

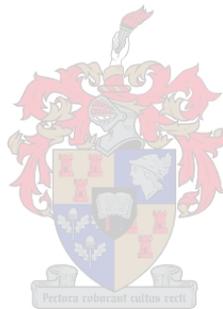
1) Title page

Investigation of first onset seizures in adults in Western Cape Emergency Centres

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2) ABSTRACT

Objectives: This study aimed to review which investigations were done on adults presenting with first onset seizures to six Emergency Centres in the Western Cape Province, South Africa.

Methods: A prospective cross-sectional study conducted from 1 July 2011 – 31 December 2011. All adults with first onset seizures were included; children and trauma patients were excluded. Subgroup analysis was conducted regarding HIV status and interfacility variation.

Results: Three hundred and nine patients were included. CT scans were planned in 218 (70.6%) patients; 96 (56.8%) had causative abnormalities (infarction, intracerebral haemorrhage and atrophy being the commonest). At least 80% of patients (n=247) received a full renal and electrolyte screen, blood glucose testing and a full haematological screen. Lumbar punctures were done in 67 (21.7%) patients; 51 (76.1%) being normal. Only 27 (8%) patients had an EEG of which 5 (18%) were abnormal. A statistically significant difference exists regarding CT scans ($p=0.002$) and lumbar punctures ($p<0.001$) in the HIV positive group (n=49).

Conclusion: This study demonstrated inconsistent, unnecessary and wide local variance for all types of investigations done. It emphasises the need for a local guideline to direct doctors to appropriate investigations, ensuring better quality patient care and potentially saving costs.

3) Main text

INVESTIGATION OF FIRST ONSET SEIZURES IN ADULTS IN WESTERN CAPE EMERGENCY CENTRES

Introduction

Seizures are a common presentation to Emergency Centres (ECs); 1 – 2% of all EC visits in the USA are seizure related. (1) The worldwide incidence of acute symptomatic seizures is 29 – 39 per 100 000 per year. (2)

The differential diagnosis of a patient presenting with first onset seizures is broad, and emergency physicians should take a careful history, conduct a thorough examination and perform appropriate investigations; not only to exclude potentially life threatening conditions, but also to correctly diagnose and appropriately dispose of these patients. (3)

High-quality guidelines regarding the investigation of adults with first onset seizures are available in the UK and the US, but similar South African guidelines are non-existent. (3,4) Local data regarding the incidence or types of seizures are also lacking. International guidelines suggest the following investigations: neuroimaging, electroencephalogram (EEG), and laboratory investigations. (3,4)

Neuroimaging can be done by either Computer Tomographic (CT) scan or Magnetic resonance imaging (MRI) to exclude organic causes such as tumours, haemorrhage and infarction. MRI is diagnostically superior to CT scans in detecting certain intracranial lesions, but is not readily available. (5) Studies investigating the use of MRIs in the emergency setting are also lacking. (6) The evidence shows a broad range of abnormal CT scans in seizures (12 – 41%); this yield increases to 59 – 82% when the patient has an abnormal neurological examination. (5,7,8) CT scan is useful to exclude catastrophic conditions in patients with first onset seizures, therefore guidelines advise CT scans instead of MRI if resources do not permit. (3,4)

There is little evidence supporting routine widespread biochemical investigations. The most common biochemical abnormalities in seizures are hypo- or hyperglycaemia and hyponatremia. (1) One should also note that some biochemical investigations (i.e. raised white cell count or hyperglycemia), may be a direct result of the seizure activity. (9) All other investigations (including toxicological screening) should be ordered as clinical circumstances dictate. (8,10,11) A lumbar puncture is indicated when an intracranial infection is suspected, the patient presents with an altered mental status and in all immune compromised patients. (12-14)

An EEG is considered an essential investigation to diagnose epilepsy; with an average abnormal yield of 29%.^(4,15) Although a normal EEG does not exclude epilepsy it can be used to predict seizure recurrence. ^(5,7) EEGs are usually only recorded at specialist units, and together with the high false positive rate, some feel it is an unnecessary investigation in the EC. ⁽¹⁶⁾

HIV/AIDS patients frequently present with seizures. ^(17,18) Physicians must adopt a low threshold for neuroimaging and lumbar puncture in the evaluation of seizures in these patients.^(13,17,19) South Africa has a high HIV infection rate (10.5%)⁽²⁰⁾ There is little data on seizures in the South African HIV positive population. ^(18,20)

There is currently no data regarding adults presenting with first onset seizures to South African EC's; nor how they are investigated. South Africa is a developing nation with limited financial and equipment resources; reviewing which investigations are being done is important as there is a potential cost saving if unnecessary investigations can be prevented. The aim of this study was to determine which special investigations are being done on adults presenting with first onset seizures to ECs in Cape Town, South Africa.

Methods

Study design

A prospective cross sectional study design was used. Approval was obtained from the Stellenbosch University Health Research Ethics Committee (Ref: N11/04/133) and from the Western Cape Health Research Committee (Ref: RF: 56/2011).

Study setting and population

Six hospitals situated within the Western Cape Province of South Africa were selected by convenience sampling. Two tertiary level hospitals, Tygerberg Hospital (Parow, Cape Town) and Groote Schuur Hospital (Observatory, Cape Town) were included. Four secondary level hospitals were also included: New Somerset Hospital (Green Point, Cape Town), Victoria Hospital (Wynberg, Cape Town), G.F. Jooste Hospital (Mannenberg, Cape Town) and Paarl Hospital (Drakenstein, Paarl). These hospitals were selected due to their close proximity; furthermore the patient load of these hospitals (a mixture of adults and children presenting with both trauma and medical conditions) are a good representation of the burden of disease within the Western Cape. ⁽²¹⁾The two tertiary level

hospitals are both large referral centres with 24-hour access to CT scans, MRI scans and specialist radiologists. The four secondary level hospitals are smaller with limited specialist services and limited access to special investigations. Three secondary hospitals (New Somerset Hospital, G.F. Jooste Hospital and Paarl Hospital) have on-site CT scanners that are operational during office hours. Victoria Hospital doesn't have an on-site CT scan and refer their patients to Groote Schuur Hospital. All of these hospitals serve a population of approximately 3.4 million people, many of whom are underprivileged or unemployed. (20)

All adults presenting to ECs with first onset seizures during the study period (1 July 2011 – 31 December 2011) were eligible for inclusion. First onset seizures were defined as the first episode of a focal or generalised seizure in a patient not known with epilepsy or any other seizure disorder. (2)

Paediatric patients (under the age of 13) were excluded due to the high incidence of febrile-related seizures and South African protocols for children with first onset seizures do exist. (22) Patients with post-traumatic seizures (presenting within one week after head injury) were also excluded as their workup differs from non-trauma patients.

Measurements

Health care personnel working in the relevant ECs were asked to help identify eligible patients. The principal investigator also reviewed the EC registers weekly to minimize missing cases. All the ECs have an EC register where the patients' details, clinical problem and disposal are recorded.

Data were extracted from the patients' folders and imported into an electronic datasheet (Microsoft Excel®, Microsoft Corporation, Redmond, WA) by the principal investigator. Variables collected included basic demographic data (age and sex), type of seizure, HIV status and investigations done. Patients with outpatient investigations that fell outside the six month study period were followed up for six weeks.

Data analysis

Statistical analyses were done by the Centre for Statistical Services at Stellenbosch University. Simple descriptive statistics were used to describe the data. The association between two nominal variables was investigated with contingency tables and likelihood ratio χ^2 tests, specifically Pearson's χ^2 test for independence. Subgroup analysis was conducted with regards to HIV status and interfacility variation. A significance level of 5% was used.

Results

A total of 1241 patients were identified during the study period. Nine hundred and thirty two patients were excluded (not first time seizures (n= 892), missing folders (n=25), paediatric patients (n=10), trauma related seizures (n=5)); thus, 309 patients were included in the final analysis. The study population's demographic details, seizure types and HIV status are presented in Table 1. Groote Schuur Hospital evaluated the most patients (n=84, 27.2%) (Table 2).

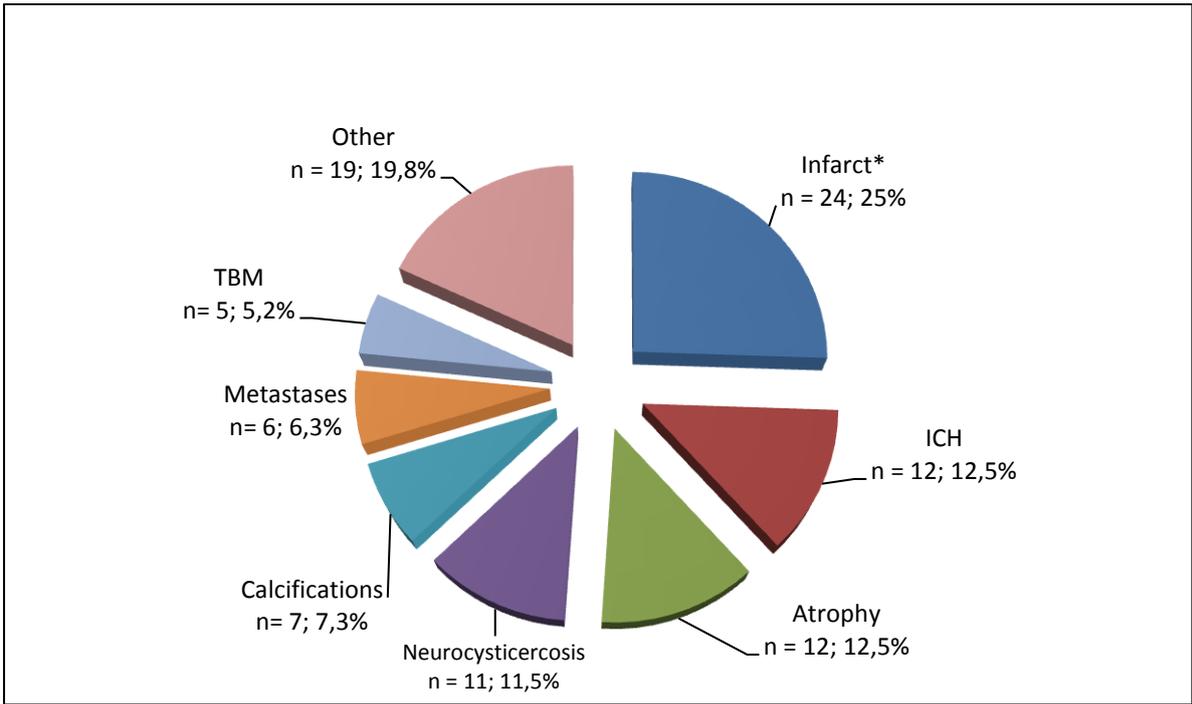
Table 1. Demographics, seizure type and HIV status of patients presenting with first onset seizures

Variable	n	%
Age (years)		
13 – 20	36	11.7%
21 – 30	54	17.5%
31 – 40	69	22.3%
41 – 50	63	20.4%
51- 60	44	14.2%
61 – 70	27	8.7%
>70	16	5.2%
Sex		
Male	120	38.8%
Female	189	61.2%
HIV Status		
Positive	49	15.8%
Negative	53	17.2%
Unknown	207	67%
Seizure type		
Focal	41	13.3%
Generalized	268	86.7%

Table 2. Distribution of patients with first onset seizures across hospitals

Hospital	n	%
Groote Schuur Hospital	84	27.2%
Victoria Hospital	56	18.1%
Tygerberg Hospital	51	16.5%
New Somerset Hospital	51	16.5%
G.F. Jooste Hospital	34	11.0%
Paarl Hospital	33	10.7%
	309	100%

CT scans were part of the investigations in 218 (70.6%) patients; 151 (69.3%) on an emergent basis and 67 (30.7%) electively. Only 18 (26.8%) of the elective CT scans were eventually done. The main reasons for this were that appointments were not made and that patients didn't attend the appointments. Ninety six (56.8%) CT scans were abnormal and interpreted as causative for seizures (Figure 1); the rest (n=73; 43.2%) were normal or had an abnormality that was not causative for seizures. All of the elective scans were normal. No patient received an MRI as part of their work-up.



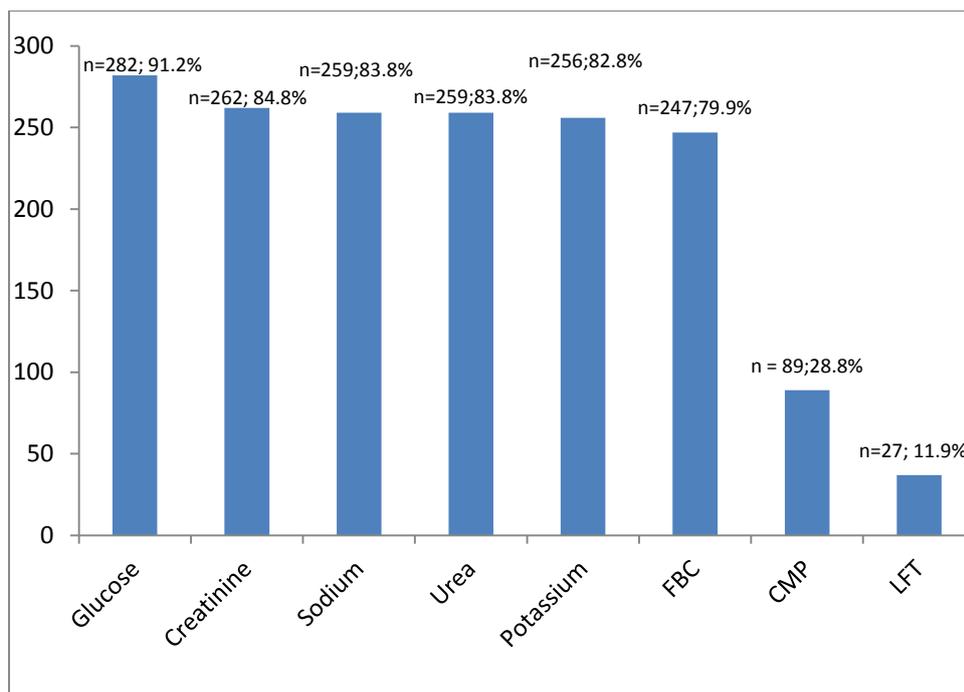
ICH, intracranial haemorrhage

TBM, Tuberculous meningitis

*Includes both old and new infarcts

Figure 1. Abnormalities on Computer Tomographic scans of the brain deemed causative for seizure activity

A total of 1762 different blood investigations were done; the commonest being serum glucose (n=282, 91.2%)(Figure 2). More than 80% of patients had renal function tests (urea and creatinine) done, with sodium and potassium the commonest electrolytes tested. Toxicology screening was done on 11 (3.6%) patients. Sixty seven (21.7%) patients had a lumbar puncture with 51 (76.1%) being normal. HIV testing was only done on 5 (1.6%) patients.



FBC, full blood count

CMP, calcium-magnesium-phosphate

LFT, liver functions test

Figure 2. Most common biochemical investigations done in patients presenting with first onset seizures

EEGs were done in 27 (8%) patients; 19 (6.2%) on an elective basis. Five (18.5%) EEGs had an abnormal result, all done urgently.

HIV status

The number of patients with a confirmed HIV status were almost equal (Table 1). A statistically significant difference exists between the HIV positive group and the other two groups regarding CT scans ($p=0.002$) and lumbar punctures ($p < 0.001$). Table 3 summarises this subgroup analysis (excluding blood investigations).

Table 3: HIV subgroup analysis in patients presenting with first onset seizures

	HIV status		
	Positive	Negative	Unknown
N	49	53	207
Seizure type			
Focal	9	10	22
Generalized	40	43	185
CT scans ordered			
Urgent	37	31	83
Elective	4	9	54
Not ordered	8	13	70
CT scan results			
Abnormal	24	20	56
Normal	13	16	40
Planned but not done	4	4	41
Lumbar punctures			
Abnormal	7	7	3
Normal	16	12	24
Not done	26	34	180
EEG			
Abnormal	3	1	1
Normal	0	12	3
Not done	47	50	192

EEG, electroencephalogram

Interfacility variability

Two thirds (n=100; 66.2%) of the urgent CT scans was done at the tertiary level hospitals . The majority of elective CT scans (n=58 ; 86.6 %) were arranged from secondary level hospitals. There was a statistically significant difference between secondary and tertiary level hospitals regarding CT scans ordered (p<0.001). Fourteen (73.7%) of all elective EEGs were from one hospital - Victoria Hospital. All eight urgent EEGs were from the two tertiary hospitals. The biochemical tests performed also varied between facilities, however these were done on very small numbers of patients and statistical significance wasn't tested. Thyroid tests were done on 16 (5.2%) patients; the majority at Tygerberg Hospital (n=7) and Victoria Hospital (n=7). Syphilis testing was done on

22(7.1%) patients, and most of these were at Tygerberg Hospital (n=15). An International Normalized Ratio (INR) was done on 8 (2.6%) patients; most at Groote Schuur Hospital (n=4) and Tygerberg Hospital (n = 3). Cholesterol levels were checked in 5 (1.6%) patients; all at Groote Schuur Hospital. A C-reactive protein (CRP) level was done on 4 (1.3%) patients at Paarl Hospital.

Discussion

Previous studies had shown a male predominance in patients presenting with first onset seizures; our study showed the exact opposite with 162 (61.2%) female patients.(9,12) The age of our patients was also similar in range to previously studied groups: the most common age of presentation was between 31 and 40 years.(9,12)

Only 71% had neuroimaging done as part of their workup. No patients in this series had MRIs – the most likely reason for this is limited access to this investigation as it is only available at tertiary hospitals during office hours. It is possible that doctors working in ECs were trying to limit costs on patients who had recovered completely by not ordering CT scans on them. It is also possible that the ECs were overcrowded and in order to facilitate patient flow, patients were discharged before CT scan.

The largest proportion of urgent scans (66%) occurred at the two tertiary centres. It may be more convenient to obtain a CT scan emergently and diminishes the need for further appointments and follow up. These hospitals are also referral centres for all the secondary level (and some primary level) facilities in the Western Cape, therefore it might just be that patients were only referred for such investigations. An alarming trend was noticed in the large percentage of patients (85%) who didn't have their elective CT scans done. The main reasons in this were: patients not attending their scheduled appointments, dates not communicated to patients, and patients being discharged prior to appointments being made. Taking the above in consideration, it may be better to complete investigations on an emergent basis in the EC to expedite patient treatment and disposition.

There is some debate in the literature regarding the appropriate timing of neuroimaging. The US guideline states that imaging could defer to an elective date, provided there is adequate patient follow up. (3) The UK guidelines are similar, requiring imaging within 4 weeks. (4) It may be more appropriate in our setting to obtain CT scans emergently (within 24 hours); however, keeping patients in the EC for these investigations contributes to overcrowding, which may lead to impaired patient care. (23) The physician should measure each case individually to give the patient the best

care. It is important to note that the debate regarding timing of imaging is only applicable to patients who have returned to a normal neurological baseline and have no significant co-morbidities; if there is any clinical suspicion of intra-cranial pathology, emergent imaging should be obtained. (15)

The yield of abnormal scans (59.6%) was higher than seen in the international data. (7-9,24) Unfortunately, data regarding abnormal neurological examinations wasn't collected, but it is possible that the higher positive yield was due to the high number of HIV positive patients in the Western Cape (particularly considering the high prevalence of neurocystercosis and TB meningitis).(20) Atrophy, traumatic brain injury and tumours were the most common CT scan abnormalities in international studies and the different ranking order in our findings are at odds with this. International data also shows an increased prevalence in those over 60, which was not our finding on this study. (Table 1) (2)

The most common biochemical abnormalities causing seizures in the literature are related to serum glucose and sodium. (8,10,11) Most international guidelines suggest plasma electrolytes, glucose and calcium if indicated. This was not reflected in our study, with more than 80% of patients receiving a full renal and electrolyte screen as well as a complete haematological profile. It is difficult to comment on whether or not all of these investigations were unnecessary as the patients' end diagnoses were not correlated to the investigations done. The patients (particularly those at tertiary centres) may have had other medical diagnoses and co-morbidities which warranted broad baseline testing. What is perhaps more worrying is the fact that essential blood tests were not done in all patients – for example blood glucose levels.

The abnormal yield of the blood tests was not reviewed and further analyses might assist in guiding a rational choice of blood investigations, particularly if ECs are trying to limit costs. The inclusion of certain tests are a reflection of the current practise at particular centres; syphilis testing at Tygerberg Hospital being a good example. The introduction of a guideline would assist doctors working in ECs to make better evidence based decisions.

Internationally there is no evidence of occult bacterial meningitis presenting as isolated seizures. A lumbar puncture is thus only needed in patients who clinically have meningitis. This may account for the small number of patients (22%) who underwent lumbar punctures. HIV positive patients who present with seizures have a high incidence of cryptococcal and TB meningitis and the physician should have a low threshold to do an LP on these patients.(18,19)

EEGs are helpful in predicting recurrence and localising lesions in complex epilepsy.(5,25) Although EEGs were only available at the tertiary hospitals, they do not appear to be part of the routine work up for any patients with first onset seizures in the Western Cape. Furthermore, the abnormal yield of EEGs (18%) was well below the 50% reported in other studies. (5,7)Recent literature suggests that an EEG should not be part of investigations ordered from the EC, but should be left to the discretion of specialist neurology services. (16)This approach seems reasonable in our setting, but also implies that we are underutilising this resource (especially in the patient group where organic causes were excluded).

HIV positive patients have a higher incidence of neurological disease causing seizures. (17) These patients may also present without any neurological abnormalities; therefore requiring more aggressive investigations.(13) Sixteen percent of our study population were confirmed HIV positive , but their HIV status didn't seem to affect the diagnostic workup or the abnormal yield of investigations (Table 3). It is unclear why the contradictory results, but the high proportion of patients (67%) with an unknown HIV status could have confounded our results. Point-of-care HIV test are readily available and more emphasis on HIV testing in this population group might be warranted.

Limitations

This study had a number of limitations. Very few cases were identified prospectively by EC staff, forcing the investigators to rely on the EC registers. The record keeping in some of the EC registers was poor and some parts were actually missing. This inadvertently led to some patients being missed. The note keeping was also below standard and the correct information was sometimes impossible to obtain. A small number of patients could have been duplicated in two hospitals' registers, predominantly when the patient was referred for urgent neuroimaging. A single data collector retrieved all the data.

The missing data may have confounded the data analysis – perhaps a greater patient number could have been obtained. This may have affected the internal validity of the study.

This study was done on small population in one province in South Africa, thus is may not be generalisable to other countries or even other provinces who do not have similar patient populations.

Conclusion

The findings of this study emphasise the need for a local guideline regarding the investigation of first onset seizures in adults. We demonstrated wide local variance for all types of investigations done. A guideline would direct doctors to the appropriate investigations, ensuring better quality patient care and potentially saving costs.

Further study as to the aetiology of first onset seizures in South Africa, particularly in HIV positive patients, is needed. The cost implication of inappropriate tests, particularly in our resource limited setting, should be further investigated.

Recommendations:

We recommend the following guideline for adults presenting with first onset seizures:

- All patients require a CT scan of the brain. Urgently when patients have focal seizures, an abnormal neurological examination or are HIV positive. Patients who have returned to a normal neurological baseline post seizure may have an elective scan. Physicians should also consider factors such as the patient's ability to follow up and EC crowding when deciding on the timing of the scan.
- Blood investigations should include at least sodium and glucose levels. HIV testing is recommended. Other blood tests should be at the treating physician's discretion; however unnecessary tests should be avoided.
- Lumbar punctures should be performed when there's clinical suspicion of an intracranial infection. Physicians should have a low threshold in the HIV positive population.
- EEGs should only be ordered at the discretion of specialist neurology services.

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The authors declare no competing interests.

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