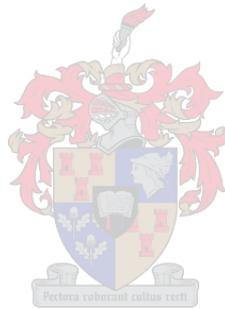


**THE VALUE OF HEAD COMPUTED TOMOGRAPHY (CT) IN
CHILDREN PRESENTING WITH FOCAL SEIZURES TO A
PAEDIATRIC AMBULATORY UNIT IN A RESOURCE
CONSTRAINED SETTING**

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*Thesis presented in fulfilment of the requirements for the
degree of Masters in Medicine (MMed) in the Faculty of
Medicine and Health Sciences at Stellenbosch University*



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March 2016

DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date:

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Date:

Signature:

ACKNOWLEDGEMENTS

First and foremost I would like to acknowledge and express my gratitude to my supervisor and mentor, Dr Liezl Smit. Her invaluable assistance whilst writing this dissertation, through providing me with guidance, words of encouragement when obstacles to data collection were faced and her exceptional support, is deeply appreciated.

I would also like to extend my gratitude to Professor Ronald Van Toorn for his guidance and advice, as well as Tonya Esterhuizen for assisting me with data analysis.

Thank you to Tygerberg Hospital Paediatric Department for allowing me to conduct my study at their institution. I would also like to acknowledge my family for their assistance and patience whilst completing the dissertation.

Finally, I would like to thank the unnamed little paediatric souls who unknowingly contributed to this study for the improvement of quality services and health care at the Tygerberg paediatric ambulatory department.

ABSTRACT

BACKGROUND

Children presenting to the ED with new onset focal seizures are often evaluated using urgent head computed tomography (CT). Although MRI is the preferred neuroimaging modality in children as it avoids the radiation risk of CT, with added superior resolution, MRI is not routinely available in the emergency setting^{1 2 3}. The recommendations for neuroimaging, and specifically CT, in children presenting with new-onset focal seizures is poorly defined and the diagnostic yields tend to vary according to study settings and population.

OBJECTIVE

This study evaluated the utility, diagnostic yield and therapeutic interventions of head CT scans in children admitted with first onset focal seizures to the Paediatric Ambulatory & Emergency Unit at Tygerberg Children's Hospital (TCH); and examined potential historical and clinical variables associated with abnormal head CT findings.

METHODS

A retrospective cohort analysis of 168 previously well children with new-onset focal seizures, admitted to TCH between January 2013 and December 2014, was undertaken. Demographic data, clinical details and head CT findings were abstracted from the radiological and medical hospital records. Data was analysed using Stata. Descriptive statistics was used to analyse demographic data and outcome. Univariate Comparisons and multiple binary logistic regression analysis were done to determine adjusted associations between historical and/or clinical findings and CT scan results.

RESULTS

Clinical significant CT scan abnormalities were identified in 32% (n=54/168) of children and head CT findings were of therapeutic significance in 81% (n=44/54) of children. The majority of CT abnormalities were related to infectious granulomas (n=21/54); followed by TB meningitis (n=12/54) and cerebral venous thrombosis (n=4/54). An abnormal neurological clinical examination as indicator for abnormal CT scan was statistically significant ($p < 0.001$). Three quarters of patients (n=26/35) with an abnormal neurological examination, had an abnormal CT scan result.

Age, HIV-status, malnutrition, duration of seizures, exposure to a household TB contact and travel history was not shown to be statistically predictive of abnormal CT

results, but the sample size was too small for multivariate logistic regression analysis to determine adjusted associations.

CONCLUSION

We recommend strongly the use of urgent CT imaging in all children with neurological abnormalities. Our findings further suggest that imaging is valuable for therapeutic decisions in children suspected of neuro-infections (other than neurocysticercosis), vascular abnormalities, and space occupying lesions based on history and physical examination. Suspected structural abnormalities in infants younger than 2 years of age are best evaluated with a MRI in the non-urgent setting.

Our findings further suggest that in a TB endemic setting, an initial CXR and tuberculin test may identify children requiring a TB work-up to diagnose tuberculous neuro-infection without the need for a CT scan.

AGTERGROND

Kinders wat by 'n noodeenheid presenteer met eerste aankoms fokale konvulsies word dikwels evalueer met behulp van 'n nood brein skandering. Alhoewel magnetiese resonansie die gekose ondersoek is in kinders as gevolg van die vermyding van die bestralingsrisiko van brein skanderings en beter resoluksie, is MRI nie roetinegeweg beskikbaar in noodeenhede nie. Die aanbevelings vir skandering in kinders wat presenteer met eerste aankoms fokale konvulsie is nie goed omskryf nie en die diagnostiese en terapeutiese waarde verskil afhangend van die plek en populasie.

UITKOMSTE

Die studie het die gebruik, en diagnostiese en terapeutiese impak van breinskanderings ondersoek in kinders wat presenteer met eerste aankoms fokale konvulsies in die Tygerberg Hospitaal se Ambulatoriese en Noodeenheid; asook gekyk na moontlike historiese en kliniese ondersoek indikasies wat geassosieer kan word met 'n abnormale brein skandering.

METODE

'n Retrospektiewe kohort studie van 168 voorheen gesonde kinders met nuwe aankoms fokale konvulsies wat toegelaat is te Tygerberg tussen Januarie 2013 en Desember 2014, is onderneem. Demografiese data, kliniese tekens en brein skanderig verslae is verkry van die hospitaal se radiologiese en pasient rekords. Data is geanaliseer met Stata. Beskrywende statistiek asook univariate en multipel binere logistiese regressie analise is onderneem.

RESULTATE

Klinies belangrike breinskanderingabnormaliteite is gevind in 32% (n=54/168) van kinders; wat tot terapeutiese intervensie gelei het in 81% (n=44/54) van gevalle. Die meerderheid abnormaliteite is veroorsaak deur infektiewe granulome (n=21/54); gevolg deur tuberkulose meningitis (n=12/54) en serebrale veneuse trombose (n=4/54). 'n Abnormale kliniese neurologiese ondersoek was statisties betekenisvol ($p < 0.001$) as aanduiding van 'n abnormale breinskandering. Driekwart van pasiente (n=26/35) met 'n abnormale neurologiese ondersoek, het 'n abnormale skandering gehad. Ouderdom, MIV status, gewig, duur van konvulsies, blootstelling aan tuberkulose kontak, en 'n onlangse reisgeskiedenis was nie statisties betekenisvol nie; die getal pasiente was egter nie genoeg om 'n assosiasie tussen geskiedenis kliniese faktore en abnormale breinskandering te toon nie.

GEVOLGTREKKING

Ons beveel aan dat 'n spoed breinskandering gedoen word vir alle kinders wat presenteer met 'n kliniese abnormale neurologiese ondersoek. Ons bevindinge verder dui daarop dat breinskandering behulpsaam is in die hantering van kinders met moontlike intrakraniale infeksies (uitsluitend neurosistiserkose), vasculere abnormaliteiete, en spasie opnemende letsels; soos vermoed na geskiedenis en ondersoek. Verder kan 'n inisiele borskasplaat en tuberkulien toets die nodigheid van 'n breinskandering voorkom aangesien dit die TB opwerk kan fokus.

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ADEM- Acute Demyelinating Encephalomyelitis

AIDS - Acquired Immuno-Deficiency Syndrome

CN – Cranial Nerve

CNS – Central Nervous system

CSF- Cerebrospinal fluid

CT – Computed tomography

CXR- Chest X-ray

ED – Emergency Department

GCP - Good Clinical Practice

HIV - Human Immunodeficiency Virus

ICP – Intracranial pressure

MRI- Magnetic Resonance Imaging

PNET- Primitive neuroectodermal tumour

PTB – Pulmonary Tuberculosis

TB – Tuberculosis

TBH – Tygerberg Hospital

TCH -Tygerberg Children's Hospital

TST- Tuberculin Skin Testing

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Figure 4.1 Flow diagram of Systematic Identification of Study Population

Seizures are the most common neurological disorder presenting to paediatric emergency departments (ED) and accounts for approximately two percent of all paediatric ED visits^{4 5}. Focal seizures accounts for twenty five percent of non-febrile seizures in children younger than six years of age^{6 7}.

Children presenting to the ED with new onset focal seizures are often evaluated using urgent head computed tomography (CT). Although MRI is the preferred neuroimaging modality in children as it avoids the radiation risk of CT, with added superior resolution, MRI is not routinely available in the emergency setting^{8 9 10}.

Studies from both developed and developing countries however report mixed results concerning the relationship between focal seizures, abnormal CT findings, and subsequent changes in acute management^{1 11 12 13 14}. These studies further use different exclusion criteria and definitions of clinically significant CT findings; making recommendations for neuroimaging difficult.

Recommendations for emergency CT scans in children presenting with focal seizures thus varies. In developing countries, with the lack of resources but high disease burden, clinical management guidelines for neuroimaging in children presenting with focal seizures, especially those presenting to the ED, need to be well defined.

This retrospective study over a two year period, evaluated the value of head CT in children presenting with first onset focal seizures to the Paediatric Emergency & Ambulatory Unit at Tygerberg Hospital, Cape Town. The utilization, timing, and yield of head CT are described. Children with known epilepsy on treatment, with previous neuroimaging and pre-existing neurological disorders, and with a history of head trauma within the last 72 hours were excluded. The study further examined as secondary outcomes, potential historical and clinical variables in children with abnormal imaging findings. This may provide further knowledge to inform the development of management guidelines and referral criteria in our resource constrained setting.

Chapter 2: LITERATURE REVIEW

Seizures are the most common neurological disorder presenting to paediatric emergency departments (ED) and accounts for approximately two percent of all paediatric ED visits^{15, 16}. Even though febrile seizures are the most common presentation of seizures in children younger than six years of age, childhood focal seizures accounts for twenty five percent of non-febrile seizures in children^{17 18}.

Children presenting to the ED with new onset focal seizures are often evaluated using urgent head computed tomography (CT), even though Magnetic Resonance Imaging (MRI) is the preferred neuroimaging modality in children as it avoids the radiation risk with superior resolution^{19 20 21}. MRI is however not routinely available in the emergency setting. CT is more accessible, but can underestimate the extent of structural brain abnormalities. The combined questionable diagnostic use of CT in children, the potential risk of sedation, radiation exposure, and adverse reaction to contrast medium, need to be balanced with the identification of potential life threatening and serious intracranial pathology requiring emergency interventions²². It remains important to identify patients in whom neuroimaging could be deferred to the non-acute setting.

The prevalence of abnormalities detected with CT neuroimaging in children presenting with focal seizures ranges widely from 0-21% in developed countries and 35-66% in developing countries^{1 23 24 25 26 27 28 29}. Subsequent change in acute management following the CT scan result is not reported on by many studies; but is as low as 2-8%.

Table 2.1 and 2.2 provides a summary of studies from developed and developing countries exploring the utility of urgent CT scans in children presenting with focal seizures in the emergency setting. These studies all use different exclusion criteria and different definitions of clinically significant CT findings, with different recommendations for neuroimaging in focal seizures in children; making universal recommendations for neuroimaging difficult.

Garvey *et al* recommended emergency CT scan for first onset unprovoked focal seizures in any previously well child after his retrospective review of 99 patients presenting to an emergency department (ED) found CT abnormalities in 19% of cases³⁰. Sharma *et al* reviewed the neuroimaging results of 475 patients with new onset afebrile seizures presenting to the ED retrospectively, and reported 8% with CT abnormalities. Her group recommended emergency CT scans in the less than 33 months age group⁷. Maytal *et al* reported abnormal results in 21% of their

retrospectively studied cohort of 66 patients, which excluded infants less than 1 month of age and those with simple febrile seizures¹. Of the 411 children with first onset unprovoked seizures evaluated by Shinar *et al*, only 53% had imaging done, of which 21% was abnormal; and only 1% required acute interventions³¹. Warden *et al* found no significant association between focal onset of seizure and CT abnormalities². Teng and colleagues found none of the 71 children presenting with complex febrile seizures to their ED to have abnormal CT findings³². Bautovich and Numa did a retrospective analysis of 89 previously asymptomatic children presenting with new-onset seizures. Children without fever were more than twice as likely to have an abnormal CT result, with a significant relationship between abnormal CT findings and multiple seizures and age less than 24 months. Focal seizures were not predictive of CT abnormalities⁹.

Table 2.1 Studies from developed countries reviewing the use of CT as Neuroimaging in first onset focal seizures

STUDY & YEAR	AUTHORS	STUDY DESIGN & POPULATION NUMBER	SETTING	FINDINGS & RECOMMENDATIONS
Emergency brain computed tomography in children with seizures: who is most likely to benefit? <i>Pediatr.</i> 1998;133(5): 664-9	Garvey MA, Gaillard WD, Rusin JA, Ochsenschlager D, Weinstein S, Conry JA, Winkfield DR, Vezina LG.	Retrospective review of 99 patients presenting to an emergency department with focal seizures	USA, Washington DC	Found CT abnormalities in 19% of case
The role of emergent neuroimaging in children with new-onset afebrile seizures. <i>Pediatrics</i> 2003;111:1-5	Sharma S, Riviello JJ, Harper MB, Baskin MN.	Retrospective review of 475 patients with new onset afebrile seizures presenting to the ED	USA	Reported 8% with CT abnormalities. Recommended emergency CT scans in the less than 33 months age group
The role of brain computed tomography in evaluating children with new onset of seizures in the emergency department. <i>Epilepsia.</i> 2000;41(8):950-4	Maytal J, Krauss JM, Novak G, Nagelberg J, Patel M.	Retrospective studied cohort of 66 patients (excluded infants less than 1 month and those with simple febrile seizures)	Israel	Reported abnormal results in 21% of patients
Neuroimaging abnormalities in children with an apparent first unprovoked seizure. <i>Epilepsy Research</i> 2001;43:261-269	Shinnar S, O'Dell C, Mitnick R, Berg AT, Moshe SL.	Ten year prospective study of 411 children with first onset unprovoked seizures	USA	Reported 21% with abnormal CT scans, (only 53% had imaging done) with only 1% requiring acute intervention
Predictors of abnormal findings of computed tomography of the head in paediatric patients presenting with seizures.	Warden CR, Brownstein DR, Del Beccaro MA.	Retrospective study of 203 patients with febrile and afebrile seizures	USA, Washington DC	Found no significant association between focal onset of seizure and CT abnormalities

Ann Emerg Med. 1997;29(4):518-23				
Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. Pediatrics. 2006;117(2):304-8	Teng D, Dayan P, Tyler S, Hauser WA, Chan S, Leary L, Hesdorffer D	Retrospective study of 71 children presenting with complex febrile seizures to an ED	USA	Found none of the children had an abnormal CT finding
Role of head computed tomography in the evaluation of children admitted to the paediatric intensive care unit with new-onset seizure. Emerg Med Australas. 2012;24(3):313-20	Bautovich T, Numa A	Retrospective analysis of 89 previously asymptomatic children presenting with new-onset seizures.	Sydney Australia	Found that children without fever were more than twice as likely to have an abnormal CT result, with a significant relationship between abnormal CT findings and multiple seizures and age less than 24 months. Focal seizures were not predictive of CT abnormalities

Studies from developing countries report a higher incidence of abnormal CT scan findings ranging from 35% - 66% which can be explained by a high prevalence of parasitic brain cysts, tuberculosis (TB) and HIV^{33 34 35}. A retrospective study from India reported 35% abnormal CT results in 23 neurologically normal children with focal seizures, but the patients were a selected group and not consecutive because of cost constraints³⁶. Baheti *et al* reported in a prospective study of 26 children presenting with first onset focal seizures abnormal CT findings in 50% of cases; from structural abnormalities to calcifications, hydrocephalus, tuberculosis, neurocysticercosis and infarctions³⁷. Similarly, a prospective study of 172 children presenting with a second onset focal seizure in Nepal reported a large percentage (62%) of abnormal CT findings ranging from neurocysticercosis and tuberculomas as the most common, and structural abnormalities, brain tumors and subdural effusions as other abnormal findings³⁸.

In the only other study from South Africa, abnormal results were reported in 66% of cases (48% single or multiple granulomas). The authors concluded however that these findings did not meaningfully change the initial clinical management as the CT abnormalities were clinically suspected. This prospective cohort study excluded children < 6 months and all CT scans were performed on an outpatient basis with one third of patients lost to follow up³⁹.

Table 2.2 Studies from developing countries reviewing the use of CT as Neuroimaging in first onset focal seizures

STUDY	AUTHORS	STUDY DESIGN	SETTING	FINDINGS
Study of EEG and CT scan in neurologically normal cases of focal convulsions. J Trop Pediatr 1989;35:113-116	Vidwas AS, Shah MD	Retrospective study of 23 children with focal seizures	India	Reported 35% abnormal CT results in 23 neurologically normal children with focal seizures (selected group of patients, not consecutive because of cost constraints)
A study of CT and EEG findings in patients with generalized and partial seizures in Western Rajasthan. Journal of Indian Academy of Clinical Medicine 2003;4(1):25-29	Baheti R, Gupta BD, Baheti R.	Prospective study of 26 children presenting with first onset focal seizures	India	Reported abnormal CT findings in 50% of cases; from structural abnormalities to calcifications, hydrocephalus, tuberculosis, neurocysticercosis and infarctions
Role of EEG and CT scan in partial seizures in children. International Journal of Medicine and Medical Sciences 2011;3(5):161-163	Jain N, Mangal V.	Prospective study of 172 children presenting with second onset focal seizures	Nepal	Reported a large percentage (62%) of abnormal CT findings ranging from neurocysticercosis and tuberculomas as the most common, structural abnormalities, brain tumors and subdural effusions as other abnormal findings
The utility of computed tomography for recent-onset partial seizures in childhood. South African Medical Journal 2006; 96(9):941-944	Swingler GH, Westwood ATR, Iloni K	Prospective cohort study (excluding children < 6 months)	South Africa	Abnormal results were found in 66% of cases (48% single or multiple granulomas)
Clinico - diagnostic and therapeutic relevance of computed tomography scan of brain in children with partial seizures. Ann Indian Acad Neurol 2013;16:352-6	Patel NH, Jain AR, Iyer VK, Shah AG, Jain DA, Shah AA	Prospective study of 50 children between ages 1month-12years presenting with first onset focal seizures	India	CT brain should be carried out in all children with focal seizures especially in developing countries.

International guidelines for emergency CT scans in children presenting with focal seizures also varies. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recommends that emergency CT is 'possibly' useful after a first seizure in children, especially where there is an abnormal neurological examination, predisposing history or focal seizure onset and in children < 6 months of age⁸. Other guidelines recommend that children presenting with first onset focal seizures known with the Human Immunodeficiency Virus (HIV) and Acquired Immuno-Deficiency Syndrome (AIDS), or with a positive TB contact, abnormal neurological signs, history suggestive of a space occupying lesion, or signs of raised intracranial pressure have a higher incidence of pathology noted on neuroimaging and should thus receive neuroimaging^{40 41 42 43 44 45 46 47 48 49}.

Recent South African guidance³ recommend urgent neuroimaging in all children presenting with status epilepticus without an obvious cause, a postictal focal neurological deficit not resolving, a child who does not return to baseline within a few hours after the seizure, and the child with suspected raised intracranial pressure. Routine outpatient imaging is proposed for all stable children with a focal seizure of unknown cause, unexplained abnormal findings, significant developmental delay of unknown cause, and children less than 1 year of age presenting with an unprovoked seizure. In the Tygerberg Hospital ED setting, referral criteria for urgent neuroimaging in children simply reads; 'new onset focal seizures'.

In developing countries, with the lack of resources but high disease burden, clinical management guidelines for neuroimaging in children presenting with focal seizures, especially those presenting to the ED, need to be well defined. This retrospective study therefore aim to evaluate the use of and incidence of abnormal CT findings in children admitted with new-onset focal seizures to a paediatric ambulatory and emergency unit in a developing country. Potential historical and clinical variables in children at risk of abnormal imaging findings was explored as secondary outcome measures. This may provide further knowledge to inform the development of management guidelines and referral criteria in our resource poor setting.

Chapter 3: RESEARCH DESIGN AND METHODOLOGY

A. Research Question

What is the utility, diagnostic yield and therapeutic interventions of head CT scans in children presenting with first onset focal seizures to a Paediatric Ambulatory & Emergency Unit in a resource constrained setting?

B. Aim & Objective

The overall aim of the study is to determine the value of head CT in children presenting with first onset focal seizures to the Paediatric Ambulatory Unit at Tygerberg Hospital over a two year period; January 2012 till December 2013.

Objectives

Primary Outcome measures

1. To describe the utilization of head CT in children presenting with focal seizures
2. To describe the timing of head CT in children presenting with focal seizure to the unit
3. To describe the yield (outcome and management) of head CT in children presenting with focal seizures
4. To describe the etiology of focal seizures in children
5. To describe the prevalence of single granulomas on head CT in children presenting with focal seizures

Secondary outcome measures

6. To determine historical and/or clinical variables (risk factors) associated with abnormal CT head findings

C. Study design

We conducted a retrospective analysis of all children presenting to the Paediatric Ambulatory Unit with focal seizures who had a head CT scan over a two year period; January 2013 till December 2014.

D. Setting

The Tygerberg Children's Hospital is situated in the G Block of the Tygerberg Hospital and is part of the larger Tygerberg Hospital, which is the academic training hospital of the University of Stellenbosch. This hospital serves the immediate surrounding areas, providing primary and secondary health care to children, as well as tertiary care to all paediatric patients in Metro East, and the Northern and Eastern rural districts of the Western Cape. Paediatric patients with primary and secondary health care problems are managed in the G-Ground Paediatric Ambulatory Unit, which is combined with acute referrals and 24hr emergency care, as well as a 24bed short stay in-patient ward. Seizures are one of the most common presenting complaints in children referred to the

Unit. The G-Ground Paediatric Ambulatory Unit sees on average a 1 000 children per month; with about a third of all patients seen admitted to the short stay inpatient ward.

E. Target population, Study Population and Sampling

The Target population were all children accessing ambulatory and emergency paediatric care services at the GGround Paediatric Ambulatory Unit. The Study population included children referred with focal seizures who subsequently had a head CT.

- *Inclusion criteria:*
 - All children between the ages of 10 days and 13 years presenting with focal seizures who subsequently had a head CT
- *Exclusion criteria:*
 - Children with known epilepsy on treatment
 - Children with previous neuroimaging and pre-existing neurological disorders
 - Children with history of head trauma within last 72 hours (as will be referred to the trauma unit)

F. Data Collection and analysis

Study participants were systematically identified from the radiological database at Tygerberg Hospital as those who had a focal seizure and head CT scans performed between January 1, 2013 to December 31, 2014. No formal sample size was calculated since all primary objectives were descriptive in nature.

Sources of Data

The primary sources of data were:

1. CT scan reports were obtained using the electronic Tygerberg Hospital Radiology databank. Each CT scan was reviewed by a registrar in radiology, then further reviewed by a qualified radiologist at Tygerberg Hospital and subsequently reported as either normal (no pathology detected as a cause of the focal seizure) or abnormal (pathology evident).
2. Routine health information as captured on the electronic management system (ECM)
3. NHLS Laboratory system using the electronic Tygerberg Hospital laboratory databank

Data Collection Methods

Routine Health Information was used to collect quantitative data and Radiology reports were obtained for each patient using the unique hospital number.

Each patient enrolled in the study was assigned a unique patient identifier number and a paper based case report form (CRF) will be used to collect the data from the radiology database and clinical records. This data will be entered into an electronic database. Patient names, hospital numbers and physical addresses will not be entered in the electronic database.

Variables collected

Personal identifier: xx-xx-xx

- Sex
- Date of Birth
- Date of Admission
- Age at presentation (months)
- Weight in kilograms
- Duration of seizure in minutes
- Number of seizures
- Family history of seizures
- Associated Fever
- Associated Developmental delay/regression/school failure
- History of TB contact
- Outcome of TB workup if performed
- HIV status
- History of recent travel e.g. Eastern Cape
- History of previous brain insult (prematurity, hypoxic, meningitis/encephalitis, trauma)
- Abnormal neurological examination (focal signs, raised ICP, meningism, developmental delay)
- Head CT findings

Operational definitions

For the purpose of the study, the following definitions will be used:

- Children: All children from ten days old to 13 years of age
- Sex: Male or Female

- Weight for age: Normal weight (+2 to -2 Z score), Underweight for age (below -2 Z score), Unknown/ Not documented
- New onset Focal seizure: First seizure isolated to one side of the body within the last year
- Duration of seizure: as documented in minutes ($>$ or \leq 15 minutes)
- Focal Status: seizure lasting more than thirty minutes or more than two seizures within the past twenty four hours of admission.
- Family history of seizures: known family member (paternal or maternal) diagnosed with a seizure condition
- Fever: Temperature $> 38^{\circ}\text{C}$
- Developmental delay/regression/school failure: a delay/regression in motor or speech skills that is appropriate for the patients' age. School failure: poor progression in school as assessed by a teacher/school psychologist
- TB contact: known relative/neighbour with symptoms of pulmonary Tuberculosis (PTB) or that has been diagnosed with PTB within the last year of patients presentation to the ambulatory unit
- Positive TB workup: radiological changes on CXR either suggestive of PTB (e.g. hilar lymphadenopathy) or millitary TB, a positive gene expert or culture on gastric washings, a positive tuberculin skin test of more than 10mm, or a positive gene expert or culture on CSF samples collected.
- HIV status: unknown, negative, exposed, infected
- Recent travel e.g. Eastern Cape within last year
- Previous brain insult: prematurity, hypoxia, meningitis/encephalitis, trauma
- Focal neurological signs: cranial nerve palsy, hemiplegia, clinical signs of raised intra-cranial pressure, meningism.
- Raised ICP: vomiting, headache, decreased level of consciousness, papilloedema, CN 6 palsy, bulging fontanelle
- Urgent CT: within 24hrs of admission
- CT scan findings: to be categorized as normal or abnormal. Abnormal findings to be documented and categorized as infective (with or without single granuloma), neoplastic, trauma, structural abnormalities (congenital), vascular, non-specific, other.
- Single granuloma to be categorized as TB, neurocysticercosis, or undetermined
- CT findings of Therapeutic value: CT scan findings leading to immediate initiation, stopping or altering of therapy, or surgical intervention.

Data Management and Statistical Analysis

All data was handled and managed according to Good Clinical Practice (GCP) requirements and ethical standards.

The database (checked for accuracy and completeness) was stored on a laptop computer, which was kept in a locked cabinet in a locked office. Copies were used to perform calculations and analysis. The database was backed up on a daily, weekly, monthly and 6 monthly basis onto a storage disk. The paper based CRFs were stored separately. All paper documents will be kept in a locked cupboard for 5 years.

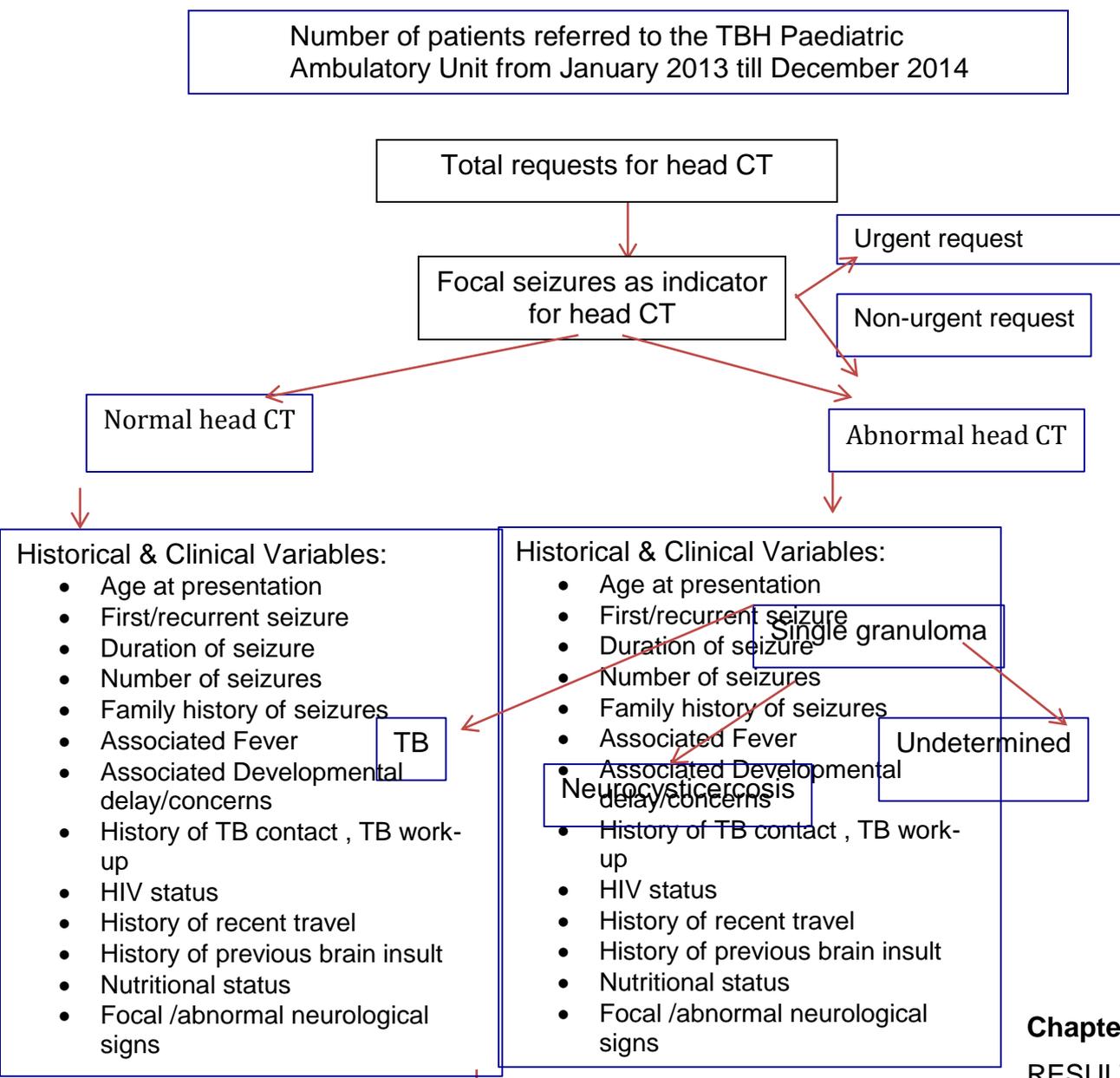
Data Analysis

Data was analysed using Stata. Descriptive statistics was used to analyse demographic data and outcome. Univariate Comparisons were based on chi-square statistical tests with the calculation of Odds Ratios and confidence limits as well a st-tests for continuous variables. Multiple biniary logistic regression analysis were done to determine adjusted associations between historical and/or clinical findings and CT scan results. Statistical techniques were utilised and a statistical prevalence was reported with 95% confidence intervals. Categorical variables (as outlined in Table 4.2) were described using frequencies and percentages. Associations between factors and binary outcomes were assessed using Pearson's chi square tests at the 0.05 level of significance.

G. Ethical considerations

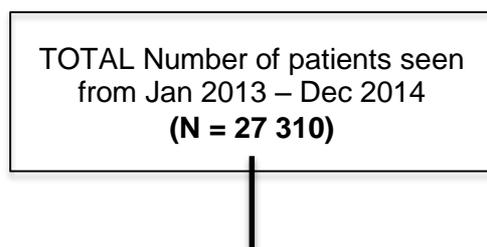
This study was approved by the Health Research Ethics Committee of Stellenbosch University (protocol number S14/05/111).

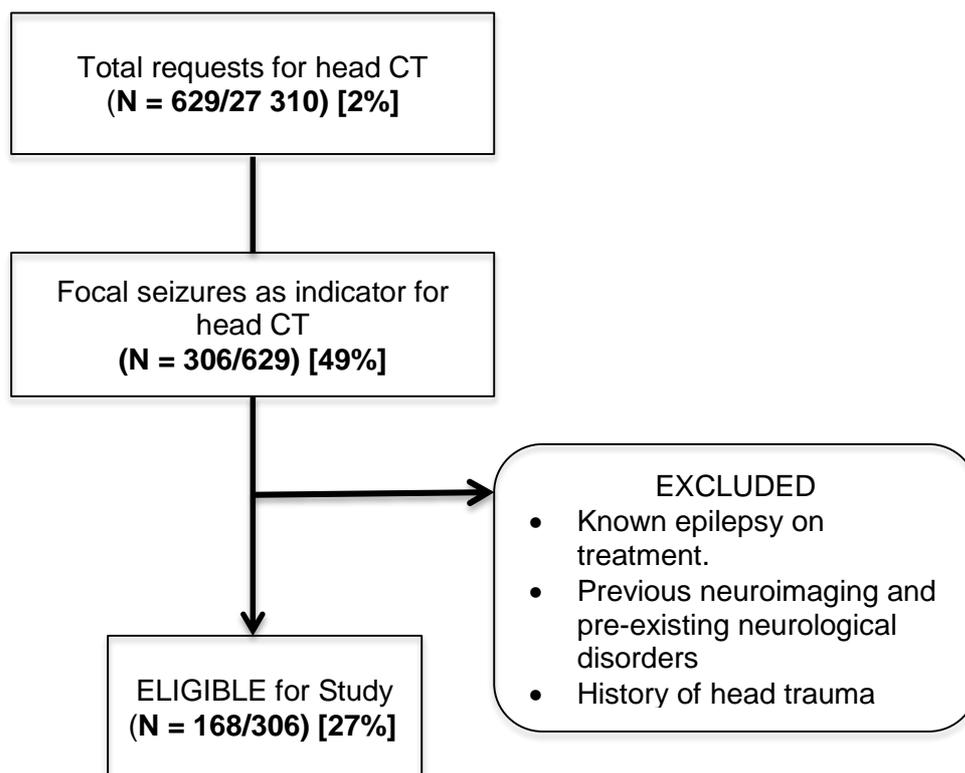
Study Population Flow chart:



During the study period a total of 27 310 children were admitted to the Paediatric Ambulatory Unit of whom 629/27 310 (2%) had a head CT done. Figure 4.1 depicts the systematic identification of the study population, with 168 children included in the retrospective review after exclusion criteria were applied.

Figure 4.1. Flow Diagram of Systematic Identification of Study Population.





A. Utilization and timing of head CT in children presenting with first onset focal seizures

Almost half (306/629) of all CT scan requests during the study period were based on a focal seizure as part of the presenting complaint. Almost a third of these (168/629) were CT requests due to first onset focal seizures with no previous neurological condition, imaging or recent trauma. CT scans were performed as 'urgent' (within 24 hrs of presentation) in most cases; 164/168 (98%).

B. Study Population Characteristics, History and Clinical Findings

Children included in our study were mostly well with normal growth and development (Table 4.1). Children between the ages of 1 and 5 years accounted for almost half (49%) of the study population. Only 5% were HIV infected, but alarmingly 60% of children's HIV status were not known or documented. Almost 1 in 5 children (19%) were exposed to a known TB case. Only 9% offered a recent travel history; but travel information was not documented in 83% of cases.

Almost half (46%) of children has had only one focal seizure at the time of imaging, with seizures lasting less than 15 minutes most prevalent (39%) although one in 5 children (21%) presented with focal status epilepticus. Fever was a common associated feature (41%), with 21% of children demonstrating an abnormal

neurological finding on examination such as focal signs, raised ICP, meningism, and /or developmental delay.

Table 4.1. Summary of Study Population Characteristics, History and Clinical Findings

Variable	Number/168 (Percentage)
Male Sex	100 (60%)
Age at presentation	
0 – 6 months	27 (16%)
6 months - 1 year	17 (10%)
1-5 years	82 (49%)
5-13 years	42 (25%)
Nutritional Category based on weight for age z-scores	
Normal (+2 to -2 Z score)	130 (77%)
Under weight (below -2 Z score)	35 (21%)
Unknown/ Not documented	3 (2%)
HIV status	
HIV exposed	3 (2%)
HIV infected	9 (5%)
HIV negative	55 (33%)
Unknown status	101 (60%)
Family History of Seizures	12 (7%)
Development Delay on History	13 (8%)
Not documented	81 (48%)
TB exposure	32 (19%)
Not documented	26 (16%)
Recent travel history	15 (9%)
Not documented	139 (83%)
Number of Seizures	
1	77(46%)
2-5	56 (33%)
> 5	32 (19%)
Not documented	3 (2%)
Seizure Duration	
< 15 minutes	65 (39%)
15 – 30 minutes	9 (5%)

> 30 minutes (Status epilepticus)	35 (21%)
Not documented	59 (35%)
Associated fever	69 (41%)
Not documented	6 (4%)
Abnormal Neurological Examination (focal signs, raised ICP, meningism, developmental delay)	35 (21%)
Not documented	4 (2)

C. Diagnostic and Therapeutic Yield of Head CT Imaging

A third, 54/168 (32%), of CT scans were reported as abnormal. Table 4.2 gives a summary of the subsequent diagnoses.

Infection was found to be the most common aetiology for focal seizures in this study population. Single and multiple granulomas (21/54; 39%) were most commonly reported; with neurocysticercosis (13/21, 62%) more prevalent than Tuberculomas (8/21; 38%). Probable Meningitis was reported in 14/54 (26%) of cases; with Tuberculous Meningitis (TBM) subsequently confirmed in 12 of these children and Bacterial meningitis in 2. Tuberculosis thus accounted for 20/54 (37%) of the intra-cranial infections.

Table 4.2 Diagnosis based on of Abnormal CT findings

Abnormal CT findings	n=54
Infectious (36/54; 67%)	
Neurocysticercosis	24% (n=13)
Tuberculomas in isolation	15% (n=8)
TB meningitis	22% (n=12)
Culture negative Bacterial meningitis	4% (n=2)
Cytomegalovirus (congenital)	2% (n=1)
Vascular (7/54; 13%)	
Cerebral venous thrombosis (Dehydration-related)	7% (n=4)
Arterial stroke	6% (n=3)
Structural abnormalities (5/54; 9%)	
Sturge Weber Syndrome (Leptomeningeal hematomas)	2% (n=1)

Developmental venous anomaly	2% (n=1)
Bilateral subdural hygromas/hematomas	4% (n=2)
Ventriculomegaly	2% (n=1)
Neoplastic (1/54; 2%)	
Primitive neuroectodermal tumour (PNET)	2% (n=1)
Other (2/54; 4%)	
Bilateral globus pallidus changes (suspected Metabolic cause)	2% (n=1)
Brain swelling (Post-ictal changes following focal status epilepticus)	2% (n=1)

9/54 patients (17%) presented with a history of acute gastro enteritis accompanied by first onset focal seizures, and were found to be clinically shocked. 7 of these patients (77%) had abnormal CT scans, the majority showing sinus venous thrombosis (4/7) and the remainder abnormality being extensive cerebral infarctions.

Two thirds (3/5) of the children diagnosed with structural abnormalities were younger than one year of age.

One patient (n=1/54) was diagnosed with a primitive neuro-ectodermal tumour (PNET). This patient was over the age of one year, was found to be under weight for age (weight less than the minus 2-Zscore), presented in focal status, had a known TB contact, and an abnormal neurological examination with signs of raised ICP.

In this study, initial therapy was adjusted (stopped, initiated, or altered) in all the children diagnosed with infectious, vascular and neoplastic aetiology of the seizures. The abnormal CT findings thus had a therapeutic significance of 81% (44/54) in the emergency/acute setting.

D. *Historical and Clinical Variables associated with abnormal head CT findings*

Historical and clinical variables of the 168 children who underwent neuroimaging were analysed (Table 4.2). An abnormal neurological clinical examination was statistically significant in predicting an abnormal CT scan result. Three quarters (26/35; 74%) of patients with an abnormal neurological examination had an abnormal CT scan result.

Of the 9 patients who had a documented abnormal neurological examination on presentation but a normal CT scan result, one presented with a left hemiplegia that resolved within twenty four hours of presentation (Todd's paralysis), four patients had

a documented abnormal level of consciousness which resolved within six hours of presentation, with three patients initially examined by junior staff at night and incorrectly assigned abnormal neurological clinical signs. When reviewed by a senior clinician the following morning, neurological examination was noted to be normal. One five year old patient presenting with a depressed level of consciousness, choreo-athetoid movements, and a left hemiplegia, was found to have a normal CT scan. Subsequently, a MRI was performed and the patient was diagnosed with Acute Demyelinating Encephalomyelitis (ADEM).

On the other hand, 129/168 (77%) of children had a normal neurological examination, of whom a third (37/129; 29%) had an abnormal CT scan result. Multivariate logistic regression analysis to determine adjusted associations between historical and/or clinical findings and CT scan results did not yield statistically significant data because of the small sample size. We are thus unable to make recommendations for the need of urgent CT scan in these children.

Table 4.3. Comparison of Historical and Clinical variables of Normal and Abnormal CT scan results

Variable	Normal CT (N=114/168)	Abnormal CT (N=54/168)	Statistical Relevance
Age			p = 0.599
0 – 6 months	15 (56%)	12 (44%)	
6 months - 1 year	11 (65%)	6 (35%)	
1-5 years	57 (70%)	25 (30%)	
5-13 years	35 (31%)	11 (20%)	
HIV infected	5 (56%)	4 (44%)	Invalid test
Malnutrition	20 (57%)	15 (43%)	p = 0.165
Duration of Seizure			p = 0.883
< 15 minutes	46 (71%)	19 (29%)	

> 15 minutes	6 (67%)	3 (33%)	
Focal status	22 (63%)	13 (37%)	
Number of Seizures			p = 0.390
1	55 (72%)	22 (29%)	
2-5	37 (66%)	19 (34%)	
>5	19 (59%)	13 (41%)	
Family History of seizures	7 (58%)	5 (42%)	p = 0.698
Developmental delay	7 (54%)	6 (46%)	p = 0.410
TB contact	18 (56%)	14 (44%)	p = 0.242
Travel history	8 (53%)	7 (47%)	p = 0.174
Abnormal neurological examination	9 (26%)	26 (74%)	p<0.001

On further examination of the 8 patients diagnosed with Tuberculoma, 2/8 (25%) had both a known TB contact and failure to thrive and one (13%) a TB contact only. These findings would have prompted a TB workup including a CXR, TST, and Gastric washing/sputum in our unit. 5/8 (63%) of patients diagnosed with Tuberculoma had however no initial indication of TB exposure or disease, with the TB work-up only performed after the CT report.

Interestingly, the CXR and TST yield suggestive of TB were very high at 100% and 75% respectively. Our findings suggest that in a TB endemic setting, an initial CXR and tuberculin test may identify children requiring a TB work-up to diagnose tuberculous neuro-infection without the need for a CT scan.

Looking at the larger study population, 44% (14/54) of patients with an abnormal CT scan had a known TB contact, 56% (18/114) of patients with a TB contact had a normal scan. TB contact per se was thus not shown to be predictive of intracranial TB in this study population.

Table 4.4 TB Risk Factors and TB workup results in patients with TB granulomas on head CT

	Known TB contact	Suggestive CXR	Reactive TST	Positive gene expert-Gastric Washing Result	Positive Sputum Result	Positive CSF Result	Failure To Thrive
Patient 1	+	+	+	+	-	-	+
Patient 2	-	+	+	+	-	-	-
Patient 3	-	+	Not documented	+	-	+	-
Patient 4	-	+	+	+	-	-	-
Patient 5	-	+	+	+	-	+	-
Patient 6	-	+	+	+	-	-	Weight not documented
Patient 7	+	+	+	-	-	-	+
Patient 8	+	+	Not documented	+	-	-	-

Chapter 5: DISCUSSION

CT scans are an important diagnostic tool in the diagnosis and management of many conditions. The recommendations for neuroimaging, and specifically CT, in children presenting with new-onset focal seizures is poorly defined and the diagnostic yields tend to vary according to study settings and population.

This study aimed to determine the utility, diagnostic yield and therapeutic interventions of head CT scans in children presenting with first onset focal seizures to a Paediatric Ambulatory & Emergency Unit in a resource constrained setting.

Our study confirmed the burden of focal seizures in ED settings, with almost half of all CT scan requests during the study period based on focal seizures as part of the

presenting complaint. A third of the CT scans reported were abnormal (32%); which is lower than other studies from developing countries (50 - 66%)^{6,7,8}, but higher than studies reported from developed countries (0-21%).^{1,2,3,4,5}

Higher diagnostic CT yields in children residing in developing countries have been reported due to a higher prevalence of neuroinfectious diseases (TB and neurocysticercosis). Similar to studies from other developing countries, single and multiple granulomas were most commonly reported in our study; with neurocysticercosis more prevalent than tuberculomas. In contrast to the only other study from South Africa, Tuberculous infection (either meningitis or tuberculous granulomas) were the most common aetiology of focal seizures in our study.

In this study, initial therapy was adjusted in 81% of children in the emergency/acute care setting. This is much higher than reported before, but also points to different operational definitions of therapeutic importance used in reports. Although intracranial pathology was clinically suspected in many of the children, a definite diagnosis with a specific management plan was only possible after the CT scan results were available. It can be argued that only the children with Tuberculosis (20), Meningitis (3), neoplastic (1) and vascular pathologies (7) requires urgent neuroimaging.

Almost one in 5 (24%) children presenting with focal seizures to our unit had neurocysticercosis changes on CT scan which influenced further investigations and treatment. It can be argued though that this finding should not be considered to be of therapeutic relevance since there is insufficient evidence that cysticidal therapy is of any clinical benefit²⁷. The evidence regarding the use of anti-epileptic therapy as prophylaxis for preventing seizures in children diagnosed with neurocysticercosis is also lacking^{27,31}. Uni- and multivariate analysis in our study could however not identify those children at risk of neurocysticercosis from history and clinical examination; making specific recommendations for CT scan in children suspected of neurocysticercosis difficult. Neuroimaging could however be deferred to the non-acute setting.

Tuberculomas (TB granulomas), especially those close to the surface of the brain, may potentially rupture into the subarachnoidal space and result in TB meningitis. Radiological identification of tuberculomas not associated with TB meningitis is therefore of diagnostic and therapeutic importance. A quarter of children with Tuberculomas had a history of a TB contact and poor weight gain in our study, but

conversely two thirds of patients diagnosed with Tuberculoma had no initial indications of TB exposure or disease. No TB specific historic and clinical markers could be identified in our study even though the yield of the TB workup in children with tuberculoma was almost double than that reported in other studies⁵⁰. Our findings further suggest that in a TB endemic setting, an initial CXR and tuberculin test may identify children requiring a TB work-up to diagnose tuberculous neuro-infection; without the need for a CT scan.

Most physician guidelines recommend anticoagulant therapy in children with arterial ischemic stroke and cerebral venous thrombosis^{32,33}. Such CT findings were therefore deemed of therapeutic value and an appropriate request in the acute setting when suspected.

Epilepsy may be the earliest and sole clinical manifestation of brain tumours. Numerous studies describe epileptic seizures as the first symptom of brain tumours in approximately 1-10% of cases in children^{34,35,36,37}. The low incidence of epilepsy and seizures in children with tumours of the brain can be attributed to the higher proportion (70-80%) of infratentorial localization. Most childhood seizure-related supratentorial tumours are of neuroepithelial origin (as seen in the case of the patient in our study diagnosed with PNET) or Astrocytomas. Often, these children have intractable or recurrent seizures which would warrant further investigations. In addition, a normal EEG excludes the presence of supratentorial tumours. Thus, in children with isolated first onset focal seizures, urgent CT as a means of excluding brain tumours is not cost effective.

In this study, age of seizure onset was not predictive of an abnormal CT scan. However, most children with cerebral malformations manifested their focal seizures at an early age (< 2 years)^{4,5,7}. This supports findings from other studies, but indicate that these children may benefit more from an elective MRI scan than an emergency CT scan.

An abnormal neurological clinical examination was statistically significant in predicting an abnormal CT scan result and should be an indication for neuroimaging.

Other historical and clinical variables were not statistically significant in predicting an abnormal CT scan in this study due to sample size.

Study limitations

Due to the selection method of using the hospital radiology database to identify patients with focal seizures who underwent imaging, we were unable to calculate the

prevalence of focal seizures as presenting complaint in our unit. Our admission book only contains the diagnosis at discharge and not the presenting symptom. We thus do not know if all children presenting with focal seizures received neuroimaging and were subsequently included in this study. This study looked at retrospective routinely collected paper based data in a busy short stay inpatient ward with possible lack of completeness of the data. Due to limited patients the study was not powered to calculate historical and clinical variables (risk factors) associated with abnormal head CT findings in children presenting with focal seizures. Further, this was a single center review that may not be applicable to a wider population.

Chapter 6: CONCLUSIONS AND RECOMMENDATIONS

Despite no clear guidance in our unit, a significant percentage of CT scans were reported as abnormal (32%) in our study. These CT scan reports influenced the management team's management decision in the majority of cases.

A clinically abnormal neurological examination was found in a third of patients with an abnormal CT scan and is an indication for an urgent CT scan.

Based on our findings, we recommend strongly the use of urgent CT imaging in all children with neurological abnormalities. Our findings further suggest that urgent imaging is indicated in children suspected of neuro-infections other than neurocysticercosis, vascular abnormalities, and space occupying lesions. Suspected structural abnormalities in infants younger than 2 years of age are best diagnosed with a MRI in the non-urgent setting. Our findings further suggest that in a TB endemic

setting, an initial CXR and tuberculin test may identify children requiring a TB work-up to diagnose tuberculous neuro-infection; without the need for a CT scan.

Follow up research should be conducted in order to determine positive and negative predictive values with regards to historical and clinical variables associated with abnormal neuroimaging. Evidence-based guidelines for neuroimaging in patients presenting with first onset focal seizures will influence both patient outcome and health costs.

Appendix 1

DATA COLLECTION SHEET

Personal identifier:

• Sex	
• Date of Birth	
• Date of Admission	
• Age at presentation (months)	

<ul style="list-style-type: none"> • Weight in kilograms 	
<ul style="list-style-type: none"> • Duration of seizure in minutes 	
<ul style="list-style-type: none"> • Number of seizures 	
<ul style="list-style-type: none"> • Family history of seizures 	
<ul style="list-style-type: none"> • Associated Fever 	
<ul style="list-style-type: none"> • History of TB contact 	
<ul style="list-style-type: none"> • Outcome of TB workup if performed 	
<ul style="list-style-type: none"> • HIV status 	
<ul style="list-style-type: none"> • Associated Developmental delay/regression/school failure 	
<ul style="list-style-type: none"> • History of recent travel 	
<ul style="list-style-type: none"> • History of previous brain insult 	
<ul style="list-style-type: none"> • Emergency CT brain 	
<ul style="list-style-type: none"> • Abnormal neurological examination 	
<ul style="list-style-type: none"> • Head CT findings 	
<ul style="list-style-type: none"> • Abnormal MRI 	
<ul style="list-style-type: none"> • Shocked 	

Appendix 2

DATA CODING SHEET

Personal identifier: xx-xx-xx

- Sex :
 - 1- Male
 - 2- Female

- Date of Birth

- Date of Admission
 - 1- 2012
 - 2- 2013

- Age at presentation (months)
 - 1- 0-six months
 - 2- Six months – 1year
 - 3- 1 year to five years
 - 4- 5 years to 12 years
 - 5- 12 years to 18 years
 - 9- Unknown

- Weight in kilograms
 - 1- Normal weight for age
 - 2- Under weight for age
 - 3- Over weight for age
 - 9- Unknown

- Duration of seizure in minutes
 - 1- Less than fifteen minutes
 - 2- Longer than fifteen minutes
 - 3- Focal status- more than thirty minutes
 - 9- Unknown

- Number of seizures

- 1- One
- 2- More than one but less than five
- 3- More than five

- Family history of seizures:

- 1- Yes
- 2- No
- 9- Unknown

- Associated Fever

- 1- Yes
- 2- No
- 9- Unknown

- History of TB contact

- 1- Yes
- 2- No
- 9- Unknown

- Outcome of TB workup if performed

- 1- Positive
- 2- Negative
- 9- Unknown

- HIV status

- 1- Exposed
- 2- Infected
- 3- Negative
- 9- Unknown

- Associated Developmental delay/regression/school failure

- 1- Yes
- 2- No
- 9- Unknown

- History of recent travel
 - 1- Yes
 - 2- No
 - 9- Unknown

- History of previous brain insult
 - 1- Yes
 - 2- No
 - 9- Unknown

- Emergency CT brain
 - 1- Yes
 - 2- No
 - 9- Unknown

- Abnormal neurological examination
 - 1- Yes
 - 2- No
 - 9- Unknown

- Head CT findings
 - 1- Normal
 - 2- Abnormal infective(with or without single granuloma)
 - 3- Abnormal neoplastic
 - 4- Abnormal trauma
 - 5- Abnormal structural abnormalities (congenital), vascular, non-specific
 - 6- Abnormal other

- Abnormal MRI
 - 1- Yes
 - 2- No
 - 9- Unknown

- Shocked

1-Yes

2-No

9-Unknown

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