Presentation of first onset seizures in Adults at a Tertiary Hospital in South Africa

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A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Emergency Medicine.

April 2019

CANDIDATE'S DECLARATION

I Dr. Sunday Oladapo Sofola-Orukotan student no 1308916 declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (MMED) Emergency Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

 Signed on this 11th day of April, 2019

DEDICATION

This work is dedicated to God for His Grace and Mercy and to all who believes in my vision.

ABSTRACT

Background: First-onset seizure is not a diagnosis per se but may be an indication of a potentially life-threatening underlying illness. The symptoms and presentation may indicate certain types of seizures. The aim of this study was to describe adults presenting with first-onset seizures to an Emergency Department in Johannesburg.

Method: A prospective review was performed on the medical records of patients >18-years who presented over a 6-month period to the study centre with first-onset seizures. Patients with post traumatic seizures and epilepsy were excluded.

Results: A total of 60 patients, with a median age of 37.4 years (IQR; 29.3-47.7 years) presented over the study period. More than half the number of subjects (58.3%) were male, 43.6% were HIV positive, 84.2% had a generalised tonic-clonic seizure, 57.6% presented to hospital more than 2 hours after the seizure, 41.1% returned to baseline neurological function within 30 minutes of the seizure and 56.7% required admission. A decrease in the level of consciousness (77%), foaming around the mouth (37%), urinary incontinence (33%) and tongue biting (32%) were the most common symptoms. A full blood count (97%), urea & electrolytes (88%), blood glucose level (72%), CT scan of the brain (75%) and lumbar puncture (68%) were the most common diagnostic procedures performed. Hypoglycemia (26.7%), ring enhancing space occupying lesion/s (16.7%) and cerebrovascular infarction (11.7%) accounted for approximately two-thirds of abnormalities found on CT in our study subjects.

Conclusion: Patients presented with multiple symptoms and multiple different possible causes of first onset seizures. Although most studies showed low yield for glucose and CTB, our study showed that in resource limited settings, glucose and CTB are key diagnostic investigations among patients presenting with first onset seizures.

ACKNOWLEDGEMENT

Except the Lord builds a house, they labour in vain that build… (Psalm 127 v1). My appreciation goes to the Almighty God, the builder of my life and this career pathway, for without God this work wouldn't have been completed.

I would like to thank my supervisors Prof F. Motara (Division of Emergency Medicine) and Dr. A. Bentley (Department of Family Medicine) at the University of Witwatersrand, for their support and encouragement at ensuring that this paper is entirely my own work.

My appreciation goes to my extended family (The Orukotans) for their financial assistance at ensuring that my stay in South Africa remains smooth. Without their passionate input, this dream would not have seen the light of the day. God will never forget your labour of love.

A very big thank you to Dr. Gbenga Olorunfemi, who rather than gave me the statistical fish, taught me how to fish statistically.

Nobody has been more important to me in the pursuit of this project than the members of my nuclear family. To my darling wife (Omobolanle), you are a rare woman. I sincerely appreciate your support. You stood by me all the way through. You assumed the role of both mother and father to the wonderful kids I left Nigeria to pursue this career. To my special and wonderfully created children, Onaopemipo, Olanrewaju, Ibunkunola and Ilerioluwase, I appreciate you all. You all stood by me and supported my career pathway. I will always love you all.

Once again to the Author of life, I return all the glory

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1. CHAPTER ONE: INTRODUCTION TO THE RESEARCH REPORT

This Master of Medicine (MMed) report is presented in a 'submission-ready' article format as approved by the Faculty of Health Sciences, University of the Witwatersrand.

This is a prospective chart review over a 6months period assessing the presentation of first onset seizures among adults presenting to the emergency department of a tertiary hospital in Gauteng, South Africa.

The content of a "submission –ready" article as required by the faculty of Health Sciences are as follows:

- The protocol with extended literature review
- Journal article
- Author's instruction from the chosen Journal (Journal chosen: African Journal of Emergency Medicine).

2. CHAPTER TWO: PROTOCOL WITH EXTENDED LITERATURE REVIEW

2.1. Title of protocol: Presentation of first-onset seizures in adults at tertiary hospital in South Africa

2.2. Introduction

Seizures are defined as an abnormal, excessive, paroxysmal discharge of the cerebral neurons (1). Adult first-onset generalized seizure is a common cause of admission in the Emergency Department (ED), accounting for 1% of all ED visits (2). First-onset seizures are defined as the first episode of a focal or generalized seizure in a patient not known to have epilepsy or any other seizure disorders (3). Also, a first onset seizure is a traumatic physical and psychological event that poses difficult diagnostic and treatment questions, and has major social consequences such as loss of driving privileges and limitations for employment opportunities. Recurrent seizures cause even more serious and costly problems, with a 2-year risk of recurrence of greater than 40% (4, 5). In view of the diagnostic and social challenges posed by first-onset seizures, it is crucial not only to abort the seizure but efforts must be made to find a treatable cause, so that a recurrence can be prevented.

2.2.1. Epidemiology

Epilepsy affects 1 out of 100 people in South Africa (6). In Sub-Sahara Africa, the annual prevalence of epilepsy is higher (63-158/100,000 inhabitants) than that found in industrialised countries (40-70/1000, 000 inhabitants) (7). The wide variation in prevalence across sub-Saharan Africa is due to differences in the distribution of risk factors, which could either be parasitic (malaria, cysticercosis, onchocerciasis, toxocariasis and toxoplasmosis) or non-parasitic (hypertension and head injury) (8)

2.2.2. Age and Sex differences in seizure disorder

Age at seizure onset is reported in a few studies and when available, seizure onset occurs before the age of 20 years in more than 60% of cases. In contrast the most common age at presentation in the Western Cape Province in South Africa was between 31 and 40 years

(3). Male patients were reported to have more first-onset seizures than females, and this may be attributed to the fact that males are trauma prone (8)

Elderly patients (60 years and above) presenting with first onset seizures constitute another challenge. They often present with focal seizures with less prominent auras and a longer duration of post-ictal confusion. Status epilepticus is common in this group of patients with a high mortality rate. The aetiology remains unknown in most cases, but cerebrovascular disease is a common aetiology (9).

2.2.3. Retroviral Status and First Onset Seizures

The total number of persons living with HIV in South Africa as at 2017 is 7.06 million (12.6% of the total population) (10). Seizures are among the neurological manifestations or complications of HIV infection. About 3% to 17% of HIV patients in South Africa have seizures as a manifestation of HIV. This group of patients tends to have generalized seizures and cerebral toxoplasmosis was the most common aetiology (11).

The incidence of first onset seizures in HIV positive patients has been reported as 4-11% by most studies. A study in southern India reported an incidence of 20% (12,13). Although generalized seizures are common in HIV patients, focal seizures can also occur and this does not necessarily mean that there is a focal lesion. About 8-18% may present in status epilepticus, which is associated with a poorer prognosis. HIV encephalopathy is the most common aetiology of seizures in HIV positive patients, while the most common intracranial lesion associated with first onset seizure is toxoplasmosis followed by primary CNS lymphoma (8, 10, 11).

2.2.4. Classification of Seizure disorder

Accurate diagnosis and classification of seizure type are essential in order to provide quality patient care and good control (12). Seizures are categorized based on presentation and aetiology.

In term of clinical presentation, seizures can be classified broadly into three major groups: focal, generalised and unknown (13). A population based study in sub-Sahara Africa showed a higher prevalence of generalized tonic clonic seizures (14) and generalized seizures are twice as likely as focal seizures (15).

2.2.4.1. Focal seizures

These seizures can often be subtle or unusual, and may go unnoticed or be mistaken for anything from intoxication to daydreaming. Seizure activity starts in one area of the brain and may spread to other regions of the brain (this is often referred to as focal seizures with secondary generalization).

2.2.4.2. Generalised seizures

Generalised seizures are the result of abnormal activity in both hemispheres of the brain simultaneously. Due to this, consciousness is lost at the onset of the seizure. Examples of generalized seizures includes; Absence, Tonic-Clonic, Clonic, Tonic, Atonic, and Myoclonic seizures.

2.2.4.3. Unknown

This is a group of seizures that cannot be diagnosed as either focal or generalised seizures and are thus grouped as unknown, for example, epileptic spasms.

2.2.5. Aetiology of Seizure disorder

The aetiologies of adult first-onset seizures and usefulness of metabolic screening (for uraemia, hypoglycaemia, drug intoxications, and electrolyte disorders), electroencephalograms (EEGs), and computer tomography(CT) scans in the ED have been rarely reported (2). Seizures can be considered to be provoked or unprovoked (Table 2.1).

Table 2:1: Causes of Seizure disorders (16)

Causes of seizure disorders	Definition	Examples
Provoked seizure (acute symptomatic seizure)	Equivalent to acute symptomatic seizure: seizure occurs at the time or within 7 days of an acute neurologic, systemic, metabolic or toxic insult.	Seizures from hyponatraemia or other electrolyte abnormalities, alcohol or drug withdrawal, toxic ingestions, encephalitis, CNS mass lesions and many others.
Unprovoked seizure (including remote symptomatic seizure)	Seizure occurs without acute precipitating factors; unprovoked seizures include, but are not limited to, remote symptomatic seizures if seizure is thought to result from Central Nervous System or systemic insult that occurred more than 7 days in the past.	Idiopathic seizures. Epilepsy (if recurrent) Seizure attributed to history of stroke, traumatic brain injury, or other past events.

The causes of first-onset seizures differ from country to country and there are also variations within the same country. For instance, alcohol withdrawal was identified to be the most common cause of first onset seizure in the United Kingdom while parasitic infections (Toxocara, toxoplasmosis) Human Immunodeficiency Virus (HIV) and malaria were more prominent in Sub-Sahara Africa. In most parts of Asia, neurocysticercosis and Japanese encephalitis are widespread as dominant causes of seizures (17). In Sub-Sahara Africa, there are local variations in parasitic infections as the aetiological agent in patient with first-onset seizures. In a study by Ngugi (7), it was noted that, the prevalence of parasitic risk factors was higher than non-parasitic risk factors among adults in Sub-Sahara Africa. It was

observed in the study that, the proportion of individuals exposed to Onchocerca volvulus ranged from 9% in Iganga-Mayuge, Uganda to 38% in Ifakara, Tanzania, and for Toxoplasma Gondi from 11% in Agincourt, South Africa to 67% in Kintampo, Ghana and for Toxocara canis from 8%in Agincourt, South Africa to 62% in Ifakara, Tanzania. Awareness of these variations is helpful for clinicians to determine causality in the different regions (8, 18).

2.2.6. Investigation of First-onset seizures

Although no single blood test can give a final diagnosis of first-onset seizure, routine blood tests are important as any abnormality detected may influence management and/or the need for admission (17).Venous blood gas analysis within the first hour has been identified as a useful tool in patients with first onset seizures. Kılıc, Yesilaras, Atilla, Sever and Aksay (19) noted that a venous blood gas analysis with a pH of<7.245, base excess<-11.1mEq/L, lactate>7.65mmol/L and bicarbonate<17.1mmol/L one hour after the last epileptic seizure episode, may be associated with a higher risk of having recurrent seizures and such patients may ultimately need to be hospitalized.

Acute and/or severe electrolyte imbalances frequently cause seizures, and these seizures may be the sole presenting symptom. Seizures are especially common in patients with sodium disorders, hypocalcaemia, and hypomagnesemia. An accurate diagnosis of the underlying electrolyte disturbance is vital for successful management of a patient with seizures, because rapid identification and correction of the disturbance is necessary to control seizures and prevent permanent brain damage. Rapidly evolving electrolyte abnormalities are more likely to cause seizures than are those occurring gradually and because of this it is not possible to assign absolute levels of electrolyte above or below which seizures are more likely to occur (20).

Seizures frequently induce an increase in body temperature, white blood cell count, or C-reactive protein levels, making it challenging to distinguish these changes from those

associated with infection. Nonetheless, elevated body temperature in the absence of generalized tonic-clonic seizures, above 39℃, or persisting for more than eight hours after recovery of consciousness, and C-reactive protein levels above 6 mg/dl warrant close observation and consideration for concurrent infection (21).

In fact, elevated CRP has been shown to be useful in identifying underlying infection. According to McCarthy, the evaluation of an ambulatory, febrile child with acute-phase reactants should include at least determination of CRP since high CRP demonstrated the best balance of specificity and sensitivity for bacteraemia (22). While the CRP and WBC may predict the possibility of infectious cause of seizures, it is important to note that single levels of CRP and WBC are not reliable for diagnosis of infections during status epilepticus but their linear changes over time significantly correlate with the presence of infections (23).

There are guidelines for investigation of adults presenting with first-onset seizures in the United Kingdom and the United States of America, but no guideline exists in South Africa (3). The American College of Emergency Physicians clinical policy and the College of Emergency Medicine in the United Kingdom recommend that emergency physicians obtain serum glucose, a sodium level, and pregnancy test in women of childbearing age and that neuroimaging in the ED should be performed on all patients with first episode seizures, except when reliable follow-up is available.

A lumbar puncture should be considered for patients with immunocompromised states, severe headache, fever, suspicion of HIV/AIDS infection, or status epilepticus. These factors increase the likelihood of positive results. The electroencephalogram (EEG) is an important aid in the evaluation of seizure patients, but the waiting median time was found to be about 5 days (12). In view of this, it has been recommended that an EEG should not be routinely performed in the ED or requested by the emergency physician (15, 24). However, an EEG should be considered in patients suspected of being in non-convulsive status epilepticus or in subtle convulsive status epilepticus (25).

The added value of an EEG includes the ability to detect local lesions, predict recurrence and indicate a specific epilepsy syndrome. The yield is often low with a longer delay after the seizure and when the EEG is negative, studies have suggested that an EEG under conditions of sleep deprivation can improve the positive yield in 13 - 31% of cases. A study by Pooja et al showed the yield of the EEG versus time since seizure to drop significantly with the passage of time (Table 2.2) (26, 27).

Table 2:2: Yield of EEG versus Time since seizure

Interval between seizure and EEG (hours)	Positive Result (%)
1-6	67
6-12	52
12-24	31

The EEG can also be used to determine the average time interval for the patient to return to baseline after a seizure episode. In a study in which the time to return to baseline was monitored on EEG, the study showed an average time of 35-109 minutes for focal seizures and 53 – 158 minutes for generalized seizure (28).

Magnetic Resonance Imaging (MRI) is considered the imaging modality of choice in patient with new onset seizures. However, due to cost and non-availability in most hospitals, a CT scan is considered adequate as an alternative to MRI when neuroimaging is required. Previous literature has shown abnormal CT scan results in 3 to 41% of patients with first time seizures. In a study by Lalchan, Shrestha, Jwarchan, Sharma, K.C., Gyawali and Tiwari (29), Abnormal CT scans were seen in 89.3% of patients with focal seizure as compared with 25.9% of patients with generalized seizure. The most common abnormality in this study was neurocysticercosis (37%). Other significant findings were infarcts (8%), tumours (5%), bleed (4%) and calcified granuloma (3.6%) (29, 30).

In elderly people, a first seizure may be caused by a silent stroke only recognizable on MRI (27). However, Paliwal, Wakerley, Yeo, Ali, Ibrahim, Wilder-Smith, Sim, Pohlmann-Eden and Rathakrishnan (31) suggested that an early (and not necessarily ED) EEG and MRI contribute to decision-making regarding treatment at specialist review, especially if the results are abnormal. Major guidelines suggest that, in the absence of a history of trauma, malignancy, or immunocompromised, and if the patient returns to a normal conscious level without any persistent headache or focal neurologic deficit, neuroimaging can be deferred to an outpatient clinic as long as follow-up is reliable (32).

Electrocardiography (ECG) is also recommended in patients with seizures because it is cheap, non-invasive, and readily available. An ECG can be used in early screening for drug toxicity and identification of abnormal patterns (16, 24). In the ED, Tricyclic Antidepressant (TCA) overdose and isoniazid (INH) overdose are two of the most common causes of drug-induced seizures. An electrocardiogram (ECG) will show a widened QRS and prominent R wave in lead aVR, prompting immediate intervention with the appropriate antidotes. In a study by Wong, Adams and Jackson (33), abnormal ECGs were found in 13% of patients presenting to first seizure clinic with no evidence of significant cardiac disease. Some of the patients in this study were found to have a long QTc that was attributed to a metabolic abnormality (idiopathic hypocalcaemia). It has been recommended that, in patients with unexplained or refractory seizures and possibly in all patients with seizures, a 12-lead ECG should be part of the evaluation (15, 16, 24, 33, 34).

There are a few ED-based studies to guide patient disposition. The indication for admitting a critically ill patient with seizures can easily be justified, but the challenge arises with patients who returned to baseline neurological activity after the first seizure episode. The aetiology of the seizure combined with the EEG findings remains the best predictor of seizure recurrence. Since an EEG is not readily available (28), the clinician must do a thorough assessment of all patients with first onset seizures. The American College of Emergency Physicians clinical policy recommends that, a patient with generalized seizure disorder with

normal results (blood, ECG, CT scan) may be discharged, provided the following criteria are satisfied: full recovery without abnormal neurologic signs and/or symptoms, normal vital signs, received advice not to drive, availability of a responsible adult to watch him or her, follow-up arranged and follow-up likely (16).

Hospital based studies on the aetiology of first-onset seizures in adults are scanty. Chalasani and Kumar (35) observed that only a few prospective incidence studies of cases with a first unprovoked seizure or a newly diagnosed unprovoked seizure in the adult population exist and that, there were no major hospital based studies which evaluated new onset seizures in adults especially from developing countries.

A recent study conducted in Cape Town, South Africa revealed that there was local variance for all type of investigations performed on patient with first-onset seizures and that there is a need for local guidelines to guide doctors in respect of appropriate investigations, thus ensuring better quality patient care and potentially saving costs. This study showed that the investigations ordered varied based on the level of care (secondary or tertiary). The majority of the CT scans, thyroid function tests and serological tests were performed at the tertiary hospitals when compared to the secondary hospitals.

The same study suggested a further study investigating the aetiology of first onset seizures in South Africa, especially in HIV positive patients (3). Therefore, the aim of my study is to describe the presentation of first-onset seizures in adults to a Tertiary Hospital in Gauteng.

2.3. Study objectives

1. To determine the demographics and clinical characteristics of patients with first-onset seizures
2. To determine the incidence of first-onset seizures in patients presenting to the ED.
3. To determine the type of seizures (focal, generalized or unknown) in adults with first time seizures, that present commonly to the study centre

4. To determine the tests performed in order to investigate adult patients who presented with first onset seizures and the treatment given in the ED.
5. To compare seizure types and HIV positive and negative patients

2.3.1. Materials and methods

2.3.2. Study Design

Prospective patient record review was used in this study.

2.3.3. Study Site

Medical Emergency Department, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The Charlotte Maxeke Johannesburg Academic Hospital is a tertiary-quaternary hospital in the Northern suburbs of Johannesburg. It is a 1088-bed hospital with doctors at all levels of qualification, from interns, medical officers and registrars to academic professors. The Medical Emergency Department of CMJAH sees approximately 3000 adult patients monthly.

2.3.4. Study Population

Adult patients presenting to the Medical Emergency Department of Charlotte Maxeke Johannesburg Academic Hospital, with first-onset seizures between 1st of May and 30th October 2016 (Dates were changed, due to delay in protocol approval and ethics submission, to November 2016 to May 2017).

Inclusion criteria: All adults (18years and above), who present with first-onset seizures.

Exclusion criteria: known epileptic patients and trauma related seizures.

2.3.5. Sampling

Based on anecdotal record review of the CMJAH ED, it is estimated that about 10-15patients present with first-onset seizures per month. This translates approximately to 60-80 patients over a 6-month period.

2.3.6. Data Collection

Data will be collected using the data collection tool (Appendix 1). Medical doctors involved in the management of patients that present to the ED, will assist with data collection. The doctors will be asked to keep records of patients with first-onset seizure seen on a daily basis to enable the researcher to follow-up on the record and extract the necessary information from the patient's file within 12-24 hrs while the patients are still in the emergency ward (Area 165). However, patients admitted to the wards very early will be followed up to extract the needed information from their files.

The data collection tool is divided into eight sub-headings namely; the demographics, the seizure type and predisposing factors.

- Demographics: the information about the age, sex and the retroviral status of the patient will be recorded.
- HIV status
- Informant information
- Seizure type: this will be recorded as generalized, focal or unknown (seizures that cannot be categorized as generalized or focal, e.g. epileptic spasm)
- History of presenting complaints
- Findings on physical examination and vital signs.
- Investigations carried out to determine the predisposing factor/s to first onset seizure.
- Disposition

2.4. Data analysis

Data will be entered electronically into Microsoft Excel (Microsoft office 2010, Microsoft Corporation). Data will be analysed using STATA 13 (StataCorp.2013). The incidence will be determined by dividing total number of patients with first onset seizures/total number of patient seen over the study period x100.The statistics of continuous variables will be expressed as means and standard deviations. The statistics of categorical variable will be expressed as proportions (and percentages). Comparison between seizure types and

between HIV positive and negative patients will be done using Mann-Whitney or Unpaired t-tests for numerical data and Fisher's exact tests for categorical data.

2.5. Ethical considerations

Written informed consent will be obtained from the participant prior to enrolment in the study (Appendix 2), to use the data after they have been seen by the doctor. There will be no influence on how they are managed and the tests that are done. Informed consent will be requested and obtained from the patient or relative (s), by the attending doctor for inclusion in the study. If patient is unable to give consent due to severity of the condition at presentation, consent will be obtained when patient is fully conscious.

Approval for the study will be obtained from the postgraduate accessor group. Once granted, ethical approval will then be requested from the Human Research Ethics Committee (Medical) prior to commencement of the study. Once the study is approved at HREC, then permission will be sought from the Chief Executive Officer (CEO) of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and head of department of the Medical Emergency Department of CMJAH to proceed with the research.

2.6. Problems

- As the Medical Emergency Department functions as a 24hours facility, the researcher will not be on the premises at all times and thus, the researcher will be reliant on colleagues in the Medical Emergency Department to keep an accurate record of patients who fulfil the inclusion criteria for him to follow-up.
- Potential down time in the National Health Laboratory Services who provide the blood/CSF results might hamper data collection.
- Obtaining informed consent before the various procedures may not be feasible on all patients because some may remain post-ictal or unconscious when these procedures are done. These procedures will be carried out as part of the departmental protocol for the investigation and treatment and consent will be obtained after their management for inclusion in the study.

2.7. Timing

Date of Activities	2015		2016						2017			2018				2019		
	Oct-Nov	Dec	Jan	Feb	Mar	Apr-May	Nov-May	Jun	July-Sep	Oct-Mar	Apr	Sep	Oct- Feb		Mar	Apr		
Literature review																		
Protocol preparation																		
Protocol Assessment																		
Ethics application																		
Data collection																		
Data Analysis																		
Writing up paper																		
Correction and submission by Supervisors																		
Submission for Marking																		
Examiner's Feedback																		
Corrections and Supervisor's approval.																		
Re-submission for mark																		
Examiner's Feedback and approval																		
Final submission to the faculty																		

2.8. Funding

ITEM	QUANTITY	UNIT PRICE	AMOUNT(R)
Printing of data collection tool	1x60=60	2	120
Printing of protocol for approval	2x19=38	2	76
Photocopying and printing of protocol for Ethics approval	20x19=380	2	760
Photocopying of information sheet and consent paper	2x60=120	2	240
TOTAL			**R 1196**

All expenses related to the study will be borne by the investigator.

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3. CHAPTER THREE: JOURNAL ARTICLE

3.1. Cover letter

Dear editor and reviewers,

Thank you for considering our manuscript entitled “Presentation of first-onset seizures in Adults at a Tertiary Hospital in South Africa”. The authors hereby certify that this submission is not under publication consideration elsewhere, and is free from any conflict of interest.

A first-onset seizure is not a diagnosis per se but may be a harbinger of a potentially life-threatening underlying illness. Since the potential causes are vast, unravelling the aetiology of first-onset seizures remains a challenge. Furthermore, South Africa is unique in that there are more people living with HIV than any other country in the world. New-onset seizures have been reported to be more common in the HIV-infected population.

Local data and guidelines regarding the presentation and management of first-onset seizures is lacking. In this study, we humbly present findings of a prospective audit of medical records. The study was aimed at describing the presentation and overall management of patients presenting to our emergency department over a 6-month period with first-onset seizures. We are confident that this manuscript will be of interest to the readership of this journal. Furthermore, it carries a high citation potential, as it is applicable to those in the fields of emergency medicine, neurology, internal medicine and family medicine.

S Sofola-Orukotan

F Motara

A Bentley

3.2. Abstract

Background: First-onset seizure is not a diagnosis per se but may be an indication of a potentially life-threatening underlying illness. The symptoms and presentation may indicate certain types of seizures. The aim of this study was to describe the presentation of adults presenting with first-onset seizures to an Emergency Department in Johannesburg.

Method: A prospective review was performed of the medical records of patients >18-years who presented over a 6-month period to the study centre with first-onset seizures. Patients with post traumatic seizures and epilepsy were excluded.

Results: A total of 60 patients, with a median age of 37.4 years (IQR; 29.3-47.7 years) presented over the study period. More than half the numbers of subjects (58.3%) were male, 43.6% were HIV positive, 84.2% had a generalised tonic-clonic seizure, 57.6% presented to hospital more than 2 hours after the seizure, 41.1% returned to baseline neurological function within 30 minutes of the seizure and 56.7% required admission. A decrease in the level of consciousness (77%), foaming around the mouth (37%), urinary incontinence (33%) and tongue biting (32%) were the most common symptoms. A full blood count (97%), urea & electrolytes (88%), blood glucose level (72%), CT scan of the brain (75%) and lumbar puncture (68%) were the most common diagnostic procedures performed. Hypoglycemia (26.7%), ring enhancing space occupying lesion/s (16.7%) and cerebrovascular infarction (11.7%) accounted for approximately two-thirds of abnormalities found in our study subjects.

Conclusion: Patients presented with multiple symptoms and multiple different possible causes of first onset seizures. Although most studies showed a low yield for glucose and CTB, our study showed that in resource limited settings, glucose and CTB are key diagnostic investigations among patients presenting with first onset seizures.

3.3. Full article: Presentation of first onset seizures in Adults at a Tertiary Hospital in South Africa

3.3.1. Introduction

'Electricity is life, but electricity is an invisible fist punching up your spine, knocking your brains right out of your skull (1). Seizures are defined as an abnormal, excessive, paroxysmal electrical discharge of the cerebral neurons (2). A first-onset seizure is described as the first episode of a focal or generalized seizure in a patient not known to have epilepsy or any other seizure disorders (3). A first onset seizure is more likely to be generalized than focal (4). In South Africa the most common age at presentation was between 31 and 40 years (3). Males reported seizures more frequently than females (5).

There are many causes for first onset seizures but in South Africa the high prevalence of HIV may be a factor. The total number of persons living with HIV in South Africa in 2017 is 7.06 million (12.6% of the total population) (6). Seizures are a common neurological manifestation or complications of HIV infection, with a prevalence of 9.5 %. About 3% to 17% of HIV patients in South Africa had seizures as a manifestation of HIV. The prevalence of seizures increases with advanced HIV disease due to opportunistic infections, side effects of antiretroviral medications and other metabolic derangements (7).

There are no guidelines in South Africa for investigation of adults presenting with first-onset seizures (3). Internationally, Magnetic Resonance Imaging (MRI) is considered the imaging modality of choice in patients with new onset seizures. However, due to cost and non-availability in most hospitals, CT scans are considered adequate when neuroimaging is required (8). The yield of the CT Scans in first onset seizure varies in the literature from 12% to 41% (3, 9, 10).

Even though no single blood test can give a final diagnosis of first-onset seizure, routine blood tests (Full Blood Count, Electrolyte and Urea, C - reactive protein) are important as any abnormality detected may influence management and the need for admission (11).

However, seizures frequently induce an increase in body temperature, white blood cell count, or C-reactive protein levels, making it challenging to distinguish these changes from those associated with infection. Elevated body temperature in the absence of generalized tonic-clonic seizures, above 39℃, or persisting for more than eight hours after recovery of consciousness, and C-reactive protein levels above 6 mg/dl warrant close observation and consideration for concurrent infection. It is important to note that single levels of CRP and White cell count (WCC) are not reliable for diagnosis of infections during status epilepticus but their linear changes over time significantly correlate with the presence of infections (12, 13).

Venous blood gas analysis within the first hour has been identified as a useful tool in patients with first onset seizures (14). The most common electrolyte abnormalities associated with seizures are disorders of sodium and glucose particularly if the sodium level is less than 120ml/l although it is not possible to assign absolute levels of electrolyte above or below which seizures are likely to occur (15, 16). Other investigations recommended in patients with first onset seizures included Lumbar puncture, Electroencephalograms (EEG) and Electrocardiography (ECG) (15, 17).

In the ED, Tricyclic antidepressant (TCA) overdose and isoniazid (INH) overdose are 2 of the most common causes of drug-induced seizures. An electrocardiogram (ECG) may show a widened QRS and prominent R wave in lead aVR, prompting immediate intervention with the appropriate antidotes. In a study by Wong et al, abnormal ECGs were found in 13% of patients presenting to a first seizure clinic with no evidence of significant cardiac disease. It has been recommended that, in patients with unexplained or refractory seizures, and possibly in all patients with seizures, a 12-lead ECG should be part of the evaluation (18-20)

There are few Emergency Department (ED)-based studies to guide management of first-onset. Understanding the scope of the presentation and the usefulness of various investigations may assist in laying the data required to establish guidelines. Therefore the

aim of this study was to describe the presentation of first onset seizures among adults in the ED of a tertiary Hospital in South Africa.

3.3.2. Materials and Methods

This was a prospective record review of patients with first onset seizures from November 2016-May 2017. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M160502). The study was conducted at the Medical Emergency Department, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The CMJAH is a tertiary-quaternary hospital in the Northern suburbs of Johannesburg, South Africa. The ED does not manage paediatric, obstetric and acute trauma patients. The inclusion criteria were all adult patients, 18 years and above, who presented to the study centre with a history of first onset seizures. Exclusion criteria included patients with epilepsy and all trauma related seizures.

A data collection tool was designed to extract information from the patient files after the treating doctors had concluded treatment plans for the patient. Information retrieved from the file included the demographics, HIV status, the informant, details of the seizure, the time of presentation to the emergency department following the seizure episode, the result of physical examination, the time for patients to return to baseline following the seizure episode, the investigations conducted and the disposition of the patient from the emergency department. The investigations conducted included: routine blood analyses (Full blood count, glucose, Electrolyte and Urea, magnesium, calcium, C - reactive protein), venous blood gases, lumbar punctures, CT scans of the brain, ECG and EEG. The laboratory investigations done were retrieved electronically from the National Health Laboratory Science portal and the results of the CT scans were retrieved from the Picture Archiving and Communicating System (PACS) system in the study area, using the patient hospital numbers.

3.3.3. Data Analysis

Data was entered electronically into Microsoft Excel (Microsoft office 2010, Microsoft Corporation, Armonk, NY). The statistics of continuous variables were expressed as means (standard deviations) and values that were non-normally distributed were presented as median (interquartile range). Categorical variables were expressed as percentages. Associations between categorical variables and seizure type were assessed using Fischer's exact test. Comparisons between numerical variables were done using an unpaired t-test. The level of significance was set at $p < 0.05$. Statistical analysis was performed using STATA 13 (StataCorp LLC).

3.3.4. Results

A total of 103 case files of suspected first onset seizures were reviewed. Forty-three patients were excluded. Of these, 23 cases were recorded as first onset seizures, but a full review of the case file showed a different diagnosis. The remaining 20 cases excluded were either known epileptics (11cases) or less than 18years of age (9 cases)

A total of 60 patients with a median age of 37.4 years (IQR; 29.3-47.7 years) who fulfilled the inclusion criteria were recruited during the study period. The youngest patient was 18 years old whilst the oldest was 89 years. The proportion of subjects per age group category is described in Table 3.1. The gender distribution comprised thirty-five (58.3%) males. The majority of the patients (84.2%) had one or more generalised seizures whilst 5 (8.3%) patients had focal seizures only. The seizure type was unknown in 4 (7.6%) patients. Of the 39 (65.0%) subjects in whom the HIV status was known, 17 (43.6%) were HIV positive.

The clinical history was provided mostly by the patient after consciousness was fully regained (36.7%) followed by a pre-hospital crew member in a further 20 (33.3%) cases. With regards to the presence of clinical features suggestive of a recent seizure, more than three-quarters of subjects (76.7%) presented with a decreased level of consciousness whereas, foaming around the mouth (36.7%), tongue biting (31.7%), and urinary

incontinence (33.3%) was evident in approximately a third of subjects each. Most subjects (90.0%) presented with 2 or more of these features.

The median (IQR) for time of presentation to the ED after a seizure episode was 120 (50-240) minutes. About 31% of the study population presented 2 hours after the seizure episode. More than half the number of study subjects (56.7%) required admission to the ward for further work-up and management (Table 3.2). Table 3.3 details the association between the seizure types, demographic characteristics and some laboratory parameters.

Table 3:1: Characteristics of study patients

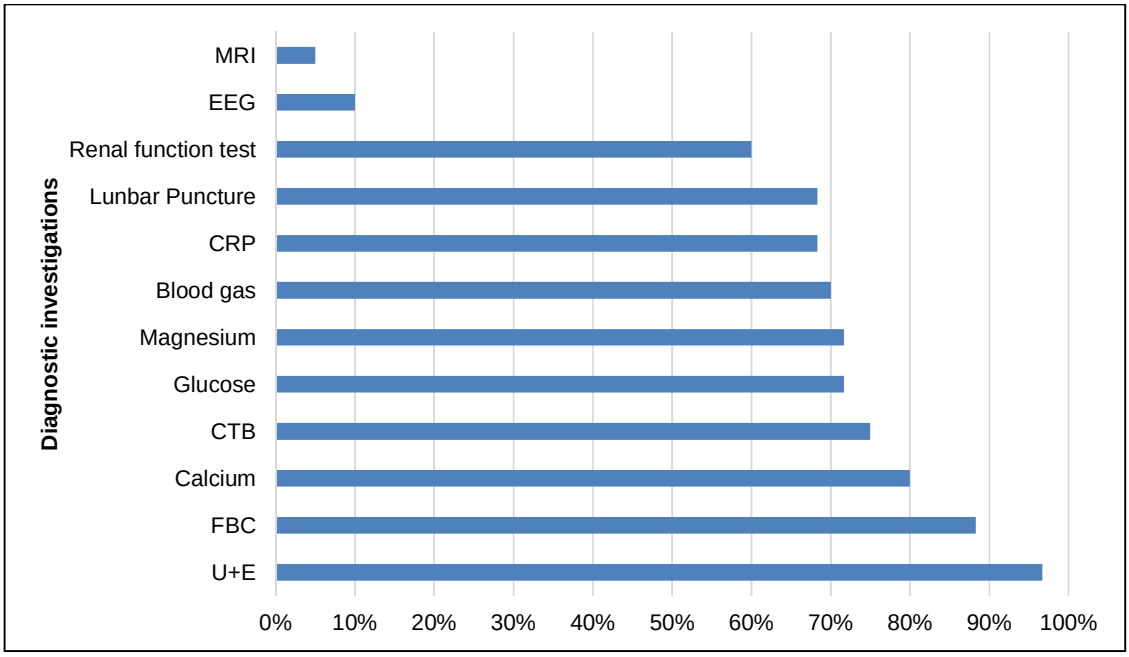
Variable	**n (%)**
Age	
18-29	15 (25.0)
30-39	20 (33.3)
40-49	12 (20.0)
50-59	9 (15.0)
60-69	(5.0)
> 70	1 (1.7)
Gender	
Male	35 (58.3)
HIV status	
Positive	17 (28.3)
Negative	22 (36.7)
Unknown	21 (35.0)
Time to ED presentation after the seizure	
< 60 minutes	13 (21.7)
61-120 minutes	1 (1.7)
> 120 minutes	19 (31.6)
Unknown	27 (45.0)
Number of symptoms among the study population	
<2	10 (6)
2-4	35 (58.3)
> 4	31.7 (19)

Table 3:2: Features of seizures

Time taken to return to baseline neurological function after the seizure	
<30min	16 (26.7)
30min-60min	11 (18.3)
>60min	7 (11.7)
Unknown	26 (43.3)
Individual providing the clinical history	
Patient (self)	22 (36.7)
Pre-hospital crew member	20 (33.3)
Relative	13 (21.70)
Friend or passer-by	5 (8.3)
Presence of clinical features suggestive of a recent seizure	
Decreased level of consciousness	46 (76.7)
Mouth foaming	22 (36.7)
Tongue biting	19 (31.7)
Urinary incontinence	20 (33.3)
Anticonvulsant agents Prescribed in the ED	
Phenytoin	30 (50.0)
Sodium Valporate	10 (16.7)
Levetiracetam	0 (0.0)
No anticonvulsant prescribed	20 (33.3)
Patient disposition	
Admitted	34 (56.7)
Discharged	26 (26.3

The proportion of study subjects in whom various diagnostic investigations were performed in the ED varied from 97% who had Urea and Electrolyte (U and E) to 5% who had an MRI. Over 75% pf patients had U and E, FBC, blood calcium and CT scans performed. Between 60 and 75% of patients had renal function tests, lumbar punctures, C-reactive protein, venous blood gases, magnesium and blood glucose done. EEGs were only done in 10% of patients. Abnormalities of selected laboratory parameters found in the study population were; hyponatraemia (43%), hypocalcaemia (58%), elevated urea (18%) hypoglycaemia (27%), elevated white cell count (15%) and high C-reactive protein (63%). All blood tests

were performed in the majority of patients with the highest number for a full blood count and the lowest C-reactive protein (Figure 3.1).



U+E = electrolytes and urea, FBC = full blood count, CTB = computed tomography scan of the brain, CRP = C-reactive protein, EEG = electroencephalogram, MRI = magnetic resonance imaging scan

Figure 3:1: Diagnostic investigations performed in the study population

Very few patients had an EEG or an MRI done. No patients had an ECG done. Among the subjects that had a CTB performed, 31 (68.9%) scans yielded positive findings whereas, only 2 of the 41 lumbar punctures (4.9%) that were performed yielded positive findings. Cryptococcus neoformans was the organism identified in both cases.

Table 3:3: Association between Seizure type and socio-demographic factors and biochemical parameters

	Generalized n=48	Focal n=5	P value#
Variables	**No (%)**	**No (%)**	
Gender			0.08
Male	29 (60.42)	1 (20.0)	
HIV status			0.67
Positive	12 (25.0)	2 (40.0)	
Negative	18 (37.5)	2 (40.0)	
Unknown	18 (37.5)	1 (20.0)	
Patient Disposition			0.93
Admitted	28 (58.3)	3 (60.0)	
Discharged	20 (41.7)	2 (40.0)	
Individual providing the clinical history			
Patient (self)	16 (34.04)	4 (80.0)	0.36
Relatives	11 (23.4)	0.00	
Friends or passer-by	4 (8.51)	0.00	
Prehospital crew member	16 (34.04)	1 (20.0)	
Biochemical parameters (Mean(SD)			P value*
Sodium (mmol/L)	137 (7.7)	138.3(5.1)	0.79
Potassium (mmol/L)	4.0 (3.8)	4.0 (0.7)	0.86
Calcium(mmol/L)	1.5 (0.6)	1.7 (0.5)	0.51
Urea (mmol/L)	5.6 (3.8)	3.7 (1.0)	0.16
Glucose (mmol/L)	7.0 (3.1)	7.1 (3.7)	0.91
White blood cell (X109)	9.6 (4.0)	9.8 (8.5)	0.93
C-Reactive Protein (mg/L)	41.9 (55.7)	56 (64.5)	0.63

=Fischer's Exact test *=unpaired T-test.

Hypoglycaemia (26.7%), ring enhancing space occupying lesions (16.7%) and cerebrovascular infarctions (11.7%) accounted for approximately half of possible causes of first-onset seizures (Figure 3.2). Neurocysticercosis was attributed as the cause of the ring enhancing space occupying lesions in 2 (3.33%) of the cases. There was no obvious cause for the seizure in 13 (21.7%) cases.

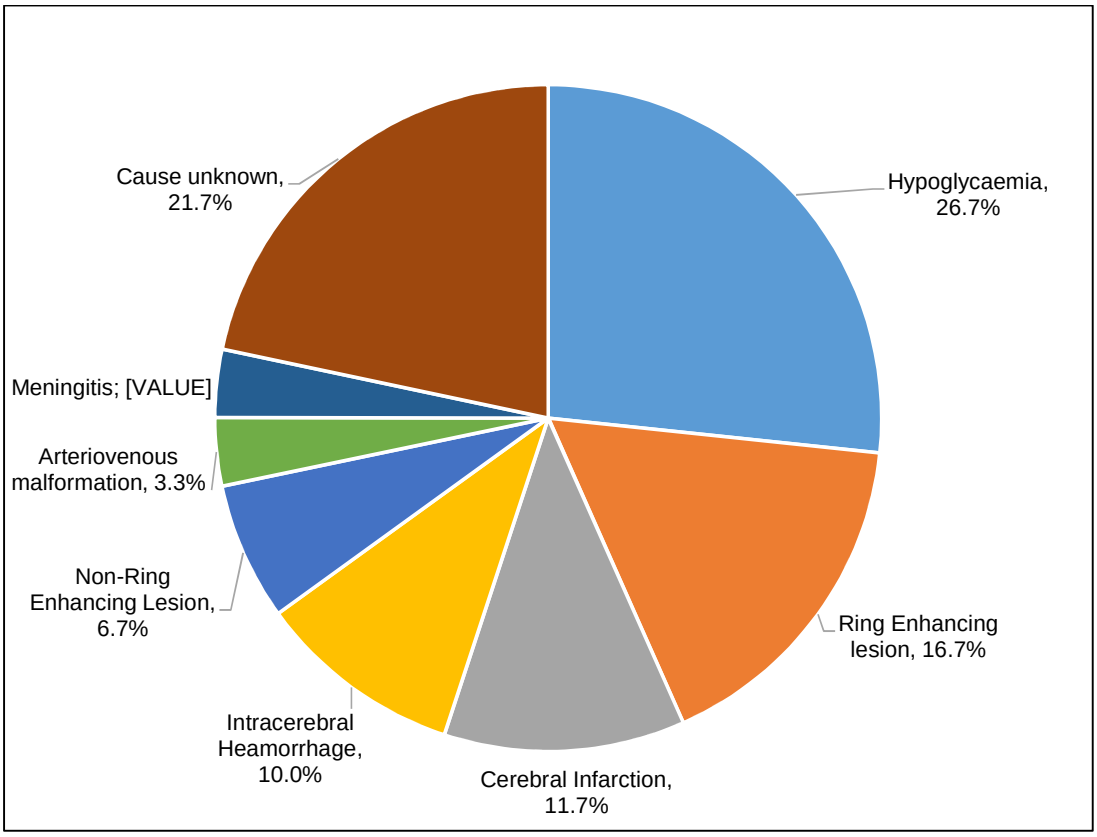


Figure 3:2: Underlying potential aetiology of first-onset seizures in the study population

Phenytoin was the most commonly prescribed long-acting anticonvulsant agent in the ED, whereas sodium valproate was the most commonly prescribed long-acting anticonvulsant agent prescribed at hospital discharge (15.0%). No anticonvulsant agent was prescribed by the ED doctor in 20 (33.3%) subjects. There was no significant association between the seizure type and other parameters with retroviral status in this study (Table 3.4).

Table 3:4: Comparison of HIV positive and negative patients with some selected variables

	Generalized n=48	Focal n=5	P value#
Variables	No (%)	No (%)	
Gender			0.08
Male	29 (60.42)	1 (20.0)	
HIV status			0.67
Positive	12 (25.0)	2 (40.0)	
Negative	18 (37.5)	2 (40.0)	
Unknown	18 (37.5)	1 (20.0)	
Patient Disposition			0.93
Admitted	28 (58.3)	3 (60.0)	
Discharged	20 (41.7)	2 (40.0)	
Individual providing the clinical history			
Patient (self)	16 (34.04)	4 (80.0)	0.36
Relatives	11 (23.4)	0.00	
Friends or passer-by	4 (8.51)	0.00	
Prehospital crew member	16 (34.04)	1 (20.0)	
Biochemical parameters (Mean(SD)			P value*
Sodium (mmol/L)	137 (7.7)	138.3(5.1)	0.79
Potassium (mmol/L)	4.0 (3.8)	4.0 (0.7)	0.86
Calcium(mmol/L)	1.5 (0.6)	1.7 (0.5)	0.51
Urea (mmol/L)	5.6 (3.8)	3.7 (1.0)	0.16
Glucose (mmol/L)	7.0 (3.1)	7.1 (3.7)	0.91
White blood cell (X109)	9.6 (4.0)	9.8 (8.5)	0.93
C-Reactive Protein (mg/L)	41.9 (55.7)	56 (64.5)	0.63

All comparisons done with a Fischer's exact apart from # which was done by a Mann-Whitney test

3.3.5. Discussion

We recruited a total of 60 patients with a history of first-onset seizures who presented to the emergency department at CMJAH over a period of 6months. There were more males than females in this study and the median age of the study population was 37 years. Most of the patients had more than 2 symptoms. The median time of presentation to the ED after the seizure was 2 hours. Hypoglycaemia accounted for possible cause of seizure in a good number of the study subjects. Though there was a high yield of positive CT scan in this

study, there was no association with the HIV status. Despite the utility, cost effectiveness and ready availability of ECG in our ED none of the study subjects had an ECG on done in the ED.

In our study, the most common age at presentation was between 30-39years of age which was similar to a study done in the Western Cape Province in South Africa (3). More males than females' patients presented with first onset seizures in this study which was also comparable to other studies (21, 22), but was in contrast to the data from the Western Cape Province, South Africa (3). A study conducted in rural North-East South Africa showed that males were more than twice as likely to develop active convulsive epilepsy (5).Similar to findings of a French based study, where a first-onset seizure was twice as likely to be generalized than focal (4, 23), generalized seizures were also the predominant seizure type in this study. This proportion does not occur in all studies. A study from South India showed that partial seizures made up the majority (56%) of first-onset seizures (21).

New-onset seizures in HIV positive individuals may be secondary to intracranial opportunistic infections, other non-infection related intracranial space occupying lesions, metabolic derangements and antiretroviral medications (22). New-onset seizures have been reported in up to 20% of HIV-infected individuals (24). As expected due to the high incidence of HIV in South Africa, 28% of the study population were HIV positive. However, the high incidence of HIV in our study has no statistical significance with seizure type or abnormal CT scan findings. Our result was similar to finding by Wagner et al in which HIV was not found to be a risk factor for acute convulsive epilepsy in the rural Northeast of South Africa (5).

Our study showed a median time of arrival to the ED to be 2 hours after the onset of seizures. This was similar to a study by Hillman et al in which the median delay for

paramedic arrival at the scene for patient with seizure episodes was 30 min, initiation of out-of-hospital Anti –Epileptics Drugs (AED) 1 h 10 min, arrival at the ED 1 h 45 min, and initiation of AED in the ED 2 h 11min (25). A median time of 2h 25minutes was found in a study by Kämppi, Ritvanen, Mustonen and Soinila (26) for patient's arrival at the tertiary hospital in Helsinki, Finland after seizure onset (26). This shows that the challenges of the paramedics with regards to patients transport are similar in other parts of the world.

Based on clinical observation, the time taken to return to baseline neurological function after the seizure episode witnessed in the ED was 30 mins in this study compared to a study that made use of EEG monitoring that reported the average time as 35-109 minutes for focal seizures and 53-158 minutes for generalized seizure (15).This means that an average of about 160 minutes may be allowed before concluding that a patient failed to return to baseline, provided there is no ongoing seizures during this observation time in which case it will be termed status epilepticus and immediate intervention will be required to avoid further brain damage.

According to the literature the most common electrolyte abnormalities associated with seizures are disorders of glucose and sodium, particularly hypoglycemia and hyponatremia of less than 120 mmol/l (4, 26). Between 18 and 58% of patients in our study had at least one of these abnormalities. Although the renal and electrolyte profile were measured in almost all (96.7%) subjects, it is concerning that the glucose was only documented in 71.7% of subjects even though hypoglycemia was suspected to be the largest possible single cause (26.7%) of first-onset seizures in our study. Since determination of finger prick glucose is quick, easy and inexpensive and hypoglycemia can be easily reversed, the blood glucose level should be routinely measured in all new-onset seizure patients.

There are no guidelines in South Africa for the investigation of adults presenting with first-onset seizures (3). While Magnetic Resonance Imaging is considered the imaging modality of choice in patient with new-onset seizures due to cost and non-availability in most hospitals, CTB is done (8). The yield of positive CTB findings in our study was 68.9%, which was comparable to a study conducted in India [9]. Positive CTB findings have ranged from 12% to 41% in other studies (8-10). The higher yield in our study has no association with the HIV status of the study population. Compared to the study by Lalchan et al. that was conducted in India where neurocysticercosis was detected on 36.8% of CTB's, neurocysticercosis was only diagnosed in 2 subjects (3.3%) in our study. Despite the utility and recommendations, an ECG was not done in any of the study subjects. Since ECG is cost effective and readily available in our ED, its omission is likely related to lack of awareness of its value amongst clinicians working in the facility (18-20).

About 67% of study subjects were prescribed long-acting anticonvulsants in the ED as compared to 2% in a study by Breen (11). The routine use of long-acting anticonvulsant agents in a patient with new-onset provoked or unprovoked seizures is not recommended, but each patient should be considered on their own merit (17). The study population were prescribed anticonvulsants as part of the study centre's protocol for patient with seizures.

The rate of admission following first-onset seizures in the literature ranges between 15-46% (11, 27). Our study showed a higher admission rate (56.7%) as compared to these studies. These patients were admitted for further in-hospital management in order to determine the underlying cause of the seizure. The attending doctors ensured that those that were discharged had normal blood test parameters and negative CT scans as recommended by the guideline (17).

In addition to detailed history and thorough physical examination in guiding the management of adults with first onset seizure, basic investigations such as blood glucose, ECG and CT

scan add additional values to the diagnosis and further management in this group of patients in the Emergency Department.

3.3.6. Limitations

Data collection was reliant on the ED doctors entering adequate information in the file, this may have been difficult to achieve due to the busy schedule during most ED shifts. The study is a single-centre study and the result may not be generalizable to other centres in South Africa.

3.3.7. Conclusion

Patients presented with multiple symptoms and multiple different possible causes of first onset seizures. Although most studies showed a low yield for glucose and CTB in patients presenting with first onset seizures, our study showed a high yield from these diagnostic tests. Thus, in resource limited settings, glucose and CTB are suggested as key diagnostic investigations among patients presenting with first onset seizures.

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4. CHAPTER FOUR: GUIDELINE FOR SUBMISSION OF ORIGINAL ARTICLE TO AFRICAN JOURNAL OF EMERGENCY MEDICINE (AFJEM)

Original Article: Original studies of basic or clinical investigations in areas relevant to emergency medicine. Reference to the relevance of the research in a resource poor setting is essential and should be alluded to in the discussion section. References and a structured abstract (see Preparation below) are required. Maximum length: 3,000 words, 5 tables and/or figures, plus the abstract (300 words) and references (max 50). The checklists found on the following websites should be used to structure your manuscript (a copy of the checklist indicating which elements of the reporting format you adhered to, a signed conflict of interest form and Author statement form - see below- should be submitted with your manuscript):

a) For randomised control trials: http://www.consort-statement.org
b) For cohort, case-control, and cross-sectional studies: http://www.strobe-statement.org/
c) All other studies: http://www.equator-network.org/

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Please submit your article via https://www.evise.com/profile/api/navigate/AFJEM

Submission Checklist

You can use this list to carry out a final check of your submission before you send it to the

journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

• E-mail address

• Full postal address

All necessary files have been uploaded:

Title page

Cover letter

Manuscript:

• Include keywords

• All figures (include relevant captions)

• All tables (including titles, description, footnotes)

• Ensure all figure and table citations in the text match the files provided

• Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)

Conflict of Interest Form

Supplemental files (where applicable): Author Statement document and relevant reporting checklist

Further considerations

• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet)

• A competing interests statement is provided, even if the authors have no competing

interests to declare

• Journal policies detailed in this guide have been reviewed

• Referee suggestions and contact details provided, based on journal requirements

STROBE Statement—checklist of items that should be included in reports of observational studies

Table 4:1: STROBE checklist

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Yes**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Yes**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Yes**
Objectives	3	State specific objectives, including any pre-specified hypotheses	**Yes**
Methods			
Study design	4	Present key elements of study design early in the paper	**Yes**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Yes**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**Yes**
		(*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**Yes**
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**Yes**
Bias	9	Describe any efforts to address potential sources of bias	**Yes**
Study size	10	Explain how the study size was arrived at	**Yes**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**NA**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Yes**
		(*b*) Describe any methods used to examine subgroups and interactions	**Yes**
		(*c*) Explain how missing data were addressed	**Yes**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**N/A**
		(*e*) Describe any sensitivity analyses	**N/A**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	**Yes**

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	**Yes**
		(c) Consider use of a flow diagram	**N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Yes**
		(b) Indicate number of participants with missing data for each variable of interest	**Yes**
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	**N/A**
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures	**Yes**
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**N/A**
		(b) Report category boundaries when continuous variables were categorized	**Yes**
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**Yes**
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of

PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

APPENDIX ONE: DATA COLLECTION TOOL

Study code:_____

1	**Demography**	Age: Sex: Male Female
2	**HIV Status**	Positive Negative Unknown
3	**Informant**	Patient Relative(s) Friend(s) Passer-by EMS crew
4	**Seizure Type**	Generalized Focal Unknown

5

History of presenting complaints (Time of seizure episode)

		Sec	Min.	Hours
a	Time of onset of seizures			
b	Duration of seizures			
c	Time of presentation to the ED after commencement of seizures			

B. Description of the seizure type

Any warning signs noted before the seizure? **Yes** **No** **If Yes,**
List:_____
What did the patient do during the seizure? **[Tick as many of the following that apply in this case]**

	Tick		Tick		Tick
Loss of consciousness.		Wets pant		Tongue biting	
Foaming from the mouth		Rigid extremities		Lip smacking	
Sweating		Unable to talk		Noisy breathing	
Head banging		Staring			

Was the patient able to respond to questions during the seizure? **Yes** or **No**
How long does it take for the patient to get back to baseline condition? _____
Is anything known to precipitate the seizures? **Yes** or **No**. If yes, list_____

C. Past Medical History

	Tick		Tick
Hypertension		Renal failure	
Diabetics		Liver failure	
Others (List)			

6	Examination	General Examination.				(b) CNS Examination	
			Record here		Tick		Tick/record
		Temp.		Jaundice		Neck stiffness	
		Resp. Rate		Palor		GCS	
		Pulse Rate		Cyanosis		Pupil Size & reaction	
		B.P		Sweating		Post-ictal paralysis	
		Oxygen Sat in room Air		Others			

(C) Associated injuries following the seizure episode (List)

(D) Other systems: List abnormalities.

7. **Investigations done for patients with first onset seizures**

ABG		BLOOD TESTS		CSF ANALYSIS				CT SCAN	
	VALUE		VALUES		YE	NO	NAD		YE
PH		Glucose		Meningitis				Neurocystioercosis	
PCO2		Sodium		TBM				TBM	
PaO2		Potassium		Crypto				Infarct	
BE		Calcium		Neurocysticercosis				Raised Intracranial	
HCO3		Urea		Malaria				Bleed or	
Hb		White cell		Viral				Other	
Lactate		CRP		**CSF**	**VALUES**				
		Malaria		WCC					
		Creatinine		Red cells					
				Glucose					
				Protein					
				Pressure					
				Colour					

8	**Disposition**	**(a)** Admitted		(b) Discharge	

APPENDIX TWO: INFORMATION SHEET AND INFORMED CONSENT

Introduction

Good day, my name is Dr. Sunday Sofola-Orukotan and I am a registrar in emergency medicine at the University of the Witwatersrand. I would like to invite you to consider participating in a research study, entitled "**Presentation of Adults with First-Onset seizures at a Tertiary Hospital in Gauteng".**

1. Before agreeing to participate, it is important that you read and understand what is involved. This information leaflet is to help you understand and decide if you would like to participate. If you have any questions, do not hesitate to ask the Doctor who asked you to participate in the project.
2. You should not agree to take part unless you are satisfied about all the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

Purpose of the study:

Adult first-time seizure is a common reason for admission into the Emergency Department (ED). This study aimed at investigating the predisposing factor/s responsible for first-time seizures among adults presenting to the Emergency Department. The information learned from this study will be used to improve care for adult patients presenting with first time seizures to the public hospitals in future

Procedures:

If you agree to take part in this study, your file will be reviewed after your doctor has concluded treatment on you and necessary information will be extracted from the file.

Will any of these study procedures result in discomfort or inconvenience?

No. Your hospital file will be used after the treatment is completed.

Unforeseen Risks: There are no unforeseen risks that agreeing to partake in this study places you in, over and above those normally encountered in the routine treatment and investigation of patients with first time seizures.

Benefits: There is no direct potential benefit that you will derive from agreeing to partake in this study.

Rights as a participant in this study: Your participation in this study is entirely voluntary and you can decline to participate without stating any reason. Your withdrawal will not affect your access to other medical care.

Ethical Approval: This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee. They can be contacted via Zanele Ndlovu, at 011-717-1234. Email;**zanele.ndlovu@wits.ac.za**

For **research information** you can contact Dr Sunday Sofola-Orukotan at 0630652008, email:ssofola@yahoo.com

Confidentiality: We will not write down your name or other personal information. The information you give us is anonymous and all information obtained during the investigation will be strictly confidential.

INFORMED CONSENT

- I hereby confirm that I have been informed by the study doctor, _____, about the nature, conduct, benefits and risks of clinical study "**Presentation of Adults with First-Onset seizures at a Tertiary Hospital in Gauteng**."
- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- I understand that if I have concerns about the project, I may contact the administrator of the Human research committee Ms Zanele Ndlovu on 011-717-1234 or email: zanele.ndlovu@wits.ac.za .

PARTICIPANT:

Printed Name	Signature / Mark or Thumbprint	Date and Time

I, _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY DOCTOR:

Printed Name	**Signature**	**Date and Time**

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT…… (DESIGNATION):

Printed Name	**Signature**	**Date and Time**

APPENDIX THREE: WITS PLAGIARISM STATEMENT

I **DR. SUNDAY OLADAPO SOFOLA-ORUKOTAN** (**Student number: 1308916**), a Master of Medicine (MMED) in Emergency Medicine student at the Division of Emergency Medicine, University of the Witwatersrand declare that;

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted by me for assessment for the above programme is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I confirm that I understand that my work may at any time be submitted to an electronic plagiarism detection system.
- I understand that the University of the Witwatersrand will not award me the desired degree if there is a belief or evidence that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:  **Date: 11th January, 2019**

APPENDIX FOUR: ETHICAL CLEARANCE CERTIFICATE

R14/49 Dr Sofola-Orukotan Sunday Oladapo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160502

NAME: (Principal Investigator)	Dr Sofola-Orukotan Sunday Oladapo
DEPARTMENT:	Emergency Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Presentation of Adults with First-onset Seizures at Tertiary Hospital in Gauteng, South Africa
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Feroza Motara and Dr Alison Bentley
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/08/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

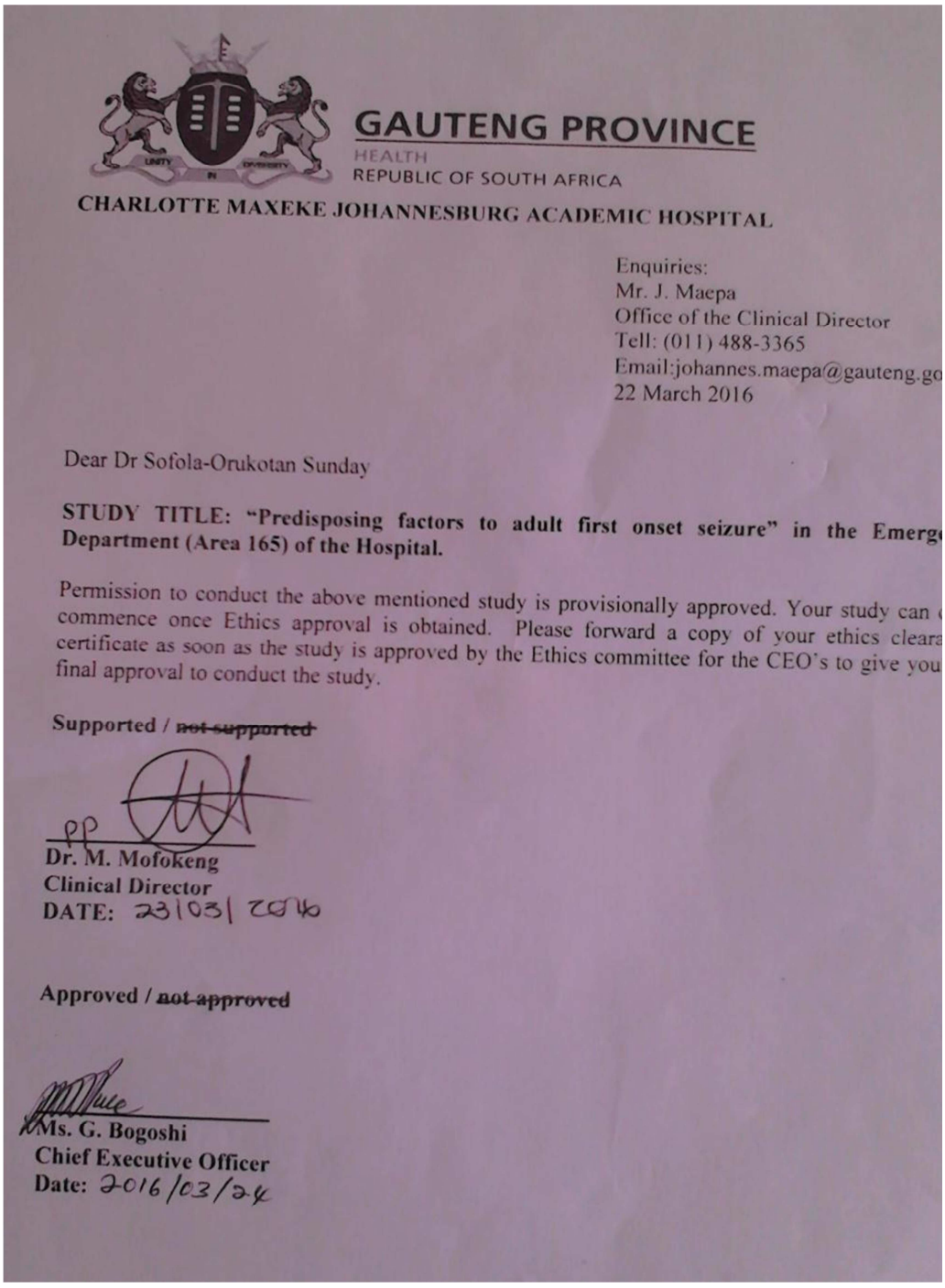
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year.

Principal Investigator Signature

Date 21/08/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX FIVE: APPROVAL FROM THE CEO OF THE STUDY CENTER



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.go
22 March 2016

Dear Dr Sofola-Orukotan Sunday

STUDY TITLE: "Predisposing factors to adult first onset seizure" in the Emerg Department (Area 165) of the Hospital.

Permission to conduct the above mentioned study is provisionally approved. Your study can commence once Ethics approval is obtained. Please forward a copy of your ethics clearance certificate as soon as the study is approved by the Ethics committee for the CEO's to give you final approval to conduct the study.

Supported / ~~not supported~~

pp
Dr. M. Mofokeng
Clinical Director
DATE: 23/03/2016

Approved / ~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
Date: 2016/03/24

APPENDIX SIX: APPROVAL OF RESEARCH TOPIC

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050

Fax: 027117172119

Tel: 02711 7172076

Reference: Mrs Sandra Benn

E-mail: sandra.benn@wits.ac.za

04 January 2019

Person No: 1308916

PAG

Dr SO Sofola-Orukotan

1508 Fitzpatrick Residence,

Johannesburg Hospital Quarters, Jubilee Road

Parktown

2193

South Africa

Dear Dr Sunday Sofola-Orukotan

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Presentation of first onset seizures in Adults ata tertiary hospital in South Africa* has been approved. Please note that any amendments to this title haveto be endorsed by the Faculty'shigher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn

Faculty Registrar

Faculty of Health Sciences

APPENDIX SEVEN: APPROVAL CHANGE OF TITLE OF RESEARCH

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050

Fax: 027117172119

Tel: 02711 7172076

Reference: Mrs Sandra Benn

E-mail: sandra.benn@wits.ac.za

04 January 2019

Person No: 1308916

TAA

Dr SO Sofola-Orukotan

1508 Fitzpatrick Residence,

Johannesburg Hospital Quarters, Jubilee Road

Parktown

2193

South Africa

Dear Dr Sunday Sofola-Orukotan

Master of Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From: **Predisposing factors to adult first-onset seizures in a tertiary hospital in Gauteng Province, South Africa**

To: **Presentation of first onset seizures in Adults at a tertiary hospital in South Africa**

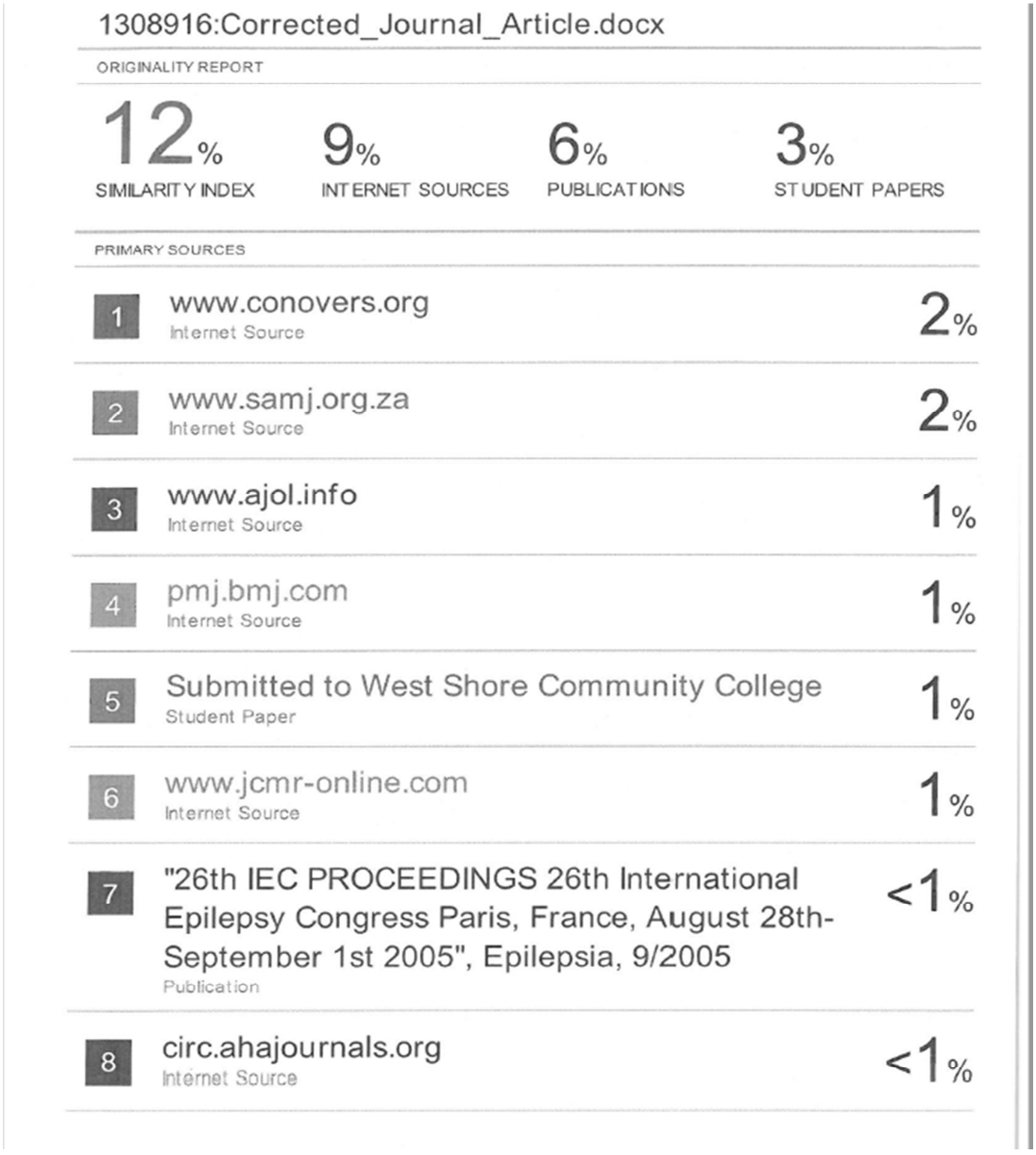
Yours sincerely

Mrs Sandra Benn

Faculty Registrar

Faculty of Health Sciences

APPENDIX EIGHT: TURNITIN REPORT



1308916:Corrected_Journal_Article.docx

ORIGINALITY REPORT

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