Dentate nucleus. A**. Equivocal neuronal inclusion of uncerrtain significance, associated with neuronal loss without significant gliosis;**
B**. Inclusion Body.**

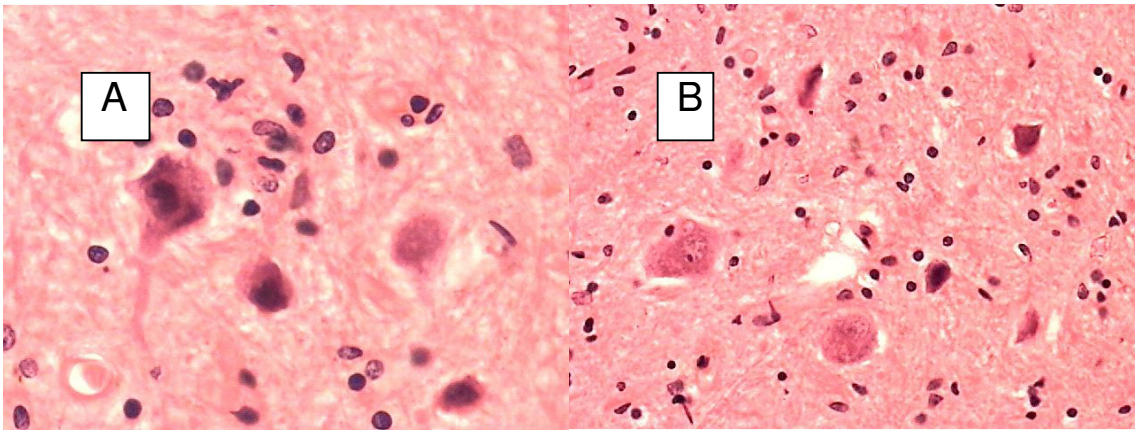

Figure 57. Dentate nucleus. A. **Relatively normal neurons;** B. **Dying neuron surrounded by reactive cells (astrocytes and microglia); hematoxylin and eosin staining x 400.**

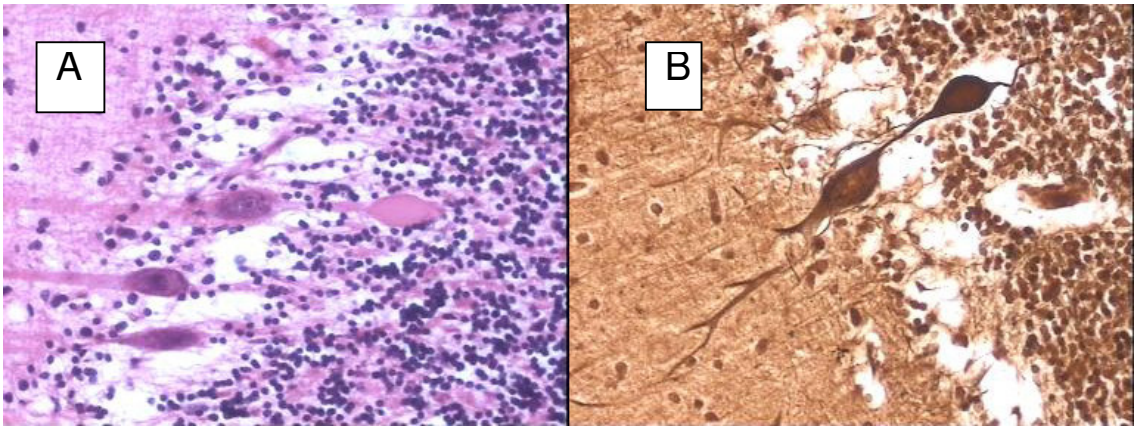

Figure 58. Cerebellar cortex. A. **Purkinje cell with axonal swelling torpedo (hematoxylin and eosin staining x 200)** B. **Purkinje cell with axonal swelling torpedo (Palmgren silver stain x 400)**

3.4 MAGNETIC RESONANCE IMAGING

Eight of the ten participants showed cerebellar atrophy, varying from mild to severe in the oldest patient (Figure 59-62). The atrophy was typically characterised by widening of major fissures and vermal atrophy. STIR sequences were performed in participants B-V-10, B-IV-23 and B-IV-26 and showed normal hippocampal formations. Individual findings are summarised in Table 15.

In addition, patient B-IV-26 also had partial callosal agenesis of the genu and body of the corpus callosum. Patient A-II-6 had bilateral T2/FLAIR hyperintense signal change in the basis pontis, a focal cortical defect in the left opercular cortex and lacunar infarctions in the right striatum and thalami (Figure 62-B). Patient B-IV-23 had periventricular T2 and FLAIR signal change, with multiple basal ganglia lacunes, and a single brainstem lacune (Figure 61, A, C, D & E). Patient B-V-10 had an area of T2/FLAIR hyperintense signal in the periventricular white matter (Figure 62-F). Two studies were normal (A-III-8, B-V-13) (Figure 59, 60).

Table 15. Results of MRI studies.

A-II-6	Focal cortical defect in the left opercular cortex, and focal, circumscribed T2 hyperintensities (T1 hypointense) in the right striatum and the thalamus bilaterally. Mild dilatation of the lateral and third ventricles. Striking widening of the fissures of the posterior fossa with marked cerebellar atrophy and bilateral T2/FLAIR hyperintense signal change in the basis pontis with dilatation of the IVth ventricle
A-III-4	Cerebellar atrophy; marked increase in CSF signal in cerebellar hemisphere, folia and posterior fossa cisterns.
A-III-8	Normal (repeat studies in 1992 and 1998)
B-IV-6	Cerebellar atrophy, predominantly with widening of major fissures and vermal atrophy
B-IV-10	Cerebellar atrophy, predominantly with widening of major fissures and vermal atrophy
B-V-13	Normal
B-V-10	Generalized atrophy, marked in cerebellum; lacune in paraventricular white matter.
B-IV-25	Cerebellar Atrophy with widening of major fissures and vermal atrophy
B-IV-23	Extensive cavitation of the striatum, thalamus and pons with T2-FLAIR hyperintensity.
B-IV-26	Cerebellar Atrophy. Callosal agenesis.

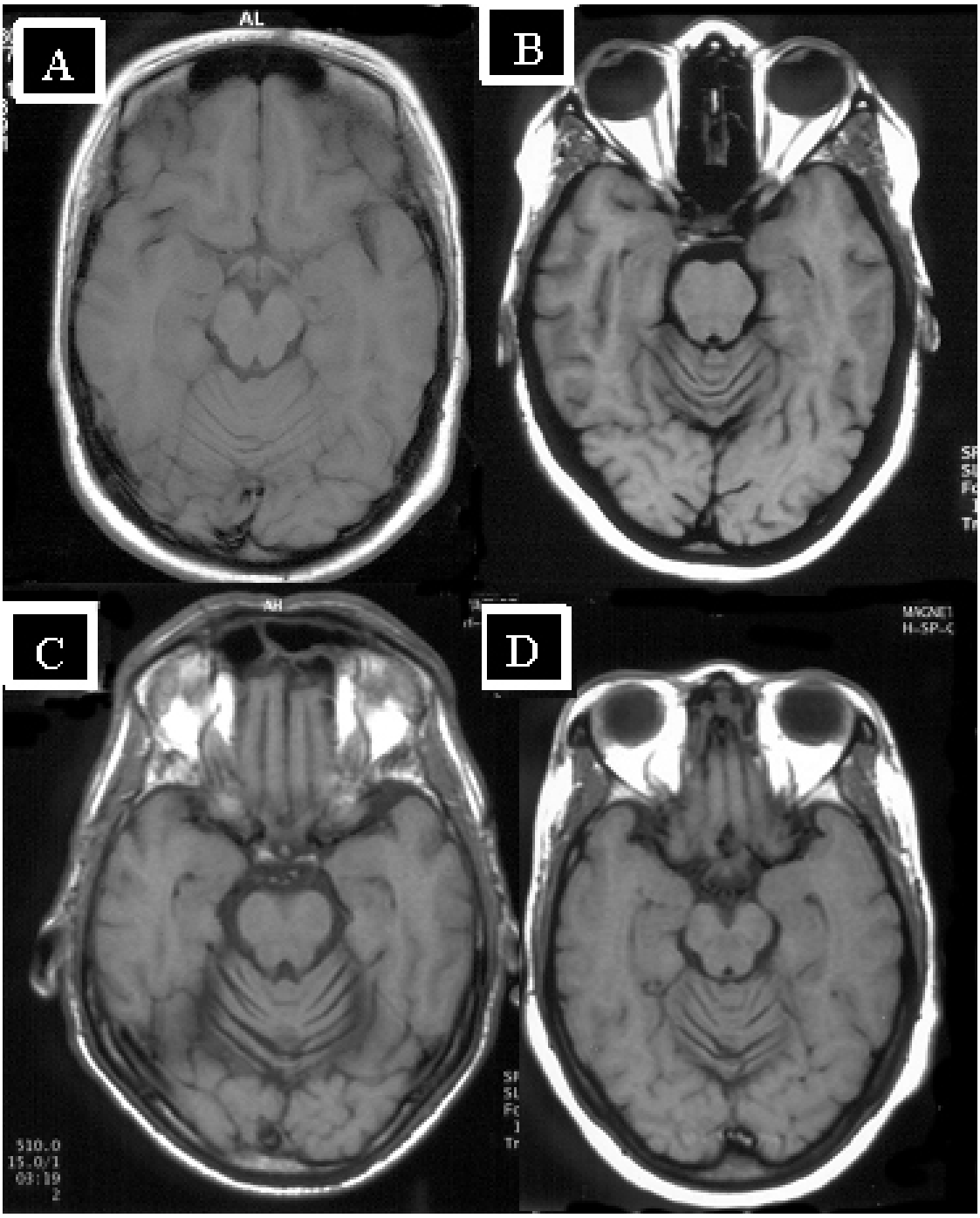

Figure 59. T1 weighted Axial Studies at level of midbrain and pons illustrating moderate cerebellar atrophy involving the vermis and anterior lobe. A **A-III-8 (normal) ;** B **B-IV-25;** C **A-II-6;**D **B-IV-10**

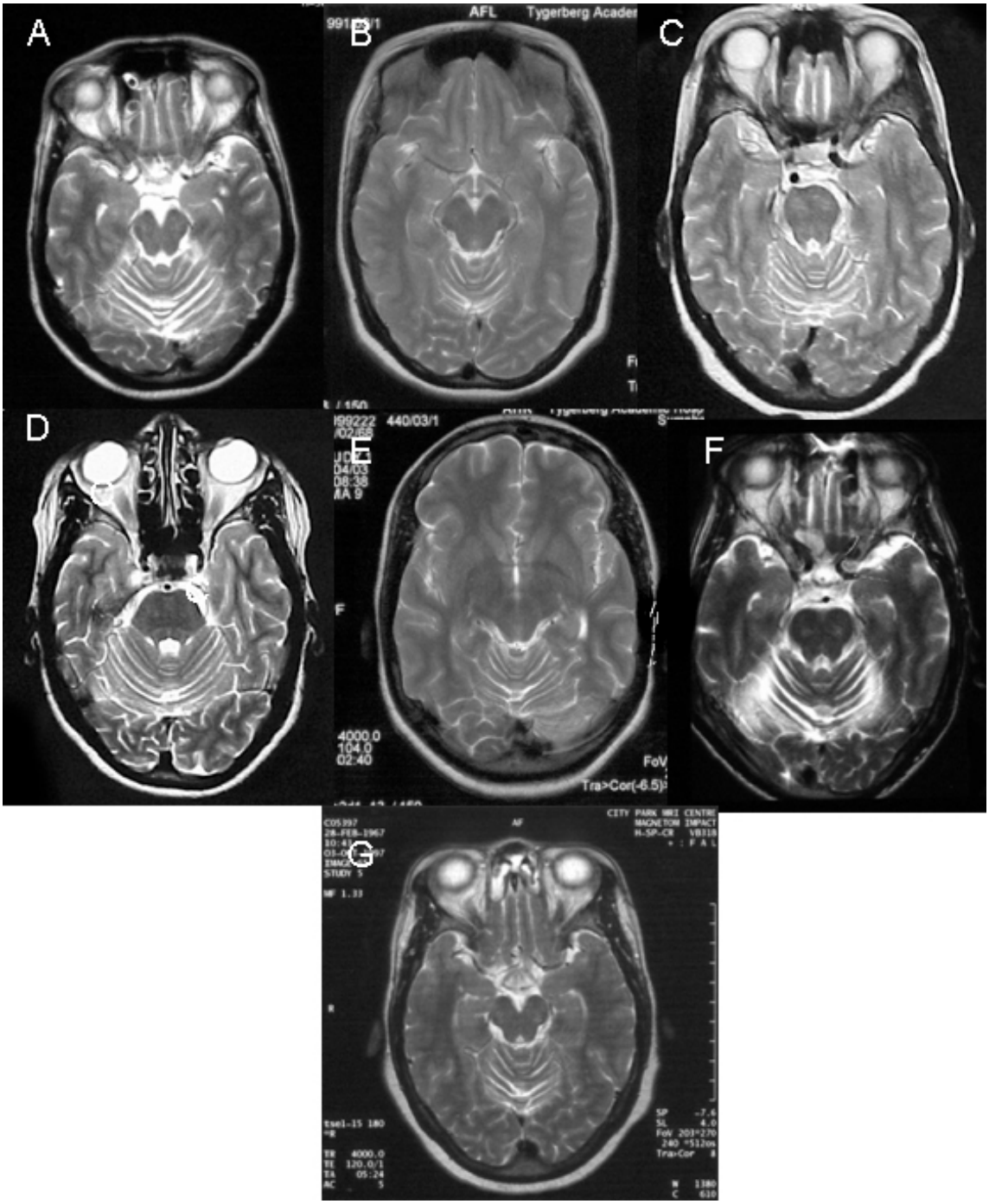

Figure 60. T2 weighted axial studies illustrating mild to moderate degrees of cerebellar atrophy. A **B-IV-6;** B **B-V-13 ;** C **B-IV-23;** D **B-IV-25;** E **B-IV-26;** F **A-III-4;** G **B-IV-10.**

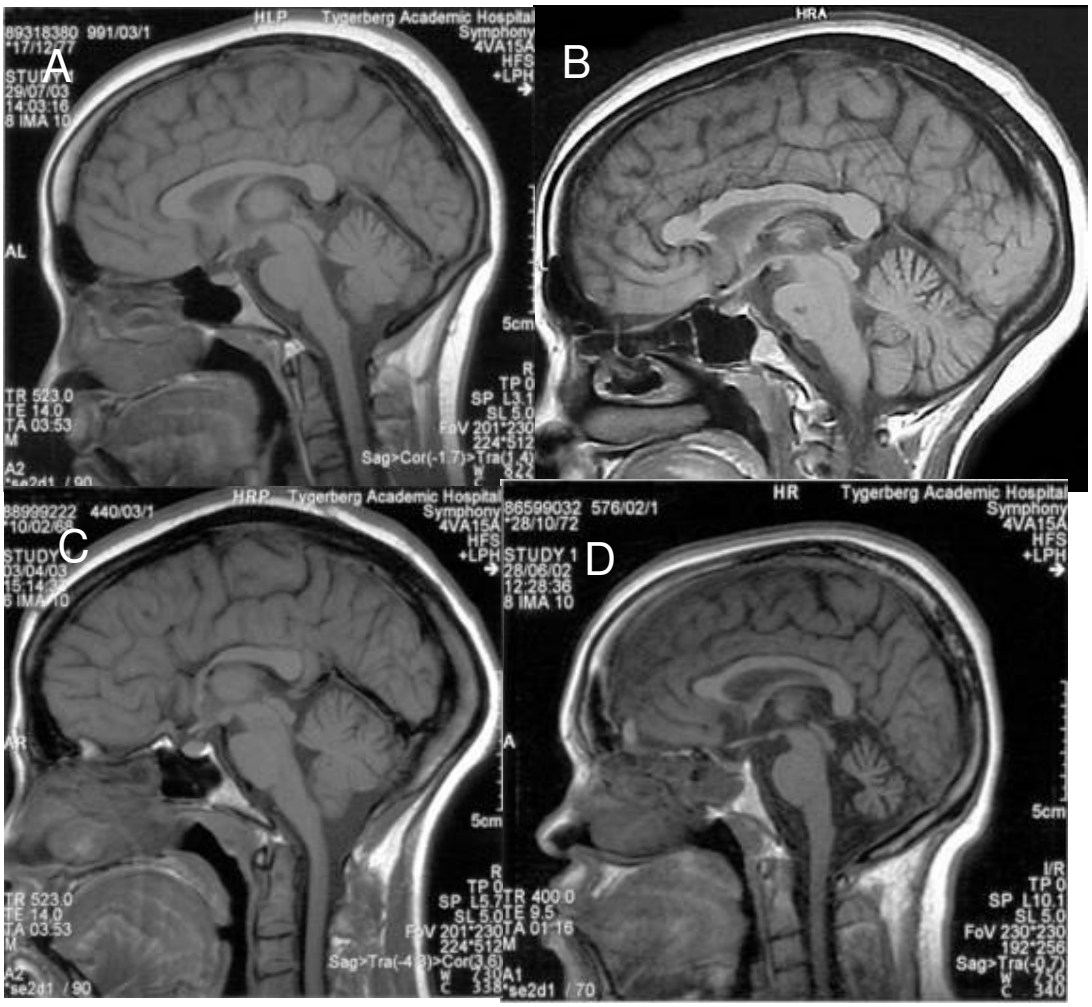

Figure 61. T1 weighted sagittal sequences showing mild to severe degrees of cerebellar atrophy. A **B-V-13;** B **B-IV-23;** C **B-IV-26;** D **B-V-10.**

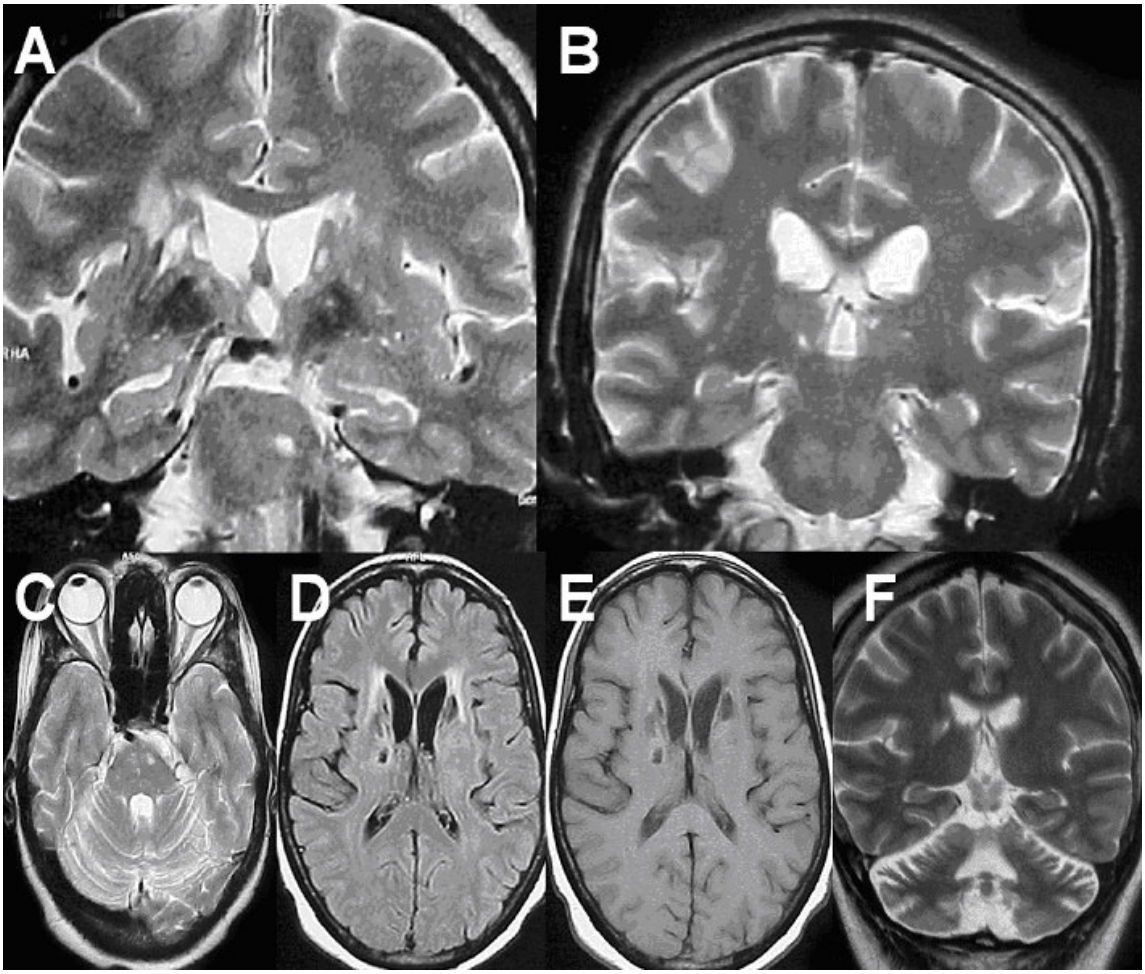

Figure 62. MRI demonstrating lacunes and white matter changes. A: patient B-IV-23 (coronal T2), C (axial T2), D (axial FLAIR), E (axial T1): extensive cavitation of the striatum, thalamus and pons with T2-FLAIR hyperintensity. B: patient A-II-6 (coronal T2) showing lacunar infarctions in the striatum and thalamus. F: patient B-V-10 (coronal T2) showing areas of periventricular T2 hyperintensity.

3.5 GENETICS

In family A, the generation of strongly negative two-point LOD scores at three markers tightly linked to the EPM1 locus excluded this candidate locus from involvement with FAME 3. The DRPLA locus was also eliminated as a candidate locus in this family, both by the generation of a strongly negative LOD score and the absence of expansion of the triplet repeat in the atrophin gene. These loci were not analyzed in family B.

Analysis of genotypes for markers at the FAME 1 and FAME 2 loci on chromosomes 8 and 2 excluded these as the region containing the same locus in family B. In the smaller family A the chromosome 2 locus was excluded, however, the chromosome 8 locus could not be excluded in family A since there was a shared haplotype among the five affected samples that were available for genotyping.

The results of the lods score for families A and B at various recombinant fractions are listed in Appendix 4.

4. DISCUSSION

The disorder described in this thesis was first identified as part of a search for patients with juvenile myoclonic epilepsy[410], and the core features of the condition remain the presence of myoclonus and generalised tonic clonic seizures. The differential diagnosis of this presentation includes the progressive myoclonic epilepsies and familial adult myoclonic epilepsy. However, disorders presenting with seizures and myoclonus also include the progressive myoclonic ataxias. PME and progressive myoclonic ataxias overlap, but are typically distinguished by the presence of prominent seizures and cognitive impairment in the former.

Results of linkage analysis demonstrated negative lod scores for the two known loci associated with FAME, the FAME 1 and FAME 2 loci. This novel condition was therefore assigned the designation FAME 3. The major distinguishing features between FAME 3 and other forms of FAME include progression, age of onset, clinical features and certain special investigations, notably MRI.

FAME appears to be a fairly uniform and relatively benign syndrome, characterized by myoclonus and rare seizures and mild or no progression of disease, and without associated neurological features except tremor[5;7;9;10;107]. Progression and neurological impairment typically go hand in hand, and, FAME 3 appears on a continuum between PME and PMA on the one hand and FAME on the other. PME and PMA are characterised by significant progression and neurological disability, whereas in FAME progression and neurological disability are either absent or trivial.

4.1 FEATURES OF FAME 3

4.1.1 PROGRESSION OF DISEASE

In FAME 3, there is a significant evidence to suggest progression:

1. Historically, participants reported that their affected parents died young and had neurological impairment. Three of the patients died during this study, at age 31, 35 and 39.
2. Participants had evidence of significant neurological impairment at the time of first assessment. For example, patients B-V-10, B-IV-26 and A-II-6 were cognitively impaired when first assessed.
3. At time of presentation, certain patients had evidence of unequivocal neurological impairment. Patient B-V-10 and A-II-6 had significant ataxia when they presented.
4. During the course of the study, participants' neurological status was noted to deteriorate. Patient A-III-5 was noted to have worsening coordination and to have developed gait ataxia. Patient B-IV-25 became forgetful and developed dysarthria.

There are two important caveats that need to be considered:

1. Assessment of cognitive state. The majority of participants in this study had very poor or very limited schooling. Assessment of cognitive function in this situation is extremely difficult and there are no well validated mechanisms for obtaining accurate data. In general, the MMSE requires eight years of school education in order for it to be valid. Interpretation of borderline or low normal MMSE scores in this study is difficult, but they are likely to represent normality. However, it is likely that scores below 20 are abnormal.
2. Effect of anti-epileptic agents and alcohol. Both phenytoin and alcohol are cerebellar toxins. Alcohol is also a cause of fronto-temporal dementia. Estimation of alcohol consumption is difficult, particularly in cases where alcohol abuse may have happened several years prior to assessment. At least one patient was known to have toxic levels of phenytoin (A-II-6). Given these factors, it is possible that either or both dementia and signs of cerebellar disease may have been related to extraneous causes other than FAME 3. In addition, Eldridge[74] has reported on cases of PME whose condition worsened when on phenytoin, and it is possible that phenytoin may have had a similarly deleterious effect in these cases. However, it is unlikely that certain patient's neurological status may be explained on the basis of these factors alone. For example, B-V-10 presented with marked ataxia and gross cognitive decline. The ataxia was not compatible with an alcohol induced phenomenon, in which damage to the anterior lobe

of the cerebellum results in truncal ataxia and relative sparing of the upper limbs. Similarly, the degree of dementia appeared profound and out of keeping with that seen typically as a result of alcohol abuse. Patient B-IV-25 developed change in her voice as a result of worsening myoclonus and was noted to have cognitive decline despite reporting no alcohol intake.

In comparison to most families reported, there appears to be a greater degree of progression in FAME 3 than in other forms of FAME (Table 16). In general, the patients from Japan appear to be less severly affected than those from Europe[11]. Van Rootselaar reported moderate functional disability with increasing myoclonus in the elderly, and impaired walking in two patients[11;117]. Labauge et al reported on slight to moderate progression leading to mild to severe handicap with complaints of memory deterioration[7]. Certainly, despite claims that the disorder is benign, a number of reports have documented some deterioration, but this seems to be to a lesser degree than that seen with FAME 3.

Table 16. Progression in FAME; (documentation of benign course in italics and parentheses).

Reference/ TERM	PROGRESSION
Ikeda, 1990 **Cortical Tremor**	Patient 1. Developed seizures five years after tremor, and then seizures every 1-2 years. Had seizures several times a month and finger tremor then became pronounced, so that writing was not possible. Patient 2. Fine tremor became worse, and developed seizure age 73.
Okino, 1997 **Familial Benign Myoclonus Epilepsy Of Adult Onset**	Patient 1. Developed tremor age 40; this worsened later, and spread to legs, and she was unable to walk by herself by age 78. Myoclonus was too severe for her to do anything by herself (but relieved by medication). Patient 4. Myoclonus gradually worsened, involving limbs and face. His level of consciousness and myoclonus frequently deteriorated., but responded to medication.
Manabe, 2002 **BAFME**	*(61 year old had no difficulty in working or daily life)*

Table 16 continued. Progression in FAME; (documentation of benign course in italics and parentheses).

Reference/ TERM	PROGRESSION
Okuma, 1997 **FCTE**	*(Tremor not progressive; younger brother of the proband able to work as engineer 20 years after first seizure)*
Terada, 1997 **FCMT**	Tremor became progressively worse; only difficulties with skillful finger movements. *(3/6 patients had from one to three seizures throughout clinical course)*
Okuma, 1998 **FCTE**	*(seizures well controlled)*
Uyama, 1996 **FAME**	No progression, but degree of myoclonus increased over 10-15 year follow-up, especially in patients over age 70. *(Lifespan normal)*
Mikami, 1999 **BAFME**	*(No ataxia or dementia over ten years)*
Elia, 1998 **Familial Cortical Tremor, Epilepsy and Mental Retardation**	*(Tremor did not worsen; seizures became rare after treatment with phenobarbital:* *Finger tremor in one patient reported not to have worsened since childhood)*
Guerrini, 2001 **ADCME**	Three had resistant complex partial seizures *(Maximum severity of myoclonus was reached within a year of onset)*
Labauge 2002 **FAME**	Increasing myoclonus in elderly; functional disability was moderate with impaired skilled movements such as writing. Walking was impaired in two patients.

Table 16 continued. Progression in FAME; (documentation of benign course in italics and parentheses).

van Rootselaar, 2002 **FCTE**	Slight to moderate progression leading to mild to severe handicap; complaints of memory deterioration. Several affected relatives with seizures had deterioration of memory.
de Falco, 2003 **BAFME**	Seizures develop in 85% of those aged > 25 years. *(Tremor was not significantly progressive; syndrome described as "nonprogressive")*

4.1.2 AGE OF ONSET

The median age of onset of disease in the two familes in this study was 20 years. This can be compared with that reported in other series, in which patients typically have an older age of onset (Table 17).

Table 17. Age of onset (mean age in bold)

	Onset myoclonus	Onset seizure
Ikeda, 1990	**+/-50**	**59**
	+/- 35	45
	+/- 65	73
Manabe, 2002	**24**	
	Case 1:16	None
	Case 2:30	33
	Case 3:27	None
Okino, 1997	**32**	**35**
	Case 1:40	?
	Case 2:	41
	Case 3:26	26
	Case 4:40	+/-40
Okuma, 1997	**32**	**27**
	Case 1:29	25
	Case 2:	20
	Case 3:?	None
	Case 4:32	32
	Case 5:34	32
Okuma, 1998	**25**	**29**
	Case 1:21	20
	Case 2:25	19
	Case 3:21	20
	Case 4:30	40
	Case 5:28	48

Table 17 continued. Age of onset (mean age in bold)

Terada, 1997	**37**	
	Case 1:24	
	Case 2:33	
	Case 3:35	
	Case 4:40	
	Case 5:42	
	Case 6:48	
Uyama, 1996/Plaster, 1999		**Mean age 37.5**
Mikami, 1999		**Mean 30.5 years(range 18-45)**
Elia, 1998	Case 1:57	None
	Case 2:18	18
	Case 3:12	5
	Case 4:Childhood	5
Guerrini, 2001	**23**	**25**
	Case 1:50	59
	Case 2:12	12
	Case 3:15	15
	Case 4:30	34
	Case 5:20	27
	Case 6:20	20
	Case 7:20	15
	Case 8:17	20
De Falco, 2003	**Family A:Mean 25.1 (15-40)**	**Mean 42.5 (30-50)**
	Family B:Mean 18 (11-25)	
Labauge, 2002	**41 (30-60)**	**44.6 (30-67)**
Striano, 2004	**14.6 (13-18)**	**30**
	Case 1:18	-
	Case 2:14	46
	Case 3:13	18
	Case 4:13	25
	Case 5:15	30
Van Rootselaar, 2002	**12-45 (23.5)**	**42**
	Case 1:	63
	Case 2:	44
	Case 3:	37
	Case 4:	43
	Case 5:	52
	Case 6:	44
	Case 7:	43
	Case 8:	42
	Case 9:	20
	Case 10:	31

4.1.3 SEIZURE FREQUENCY

Compared with the disease in the South African families, the seizures associated with FAME may occur at a later age[7 9;107]. Although seizure frequency varied, many patients with FAME 3 had frequent seizures. In contrast, most reported families with FAME have had infrequent seizures, as presented in Table 18. For example, in Ikeda's initial report, one patient had only two seizures[107]. Similarly, in the family reported by Terada, episodes of loss of consciousness were reported to be extremely rare[108]. Of European families, that reported by de Falco had rare attacks[9], and in ADCME, of eight affected patients, two had only one or two isolated GTCS, and three had seizures in remission on treatment, in two of whom remission was present for 20 years. The proband of the family reported by van Rootselaar was reported to have rare seizures[117].

4.1.4 NEUROLOGICAL FINDINGS

Other features which suggest that FAME 3 is unique compared to more benign forms of familial myoclonic epilepsy include the presence of dementia and corticospinal and cerebellar dysfunction (table 12). Neurological findings included nystagmus, dysarthria, ataxia and corticospinal tract dysfunction manifesting as hyperreflexia and the Babinksi sign. These findings may be contrasted with those reported in other forms of FAME, outlined in table 19.

4.1.5 EEG

The EEG background is normal in ADCME and not infrequently patients with FAME have normal EEGs [7;10,117] , whereas abnormal EEG backgrounds and abundant polyspike discharges were the rule in the participants described in this report (Table 19, Appendix 2). However, as opposed to findings in the South African participants, photosensitivity appears to be common in both FAME and ADCME [5,6,8;10].

4.1.6 MRI

Further distinctive features included MRI findings of cerebellar atrophy. An additional radiological feature was that three patients had lacunar infarctions in the basal ganglia, brainstem and white matter changes, notably in the absence of a history of hypertension. The results of neuroradiological tests are reported in Table 15 and are shown in Figures 59-62. Interestingly, the family reported by Okino also reported multiple lacunar infarctions in one patient and cerebellar hemisphere infarction in another[111].

In FAME, MRI is generally reported to be normal[7;10], whereas cerebellar atrophy, ranging from mild to severe, was found in eight of ten patients from the two families reported here. Mild cerebellar atrophy on MRI was seen in two of four patients in a Dutch family with FAME, and a 68 year old patient from this family had cerebellar degeneration at autopsy[122]. However, this family had typical features of FAME in other respects, with mean age of onset of seizures at 43 years, and no other features of neurological disease other than mild cognitive impairment[11;117].

4.1.7 NEUROPATHOLOGY

In FAME 3, pathological findings included Purkinje cell loss and dentate atrophy in the cerebellum, and neuronal loss and gliosis in the pallidum and olives (Figures 55-58). In the Japanese literature, normal findings were reported in three patients with myoclonus and epilepsy, some of whom had “myoclonic tremor” ([121]cited in [110]).

Van Rootselaar reported on a case of FCTE, in whom linkage was negative for both the FAME 1 and 2 loci. The cerebellum showed Purkinje cell loss with Bergmann gliosis, atrophy of the molecular layer and abnormal Purkinje cell morphology. Gliosis of the cerebellar white matter and cell loss and gliosis of the dentate nucleus were present There was extensive mineralization of vessel walls and neurons in the globus pallidus[122]. A second case showed similar features, and some gliosis in the claustrum[411].

Table 18. Clinical characteristics of patients with FAME and allied conditions.

Number Affected	Reference	Term	Myoclonus Description	Tremor Description	Enhanced by:	Seizures	Cerebellar Signs	Dementia
10 living 3 dead	Labauge, 2002	**FAME**	Sometimes at rest; Oscillatory, brief and irregular.	Involuntary rhythmic movements of the extremities	Action Posture	8/13 Infrequent (2-5 seizures/lifetime)	Absent	Absent
13 definite, 3 possible from one family	van Rootselaar, 2002	**FCTE**	Present in fingers, arms feet and legs	Kinesogenic tremor resembling essential tremor with superimposed myoclonus	Action Stress	(11/16)	Absent	Complaints of memory deterioration Slight Cognitive impairment (short term memory and attention deficit) in 4 (all on AEDs)
2 families 15 in two families	de Falco, 2003	**BAFME**	Distal Arrythmic Myoclonus of arms	Cortical tremor	Posture	7/15 Rare (1-5) Eight had no GTCS	Absent	Absent
7	Striano, 2004	**BAFME**	Continuous, distal fine twitches of hands	Cortical tremor	Emotion Fatigue	Rare(1-4) One had no GTCS	Not reported	1 had IQ of 79

Table 18 continued: Clinical characteristics of patients with FAME and allied conditions.

Number Affected	Reference	Term	Myoclonus Description	Tremor Description	Enhanced by:	Seizures	Cerebellar Signs	Dementia
Patient 1. 3/6 Siblings in one family Patient 2 No family history	Ikeda 1990	**Cortical Tremor**		Fine, shivering-like twitchings	Posture Action	Patient 1. Several every one-two years Patient 2. Two (Age 73,74)	Absent	Absent
4 patients from 3 different Families	Okino 1997	**Familial benign myoclonus epilepsy of adult onset**	Patient 1. 84 year old mother : marked, generalised Previously in arms and Eyelids Patient 2,3&4 Myoclonus of limbs and face		Movement Intention	Rare	Absent	Absent
5 in 3 generations	Manabe 2002	**BAFME**	Myoclonus in arms and legs at rest	Fine tremor in fingers		Rare		Absent

Table 18 continued: Clinical characteristics of patients with FAME and allied conditions.

Number Affected	Reference	Term	Myoclonus Description	Tremor Description	Enhanced by:	Seizures	Cerebellar Signs	Dementia
5 in 3 generations	Okuma 1997	**FCTE**		Tremulous shivering-like movements		Extremely rare, 1-3 times during clinical course.		
6 from 3 families	Terada 1997	**FCMT**		Rhythmic involuntary movements in the distal arms and legs	Posture Fine movements	3 only had 1-3 events	Absent	Absent
7 from 3 families	Okuma, 1998	**FCTE**	Present in arms when anticonvulsants stopped	Tremulous finger movements		Well controlled, infrequent		
27 in four families	Uyama 1996	**FAME**	Myoclonus in arms and legs	Tremulous finger movements	Fatigue, Photic stimuli	Rare	Absent	Absent
17 affected out of 27 in one family	Mikami, 1999	**BAFME**	Myoclonus of extremities 50% upper body 50% whole body	Tremulous finger movements		2 had none Infrequent(often fewer than 4 during lifespan)	Absent	Absent

Table 18 continued: Clinical characteristics of patients with FAME and allied conditions.

Number Affected	Reference	Term	Myoclonus Description	Tremor Description	Enhanced by:	Seizures	Cerebellar Signs	Dementia
7 in 6 Generations of one family	Elia 1998	**Familial Cortical Tremor, Epilepsy and Mental Retardation**		Fine tremor involving the fingers	Stretching hands or movement	1 had no seizures Seizures well controlled in 2/3		Mental Retardation in two
11 in 5 generations	Guerrini 2001	**ADCME**	Distally, at rest in severe caes Arrythmic, multifocal proximal arms Eyelid twitching	"tremor-like"	Posture maintenance	2 had 1/2 isolated GTCS 3 had Sz in remission 1 resistant GTCS 2 resistant CPS		All had low IQ (Two<70)
14 from 4 families.	Plaster 1999	**FAME**	Varying degrees of myoclonus	Fine finger tremulous movements		1-4/ lifetime	Absent	Absent

4.2 GENETICS OF FAME

Linkage analysis was used to investigate the genetic localization of FAME 3. If a single alteration in a gene, an allele, is responsible for the production of a disease trait, then that allele should be present in the DNA of all carriers of the condition. A marker is a gene of sufficiently high prevalence that it is likely to be found in the family under study, and if two affected members of that family should have the *same* allele at the marker locus more often than would be expected, this finding increases the probability that there is linkage between that marker allele and the trait being investigated, for example, myoclonic epilepsy.

Genes may be said to be closely or loosely linked, depending on their distance apart from one another. A frequent occurrence during meiosis is the process known as crossing over, which consists of the exchange of parts between the chromatids of homologous chromosomes. Crossing over of chromosomes between two linked genes results in a new combination, known as a *recombination*, between the two loci. The frequency with which these recombinations increases with increasing distance between two genes. The genetic map distance between two genes is defined as the expected number of crossovers occurring between them, observable as regions of contact known as chiasmata. At any given meiosis, there is a 1% chance that recombination will occur between two genetic markers that are separated in the DNA by one centimorgan, representing approximately ten million base pairs of DNA. Two genes located one centimorgan apart will be passed on together from parent to offspring 99% of the time [412].

Linkage describes a distance relationship between two genetic loci and quantifies the location of a polymorphic marker relative to a gene for a disease [412]. The process of meiosis is associated with the separation of alleles so that each gamete ends up with only one of an allele-pair. Linkage analysis is a test to determine whether in this process, known as segregation, a trait or disease associates with some known genetic marker within families more frequently than would be predicted by Mendel's law of independent segregation. The probabilities that the observed associations are caused by linkage or arose by chance (no linkage) are calculated. The ratio of these two possibilities is expressed as a logarithm (base 10) and is termed the odds ratio for linkage (lod) [413].

The lod scores either support or reject the hypothesis that the disease locus is near the marker locus. Support for linkage is suggested by positive lod scores, where a result of more than 3 is a threshold value for accepting the existence of linkage, representing odds of 1000 to 1 in favour of linkage, whereas scores of less than -2 are indicative of odds of 10 to

1 against linkage. Since recombination between two loci becomes more likely the further apart they are on a chromosome, the genetic distance between the disease locus and a given marker locus can be estimated by the recombination frequency (θ) which is the rate of recombination between them. The recombination frequency has an upper limit of 0.5, which is equivalent to no linkage (random assortment). For a given data set at a particular recombination fraction tight linkage may be excluded, but this does not exclude linkage at a greater.

Linkage analysis requires the identification of an unequivocal phenotype, a familial clustering of this phenotype, and the availability of a sufficient number of adequate informative pedigrees.

Genetic analysis becomes more difficult when the penetrance of the disease phenotype is low or when the penetrance is an unknown function of age. Errors in the assessment of the phenotype can obscure linkage findings because they may lead to the mis-scoring of recombinant events [414]. Genetic or locus heterogeneity may also obscure linkage findings, if a similar phenotype is caused by separate genes in unrelated families, since one family may give a positive lod score with a given close marker whereas another family may give a strongly negative lod score with the same marker[414].

In general, samples for the establishment of genetic linkage should be obtained from a minimum of 10 to 12 affected individuals within a family, for evidence of linkage to be demonstrable. A single large family of a given size provides more potential linkage information than does a combination of several smaller families with the same total number of individuals[415], large families being better suited for linkage analysis because they contain potentially fewer unrelated individuals than do smaller families. Pedigrees with larger sibship sizes are more efficient than those with smaller sibships because the proportion of meioses scored per genotype is higher when many offspring are available for inclusion in the analysis[414].

In FAME 3, the initial assessment that the phenotype was a pure one of a core syndrome of epilepsy and myoclonus was found to be erroneous when patient Patient B-V-11, who was asymptomatic, was noted to have a single spike discharge on a standard EEG recording. Subsequent long term EEG monitoring established the presence of abundant spike discharges. Similarly, patient B-IV-26, who was a poor historian, was initially felt to be asymptomatic until her EEG was noted to be abnormal. Subsequently, she was noted to have mild postural tremor, and on follow-up, reported having a generalized seizure.

Five problems in establishing affectedness status were identified:

1. The disorder is age dependant. For example, the offspring of patient A-III-4 were initially presumed to be unaffected. However, one of them (A-IV-1) developed myoclonus at the age of 13. Given that the age of presentation for FAME 3 is quite wide, ranging from early adolescence to the fourth decade, determining the affectedness status in family members in their first three decades may be difficult.
2. Patients may be clinically asymptomatic. As noted, patients B-V-11 and B-IV-26 were either normal or had trivial physical findings. Similarly, when last assessed, patient A-III-10 appeared to be normal, although she was on treatment at the time.
3. Although the vast majority of cases have an abnormal EEG, this may represent a circular argument, since the "gold standard" test is an EEG, and affectedness is determined by whether the EEG is normal or not. Patient B-V-11 initially had a normal EEG, and a second recording showed a single spike discharge. The question of the optimal duration of EEG recording is unanswerable, and presumably is related to age: it is reasonable to assume that the older the patient, the more advanced the disease, and the more likely that the EEG will be abnormal. However, this is unproven. Extrapolating from the experience with patient B-V-11, it is possible that some patients classified as asymptomatic on a the basis of a single normal EEG may well be abnormal, either because they are too young to manifest the disease, or because they are clinically asymptomatic and a single EEG is insufficient to indicated affectedness. If the EEG is to some extent a marker of severity of disease, it seems plausible that those patients on the mild end of the spectrum of affectedness might have not only minimal or no clinical signs but also a normal or minimally abnormal EEG.
4. One patient (B-V-9) was identified as having focal temporal spikes and focal slowing in the temporal region. Apart from Guerrini's report of ADCME, in which patients had FAME associated with complex partial seizures and focal temporal spikes[8], other forms of genetic epilepsy have been associated with focal seizure types, for example, autosomal dominant nocturnal frontal lobe epilepsy and GEFS plus[416;417]. The affectedness state of this patient is unknown. He is believed not to have FAME 3 since he lacks typical clinical manifestations, and his EEG findings would be unique. However, the possibility that some patients may manifest with focal spikes cannot be excluded.
5. In general, determining affectedness on the basis of history was relatively straightforward, with many reports being that of individual who were severely neurologically impaired, with frequent seizures. However, mildly affected patients may not have been identified by their relatives. The converse also holds true, in that

some patients may have been incorrectly determined to be affected on the basis of history. However, all patients who were affected had abnormal EEGs. Given that seizures occur in approximately 10% of the population at some stage, and are likely to be more prevalent in a population prone to alcohol abuse and violence, the possibility exists that, similarly to patient B-V-9, who is presumed to have epilepsy not related to FAME 3, patients may have developed secondary epilepsy on the basis of an acquired lesion.

The inheritance pattern of FAME 3 appears to be clearly autosomal dominant, and the penetrance of the condition is high. Affectedness status is determined by multiple factors including history, clinical features, EEG and MRI scan. These factors are largely congruent, in that patients would report seizures, have clinical evidence of myoclonus, be shown to have a typically abnormal EEG, and MRI would demonstrate cerebellar atrophy. It is therefore highly unlikely that patients who were examined and investigated would have been incorrectly assigned as having the disease.

The apparent high penetrance of the condition (Figures 41 and 42) may also be an indication that determination of affectedness is accurate, with a low false negative rate. However, an exception to this is related to determination of affectedness in the offspring of B-IV-14, where of eight individuals, only one was thought to be affected. The affected individual, B-V-3, had died before the study commenced, and of the remaining seven siblings, five had normal EEGs. The most parsimonious explanation is that the positive affectedness status of patients B-IV-14 and B-V-3, in both of whom the determination was historical, is incorrect.

Given that FAME 3 overlaps with the group of PME conditions and with FAME, the number of candidate loci was limited, since in PME dominant inheritance has only been reported in DRPLA[2], a single family with Kufs disease[3] and mutations in the neuroserpin gene [4]. All of these conditions are rare, with the exception of DRPLA, which is, however, uncommon in non Japanese populations[140;418]. Clinically, all three of these conditions appeared possible candidate genes, although neuroserpin gene mutations are typically associated with a greater degree of dementia.

Kufs disease is characterized by PAS positive material in cortical neurons. Similarly, in patients carrying mutations in the neuroserpin gene, intraneuronal eosinophilic homogeneous bodies are seen in neurons in cerebral cortex. Sections of cortex from patient A-III-9 were normal, excluding both Kufs and neuroserpin mutations as possible causes for FAME 3.

In the early stages of investigation of the disease, it was felt that Unverricht-Lundborg disease was a plausible candidate locus. In family A, two point LOD scores of -14.24, -12.83 and –6.82 were generated at the DNA markers D21S2040, D21S1912 and D21S1959[419]. These markers are tightly linked to the EPM1 locus[409] and excluded this candidate locus from involvement with FAME 3 (Table 31, page 274).

With regard to DRPLA, in family A the two point LOD score derived at the *DRPLA* locus was -14.50. In addition, there was no evidence of expansion of the triplet repeat in the atrophin gene, with two normal sized alleles being present. The DRPLA locus was therefore eliminated as a candidate locus (Table 32, page 275). The EPM1 and DRPLA loci were not analyzed in family B.

In the smaller family A the chromosome 2 locus (FAME 2) was excluded (Table 32, page 275). However, the chromosome 8 locus (FAME 1) could not be excluded in family A since there was a shared haplotype among the five affected samples that were available for genotyping (Table 32, page 275).

In family B, Analysis of genotypes for markers at the FAME 1 and FAME 2 loci on chromosomes 8 and 2 excluded these as the regions containing the same locus (Table 33, page 276).

4.3 CAUSATION OF MYOCLONUS

Myoclonus is a phenomenon that is key to a widely disparate range of conditions, but of these, perhaps the overlap between epilepsy and myoclonus is the most striking. The occurrence of epileptic seizures is intrinsic to the definition of PME, and many patients with PME describe not only myoclonus and epilepsy, but also that increasing runs of myoclonus may terminate in a seizure[78;103;104;126;126;166;227;420-422]. In cortical myoclonus, the EEG findings of generalized spike and wave, "giant" evoked potentials and enhanced late responses are likely to indicate that in this condition the cortex is abnormally excitable, or abnormally disinhibited, a feature of idiopathic generalized epilepsies[343;345]. Although myoclonus and epilepsy may be related independently to increased cortical excitability, their close temporal relationship is striking and suggests that the underlying pathophysiology is very similar.
Thus, with regard to epilepsy, myoclonus has unique features, which include:

1. Frequent accompaniment by epileptic seizures.
2. Increasing frequency and amplitude of myoclonus culminating in a generalized seizure.

Similarly, with regard to the movement disorder of myoclonus itself, again there are two striking characteristics:

1. Overlap between myoclonus and tremor.
2. Tendency for myoclonus to be brought out by voluntary movement.

The relationship between tremor and myoclonus is a complex one. For example, rhythmic myoclonus cannot be distinguished from tremor[311]. Apart from the fact that cortical myoclonus is described as either rhythmic or irregular, the current definition also explicitly states that cortical tremor is not a tremor at all, but is a myoclonic phenomenon[311]. Emphasizing this point, the consensus statement from the Movement Disorder Society on tremor notes "It must be emphasized that so-called jerky tremors are often not tremors but rather, myoclonus or asterixis"[311].

When viewed from either a phenomenonological perspective or a pathophysiological one, myoclonus can range from being a type of tremor to a type of epilepsy. In attempting to unravel the cause of myoclonus, it will prove useful to examine both aspects in greater detail.

4.3.1 MYOCLONUS AND EPILEPSY

Apart from our understanding of myoclonus and cerebellothalamocortical pathways, reviewed in the following section, relatively little is known about many of the basic mechanisms of myoclonus. In contradistinction, the pathophysiology of generalized seizures, notably absence seizures, has been explored in greater detail, and this knowledge may therefore lead to greater understanding of the pathophysiology of myoclonus. Absence seizures serve as a model for the primary generalized epilepsies as a whole, which may present with absence, generalized tonic-clonic seizures or myoclonus.

The major shared EEG correlate between primary generalized epilepsy and FAME is the presence of generalized spike and wave discharges. There are clear distinctions between the two conditions, in that the EEG in FAME 3 is associated with a slow background and the frequency of the generalized spike and wave discharges is not 3 Hz, as is typically found in absence epilepsy. However, the generalized epilepsies themselves may be best regarded as part of a spectrum of epileptic conditions. One extreme constitutes pure primary generalized epilepsy, where the major etiologic factor is an inherited trait that is expressed electroencepholographically as generalized spike-wave discharges at 3 Hz or faster. The other extreme is made up of secondary generalized epilepsies where there is diffuse grey matter disease, usually due to acquired factors. Lying between these are a considerable number of patients with a heterogeneous mixture of features.

Of greater relevance to the question of the relationship between generalized spike and wave discharges in epilepsy and myoclonus are the conditions referred to as borderline syndromes with absence. These include idiopathic myoclonic astatic epilepsy of childhood (syndrome of Doose) and epilepsy with myoclonic absences.

i) Intermediate petit mal is a condition of absence seizures which is clinically similar to childhood absence, but is associated with atypical spike and waves. These are irregular, with a frequency of less than 2.5 Hz and are asymmetrical. The interictal EEG has a theta background and frontal bursts of polyspike and wave activity. The condition is characterised by a myoclonic jerks which may be prominent or may be a minor symptom amongst daily convulsive seizures, and some patients are mentally retarded. The disorder begins usually between the age of 2 and 5 years and, although classified as a generalized cryptogenic or symptomatic epilepsy, there may be a large subgroup caused by idiopathic epilepsy or IGE [423].

ii) Epilepsy with myoclonic absences is a rare condition which usually has its onset at the age of seven years, has a male preponderance, and is noteworthy for the

presence of mental deterioration. The seizures consist of absences with prominent myoclonus or clonic jerks, frequently associated with tonic contractions. The ictal EEG displays a typical 3 Hz pattern which may be precipitated by hyperventilation.

Absence seizures are also described in secondary generalized epilepsies, in which case there are usually associated tonic and atonic seizures or myoclonus. Such patients [424] may have focal signs, cognitive impairment, and evidence for an acquired aetiology, and the EEG has a slow background and the spike and wave discharges are of a frequency of 2 Hz or less. Similarly, absences are described in subacute sclerosing panencephalitis, in which they have a frequency of 2.5 Hz with periods of desynchronization [425], and are also seen in lysosomal storage diseases [426]. Of note, a case of Batten's disease, which is one the conditions linked to PME, has been described with a 3 Hz spike and wave discharge, indicating that typical EEG patterns of primary generalized epilepsy may occur as a manifestation of diffuse neuronal disease. Metabolic encephalopathies such as renal failure[255] hypoglycaemia and metrizamide use [427] are also reported to cause absence seizures, although in the case of the latter, a slow 2 Hz sharp and slow wave pattern was noted.

Considerable basic research has been carried out in investigating the pathophysiology of absence seizures. Gloor described the fundamental pathogenesis of the generalized epilepsies as an abnormal response pattern of cortical neurones to the afferent thalamocortical volleys which are normally involved in the elicitation of spindles[428]. This aberrant response occurs under conditions of diffuse mild cortical hyperexcitability, and results in an increased number of action potentials generated as a result of the afferent input from the thalamus. These findings were based on experimental studies of penicillin-induced seizures in the cat, in which thalamic structures were stimulated directly, with the additional administration of penicillin either systemically or applied topically to the cortex. In the cat, generalized spike and wave discharges can be produced experimentally by stimulation of the midline and intralaminar nuclei of the thalamus. In humans, direct recordings have demonstrated that spike and wave discharges as part of an absence seizure can be simultaneously recorded from both cortex and thalamus [429;430].

However, electrical stimulation of human frontal cortex, particularly the mesial aspect, may also produce EEG activity indistinguishable from spontaneous spike and wave and attacks, and which clinically resemble either simple or complex absences, suggesting that subcortical structures may not always be required for the generation of the spike and wave discharge[431].

In summary, three levels of the central nervous system are involved in the genesis of the discharges[428]:

i) the cortex, which is hyperexcitable.

ii) the thalamus, particularly the midline and intralaminar nuclei.

iii) the brainstem reticular formation, which allows for facilitation of generalized discharges if its activity is depressed.

Oscillatory activity in the thalamus, such as that resulting in sleep spindles, is dependant on the intrinsic ability of neurons within the NRT to impose their oscillatory behaviour on thalamo-cortical circuitry (Figure 63). The NRT forms a shell surrounding the dorsal thalamus, made up of GABAergic neurons projecting both amongst each other and also to the thalamic relay nuclei. These NRT neurons are stimulated by thalamocortical and reciprocal cortico-thalamic projections.

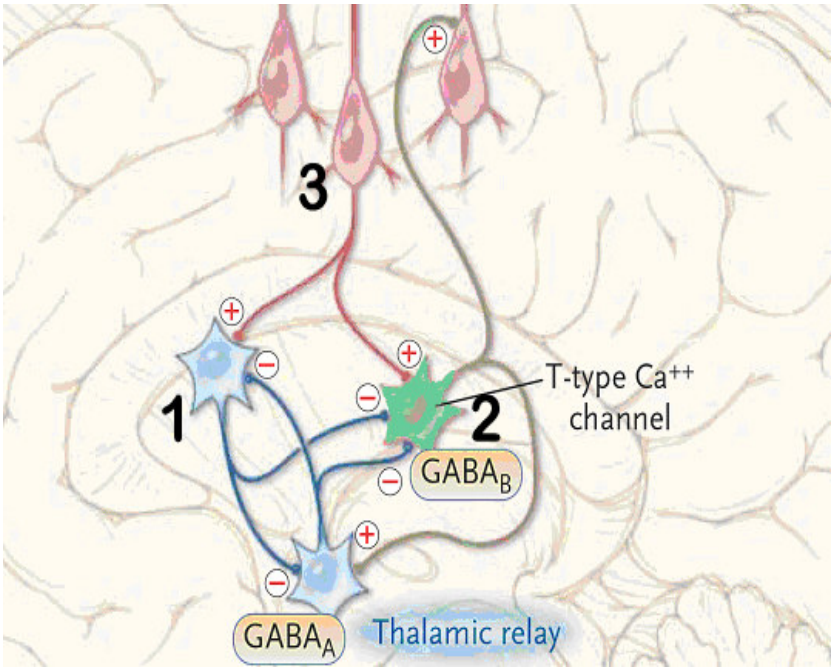

Figure 63. Thalamo-cortical interactions. (Redrawn from Chang & Lowenstein, 2003)

1. Thalamic reticular neurons (in blue) hyperpolarize the thalamic relay neurons, acting at GABAB receptors.

2. Thalamic relay neurons (in green) activate the cortical pyramidal neurons.

3. Cortical pyramidal neurons activate the thalamic reticular neurons in a feedforward loop.

If the thalamus is inactivated, spike and wave discharges in both the thalamus and cortex are abolished[432]. In turn, when cortical activity is abolished or suppressed, spike and wave discharges are suppressed in the thalamus [433] although spindles continue to be present [434]. The spike and wave burst appears to be initiated in the cortex with secondary involvement of the thalamus, and is seen more clearly in neurons of the specific nuclei[435]. Once initiated, both thalamus and cortex are essential to the maintenance of the spike and wave discharge[430]. Studies using time computation histogram techniques of cortical and thalamic neurons have demonstrated that firing takes place in an oscillatory, phase-locked manner[436]; intracellular discharges recorded during spike and wave bursts demonstrate a marked increase in the firing probability of both thalamic and cortical neurons during the spike, and the converse holds true during the slow wave component[430]. Corticothalamic neurons fire bursts of action potentials during the spike (of the spike and wave discharge) and hence entrain thalamic neurons to the oscillatory discharges which underlie the spike and wave discharge, with some thalamic cells reciprocally projecting back to cortex[437]. In spike and wave discharges recorded from thalamus and cortex there is preservation of GABAergic function, with preserved IPSPs, thereby contributing to synchronisation of spike and wave discharges which are dependant on rhythmically recurring inhibition in both cortex and thalamus [438].

4.3.2 MYOCLONUS AS RELATED TO THE MOTOR SYSTEM

Wolfhart and Hook [422] appear to have been the first authors to observe that myoclonus was brought out clearly by action: “at every volitional movement there were violent jerks and shakings, sometimes of a tremor type”. Bonduelle observed that "in a great variety of diseases myoclonus may be intensified or elicited by voluntary movement of the affected segment of a limb or maintaining the limb in a given posture "[22] and also drew attention to the "infinite gradation between pure postural tremor, as seen in essential tremor, and the major forms of dyskinesia such as the syndrome described by Lance and Adams, methyl bromide poisoning and hepatolenticular degeneration"[22].

Similarly, Gilbert found that myoclonus occurs upon a background of shifting posture or changing direction of movement, and suggested that this implied a relationship to cerebellar function[439]. Harriman[96] and Gilbert[440] noted that maneuvers which worsened tremor would worsen myoclonus. Shibasaki also commented on the fact that cortical reflex myoclonus is commonly enhanced by posturing and/or volitional movement, possibly suggesting a role for the cerebellum in the production of myoclonus[401].

Regarding the role of the cerebellum in myoclonus, Mima reasoned that since most patients with PME had cerebellar ataxia, most would also have deficits in the cerebellothalamocortical system [441]. However, Ugawa, studying patients with hereditary cerebellar ataxia, showed that cortical excitability was normal in these conditions, using a technique of a cerebral hemispheric conditioning stimulus followed by magnetic stimulation (cortico-cortical inhibition). Since cortical excitability was normal, it was inferred that cerebellar systems did not contribute to cortical excitiability or cortico-cortical inhibition via the cerebello-thalamo-cortical pathway. However, in a different experimental set-up, in which electrical stimuli over the posterior fossa were followed by transcortical stimulation, the normal degree of cerebellar inhibition of motor cortex was absent in DRPLA and other forms of hereditary cerebellar ataxia [442;443].

Other studies have contributed further evidence to suggest a role for the cerebellum in patients who develop myoclonus. In a patient with RHS studied with a 3-dimensional positional analysis system, myoclonic jerks were noted to be more frequent when directed to a target and appeared to be triggered primarily by external sensory inputs relevant to the movement rather than the movement itself[444]. Myoclonic jerks followed finger contact with a target after about 100 msec: given that many cells in the dentate nucleus respond to visual and somatosensory inputs, this long latency might be accounted for by processing in cerebellar structures prior to motor cortex activation[444]. The authors postulated that loss of Purkinje cell inhibition, with consequent abnormally synchronized sensory related inputs from cerebellar nuclei, could affect cerebellar projections to the cortical motor regions[444]. Similarly, the bereitschaftpotential, which is generated by activation of the motor cortex through dentato-thalamic connections, was found to be absent in some forms of PME (RHS) [445]. Silen et al. comment that loss of Purkinje cells in the cerebellum is the major finding in patients with Unverricht-Lundborg disease[78], and that loss of their inhibitory effect could lead to enhanced cerebello–thalamo–cortical output, which might affect the oscillatory activity of the motor cortex[446].

In keeping with these observations, in 1930, Hodskins and Yakovlev reviewed the literature on the pathologic findings in myoclonic epilepsy and found that, in all 12 of the adequately studied cases in the literature, a lesion had been found in the dentate nucleus or in its efferent pathway, the brachium conjunctivum. In 7 of the 12 cases, the dentate nucleus was “the point of election of the disease”[235]. Obeso et al observed in their review of cortical myoclonus that 7 of their 11 patients had radiological evidence of cerebellar damage, and considered that “myoclonus was due to abnormal cerebellar input into, perhaps, a normal sensorimotor cortex”[60]. As was also noted, Dawson’s original case who had presented with

giant SEPs, focal myoclonus and seizures, had Purkinje cell loss at postmortem [253]. Similarly, Brown found that cerebellar pathology seemed to be the only consistent pathological finding in many cases of PMA, as well as in the few cases of postanoxic myoclonus in which there was histology, contrasting with the "physiological abnormalities which seem to be primarily cortical"[447]. Correspondingly, features of cortical reflex myoclonus such as giant SEPs and C reflexes have been recorded in olivopontocerebellar atrophy (in which the pathology primarily involves the brainstem and cerebellum)[42] and a presumptive cortical origin for visual evoked potentials can be demonstrated in the same condition[395]. Obeso proposed that features of cortical myoclonus, such as bilaterally enlarged SEPs, may be related to loss of inhibition from other centres, such as a loss of cerebellar inhibition of the sensorimotor cortex [374].

Lesion studies may be useful in a reductionist approach to the causation of physiological phenomena, such as myoclonus. In the sparse surgical literature on myoclonus, there is a single case-report of a lesion of the cerebellar dentate nucleus in a 28 year old patient with severe myoclonus. For the first ten post-operative days the patient was free of myoclonus, but thereafter it returned to her arms[448]. Laitinen reported on seven patients with PME (probably Unverricht-Lundborg disease), who underwent subventrolateral thalamotomy, (presumably involving Vim and the cerebellar-thalamic outflow) with an improvement in ataxia and intention tremor, but “the effect of surgery on the myoclonias was less marked”. In two cases with myoclonus and ataxia who underwent thalamotomy, the myoclonus ceased initially, only gradually to return to a lesser degree[449]. In a case of neuroaxonal dystrophy, ventrolateral thalamotomy did not affect myoclonus[203]. Based on the rationale that increased Purkinje cell activity should decrease cerebral activity, Cooper performed cerebellar stimulation over the cortex of of the anterior lobe of the cerebellum[450]. In one patient, whose condition was the result of anoxic brain damage, myoclonus gradually diminished until the patient was able to sit without involuntary movements; “the flapping violent movements of her head, neck and upper extremities ceased and she could feed herself, drink from a glass without difficulty, and carry on unaided all activities of daily living, except walking”[450]. Two other patients also had reported improvement in their condition.

However, there is virtually no indication as to how cerebellar lesions might cause myoclonus. Clearcut involvement of the dentato-rubral system need not give rise to myoclonus epilepsy [125;451], and the majority of diseases involving the cerebellum are not associated with myoclonus, for example, spinocerebellar ataxias and paraneoplastic cerebellar degeneration. Furthermore, the spectrum of conditions giving rise to myoclonus associated

with cerebellar pathology is wide and ranges from relatively mild diseases manifesting with cortical tremor (FAME, coeliac disease) to severe forms of PME, such as DRPLA.

Similarly to theories invoking a broad framework incorporating cortical and subcortical structures in addition to the cerebellum in the genesis of essential tremor[452], there is theoretical and experimental evidence for interactions between the cortex and subcortical structures in myoclonus. Myoclonus overlaps phenomenologically with tremor, and tremor has been frequently associated with various types of myoclonus, notably manifesting as cortical tremor, which may be clinically indistinguishable from other types of tremor, such as essential tremor. It is therefore not unreasonable to speculate on the involvement of distributed networks in the production of myoclonus, analogous to networks associated with tremor, including the cerebellothalamocortical pathway[453].

In terms of cortical involvement in the genesis of myoclonus, there is substantial evidence for a reduction in cortical inhibition (reviewed in section 1.8.12). With regard to cortical reflex myoclonus, Ashby has proposed that a single stimulus may result in the synchronous discharge of many neurons, and recurrent discharge and subsequent after hyperpolarization and reexcitation might lead to recurrent myoclonus[295]. Decreased inhibition in motor cortex could cause an increase in the tendency of neurones to become synchronised. Similarly, Brown has observed that during voluntary motor contraction, motor units are subject to the effect of different drives, tending to synchronize the discharges of the motor units at different frequencies[454]. In line with this, patients with cortical myoclonus and multifocal myoclonus have been shown to have coherence of cortical and muscle discharges[400]. Coherence analysis has also shown stong corticomuscular coherence in familial cortical tremor[455]. Strong *intermuscular* coherence has also been described which may represent rhythmical cortical output to target muscles, leading to tremulous movements in conditions with cortical tremor[455].

With regard to specific subcortical and cortical interactions, the amplitude of the P30m evoked potential and spectral amplitudes of 10 Hz activity are correlated in Unverricht-Lundborg disease, suggesting that both signals are derived from overlapping neuronal populations or have common subcortical input[349]. More direct evidence in cases of cortical myoclonus consists of coherent oscillatory activity in the 8-27 Hz range obtained from the cerebellar thalamus (Vim nucleus) and sensorimotor cortex by recording local field potentials and EEG[456]. The authors proposed that this activity may represent a mechanism for "temporal sampling of movement-related activities within the sensorimotor cortex and cerebellar systems…..the sensorimotor cortex would be continuously digitizing activity in the

cerebellar thalamus, perhaps via a corticocerebellar-thalamic loop, explaining why coherence was present between the cortex and the cerebellar thalamus at rest as well as during activity"[456]. High frequency cortical oscillations may be of cortical origin, but, in particular, the basal ganglia are said to "have a critical role in supporting and controlling the synchronization of cortical activity at high frequencies"[454].

Coherence has also been reported between essential tremor and cortical EEG activity[457]. However, as McAuley pointed out with regard to essential tremor (Figure 64) "even a simplified scheme of the various neuronal pathways potentially relevant in the generation of essential tremor indicates that didactically attempting to attribute its origin to a single lesion in a single nucleus by means of simple recording is likely to be difficult, and that it may be more realistic to appreciate that tremors probably arise through interactions between central and peripheral neuromuscular systems"[458]. The findings of coherence between cortical activity and tremor or myoclonus do not indicate that the cortex is the origin of either activity[458].

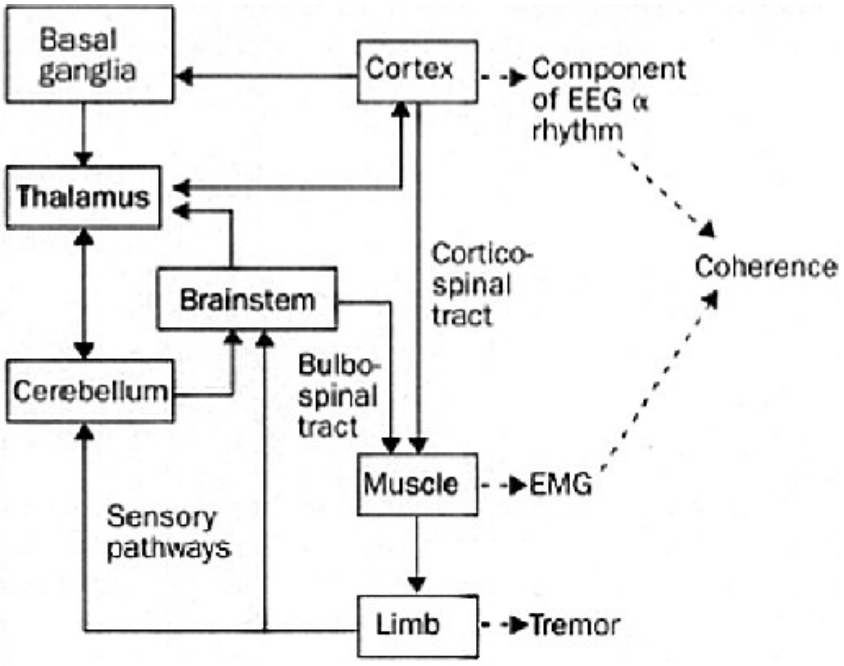

Figure 64. Diagram indicating the pathways involved in recording coherence. From McAuley [458].

Although Shibasaki initially described a single spike-like discharge when performing JLA recordings (Figure 35), many reports have either shown or commented on findings of multiple wavelets associated with the EMG burst, as seen also in FAME 3 (Figures 48-53). This is a similar pattern to that described initially in primary generalized epileptic myoclonus

(Figure 19) and has also been described as a manifestation of ADCME (Figure 25), Angelman syndrome (Figure 3), in HIV associated myoclonus (Figure 27), and in familial myoclonus epilepsy (Figures 22, 23, 26). Similar rhythmic myoclonus has also been reported with findings from JLA of a complex shape that included multiple waves, and with coherence between rhythmic EEG discharges and EMG bursts, with a peak at a frequency of 10.8 Hz [317]. The authors proposed that since rhythmic activity was visible on EEG, and significant coherence was demonstrable, the oscillations were generated by large, synchronous discharges of hyperexcitable cortical neurons[317]. Clearly, these discharges are related to the myoclonic jerk, but equally, the latency of the discharges is too long for there to be a direct relationship between a discharge in the motor cortex and a resultant myoclonic jerk, as is postulated to be the case in JLA when simple spikes are detected.

4.4 CLASSIFICATION OF MYOCLONUS

In recent years, the concept of myoclonus as consisting of two major entities, cortical and reticular reflex, has been prevalent. This may largely be for historical reasons, in that the dominant group working on myoclonus held that exaggerated long loop reflexes were a major factor in the causation of myoclonus[228;243;253]. Prior to that finding, the presence of enlarged evoked potentials had been noted in myoclonus, and were presumed to be indicative of cortical dysfunction. The additional detection of cortical potentials by jerk locked averaging appeared to seal the argument that myoclonus was of cortical origin[60].

These modalities, namely, evoked potentials, long loop reflexes and jerk locked averaging had been applied initially in the investigation of discrete cortical lesions presenting with focal jerks, and found to be abnormal. Abnormal results on these tests appeared to indicate cortical dysfunction. Subsequently, this interpretation was extrapolated to incorporate most other forms of myoclonus. The abnormal findings that had implicated the cortex as the site of origin of cortical reflex myoclonus in the setting of focal cortical lesions were replicated in diffuse myoclonus, leading to the deduction that diffuse myoclonus was also of cortical origin.

However, the problem of the neuropathology of the conditions associated with myoclonus has been noted persistently to be relatively inconsistent with the concept of a purely cortical process causing myoclonus. In his review of myoclonus, Symonds pointed out that “the involvement of the cerebellum is of particular interest in view of Ramsay Hunt’s observations, and of the finding by Greenfield (1953) of an almost complete disappearance of the Purkinje cells in the case of reported by Dawson (1946), in which myoclonus was proven to be provoked by muscle stretch[421]. In general, the predominant neuropathology has tended to involve subcortical and cerebellar structures, and to spare the cortex[60].

With respect to the neurophysiological criteria for diagnosing cortical myoclonus, the traditional argument has been that since the initial cortical response, N1 or N20, is normal and represents the incoming thalamic volley, and that subsequent abnormally enlarged responses are indicative of a purely cortical process. However, as reviewed (section 1.8.14), the initial response is not always normal, and may be enhanced, although to a lesser degree than other components of the SEP[242]. Perhaps of greater importance, it appears probable that thalamic afferents affect later responses that arise after the N20 response[391]. It seems reasonable to assume that in the setting of an existing state of cortical disinhibition, cortical networks will amplify thalamic input. It is unknown whether the

enhanced evoked potential is due purely to abnormal cortical processing of a normal thalamic signal subsequent to the arrival of the thalamic volley, or whether the thalamic input itself is abnormal or prolonged, and that it is this interaction with an abnormally functioning cortex which results in an enlarged evoked response.

Jerk locked averaging is a useful technique, but understanding of the physiological processes that result in a spike discharge and bear a precise temporal relationship to a subsequent myoclonic jerk is limited. Many forms of myoclonus have jerks that are of too high a frequency to be interpreted. Although the peak of the positive wave has been routinely used to determine the latency from point of cortical discharge to onset of myoclonus, it is important to point out that this is an assumption based on recordings in primates in which a positive cortical potential is believed to represent the combined discharge of pyramidal neurons. Certainly, in many cases the latency from this peak to the onset of myoclonus is too short for the discharge to have originated in the cortex (table 11). It is perhaps salient to point out that Shibasaki, when initially describing the phenomenon of JLA, assumed that it was a feature of subcortical origin for myoclonus, since the latencies were so short, and only subsequently altered his position[240]. Whether the difficulty lies in determining the actual onset of the myoclonic jerk, which is established by the somewhat arbitrary setting of a trigger level, or whether the latency should be fixed from some point other than the peak of the positive potential, is unclear. It is not impossible that the cortical spike is an epiphenomenon, and is not directly related to the neuronal discharge that results in a myoclonic jerk. The finding with JLA of a pattern of multiple waves is incompatible with a single discrete discharge in the cortex resulting in a single, discrete jerk[8;216;316]. Furthermore, as EP Richardson pointed out, even if JLA demonstrates a cortical potential associated with myoclonus, this does not necessarily "preclude the possibility that subcortical structures may be crucial in making the cerebral cortex either "myoclonogenic" (Gilbert 1963) or "epileptogenic" (Ziegler 1974)" [459].

With regard to long latency reflexes, the physiological role of these reflexes, and their origin, remains controversial. It is unlikely that the long latency reflex forms part of the pathway that resulted initially in a giant evoked potential and subsequently in a C reflex, as was initially proposed[385]. Given that the latency of the long latency reflexes is typically held to be approximately 40 msec, it is appropriate to refer to the controversy regarding the origin and nature of the short latency input to motor cortex, a pathway which would presumably be required if the long latency reflex involved a transcortical loop (reviewed in section 1.8.13).

However, there is good evidence from a variety of experimental methods that indicate that the cortex is relatively disinhibited, as was demonstrated in this study in FAME 3 by using transcranial magnetic stimulation, and seen also in other forms of PME and familial cortical tremor[345;411].

In view of the known subcortical pathology, it is tempting to speculate on ascending projections arising from dysfunctional subcortical structures that may affect cortical inhibition. For example, the overall set point of thalamic and cortical excitability is modulated by ascending cholinergic pathways that project to the thalamus as well as noradrenergic and dopaminergic neurons projecting to the cortical end of the thalamocortical loop where they influence bursting cells in layer V of the cerebral cortex [460]. Rhythmic stimulation of the thalamus results in the the augmenting response, in which responses in the thalamus, as well as areas of the neocortex to which the stimulated thalamic foci project, increase in size during the first few stimuli[461;462]. Intrathalamic mechanisms might make a major contribution to cortical augmenting responses during repetitive thalamic stimulation, and cortical feedback could promote augmentation in the thalamus through mechanisms similar to those that are involved in the generation of spindles[462]. Following stimulation in the VL nucleus, activity in thalamic afferents projecting to cortical layer V initiates a sequence of events that primes the cortical network and subsequent afferent activity evokes an augmented response[463]. Thus, as Brookhart and Zanchetti noted in animal experiments in cats, recurrent thalamic stimulation may induce an augmenting response, and subsequently a discharge could be recorded in the pyramidal tract[397].

FAME 3 has features of cortical myoclonus in that evoked potentials are enlarged, long latency reflexes are present, and JLA demonstrated a series of waves linked to the myoclonic discharge. However, MRI scans showed cerebellar atrophy, and neuropathology was largely restricted to the cerebellum, with Purkinje cell loss, and involvement of the dentate nucleus.

FAME 3 is therefore a classical example of a condition in which there are subcortical and cerebellar pathological changes in the setting of neurophysiological abnormalities which traditionally have been associated with cortical dysfunction.

Although focal cortical lesions may have enhanced SEPs and spikes detected by JLA, there is evidence to indicate that these characteristics are not exclusively the domain of myoclonus arising from the cortex. As reviewed, a striking feature of many diseases associated with myoclonus is the presence of generalized spike and wave activity, and given

the substantial body of work that suggests that these discharges arise from cortico-thalamic interactions, it appears likely that similar conclusions may be drawn with regard to FAME 3 and like conditions. Given the strong association of myoclonus with epilepsy, the phenomenon of increasing myoclonic jerks prior to seizures, and EEG findings of spike and wave, it appears likely that myoclonus itself may also be associated with abnormalities in cortical-thalamic interactions.

Furthermore, FAME 3 shares many neurophysiological similarities with other forms of PME, such as DRPLA and the sialidoses. The majority of these conditions also have pathological changes affecting subcortical structures. With regard to definitions of myoclonus, it seems reasonable to emphasize that on the basis of their differing pathology and the presence of epilepsy, conditions such as the PMEs are distinct from pure cortical lesions. Although PME and FAME 3 may share neurophysiological features with those forms of myoclonus which arise from a discrete cortical lesion, it appears likely that this similarity is the result of two distinct pathophysiological processes meeting at a common point, the cortex. It would seem reasonable to argue that definitions of myoclonus, such as cortical and reticular reflex, border on being somewhat arbitrary distinctions, and that although neurophysiological testing lends support to such groupings, many of the disease processes overlap. The majority of the conditions associated with PME and FAME have pathological and physiological findings which are indicative of both subcortical and cortical dysfunction, and the usual designation of cortical myoclonus for these conditions appears to be an oversimplification.

APPENDIX 1: CASE HISTORIES

FAMILY A

A-II-2

This patient, who was born in 1942, and died at the age of 57, was seen at Groote Schuur Hospital in Cape Town on one occasion, and was referred to the neurological service with a history of generalized tonic-clonic seizures; CT scan showed previous cerebrovascular accident with left parietal infarction and atrophy. Neurology consultation reported a degree of dementia, absent ankle and knee jerks and weakness of the legs with flexion contractures.

He was reported by his children to have had an amputation and subsequently burnt to death, probably whilst smoking in bed. He was said to have had many seizures; the onset of his illness was reported to have been about the age of 30 years. He had tremor and visual hallucinations.

A-II-6

This patient's illness started at the age of 22 years and was characterized by both myoclonus and seizures. He reported that seizures were rare and tended to occur in the morning and that there was an increasing frequency of myoclonus prior to a seizure. He had been on both phenytoin and phenobarbital and had documented toxic levels of both drugs. His Minimental State Examination (MMSE) was 16, but it should be noted that he had no formal education. When he was examined at the age of 50, symmetrical tremor of the hands was present, which was brought out by action, notably posture holding. Myoclonus was present, with occasional jerks of the upper limbs. Cranial nerves showed abnormal pursuit with dysarthria. Dysmetria of the legs was present and he had truncal ataxia and difficulty walking, which had started in his early thirties. Knee and ankle reflexes were absent and he had distal loss of vibration and joint position sense. Extensor plantar responses were present.

A-III-4

This patient's illness started at the age of 20 years, and was characterized by myoclonus and rare seizures, the latter being aggravated by sleep deprivation. Medication largely consisted of a combination of phenytoin and phenobarbital and he reported an improvement in his condition using valproate. He was initially assessed in 1991 at the age of 28 years, and again in 2002. As of 2005 he was still employed as a labourer in a factory. He had a MMSE of 28. He had a Standard 4 education.

On examination, he had no nystagmus, but ocular pursuit was impaired. Blepharospasm was present. Mild dysmetria and tremor of the hands were present. Myoclonus of low

amplitude was present in his face and upper limbs. Reflexes and distal sensation were normal.

At re-examination in 2002, there was no appreciable change noted: he had changed his medication to sodium valproate in the interim period.

A-III-5

This patient's illness was characterized by the presence of myoclonus and seizures, which started at the age of 18 years. Seizures occurred two to three times per month and both morning myoclonus and seizures occurred. He reported exacerbation of his condition by sleep deprivation and alcohol. His medication was limited to a combination of phenytoin and phenobarb. CT scan was normal. He had a Standard 4 Education, and his MMSE was 9.

On examination, smooth pursuit was abnormal, and although at initial assessment he was normal, a decade later on repeat examination, dysmetria was present, affecting legs more than arms: this may have represented an anterior vermis syndrome secondary to alcohol. Tremulous movements of the lips and hands were present, as was myoclonus of small amplitude largely affecting the upper limbs.

A-III-7

This patient had both myoclonus and seizures, commencing at the age of 14 years. She reported about one seizure per month, and said that seizures would sometimes be preceded by increasing myoclonus, and were exacerbated by sleep deprivation.

On examination, she was not orientated to time or place and appeared to be demented. She had a Standard 1 education. Nystagmus and abnormal smooth pursuit were present; she was dysarthric and had dysmetria of arms and legs, difficulty walking and truncal ataxia. Typical tremor was present. Knee and ankle reflexes were difficult to elicit. Low amplitude myoclonic jerks were present in the upper limbs. Blepharospasm was present.

A-III-8

(Proband family A): This patient, first seen in 1992 at the age of 28 years, reported the onset of myoclonus at the age of 26. Myoclonus was said to come on at any time; she commented that it seemed particularly worse after going out into bright sunshine, and on one occasion, after a dance. She also had generalized seizures, and received a combination of phenobarbital and phenytoin for these. Myoclonus was not worse in the morning. She reported that she would occasionally experience a series of jerks. She had failed her final year of schooling and then left school. On examination, MMSE was 27 and testing of category fluency and motor sequencing tasks was normal. She had fine tremor of the fingers at rest, exacerbated by posture, and intermittent myoclonus, predominantly distally in the arms. Smooth pursuit was normal and there was no nystagmus or dysarthria present. There was mild blepharospasm. Examination of the motor and sensory systems was intact and there was no evidence of cerebellar dysfunction.

CSF lactate was normal and biopsies of muscle, axilla and palmar skin were normal. She was seen again at the age of 33 in 1997; a combination of valproic acid and clonazepam stopped her myoclonic jerks. At the time of her last assessment she reported having a few seizures per month, and complained of intermittent myoclonus. She commented on an increased frequency of jerks prior to a seizure. On examination, she had fine tremulousness of the hands, with a mild intention tremor and mild lower limb ataxia.

A-III-9

This patient reported the onset of myoclonus at the age of 20 years. He had nocturnal seizures at a frequency of one per month. He reported exacerbation of convulsions from alcohol, stating that his convulsions had lasted one to two hours. He had a poor response to a combination of phenobarbital and phenytoin and at the time of examination was taking phenytoin 300mg at night.

He had a grade 9 education, but reportedly had progressive intellectual impairment. Pursuit was abnormal, and he had dysarthria. Postural tremor of the hands was present.

Dysmetria was present, but it was unclear whether this related to superimposed myoclonic jerks. He had truncal ataxia and extensor plantar responses. He died in 1996, reportedly following a seizure and his brain was subsequently examined pathologically (details are given in Section 2.3).

A-III-10

This patient reported that myoclonus started at the age of 23 years. Her examination was normal, apart from mild tremulousness, and rare distal myoclonus. She noted improvement with clonazepam. She had a grade 1 education and could not read, but scored 26 on MMSE in 2001.

She lived an isolated life on a farm with her mother, and took sodium valproate religiously since 1994. She was reassessed in 2001, and reported very few seizures; her neurological examination was normal.

A-IV-1

This patient, the daughter of A-III-4, presented in 2005 at the age of 23 with a complaint that she had experienced intermittent myoclonic jerks since age 13. She had completed high school and had a job as a book-keeper at a school. Myoclonus involved arms more than legs, and was worse in the morning and associated with sleep deprivation. She had no history of seizures. The myoclonus was mild and did not trouble her particularly; she had sought medical attention largely due to her sister's insistence. She described a brief sensation of absence associated with some myoclonic jerks. On examination she had a fine postural tremor of the hands and occasional myoclonic jerks were noted in the shoulders.

FAMILY B

B-I-1

The great-grandmother of the proband, IV-6, lived near Piketberg, and was also reported as having lived in Calvinia by her grandaughter, III-1. She was reported to have had tremor and seizures, and although she was able to walk, was said to have been in bed much of the time.

B-II-1

This patient is said to have had tremor and numerous seizures and drowned after he ran into a dam, round about 1900. He lived “on the other side” of Piketberg.

B-III-9

This patient had visual hallucinations, complained of strange smells, and was said to have frequent exacerbations and remissions. She was reported to have been admitted to the Valkenburg Mental Hospital in Cape Town. She is reported to have died in her thirties. She was also reported as having myoclonic jerks starting in her early thirties.

B-III-12

This patient is described as having myoclonic jerks and generalized tonic-clonic seizures; she was also reported to wander off, disappearing for a few days at a time. She was reported by her family members to have had a normal gait, without features of truncal ataxia. She died in her late thirties.

B-III-20

This patient’s son (seen at the age of 46) said that his mother died at the age of 62, after she had set herself alight by accident. She had myoclonic jerks, and reportedly walked as though she was drunk and had postictal confusion.

B-IV-3:

(Proband family B): This patient was admitted to the hospital in 1994, initially to the psychiatry ward, where she presented with emotional lability and myoclonus. She reported that her illness had started five years previously at the age of 31. The myoclonic jerks came in clusters, and there were runs of jerks prior to seizures. The seizures were said to be infrequent. She felt that the illness was progressive, and led to impaired functioning at home. According to her sister, she had been very neat, but she was no longer able to care for herself. In the psychiatry ward, she was noted to have auditory and visual hallucinations and religious delusions. On examination, she was emotionally labile and disinhibited. She had a grade 9 education. Myoclonic jerks were present in her arms and hands and trunk, brought out by movement. She had blepharospasm and facial myoclonus. Reflexes were brisk throughout. Coordination was initially difficult to evaluate because of myoclonus, but subsequently appeared normal. Myoclonus responded to clonazepam. CSF and CT brain were normal. Although placed on sodium valproate, her compliance was poor and her response was unclear. She died aged 39; the circumstances of her death are unknown.

B-IV-6

This patient reported the onset of myoclonus and seizures at about the age of 20 years. She felt at the time of initial assessment, at the age of 30, that her condition was not progressive, although it seemed to increase with stress. Myoclonus was present only in her arms and hands and resulted in her struggling to carry things, serve up food to her children and shop. Myoclonus was typically associated with activity and did not occur at rest. There was no morning myoclonus or seizures and no series of myoclonic jerks prior to a convulsion. Sleep deprivation and alcohol did not exacerbate seizures.

Seizures were characterized by having no warning, although she reported that her neck would turn to the right initially; after the event she was confused for a few hours; seizure frequency was 2-3 times per month, although at times she would have clusters of seizures, up to 7 per day. She had a MMSE of 28/30; she had a Standard 4 education.

When initially examined in 1994 there was no truncal ataxia but 5 years later, she had developed truncal ataxia. Similarly, initially reflexes were normal, but she later developed hyperreflexia. In 2000, there were myoclonic jerks of the outstretched hands, with intermittent jerks seen all over body, especially the arms, hands, and feet. The reflexes were all brisk, but tone was normal. Postural tremor was present. Sensation was normal. There was no blepharospasm. There was mild impairment of finger to nose testing and rapid alternating movements were mildly clumsy. She had been treated with phenytoin 300mg, phenobarbital 30 nocte and clonazepam 0.5 mg nocte. As with her sister, she appeared to be only intermittently compliant with sodium valproate.

B-IV-10

This patient reported that her illness started around the birth of her fourth child, about the age of 25 years. She reported blepharospasm and tremor of her hands, followed later by tonic-clonic seizures, which occurred at a frequency of 2-3 per month. The seizures were preceded by runs of myoclonic jerks or by jerks or tonic spasms of the left arm. Seizures were not worsened by alchohol, but tended to be more frequent in the evening. She also experienced nocturnal seizures. Myoclonus was not worse in the morning. Sodium valproate improved her seizure control, both by history and on comparing spike counts on EEG. She had no formal education.

On examination, she had myoclonic jerks composed predominantly of fine, tremulous movements in the arms, particularly the hands, brought out by posture. The hands and forearms were involved, but not the legs. There was slight myoclonus of the mouth and chin and blepharospasm was present. Reflexes were slightly increased. There was mild dysmetria in legs and in the arms, possibly secondary to myoclonus. Rapid alternating movements were normal, as were smooth pursuit and saccades.

One seizure was witnessed at 9 pm: she was noted to have an increase in myoclonus, progressing to massive myoclonic jerks, predominantly of the upper body and with retained consciousness, and she was unable to stand and sat on the floor; after a few minutes she had a generalized tonic-clonic seizure, followed by post-ictal confusion.

B-IV-14

This patient was described as having generalized seizures and myoclonus. He died young.

B-IV-19

This patient died at the age of 45, just after a seizure. She had many seizures, and was reported to have had an unsteady gait. She was said to have been confused at times.

B-IV-23

This patient reported that she did not go to school at all, or that it was limited to Sub A. She was unable to remember when her illness began, but stated that it was long after her two children were born; on another occasion she reported jerks starting at age 17, and that her first seizure was at the age of 42 years. She reported if she did not take medication that she would get jerks of her body and tremor. She had approximately 1 – 2 seizures per year. At initial assessment she was taking phenobarbital 60 mg daily. She was first assessed in the year 2000, aged 44: smooth pursuit was mildly abnormal, and there was intention tremor present, with mildly brisk reflexes. Myoclonus was only evident as a fine low amplitude tremor of outstretched hands and occasional proximal jerks in the legs. There was no blepharospasm or facial jerks.

Four years later, on examination, minimal tremulousness was present. There was no nystagmus and smooth pursuit was normal. She was mildly dysarthric. There was no blepharospasm. On examination of the motor system, the reflexes were brisk, but tone was normal. The plantar responses were flexor; sensation was intact. On examination of the cerebellar system, the heel-shin, finger-nose and tandem gait were normal.

Her MMSE was 15. She was unable to name the province in which the hospital is found and identified the year, season and day of the week incorrectly. She was unable to perform serial sevens or to spell backwards. Her 3-minute recall was 1 and 0 on two separate testing periods. Language function was intact, but she was unable to read or write and unable to copy a diagram. Regarding category fluency, she was able to name seven animals in 1 minute; she was unable to identify any similarities, and verbal fluency was limited to three words beginning with S; her series of alternating motor sequences was normal.

B-IV-25

This patient, born in 1966, was last examined in November, 2004. She was born on a farm and had two years of schooling. At the age of 12 she was sent as a servant to Cape Town and returned home once a year for the next four years, at the end of which time she fell pregnant and returned to the farm.

She was unable to recall when her illness had begun, except that she had her first seizure when her son was three years old, corresponding to an age of 19. She had been an alcoholic, but after repeated physical assaults by her husband because of her drinking, she stopped. Myoclonus could occur at any time; she reported an increase of myoclonus prior to a seizure. Her husband reported that she had become somewhat more forgetful in the last few years, for example would not know what the date was.. She had very few seizures, but had severe myoclonus which was considerably improved by sodium valproate; she reported that if her medication ran out, the jerks would return. She had previously been on phenobarbital which had not controlled her seizures, and during which time she had very prominent myoclonic jerks. She had no generalized seizures since being on sodium valproate, a period of approximately 12 years. At the time of last examination in June, 2004, she had normal smooth pursuit, without nystagmus. She was noted to have a fine tremor of the hands. There was no ataxia present and she had minimal tremulousness. Reflexes were brisk, except for absent ankle jerks, and sensation and gait were normal. She had mild difficulty with tandem gait. She reported deterioration in the form of dysarthria due to myoclonus of speech. She scored 16 on the MMSE.

B-IV-26

This patient, the youngest of 11 children, had a history of severe alcohol abuse. At initial assessment she was thought to be normal, but on the basis of her abnormal EEG was given an “affected” ascertainment. She reported that she had jerks for a few years, from about the age of 30 years. She also complained of intermittent dizziness and that she was unsteady on her feet. She reported having only two generalized seizures. On examination she had a fine postural tremor and intention tremor of the hands. Smooth pursuit was abnormal and reflexes were brisk. She had only a grade 2 education. She was unable to give the year, season or date, and did not know the name of the country, province or town. She was unable to spell backwards and could not read, write or copy a diagram. MMSE score was 9.

B-V-3

This affected patient died in her thirties; she was described as having dysarthria, and epileptic seizures. She was admitted to the Stikland mental hospital. She was reported to have times when she was unable to walk and times when she was confused.

B-V-10

This patient was first seen at the age of 29 years in 2000. On examination she had a MMSE score of 10, in part related to her severe myoclonus, but she scored only 4/10 for orientation, and was unable to say the names of the days of week backwards. In addition she was disinhibited and had difficulty in performing motor sequences. Medicines included both phenytoin and phenobarbital. She had large amplitude myoclonus of predominantly the upper body and a moderate tremor of the hands, and was bed-bound. She had marked dysmetria with intention tremor. She was placed on sodium valproate and clonazepam with considerable improvement, but developed pancytopenia and sodium valproate was stopped, followed by worsening of myoclonus. She was last examined in March, 2005; at that time she was markedly demented, being unable to give appropriate answers regarding orientation to place or time, with prominent perseveration. She had been off all medication and had marked generalized myoclonus, which worsened slightly with posture-holding. Vertical and horizontal nystagmus was present and smooth pursuit was markedly impaired. All limb reflexes were absent. Assessment of cerebellar signs was difficult due to the presence of myoclonus. Nerve conduction studies were normal. She had frequent generalized seizures while in the ward. She developed difficulty swallowing and died at the age of 35 years.

B-V-13

This patient reported that her illness started about the age of 19, with myoclonic jerks.

She had a Standard 5 education. She was taking sodium valproate, 200mg x 3 daily. She reported that she only had myoclonic jerks and had no tonic clonic seizures. Her medication decreased her degree of myoclonic jerks. She reported a total of three seizures in her lifetime, the last one being about 3 years previously, at which time she had started taking sodium valproate.

On examination she had minimal tremulousness, present both with posture holding and with action. Ocular pursuit was normal and there was no nystagmus. Reflexes were increased in her arms. There was a mildly abnormal heel-shin test but tandem gait was normal.

Regarding her cognitive state, her 3-minute recall and language function were intact. However, her orientation was incorrect on all questions, both to time and place except for the name of the hospital. Her total MMSE score was 11/30.

She was seen again in 2005, at which time she was on sodium valproate CR 500 mg tds. On examination, she had minimal postural and intention tremor. Reflexes were moderately brisk and smooth pursuit mildly abnormal. MMSE had improved to 18/30.

APPENDIX 2: PHYSIOLOGY OF FAME 3

Table 19. Results of EEGs in patients and controls

Subject	Year	Background	Polyspike and Wave	Hyperventilation	IPS
AFFECTED					
A-II-6	1999	10-11 Hz alpha with moderate theta and scattered delta	Frequent spike and polyspike and wave in frontal regions	No increase in SW	No
A-III-3	1999	Slowed 7 Hz background	Frequent bursts of polyspike and wave	No increase in SW	No
A-III-4	1991	9 Hz alpha Occasional theta and delta transients	Independent spike and wave from frontal regions	Enhances SW	No
A-III-6	nd				
A-III-7	1992	6-7 widespread theta	Frequent bursts at 5 Hz	No increase in SW	No
	1998		Polyspike and wave	No increase in SW	No
	1999	Normal	Poorly formed bursts	No increase in SW	No
A-III-8	1987	“slow activity”	Single polyspike and wave	SW discharges following HV	No
A-III-9	1994	Poorly formed background	Left frontal spike discharges	Intermittent frontal spike discharges	No
A-IV-1	2005	Normal background with occasional scattered theta transients; recurrent bursts of theta and delta activity	Generalized frontally predominant spike and polyspike and wave	No increase in SW	No
B-IV-3	1989	Normal alpha with intermittent episodic rhythmic theta activity	Brief frontal spike discharges	No increase in SW	No
	1994	Background of theta and abundant delta activity	Single generalized frontally predominant spike	No increase in SW	No
B-IV-6	1994	8 Hz alpha background; intermittent brief bursts of theta frontally		No increase in SW	No

Table 19. Results of EEGs in patients and controls

Subject	Year	Background	Polyspike and Wave	Hyperventilation	IPS
B-IV-6	2000	Well developed alpha, moderate amount diffuse theta, occasional delta transients	Abundant generalized spike and polyspike and wave discharges	No increase in SW	No
B-IV-10	1997	Normal background	Recurrent bursts of 4-5 Hz spike and polyspike and wave discharges, duration 0.5-1 second.	No increase in SW	No
B-IV-23	2000	Diffuse 7-8 Hz theta activity;	Generalized frontal spike and polyspike and wave	No increase in SW	No
B-IV-25	2000	Diffuse 5-6 Hz theta background	Frequent frontal spike and spike and wave	No increase in SW	*
	2000	Slow background, mixture of theta and delta transients	Frontal spikes and polyspikes	No increase in SW	No
	2000	Theta background of 5-6 Hz	Intermittent bursts of Polyspike and wave	No increase in SW	No
	2004	Background alpha activity; occasional 0.5-1 sec bursts of theta intermixed with delta	Occasional brief bursts of S and polyspike and wave at 3-4 Hz	No increase in SW	No
B-IV-26	2003	8 Hz alpha rhythm	Recurrent bursts of 4-5 Hz bursts of S and polyspike and wave of one second duration	No increase in SW	No
B-V-10	2000	7-8 Hz theta background	Frequent frontal bursts of polyspike and wave	No increase in SW	**
	2003	6-7 Hz theta	Frontally predominant generalized polyspike and wave	No increase in SW	No
B-V-11	2001	Normal	Normal	No paroxysmal activity	No
		Normal	Single SW discharge on referential montage	No paroxysmal activity	No
B-V-13	2003	6-7 Hz theta background, with delta transients	Normal	No paroxysmal activity	No
	2003	6-7 Hz theta background, with delta transients	Normal	No paroxysmal activity	No
ABNORMAL EEG, PROBABLY NOT AFFECTED					
B-V-9	2000	Normal background; Right posterior temporal delta	Spikes at T4 and T6	No paroxysmal activity	No

Table 19. Results of EEGs in patients and controls

UNAFFECTED					
Subject	**Year**	**Background**	**Polyspike and Wave**	**Hyperventilation**	**IPS**
B-IV-16	2000	Normal	Normal	No paroxysmal activity	No
B-IV-22	2004	Normal	Normal	No paroxysmal activity	No
B-IV-24	2000	Normal	Normal	No paroxysmal activity	No
B-V-1	2001	Normal	Normal	No paroxysmal activity	No
B-V-4	2001	Normal	Normal	No paroxysmal activity	No
B-V-4	2005	Normal	Normal	No paroxysmal activity	No
B-V-5	2000	Normal	Normal	No paroxysmal activity	No
B-V-5	2005	Normal	Normal	No paroxysmal activity	No
B-V-6	2000	Normal	Normal	No paroxysmal activity	No
B-V-7	2000	Normal	Normal	No paroxysmal activity	No
B-V-12	2001	Normal	Normal	No paroxysmal activity	No
B-V-12	2003	Normal	Normal	No paroxysmal activity	No
B-V-14	2001	Normal	Normal	No paroxysmal activity	No
B-V-14	2003	Normal	Normal	No paroxysmal activity	No
B-V-14	2003	Normal	Normal	No paroxysmal activity	No
B-V-14	2004	Normal	Normal	No paroxysmal activity	No

Table 20. Results of nerve conduction studies

Subject	Peroneal Motor (latency, velocity, CMAP mV)	Tibial Motor (latency, velocity, CMAP mV)	Sural Sensory (latency/ amplitude µV)
A-II-6	3.3/49.3/4	2.8/56//8	3.2/10
A-II-10	3.9/47.1/6.9		4.2/12
A-III-4	3.1/52/5.7	3.9/56/8.4	3.5/16
A-III-8	3.3/50/10	4.2/57/4.5	3.9/15
A-III-9			4.2/14.6
B-IV-3			3.5/18
B-IV-10	3.3/51/6.6	3.4/61/6	3.0/27
B-IV-23	2.7/52.4/4	3/55/9.5	3.1/15
B-IV-25	3.4/50/3		3.6/18
B-IV-26	2.8/50/4	3.6/51/9	3.6/17
B-V-10	3.9/52.6/1	3.6/52.6/7	3.7/10

Table 21. Synchronicity of myoclonic discharges and duration of myoclonus.

Name	Synchronous	EMG duration (msec, range)
A-II-6	rare	<50(20-40)
A-III-3	nd	
A-III-7	at times	<50(30-50)
A-III-8	at times	<50
A-III-9	no	20-40
B-IV-3	Variable	20-40
B-IV-10	Frequent	30-50
B-IV-23	at times	<50
B-IV-25	at times	20-50
B-IV-26	No	nd
B-V-10	No	<50

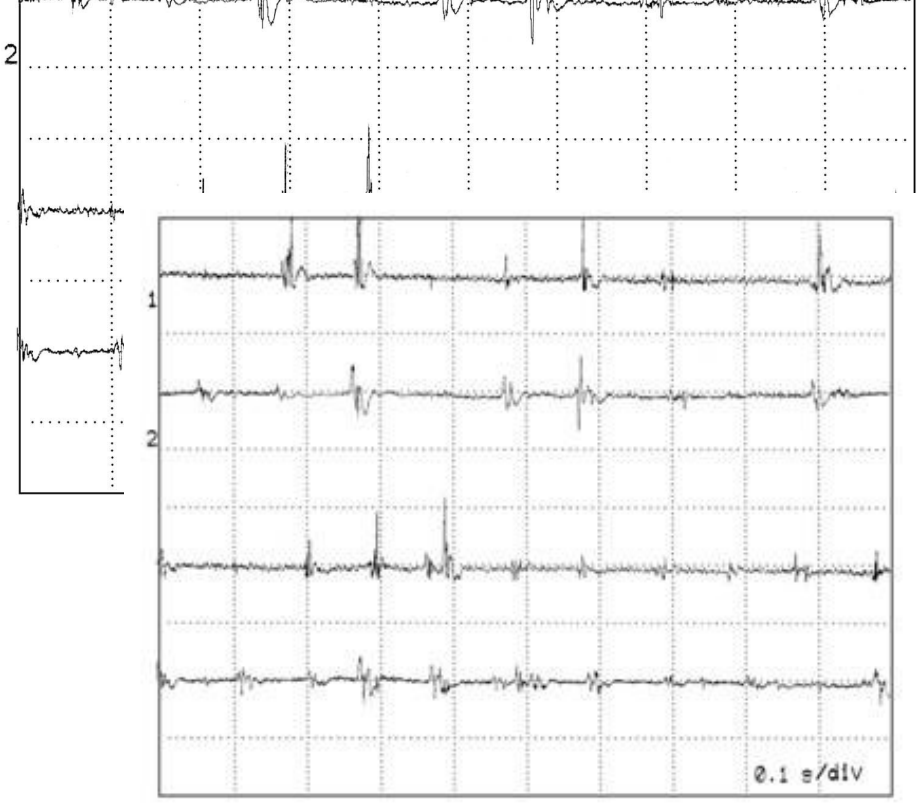

Figure 65. Assessing synchronicity and duration of myoclonus; patient A-III-8.

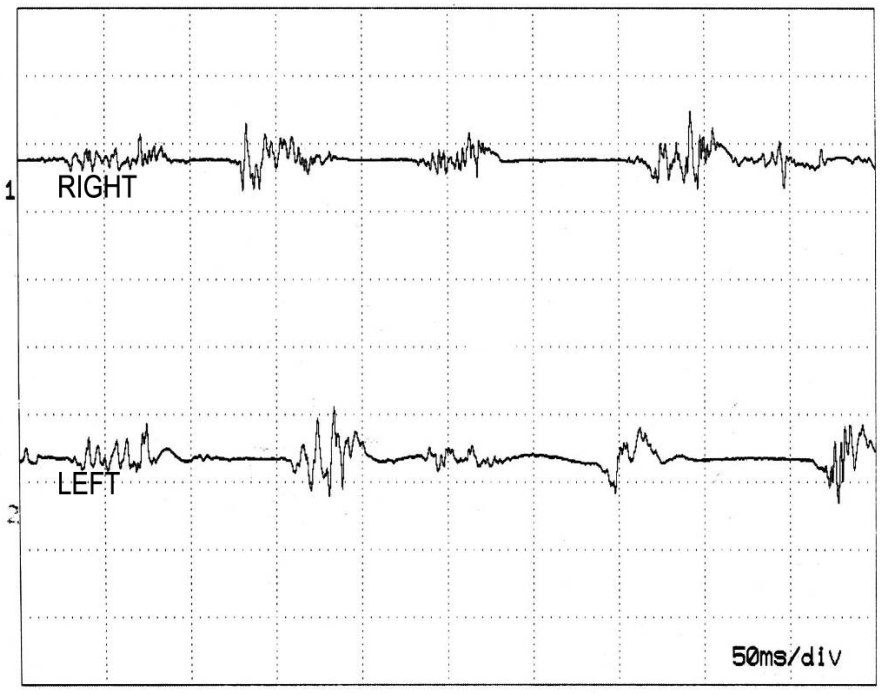

Figure 66. Assessing synchronicity and duration of myoclonus; patient B-IV-26.

Table 22. Control group for determination of SEP amplitudes (average age 39.5)

Gender/ Age	N19	N1-P1/N19-P25	P1-N2/P25-N33
Mean Values	**1.77**	**3.73**	**2.61**
M38	0.84	1.82	1.66
	0.42	2.2	1.48
	1.18	3.06	0.52
	0.81	**2.36**	**1.22**
M46	3.32	6.64	2.8
	3.4	5.88	2.52
	3.24	6.28	2.84
	3.32	**6.27**	**2.72**
M36	2.36	2.62	0.72
	2.12	2.54	0.88
	2.02	2.6	0.6
	2.17	**2.59**	**0.73**
M46	1.28	3	3.04
	1.6	3.2	3
	1.64	2.96	3.14
	1.51	**3.05**	**3.06**
M42	1.42	2.04	3.1
	1.82	2.82	2.08
	1.66	2.12	1.98
	1.63	**2.33**	**2.39**
F42	3.56	7.06	5.96
	3.08	4.92	5.84
	3.48	9.96	5.56
	3.37	**7.31**	**5.79**
F33	0.6	3.64	2.08
	0.72	3.32	3.4
	0.68	3.32	2.52
	0.66	**3.48**	**2.67**
F40	2.72	3.12	1.96
	2.1	2.88	1.5
	2.5	3.2	1.86
	2.44	**3.07**	**1.77**

Table 22. Control group for determination of SEP amplitudes (average age 39.5)

M33	1.44	2.98	1.88
	1.9	3.9	1.86
	2.6	3.88	1.7
	1.98	**3.59**	**1.81**
F21	0.54	3.96	2.72
	0.6	3.46	3.88
	0.64	3.68	3.92
	0.59	**3.7**	**3.51**
F50	1.02	1.34	1.2
	1.9	1.18	1.22
	1.56	1.3	1.26
	1.49	**1.29**	**1.23**
M52	0.96	3.4	4.12
	1.06	3.64	4.02
	1.16	3.38	4.2
	1.06	**3.47**	**4.11**
F30	1.12	4.6	4.16
	1.04	4.72	3.12
	1.52	4.44	3.76
	1.23	**4.59**	**3.68**
M32	1.08	4.04	1.52
	1.16	4.16	1.6
	1.08	4.36	1.72
	1.11	**4.19**	**1.61**
M52	3.52	4.44	2.6
	3.12	4.6	2.84
	2.88	4.84	2.96
	3.17	**4.63**	**2.8**

Table 23. Results of C reflex studies

Name	Long latency-interval (msec)	Stimulus (mA)	Amplitudeof Response (mV)	CMAP
B-IV-10	36.7		3-6	
	36.2			
	37.3.			
	37.2			
	36.85			
A-III-4	48.8	3	0.66	0
	48.7	4.2	0.62	0.54
	45.6	6.2	1.11	1.07
	45.4	8	0.28	3.14
	47.5	10.4	0.31	4.93
		12.4	0.49	4.72
	47.7	6.6	0.67	0.16
	45.3	7.4	0.56	0.53
	45.8	9	0.17	1.06
	46.9	10.8	0.86	1.27
	46.6	15.6	0.7	5.1
A-II-6	49.5	12		
	47.2	12		
	47.3	12		
	47.9	12		
A-III-8	37.8		0.03	
	39.2	4.2	2.4	0
	40.6	8.2	1	1.7
	38.9	8.6	1.8	3
	40.7	8.8	1.1	3.8
		11	.	7
	39.1	5.8	3.1	0
	38.6	7	3.6	0.3
	45.2	8.2	1.2	3
	39.7	8.6	1.7	5.5
	42.1	10.6	0.2	7.3
B-IV-6	40	4		
	39.1	4	5	Nil
	40.7	3	3	
	40	26	4.45	
	39.95			
	39	10		
	41.5	4.9		
	41	4.9		
	40.5			

Name	Long latency-interval (msec)	Stim (mA)	Amplitudeof Response (mV)	CMAP
B-IV-23	39.0 – 41.2			
B-IV-25	37.6 – 46.6			
		2.6	0.04	
		3	1.1	
		6.4	0.45	
		7.5	0.25	
		8.5	0.98	
		10	0.2	
		13.4	0.3	
B-IV-26	43.6 - 46.3			

APPENDIX 3: STATISTICAL ANALYSIS OF MAGNETIC STIMULATION RESULTS

Using Statgraphics (Manugistics, Inc), a Repeated Measures ANOVA was used to test the effects of high and low stimulus applied to patients and controls. Given the control subjects were both males and females, and the patients tested were only females, the first test was to determine whether or not there was a significant difference between males and females in the controls. Repeated measures ANOVA was run on low and then on high stimulus. On comparison there was not a direct significant difference between males and females in the full model for low stimulus; however, there was a strong effect within duration levels and a Sex x Duration interaction (Table 24). There was a significant difference between males and females at high stimulus, as well as a significant within duration and interaction term (Sex x Duration) (Table 25).

Table 24. (Controls) Summary of Repeated Measures ANOVA for low stimulus at all duration levels. Significant values are denoted by an *, an p-value < 0.05 level was used as the significance level

Test	Sum of Squares	d.f.	Mean Squares	F	p-value
Effect	5818.0	1	5848.025	3.311	0.0702
Error	374278.1	213	1757.174		

Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Sex	1	5818.025	213	1757.17	3.311	0.0702
Duration	6	908.170	1278	88.97	10.207	0.0000*
Sex x Duration	6	273.619	1278	88.97	3.075	0.0054*

Table 25. (Controls) Summary of Repeated Measures ANOVA for high stimulus at all duration levels. Significant values are denoted by an *, an p-value < 0.05 level was used as the significance level. Significant difference between genders at high stimulation.

Test	Sum of Squares	d.f.	Mean Squares	F	p-value
Effect	11284.7	1	11284.65	4.984	0.0265
Error	502634.6	222	2264.12		

Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Sex	1	11284.70	222	2264.12	4.984	0.0265*
Duration	6	3309.25	1332	123.56	10.207	0.0000*
Sex x Duration	6	694.24	1332	123.56	3.075	0.0000*

To further explore the difference between males and females, a series of one-way ANOVAs were run to compare each duration within the high and low stimuli (Table 26). These results showed that at most individual levels in a low stimulus situation, there are no significant differences, however at the high level almost all levels exhibited differences.

Table 26. (Controls) P-values for one-way ANOVA comparisons between males and females at each duration within each stimulus level. All significant p-values have an *.

Duration (mSec)	LOW	HIGH
10	0.5861	0.0037*
20	0.0010*	0.0024*
30	0.0038*	0.0226*
40	0.0378*	0.0048*
50	0.7702	0.0000*
60	0.5021	0.0249*
70	0.0884	0.2260

Examining the results from the control group analysis, it was determined that all of the data (males and females) from this group could be used to determine if there was a significant difference between patients and controls at a low stimulus level. The analysis to determine if the control and patients were significantly different was run using only females from the control group.

A Repeated Measures ANOVA was again used to determine if there was a significant difference between patients and controls. Three runs were completed, one using all the control group data at the low level of stimulus, the same analysis using only female controls at low level, and female only 'control' at the high level of stimulus. All tests determined that there was a highly significant difference between patients and controls(Tables 27 & 28).

Table 27. Repeated Measures ANOVA for low level stimulus between patients and controls, using female only control group data.

Test	Sum of Squares	d.f.	Mean Squares	F	p-value	
Effect	77224.22	1	77224.22	183.598	0.0000*	
Error	43323.46	103	420.62			
Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Group	1	77224.22	103	420.61	183.598	0.0000*
Duration	6	3139.89	618	133.72	23.480	0.0000*
Group x Duration	6	3235.84	618	133.72	24.198	0.0000*

Table 28. Repeated Measures ANOVA for high level stimulus between patients and controls, using female only control group data.

Test	Sum of Squares	d.f.	Mean Squares	F	p-value	
Effect	245402.5	1	245402.5	216.944	0.0000*	
Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Group	1	245402.5	88	1131.17	216.944	0.0000*
Duration	6	1224.5	528	160.47	7.630	0.0000*
Group x Duration	6	799.7	825	160.47	4.983	0.0000*

The number of controls was much greater than the number of patients, even when only comparing female controls. Therefore, all females in the control group that had missing values were omitted from the data, and 3 female controls were chosen to test against the 3 patients. The results supported those given above, in that there was a significant difference between the patients and the control group for both high and low stimulus levels. The results are reported in Tables 29 and 30.

Table 29. Repeated Measures ANOVA for low level stimulus between patients and controls, using 3 randomly chosen females from the control group data.

Test	Sum of Squares	d.f.	Mean Squares	F	p-value
Effect	61438.85	1	61438.85	129.249	0.0000*
Error	21866.25	46	475.35		

Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Group	1	61438.85	46	475.35	129.249	0.0000*
Duration	6	2061.71	276	161.98		0.0000*
Group x Duration	6	2459.70	276	161.98		0.0000*

Table 30. Repeated Measures ANOVA for high level stimulus between patients and controls, using 3 randomly chosen females from the control group data.

Test	Sum of Squares	d.f.	Mean Squares	F	p-value
Effect	206480.6	1	206480.6	188.021	0.0000*
Error	50516.2	46	1098.2		

Effect	d.f. effect	MS effect	d.f. error	MS error	F	p-value
Group	1	206480.6	46	1098.2	188.021	0.0000*
Duration	6	832.0	276	169.7		0.0000*
Group x Duration	6	321.6	276	169.7		0.0818

APPENDIX 4: MAGNETIC STIMULATION

Patient A-III-10 (Maximum CMAP 13.2 mV)

Level of magnetic stimulation								
				Latencies				
40	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.6		4.7	10.1	4.4	1.35	0.6	0.6
	2.6		4.7	10.3	5	0.6	0.4	1.2
	6		7	10.1	6.4	0.4	0.2	1.8
	4.5		6.9	10.2	3.2	0.4	0.6	3
	4		5.5	6.5	5.9	1	0.4	0.4
	5		6.7	10.4	4.1	3	1.2	0.4
	5		5.2	9.9	2.5	0.7	2.4	0.5
	4.9		10	9.9	4.1	0.3	1	0.5
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	12.6		11	15.6	14.1	8.3	12.4	15.1
	13.9		11	11.9	14.5	10.2	14.8	10
	13.2		12	12.3	14.3	14.3	12.5	10.3
	11.9		10	16.2	17.3	14.1	12.7	9.6
	11.3		10	14.5	12.3	13.2	14.7	9.9
	11.3		10	15	13.7	10.1	16.1	12
	11.3		10	12.6	14.5	9.4	13	17.7
	12.9		10.5	17.7	14.9	11.2	12.7	9.6

Patient B-IV-3 (Maximum CMAP 10.8 mV)

Level of magnetic stimulation								
				Latencies				
48	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	6.4		3.4	3.7	5.3	5	3.2	5.4
	6.4		4.8	5.6	5.9	1.7	6.8	3.7
	4.4		4.6	5.7	5.5	3.5	5.6	5.9
	3.8		7	5.9	6.1	4.6	7.7	2.6
	4.4		6.7	5.3	6.5	7.5	4.2	2.7
	6.2		6.2	7.6	3	5.5	6.5	5.9
	5.1		4.7	6	7.7	6.1	5	3
	7.3		6.9	7.9	4.8	6.4	6.9	5.4
75	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	8.2		8.9	9.3	5.9	8.4	8.1	1.5
	6.8		7.9	8.8	8.1	7.6	10	0.4
	8.6		8.7	8.7	7	7.1	8.6	1.9
	9		9.5	8.2	8.5	8.4	9	6.2
	9.4		9	8.8	9.3	9.2	9.7	8.3
	9.2		10.2	7.1	8.5	9.5	10	10.2
	10.4		9.7	9.2	5.6	8.7	10	7
	8.4		9.1	8.7	7.8	7.2	10	8.5

Patient B-IV-6 (Maximum CMAP 10 mV)

Level of magnetic stimulation				**Latencies**				
48	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.2		6.4	6.6	6.1	4.7	4.5	2
	3		4.9	6.1	7.1	3.8	6.7	6.2
	2.8		7	4.8	7.7	2.3	5.5	3.8
	1.5		6.6	5.8	7.2	2.2	5.1	3.7
	3.6		8.7	6.6	6.1	4.1	6.3	4.4
	1.3		6	5.4	3	3.2	4.2	5.6
	4.3		5.6	6.7	3.6	5.5	3.6	3.3
	1.4		7.2	6.9	4.6	2.8	5.7	3
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	8.6		5.6	5.7	5	4.6	4.6	5.1
	6.1		5.7	4.7	5.9	5.7	6.1	4.9
	5.8		6.9	3.8	4.7	7.1	5.9	5.7
	5.2		5.4	8.3	5.7	7	6.1	5.6
	6.1		6.2	6.6	5.3	6.3	5.5	5.9
	6.6		8	5.5	6	5.4	6.1	5.8
	7.3		7.1	5.5	6.2	5.3	4.6	5
	7.1		7.3	5.1	5.9	4.7	4.3	5.6

Control 1 (Maximum CMAP 16.7 mV)

Level of magnetic stimulation	**Latencies**							
70	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	6	0.71	4.1	2.8	4.7	1.9	4	6.6
	4.7	1.37	3.9	2.9	2.8	2.8	4.7	1.9
	2.1	0.63	1.7	1.5	3	2.8	2.9	0.8
	3.7	2.37	3.9	3.2	5.7	3.7	1.8	1.9
	5.5	2.47	2.8	3.6	4.1	2.4	3.6	3.8
	4.2	2.5	1.5	2.5	3.1	2.1	1.1	1.1
	1.2		2.6	2.7	2	6.1	2.1	4.3
	5.4		3.8	6.5	6.2	5.1	2	2.2
95	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	8.2		7.8	6.8	2.9	4.5	3.1	5
	7.6		7.6	8.3	4.2	4.2	3.3	3.8
	7.2		6.7	7.9	5.4	1.8	1.9	5.6
	5.7		5	6.8	5.2	4.9	5	4.4
	6.7		6.1	7.2	4.1	4.3	3.2	4.2
	5.5		7.7	6.8	6.2	3.8	5.8	5
	3.2		6.1	9.5	4.2	4.1	5	5.6
	3.5		6.6	7	6.7	6	6.1	5.2

Patient Control 2 (Maximum CMAP 14.5 mV) (excluded from analysis)

Level of magnetic stimulation	**Latencies**							
100	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.64		0.3	0.26	0.2	0.28	0.4	0.25
	0.73		0.26	0.36	0.23	0.41	0.14	0.76
	1.14		0.17	0.21	0.17	0.16	0.1	0.21
	0.68		0.45	0.31	0.18	0.15	0.04	0.18
	1.21		0.81	0.47	0.21	0.37	0.09	0.34
	1.06		0.5	0.41	0.18	0.12	0.06	0.17
	0.93		1.08	0.72	0.11	0.14	0.04	0.27
	1.56		0.5	0.52	0.23	0.07	0.1	0.23

Control 3 (Maximum CMAP 18.3 mV) (excluded from analysis)

Level of magnetic stimulation	**Latencies**							
95	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	2		0.5	1	0.4	2.82	3.9	
	1.1		1.2	1.45	1.55	3.46	2.6	
	1.4		0.3	0.5	0.65	0.7	4.5	
	2.1		0.3	0.89	1.72	2.3	4.2	
	2.7		0.9	0.4	0.6	2.3	4.7	
	1.8		0.4	0.62	0.95	1.5	3.8	
	1.1		1.4	0.29	1.11	3.4	3.5	
	1.6		0.8	1.39	1.45	3	5.9	

Control 4 (Maximum CMAP 12.0 mV)

Level of magnetic stimulation	**Latencies**							
55	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.14		0.26	0.02	0.2	0.36	0.33	
	0.03		0.03	0.09	0.6	0.36	0.28	
	0.02		0.22	0.36	0.38	0.36	0.63	
	0.1		0.04	0.23	0.43	0.19	0.92	
	0.13		0.06	0.1	0.26	0.38	0.26	
	0.11		0.05	0.34	0.46	0.55	0.24	
	0.04		0.07	0.24	0.32	0.29	0.42	
	0.22		0.03	0.02	0.35	0.28	0.91	
75	**10**		**20**	**30**	**40**	**50**	**60**	**70**
	0.66		1.11	1.18	2.49	2.3	1.5	
	0.94		1.08	1.32	1.75	2.82	2.6	
	0.82		1.95	1.9	2.21	1.85	3.11	
	1.18		1.37	2.17	2.11	2.49	3.5	
	0.22		1.1	1.92	0.96	1.66	1.22	
	0.65		0.96	2.17	2.17	1.85	4.06	
	0.73		0.98	0.96	2.18	2.07	3.2	
	2.51		1.78	1.99	2.8	1.46	2.7	

Patient Control 5 (Maximum CMAP 8.9 mV)

Level of magnetic stimulation					**Latencies**			
70	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.34		0.06	2.46	2.4	1	3.03	1.8
	0.49		0.3	1.63	4.6	0.6	1.9	1.5
	0.2		0.31	3.25	2	1.36	1.6	1.8
	0.56		0.37	1.6	2.3	1.13	1.6	1.1
	0.29		0.46	1	1.8	1.05	2	1.6
	0.3		0.07	2.2	1.5	1.5	1.8	1.5
	0.4		0.34	0.6	1.3	0.84	2.2	1.7
	0.24		0.24	0.8	1.6	0.66	1.9	2.9
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.4		3.1	2.01	2.58	1.11	1.37	1.63
	4.5		1.3	2.06	1.52	0.71	1.61	1.18
	4.8		1.8	1.9	2.18	0.83	3	2.06
	4.7		1.1	2.31	1.7	0.59	1.67	1.61
	4.9		1.5	1.88	2.36	1.01	1.74	1.74
	5.2		1.1	1.81	1.63	1.68	1.86	1.54
	4.9		1.9	1.67	2	0.73	1.66	2.54
	4.8		1.6	2.67	1.59	0.77	2.49	1.84

Control 6 (Maximum CMAP 9 mV)

Level of magnetic stimulation					**Latencies**			
60	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.14	0.24	0.19	0.43	2.25	1.48	1.36	
	0.93	0.53	0.16	0.2	0.22	1.23	0.25	
	0.24	0.37	0.54	0.31	1.13	0.9	0.74	
	0.79	0.38	0.64	0.13	1.26	0.41	0.32	
	0.21	0.54	0.13	0.2	0.73	0.37	1.21	
	0.47	0.51	0.2	0.38	1.18	0.55	0.24	
	0.17	0.54	0.19	1.01	0.57	0.48	0.35	
	0.31	0.16	0.25	0.21	0.32	0.45	0.59	
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	5.4	2.2	4.9	3.2	3.4	2.5	4.9	6
	4.5	3.8	4.3	5	5.1	5.8	6.6	3.4
	4.7	4	3.8	5	5.9	5.2	4.5	3.5
	4.9	5.1	3.8	6.2	5	5.7	5.9	2.9
	3.7	2.3	2.4	6.2	6.3	3.5	4.2	4.4
	5.4	3	2.2	6.6	6.3	6.4	4.5	4.3
	5.8	3.5	2.8	6.3	7.3	6.3	5.7	2
	5	4.7	1.1	3.3	6.3	4.3	5.3	5.5

Control 7 (Maximum CMAP 17.5 mV)

Level of magnetic stimulation								
				Latencies				
60	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	7		3	4.7	5.8	4.6	6	4
	1.9		3.1	2.4	6.5	4.9	4.4	3.9
	3.4		2.2	3.5	5.7	5.1	3.9	3
	5.1		4	3.7	5.2	4.1	2.9	3.3
	4.8		4.5	2.7	4.4	5.3	5.1	5.3
	3.2		3.1	3.5	5.6	4.4	5.7	3.9
	2.2		3.5	3	5.9	3.5	3.4	
	4.7		3.2	5.3	4	1.3	3.4	3.4
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	6.5		3.4	5.9	7.4	6		4
	6.5		5.3	5.3	5.2	3.8		4.8
	5.1		4.2	6	4.5	4.3		3
	7		4.7	4.9	4.9	5.5		4
	7.2		4.7	6.8	3.9	4.7		5.1
	6.7		5.4	5.3	4.9	5		4.1
	6.5		4.6	4.7	5.9	3.8		4.3
	5.1		5.6	6.4	5.2	5		4.9

Control 8 (Maximum CMAP 8.5 mV)

Level of magnetic stimulation								
				Latencies				
63	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.3		3.2	2.7	0.8	1.5	1.4	3.1
	3.2		2.3	1.6	1.03	0.18	4	1
	4.3		2	1.4	2.23	2.6	2.5	0.4
	3.3		1.7	3.4	1.7	0.8	1.1	0.46
	4.1		3.5	2.7	2.16	0.12	3.3	2.34
	3.7		2.6	2.3	2.49	2.4	3.4	1.03
	4.6		2.2	3.4	0.7	0.9	5.7	1.82
	3.7		1.2	3	1	1.6	2	2.34
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.5		0.83	0.7	1.5	3.1	3.5	0.6
	5.4		0.8	4.5	2.9	3.8	3.4	4.8
	5.4		4.6	2.1	1.7	3.3	4.8	3.4
	3.9		4.3	3.4	2.8	3.8	1.8	2.9
	5.5		4.2	1.2	3.6	3.8	3.3	0.71
	5.1		2.6	4.1	4.4	3.6	3.2	3.2
	5.5		3.2	0.9	6.3	1.5	0.7	2.9
	5.8		5.2	4.9	3.4	3.9	0.8	1.5

Control 9 (Maximum CMAP 9.2 mV)

Level of magnetic stimulation	**Latencies**							
65	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	7.8	6.6	5.4	7.4	7.9	6.6	6.2	7.2
	6.8	7.1	4.9	7.5	8	7.1	6.7	6.8
	5.5	5.6	5.4	5.5	7.5	7.1	6.9	7
	6.1	6.1	7.4	5.9	7.8	6.8	6.2	7.5
	5.1	5.2	3.7	5	7.6	6.5	7.1	6.3
	6.8	4.8	5.6	5.9	7.1	6.9	6.9	6.9
	6.1	6.7	4.6	7.3	6.6	6.7	6.6	6.2
	7.2		6.2	6.2	7	6.4	7	44
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.6	5.4	7.9	5.9	6.7	6.9	6.7	6.8
	5.2	6.5	6.9	6.7	5.1	7	7.4	5.9
	5.8	6.5	6.4	7.8	6.9	6	7.7	7.6
	5.4	6.1	6.2	7.7	6.5	5.4	7.2	8.7
	5.7	7.5	7.8	7.4	6.2	6.6	7	7.9
	5.6	6.9	6.7	7.6	6.6	6.1	7	8.1
	5.7	6	8.3	8	6.3	6.6	7.2	7.9
	5.4	6.6	7.9	6	6.4	7	7.2	8.2

Control 10 (Maximum CMAP 12.4 mV)

Level of magnetic stimulation	**Latencies**							
78	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	1.6		1	2.4	2.4	1	1.1	2.2
	1.3		3.3	2.8	1.2	1	1.1	1.6
	3.8		3.6	2.7	2.96	1.4	1	1.5
	2.2		2	1	1.42	3.2	1	0.4
	3.5		3.2	2.8	3	0.9	3.7	3.7
	1.4		4	1.5	1.7	1.1	1.4	0.4
	3.4		3	3.5	3.88	1.9	2.1	1.4
	3.3		2	5.1	1.45	2	1.6	2.3
90	**10**		**20**	**30**	**40**	**50**	**60**	**70**
	8.4		4.4	2	2.3			2.4
	7.2		4.5	4	1.7			1.7
	1.8		2.1	6.5	1.4			0.9
	3.3		4.1	1.3	2.2			2.8
	5.1		3.1	4.3	1.7			3.3
	6.1		2.1	3.8	1.1			4.6
	3		3.2	2.4	1			3.5
	3.4		4.4	3.1	1.3			0.9

Control 11 (Maximum CMAP 16.7 mV)

Level of magnetic stimulation	**Latencies**							
65	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.96		1.88	1.64	4.81	6.4	1.1	1.89
	2.53		2.38	1.92	6.1	5.4	3.3	1.84
	1.4		2.41	2.39	8.3	7.9	3.9	1.58
	1.4		0.25	1.58	3.7	5.7	0.7	1.16
	0.9		1.44	1.61	7.3	7.4	0.4	1.61
	1.2		1.06	1.89	6.5	3	1	1.29
	1.1		0.45	2.93	7.4	2.7	1.41	3.92
	2.4		0	2.66	4.2	4.6	3.01	2.05
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.1		2.6	3	6.1	2.6	3.7	1
	5.7		4.8	1.4	3.5	2.9	2.2	3.9
	4.1		3.4	1.5	3.3	1.58	2.2	2.06
	4.6		2	1.8	4.5	4.1	2.4	4.27
	4.9		1.6	6.7	4.4	2.3	3.2	3.09
	4.7		2.1	1.7	2.7	1.6	2.6	1.76
	3		2.4	4	5.6	2.1	1.8	1.89
	5.1		1.5	2.3	5.3	2.9	2.2	2.48

Control 12 (Maximum CMAP 11.4 mV)

Level of magnetic stimulation	**Latencies**							
50	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.35		0.18	0.18	0.06	0.15	0.23	0.8
	0.17		0.16	0.35	0.48	0.1	0.44	0.33
	0.32		0.31	0.15	0.26	0.11	0.61	0.67
	0.24		0.11	0.13	0.2	0.17	0.22	0.17
	0.13		0.47	0.09	0.24	0.46	0.92	0.3
	0.35		0.08	0.17	0.3	0.46	0.18	0.28
	0.08		0.65	0.17	0.12	0.16	1.18	0.19
	0.18		0.07	0.22	0.05	0.45	0.84	2.37
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	1.8		0.6	1.58	0.59	0.51	2.27	1.77
	2.1		1.2	2.01	1.28	2.92	1.73	0.42
	3.2		1.36	2.95	1	1.69	0.24	0.21
	2.1		1.13	1.17	1	2.4	2.68	1.39
	2.1		1.58	1.87	2.19	1.42	0.21	1.94
	1.9		1.14	1.88	1.25	1.5	2.31	1.72
	2.8		2.08	1.38	0.73	0.82	1.54	1.33
	1.9		2.75	1.4	1.15	1.51	3.13	1.16

Control 13 (Maximum CMAP 9.4 mV)

Level of magnetic stimulation	**Latencies**							
55	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.27		0.13	0.6	1.95	2.34	2.07	0.6
	2.47		0.7	0.37	1.73	0.16	0.7	1.44
	0.37		0.14	1.75	0.6	0.25	1.51	0.18
	1.14		0.28	1.39	2.44	0.28	0.67	0.37
	1.73		0.2	0.24	1.58	1.03	0.79	0.32
	0.15		0.16	0.27	0.63	3	1.7	1.55
	0.78		0.46	1.61	1.11	1.2	0.56	0.18
	0.96		0.13	2.44	0.22	0.71	0.85	1.91
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.72		0.7	4	5	2.9	4.5	3.9
	1.5		1	2.2	3.9	4.4	1.4	1.9
	2.3		0.4	2.3	3.6	2.2	1.7	2.5
	3.1		0.9	2.9	4	3	4.8	2.6
	2.2		0.7	2.3	4.4	4	2.3	4.7
	1.5		1.2	2.1	2.6	4.7	4.6	2.1
	2.1		0.5	3.5	3.9	3.5	4.5	4.3
	1.7		0.2	4.6	3.8	3.2	4.7	4

Control 14 (Maximum CMAP 7.8 mV)

Level of magnetic stimulation	**Latencies**							
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.4		1.37	3.4	0.71	0.92	0.84	0.52
	0.69		0.41	3.19	0.48	1.03	0.35	1.03
	4.15		0.14	0.36	0.63	0.19	0.3	0.52
	0.33		1.26	1.84	0.91	0.2	2.3	0.97
	0.67		0.47	0.28	1.84	0.31	1.29	0.88
	0.17		1.37	0.18	0.62	0.2	0.17	0.15
	0.01		1.32	1.01	0.56	0.23	0.97	0.71
	2.48		0.23	0.81	3.17	0.87	0.39	0.77
95	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.35		0.43	0.49				
	1.47		0.77	0.6				
	1.7		0.57	1.07				
	3.71		2.45	0.67				
	1.66		2.05	0.46				
	1.1		0.91	0.64				
	0.68		0.52	1.06				
	2		2.89	0.2				

Control 15 (Maximum CMAP 11.3 mV)

Level of magnetic stimulation	**Latencies**							
60	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.2		0.43	0.66	1.48	0.74	1.29	2.14
	0.3		0.35	0.36	1.36	0.51	2.04	2.59
	0.95		0.45	0.32	0.31	0.42	1.23	1.29
	0.47		0.43	0.15	0.44	0.8	0.74	0.54
	0.97		0.23	0.31	0.17	0.71	1.07	1.31
	0.26		0.66	0.63	0.45	0.43	0.4	1.5
	0.41		0.29	0.57	0.48	0.67	0.6	2
	0.4		0.29	0.35	0.33	0.48	0.2	1.2
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	2.8		2	1.75	2.7	3.65	4.41	5.4
	3.2		0.8	1.09	2.44	1.49	3.8	5.3
	3.2		1.3	4.28	1.43	1.26	4.1	5.1
	2.5		2.2	1.06	2.2	2.21	4.3	4.2
	4.2		1.84	1.63	3.12	1.83	5.4	6.1
	5.2		2.99	1.14	1.6	2.36	2.4	4.3
	3.8		1.11	2.75	2.67	2.72	5.3	5.2
	3.5		1.86	2.2	1.71	2.95	6.2	6.4

Control 16 (Maximum CMAP 14.3 mV)

Level of magnetic stimulation	**Latencies**							
70	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.46		0.91	1.02	0.08	0.05	0.49	0.16
	0.46		0.27	0.55	1.14	0.08	0.34	0.65
	1.75		0.72	0.18	0.11	0.68	0.24	0.17
	0.87		0.12	0.49	0.13	0.19	0.23	0.22
	0.7		0.55	0.85	0.69	0.57	0.24	0.26
	1.69		0.1	0.1	0.5	0.88	0.5	0.5
	0.49		0.14	0.44	0.28	0.18	0.17	0.89
	0.26		0.02	0.79	0.18	0.34	0.73	0.18
95	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	1.2		0.94	0.39	0.57	0.51	0.31	1.3
	2.2		1.34	0.48	0.15	0.18	0.29	1.33
	2.82		0.73	0.53	0.52	0.19	0.56	0.19
	1.95		0.83	4.31	0.53	0.42	0.47	1.2
	1.68		0.67	0.5	0.44	0.45	0.2	0.26
	0.91		1.06	1.15	0.69	0.5	0.31	1.95
	2.18		2.24	0.64	0.63	0.64	0.59	1.01
	2.36		0.93	0.97	0.52	0.59	0.24	0.29

Control 17 (Maximum CMAP 12.4 mV)

Level of magnetic stimulation					**Latencies**			
70	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	8		6.1	10	7.1	3.2	6.2	4.8
	9.6		5.3	3	2.6	1.5	3.2	9.6
	11.1		4.3	8	7.5	5.9	5.4	8.4
	9.9		5.1	9.4	5.4	6.6	5.2	6.3
	8.7		4.1	9.5	4.2	6	9.1	5.7
	8		2	9.4	6	8.5	5	5.8
	6.7		4.7	9	5.2	7.5	6.4	8.5
	6.6		1.9	7.8	5.9	4.6	2.7	9.1
90	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	10		20	30	40	50	60	70
	9		7.6	5.8	8.4	8.2	6.7	6.9
	8.4		7.7	7.3	7.6	8	9.5	7.8
	10.4		5.6	6.9	6.1	4.5	7.5	8.6
	9.7		7.6	8.2	7.6	6.4	4.3	6.8
	8.6		10.1	6.1	8.1	6.7	6.7	5.9
	10.1		7.7	7	8.3	6.5	9.3	5.5
	9.3		6.6	7.8	7.6	5.8	7.9	7.5
	9.6		6.2	5.4	9	6.3	8.8	5.7

Control 18 (Maximum CMAP 10.0 mV)

Level of magnetic stimulation					**Latencies**			
66	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.29		0.36	2.09	0.68	0.2	0.27	0.04
	2.28		1	1	0.64	0.96	0.45	0.04
	0.48		1.17	0.46	1.63	0.13	0.29	0.55
	0.83		0.86	0.69	2.8	0.44	0.11	0.18
	0.98		0.95	1.03	0.87	0.15	0.1	0.79
	2.34		3.18	0.51	1.35	0.07	0.11	0.11
	0.38		0.72	0.74	2.67	1.25	0.92	0.04
	0.45		0.76	1.36	0.28	0.47	0.28	0.16
90	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	2.4		1.3	2.95	0.11	0.25	0.47	0.17
	4.6		3.5	1.37	0.52	0.69	0.24	0.37
	1.2		0.5	1.47	0.27	0.69	0.68	0.37
	1.7		1.9	1.21	0.24	0.27	0.36	0.14
	4.3		1.8	0.48	0.61	0.08	0.58	0.16
	1.4		1.2	0.15	0.29	0.26	0.34	0.28
	2.5		0.8	0.2	0.6	0.67	0.46	0.84
	4.2		1.2	0.11	0.01	0.04	0.14	0.58

Control 19 (Maximum CMAP 8.3 mV) (excluded from analysis)

Level of magnetic stimulation	**Latencies**							
0	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
91	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.28		0.33	1.53	0.85	0.13	0.53	0.62
	0.37		0.58	1.87	0.96	1.22	0.62	1.79
	0.25		0.73	0.48	1.21	0.36	1.43	0.41
	0.46		0.56	1.45	0.5	1.02	0.12	0.37
	0.74		0.98	2.29	1.97	1.49	0.71	0.47
	0.24		0.17	2.17	2.19	0.39	2.01	0.54
	0.19		2.41	1.46	0.95	0.18	0.07	0.23
	0.13		1.23	0.62	0.48	0.11	0.7	0.19

Control 20 (Maximum CMAP 6.9 mV)

Level of magnetic stimulation	**Latencies**							
	10	**15**	**20**	**30**	**40**	**50**	**60**	**70**
45	3.8		3.4	1.8	3	4	2.8	2.9
	2.2		2.6	1.5	3	1.5	3.1	2.3
	2.5		3.2	2	2.8	3.6	2.3	2.9
	3		1.2	1.6	2.4	2.7	2.6	2.6
	4.2		3	1.5	3.7	1.7	3.8	3.3
	1.9		2.8	2.4	2.4	1.9	3.5	3
	2.3		3.4	1.7	3	2.1	2.7	2.2
	3.1		2.5	1.9	2.3	1.9	2.9	2.9
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.7		4	3.3	3.9	3.6	3.6	4.1
	4.2		2.4	2.8	3.5	4	4.7	4.6
	5.2		3.6	3.4	2.3	4.9	3.9	3.6
	3.9		4.1	4.5	4.7	5.1	4.4	2.7
	5.2		3.1	2.3	3	4.2	4.2	3.2
	4.7		3.7	2.9	2.3	3.7	4.9	3.8
	5.1		4.5	3.3	2.2	3.8	4.2	3.5
	3.6		3.5	3.3	5	4.6	4.6	3.3

Control 21 (Maximum CMAP 11.3 mV)

Level of magnetic stimulation	**Latencies**							
78	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.1		2.5	2.6	2.7	2.7	2.9	1.1
	3.4		2.4	4.5	2.2	4.5	3.4	2.1
	4.4		2.4	3.3	3.6	3.8	4.2	1.3
	3		2.4	3.3	5.6	5	1.7	0.3
	3.4		1.9	2.4	3.6	3.7	4.8	1
	3.6		1.8	4.5	4.5	3.3	3.8	1.3
	3		1.4	5.9	3.5	4	3.4	2
	4.8		2.9	4.7	1.4	2.7	2.9	1.6
95	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	5.3		1.4	2.5	1.1	1.2	3.2	0.6
	2		2	0.7	1.2	2.3	0.8	1.9
	3.1		1.4	0.5	0.8	0.6	1.3	0.8
	4.7		2.6	2.9	2.3	1.8	0.9	0.7
	2.2		1.6	2.4	3.2	2.5	1.1	0.9
	2.4		3.2	1.7	1.1	0.5	0.9	0.4
	3.2		2.1	2.8	1.6	2.5	0.9	0.5
	2.9		2.6	1.2	4	0.3	1.3	1.8

Control 22 (Maximum CMAP 9.8 mV)

Level of magnetic stimulation	**Latencies**							
60								
	10	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.5		3.3	4.1	4.7	5.5	6.5	3.7
	5		3.5	3.5	5.1	4.8	3.9	4.4
	3.7		3.4	3.4	4.2	4	4.2	3.6
	3.8		1.9	3.2	3.7	3.8	4.8	3.5
	2.5		3.4	2.2	5	5.1	3.7	3
	3.3		2.9	1.8	3.8	5	6.2	3.7
	3.5		2.3	3.4	4.6	3.8	5	4
	2.9		2.2	4.8	3.6	3.7	6.4	3.9
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	6.9		4.1	4.9	4.4	5.3	4.6	5
	4.7		4.7	5	5.5	5.5	4.8	4.9
	5.4		5.1	6.3	5.3	5.1	4.7	5.5
	5.2		4.2	5.5	5.9	5.5	4.2	5.7
	4.8		4.6	4.6	5	4.8	4.3	4.6
	5.4		5.4	5.2	4	5	5.2	4.7
	5.4		5.3	4.9	5	5.1	5.7	3.8
	5.6		4.1	4.7	4.9	5	3.9	5.5

Control 23 (Maximum CMAP 14.6 mV)

Level of magnetic stimulation	**Latencies**							
55	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	3.5		3.2	2.9	5.5	4.7	3.5	4.5
	4.8		3.1	3	4.6	4.6	3.9	4.5
	5.4		3.2	3.2	5.9	3.2	2.9	4.6
	5.6		2.5	2.4	4.6	4.6	4.2	2.9
	5		2.6	2	3.4	4.7	4.9	4.9
	4.7		2.4	4.1	4.7	3.7	5.1	2.4
	5.4		2.4	4.2	5.6	4.6	4.1	4.6
	6.2			5.6	4.4	4	5.1	4.1
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	5.4		6.2	5.6	4.1	5	6	4.4
	5.5		3	4.8	4.3	5.8	4.7	5.2
	4.9		3.2	4.5	4.7	6.3	5.1	5
	4.2		2.5	4.9	4.9	5	5.8	5.5
	5.3		2.6	3.1	4.2	6.2	5	5.3
	5.7		2.4	5.5	3.9	4.2	5	4.7
	5.9		2.4	3.8	3.7	3	5.7	5.7
	6.1		2.9	3.6	3.3	3	6.2	5.7

Control 24 (Maximum CMAP 14.2 mV)

Level of magnetic stimulation	**Latencies**							
52								
	10	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	1.7		1.3	1.5	2.3	3.3	2.6	1.9
	2.3		2.3	2.6	3.1	3	3.3	2.6
	2.4		2.5	1.4	2.8	3.2	2.3	1.1
	2.2		2.4	1.9	2.6	3.9	2.1	2.2
	4		1.2	1.9	2.6	3.6	2.8	1.4
	2.8		2.4	1.7	2.6	4.1	1.5	1.8
	2.5		1.6	2.2	2.8	3.2	1.2	1.2
	4.7		1.5	3.3	3.1	2.2	2.4	1.3
82	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	2.5		1.4	2.2	1.5	3.4	2.3	2.1
	1.9		1.3	1.9	2.3	2.6	2	3.9
	2.7		2.9	1.8	2.3	2.2	2.7	4.5
	1.9		1.7	2.5	2.2	1.9	4.3	3.9
	2.1		2.4	3.3	2.1	1.7	3.2	4.5
	4.1		2	2.8	3.1	2.8	3.5	4.4
	3.5		2.7	2.3	1.7	2.7	3.3	4.3
	4.5		3.3	4.3	2.9	2.9	2.7	2

Control 25 (Maximum CMAP 13.3 mV)

Level of magnetic stimulation	**Latencies**							
65	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	7.2		4.7	4.3	3.9	6	7.3	5.5
	5.5		4.9	2.9	3.7	6.9	5.9	4.8
	7.1		3.9	2.8	4.5	7.4	6.5	4.7
	3.7		5.2	3.5	4.4	6.1	6.2	5.3
	6.5		4.8	2.9	4.9	8.1	5.9	4.6
	3.8		2.9	2.8	4.4	6.4	6.4	6
	6.3		5.2	3.6	4	6.7	5.9	5
	5.6		4.6	2.7	4.3	7.1	5.7	6.3
80	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	7.4		8.7	4.7	7.6	8.5	10.8	8.5
	8.4		6.3	7.2	6.4	8.9	10.9	7.6
	9.1		7.3	6.8	7.7	9	10.9	9.1
	8.6		7.2	7.2	7.9	9.3	11.4	8.5
	9.2		7.9	7.6	10.1	7.9	10.7	8.4
	10.3		8.1	9.5	8.2	8.4	12	8.4
	8.2		8	8.5	8	8.2	10.3	8.7
	9.3		6.9	7.3	7.6	9.1	9.9	8.5

Control 26 (Maximum CMAP 9.7 mV)

Level of magnetic stimulation	**Latencies**							
49	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.2		3.1	0.7	2.8	3.3	0.9	1.3
	2.1		2.3	1.1	2.7	3.1	1.3	2.4
	2.7		2.2	1.7	2.7	4.6	1	4.7
	3.9		1.6	1.3	1.9	3.8	3.3	4.1
	3.6		1.8	0.7	1.9	1.6	1.2	1.7
	2		1.7	1.5	3.3	3.1	1.4	1.4
	3.3		1.6	0.7	1.6	2.9	1.4	3.5
	1.9		0.9	1.1	3	3	1.8	3.2
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	7.6		3.8	5	4.5	4.2	4	5.7
	10.4		4.3	3.5	5.4	3.9	7.9	4.2
	7.2		5.3	2.9	5.7	5.7	3.8	5.1
	7.1		6.6	5.2	3.3	5.3	5.8	4.3
	7.3		3.2	4	5.9	5.8	4.4	3.7
	6.7		3.7	7	4	4.2	4.1	6.2
	7.9		3.4	2.9	4.7	4.3	4.4	4
	8.8		3.3	3.6	3.3	4	5	6.6

Control 27 (Maximum CMAP 16.6 mV)

Level of magnetic stimulation					**Latencies**			
57	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.6		4.4	4.8	1.86	3.5	2.6	4.1
	3		2.5	3.4	0.35	3.4	2.6	3
	4.1		1.8	2.8	1.62	2	3.3	2.7
	3.7		1.3	3.2	1.3	1.9	1.6	2.5
	3.7		3.3	2.3	2.23	2.2	2.9	2.1
	3.9		3.3	2.4	0.43	1.6	1.3	1.7
	1.8		2	3.4	0.22	2.2	2.3	1.7
	1.6		2.8	1.2	0.78	2.7	2.5	1.4
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	5.6		3.4	5.1	4.9	2.1	4.7	2.8
	5		1.3	2.5	3	3.1	2.1	2.1
	4.1		2.5	2.8	3.7	2.2	1.7	1.6
	3.8		1.4	3.4	3.5	1.7	2.1	1.7
	3.7		2.3	3.8	4.6	2.1	4.1	2.7
	3.3		1.8	4.4	4.4	2.2	3.7	2.3
	2.3		1.6	4.2	3	3.1	2.6	2.3
	3.2		2.3	2.6	3.4	2.1	2.2	1.3

Control 28 (Maximum CMAP 10.9 mV)

Level of magnetic stimulation					**Latencies**			
55	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	1.79		0.46	1.47	1.34	1.21	0.73	1.71
	1.84		0.7	1.24	0.74	0.3	0.64	2.06
	0.59		0.61	0.58	0.71	0.79	0.81	0.65
	1.36		0.27	2.13	1.04	0.32	0.79	0.51
	0.38		1.37	2.24	1.37	2.27	1.23	1.72
	0.69		0.42	1.02	0.65	1.99	0.74	1.02
	0.67		0.34	2.64	0.53	1.77	0.25	1.16
	0.67		2.19	0.22	1.92	1.34	0.99	1.92
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	4.4	3.6	4.39	2.12	6	1.8	6.7	4.2
	8.5	3.62	2.22	2.41	2	5.2	2.4	2
	4	1.82	2.31	1.8	2.5	3.4	2.8	3.3
	3.4	1.4	1.8	2.7	3.1	3.3	3	1.6
	4	4.1	2.54	1.83	3	3.4	3.1	2.1
	2.5	2.36	1.44	4.71	1.9	6.4	4.3	4.4
	2.9	1.39	1.73	4.4	2.7	5	2	3.1
	3.4	3.14	3.24	2.1	4.4	5	2.2	1.5

Control 29 (Maximum CMAP 11.6 mV)

Level of magnetic stimulation								
					Latencies			
58	**10**		**20**	**30**	**40**	**50**	**60**	**70**
	1.14		0.97	0.92	1.4	0.52	4.26	2.26
	1.02		0.98	1.19	0.98	0.45	2.05	2.06
	0.46		2.77	2.95	3.3	0.5	0.8	2.27
	1.36		2.75	2.16	3.3	2.07	2.96	0.97
	1.01		0.75	4.01	4.9	0.46	4.93	0.46
	0.58		0.79	4.65	2.97	0.92	2.57	2.53
	0.47		1.63	1.17	2.85	2.3	0.98	0.71
	1.56		0.89	4.92	1.83	0.36	4.3	1.96
90	**10**		**20**	**30**	**40**	**50**	**60**	**70**
	4.8		4.3	1.8	3.5	4.7	7.4	5.3
	5.9		4.2	2.9	4.6	4.7	3.9	3.5
	6.1		2.3	3.9	5	5.6	5.7	2.6
	4.7		2.4	3.8	5.3	7.9	4.1	3.1
	3.7		2.8	2.3	4.8	6.1	5.9	3.4
	5.4		3.6	5	5.1	6.4	4.8	2.1
	5.5		3.4	2.1	4.5	7.7	1.8	5.1
	3.5		2.4	3.4	5.8	6.7	5.2	4.5

Control 30 (Maximum CMAP 11.5 mV)

Level of magnetic stimulation								
					Latencies			
72	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	5.6		3.1	4.5	1.2	2	3.2	1.9
	5.3		3.5	3	2.4	1.7	2.3	2.9
	4.8		2	1.6	1.4	4	3.9	2.7
	5.1		1.4	2.4	2.5	2.2	4.4	4.4
	4.5		3	2.2	2.3	3.8	2.3	2.2
	3.9		2.5	4.7	0.3	3.2	2.9	3.2
	4.8		2.6	3.9	2.3	2.4	4.2	6
	3.9		3.2	2.4	3.2	3.6	3.9	3.5
92	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	6.2		3.2	3.9	1.9	2.9	3.8	3.8
	5.4		3.2	3.3	3.8	3.3	5.3	5.3
	5.1		3	4.1	3.6	3.5	3.2	3.2
	4.9		2.9	3.8	3	4	3.1	3.1
	4.7		4.1	5	3.1	5.1	4.1	4.1
	5.4		3.3	3.6	3.4	4.2	4.5	4.5
	5.7		3.5	4.1	3.4	4.4	2.7	2.7
	5.7		4.3	2.4	4	3.3	4.2	4.2

Control 31 (Maximum CMAP 9 mV)

Level of magnetic stimulation	**Latencies**							
60	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	0.14	0.24	0.43	0.66	1.48	0.74	1.29	2.14
	0.93		0.35	0.36	1.36	0.51	2.04	2.59
	0.24		0.45	0.32	0.31	0.42	1.23	1.29
	0.79		0.43	0.15	0.44	0.8	0.74	0.54
	0.21		0.23	0.31	0.17	0.71	1.07	1.31
	0.47		0.66	0.63	0.45	0.43	0.4	1.5
	0.17		0.29	0.57	0.48	0.67	0.6	2
	0.31		0.29	0.35	0.33	0.48	0.2	1.2
85	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**
	2.8		2	1.75	2.7	3.65	4.41	5.4
	3.2		0.8	1.09	2.44	1.49	3.8	5.3
	3.2		1.3	4.28	1.43	1.26	4.1	5.1
	2.5		2.2	1.06	2.2	2.21	4.3	4.2
	4.2		1.84	1.63	3.12	1.83	5.4	6.1
	5.2		2.99	1.14	1.6	2.36	2.4	4.3
	3.8		1.11	2.75	2.67	2.72	5.3	5.2
	3.5		1.86	2.2	1.71	2.95	6.2	6.4

APPENDIX 5: RESULTS OF LINKAGE ANALYSIS

Table 31. Lod scores for Family A of pairwise Lod score for FAME 3 versus EPM1 markers and DRPLA (from Thomas[419])

EPM1 markers											
	Marshfield	Lod score at θ =									
Marker	(cM)	0.00	0.01	0.02	0.03	0.04	0.05	0.10	0.20	0.30	0.40
D21S2040		-14.24	-1.92				-0.65	-0.21	0.06	0.08	0.03
D21S1912	0.5	-12.83	-0.94				-0.29	-0.06	0.09	0.09	0.04
D21S1950	7.8	-6.82	-0.65				-0.05	0.13	0.18	0.12	0.04
DRPLA											
DRPLA CAG Repeat		-14.50	-4.13				-2.15	-1.32	-0.58	-0.23	-0.05

Table 32. Results for Family A of pairwise Lod score for FAME 3 versus 8q markers and 2p markers

Family A Pairwise Lod score for FAME 3 versus chromosome 8q24 markers											
	Marshfield	Lod score at θ =									
Marker	(cM)	0.00	0.01	0.02	0.03	0.04	0.05	0.10	0.20	0.30	0.40
D8S1784		0.70	0.69	0.68	0.67	0.66	0.65	0.58	0.42	0.24	0.07
D8S1830	1.07	0.60	0.59	0.58	0.56	0.55	0.54	0.48	0.33	0.18	0.05
D8S1779	4.32	0.59	0.58	0.58	0.57	0.56	0.55	0.50	0.36	0.20	0.06
D8S547	0.00	0.61	0.60	0.59	0.58	0.57	0.56	0.50	0.35	0.19	0.06
D8S1694	1.73	0.69	0.68	0.67	0.66	0.65	0.64	0.58	0.42	0.24	0.07
D8S342	4.73	0.70	0.69	0.68	0.67	0.66	0.65	0.58	0.42	0.24	0.07
D8S1826	0.00	0.70	0.69	0.68	0.67	0.66	0.65	0.58	0.42	0.24	0.07

: **Family A**: Pairwise Lod score for FAME 3 versus chromosome 2p11.1-q12.2 markers											
	Marshfield	Lod score at θ =									
Marker	(cM)	0.00	0.01	0.02	0.03	0.04	0.05	0.10	0.20	0.30	0.40
D2S139		-2.23	-0.41	-0.14	0.00	0.10	0.17	0.32	0.30	0.17	0.04
D2S2333	1.60	-6.20	-2.34	-1.77	-1.44	-1.22	-1.05	-0.57	-0.21	-0.08	-0.02
D2S2161	1.84	-2.60	-0.53	-0.26	-0.11	-0.01	0.06	0.22	0.23	0.13	0.03
D2S388	2.46	-2.98	-2.17	-1.64	-1.33	-1.11	-0.94	-0.47	-0.14	-0.04	-0.01
D2S2216	3.75	-6.56	-3.06	-2.46	-2.11	-1.86	-1.66	-1.06	-0.49	-0.20	-0.05
D2S2264	3.21	-6.13	-2.23	-1.66	-1.34	-1.11	-0.95	-0.48	-0.15	-0.05	-0.01
D2S135	1.60	-2.41	-2.02	-1.59	-1.30	-1.09	-0.92	-0.45	-0.10	-0.01	0.00
D2S1897	1.60	-6.13	-2.23	-1.66	-1.34	-1.11	-0.95	-0.48	-0.15	-0.05	-0.01

Table 33. Results for Family B of pairwise Lod score for FAME 3 versus 8q markers and 2p markers

Family B Pairwise Lod score for FAME 3 versus chromosome 8q24 markers											
	Marshfield	Lod score at θ =									
Marker	(cM)	0.00	0.01	0.02	0.03	0.04	0.05	0.10	0.20	0.30	0.40
D8S1784		-12.52	-7.26	-6.11	-5.33	-4.74	-4.25	-2.65	-1.09	-0.37	-0.07
D8S1830	1.07	-8.26	-3.60	-2.88	-2.42	-2.08	-1.81	-0.96	-0.26	-0.04	-0.01
D8S1779	4.32	-2.48	-1.06	-0.74	-0.54	-0.40	-0.29	0.02	0.17	0.13	0.04
D8S547	0.00	-11.72	-5.46	-4.43	-3.79	-3.32	-2.94	-1.77	-0.71	-0.28	-0.11
D8S1694	1.73	-11.52	-6.09	-5.04	-4.35	-3.82	-3.41	-2.08	-0.84	-0.29	-0.06
D8S342	4.73	-9.60	-4.42	-3.54	-2.97	-2.54	-2.20	-1.14	-0.30	0.05	0.03
D8S1826	0.00	-3.33	-1.67	-1.28	-1.03	-0.85	-0.71	-0.29	0.00	0.05	0.03
Family B: Pairwise Lod score for FAME 3 versus chromosome 2p11.1-q12.2 markers											
	Marshfield	Lod score at θ =									
Marker	(cM)	0.00	0.01	0.02	0.03	0.04	0.05	0.10	0.20	0.30	0.40
D2S139		-13.25	-2.68	-1.80	-1.30	-0.94	-0.69	0.00	0.32	0.19	0.00
D2S2180	1.06	-9.96	-0.47	0.11	0.44	0.65	0.80	1.14	1.03	0.59	0.14
D2S1387	0.54	-9.32	-1.21	-0.65	-0.34	-0.13	0.02	0.37	0.42	0.23	0.06
D2S2333	0.00	-4.31	-0.63	-0.28	-0.08	0.05	0.15	0.36	0.32	0.16	0.05
D2S2161	1.84	0.45	0.50	0.53	0.56	0.58	0.59	0.59	0.48	0.31	0.14
D2S388	2.46	-9.31	-2.34	-1.51	-1.06	-0.76	-0.54	0.01	0.24	0.17	0.05
D2S2216	3.75	-8.86	-2.01	-1.38	-1.01	-0.74	-0.54	0.02	0.35	0.30	0.12
D2S2264	3.21	-11.92	-2.99	-2.15	-1.67	-1.34	-1.10	-0.43	-0.02	-0.02	-0.09
D2S135	1.60	-4.10	-2.60	-2.20	-1.93	-1.72	-1.54	-0.97	-0.45	-0.22	-0.08
D2S1897	1.60	-5.58	-2.52	-1.81	-1.37	-1.06	-0.82	-0.14	0.22	0.11	-0.10

APPENDIX 6: ETHICAL DILEMMAS

Appropriate ethical consent was obtained for the purposes of this study, both in terms of assessing DNA for purposes of linkage and for the purpose of neurophysiological testing.

However, the fact remains that the majority of patients were ill-educated and many of them were functionally illiterate. This results in enormous difficulties for the investigator attempting to behave in an ethical fashion. The majority of patients who provided blood samples were likely to be relatively ill informed of the precise reason that they were being asked to give samples, since explanations of linkage analysis and understanding the nature of DNA analysis were difficult. It would be an interesting study in itself to return to the participants and ask if they knew why they had given blood samples at the time of the study.

Similarly, although participants were informed that the purpose of this research study was to establish the cause of the genetic illness in their families, as with virtually all other genetic illnesses, the results of such a study would be likely to have no or very little impact on their future behaviour. At the time this study was performed, no gene therapy was available for genetic conditions of this nature. The only likely practical outcome of the genetic analyses would be to establish a genetic marker for identifying disease in future generations. The implications of this would be that in those who were affected, they could elect not to have children at all, or in the event that a pregnancy occurred, genetic testing could be performed, and, if they were so willing, they could elect to undergo abortion. It should be noted that even in conditions with far worse prognoses than FAME 3, such as Huntington's disease, the option of undergoing in utero testing is virtually unheard of in the state sector of the Western Cape.

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