

An audit of CTB findings in adults with new-onset seizures in a resource restricted setting in South Africa

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Declaration

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25/01/2022

Student's contribution to article

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- Study concept and design.
- Primary compilation of the protocol and literature review.
- Data collection and analysis.
- Compilation of the manuscript.
- Submission of the manuscript to the publishing journal.
- Corresponding author in editing process of the published article.
- Primary author of the published article.

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, **Sabelo Herbert Mabaso**, student number **1822378**, declare that this Dissertation is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my Dissertation.

Signature of Student  Date **21/01/2022**.....

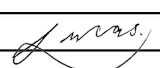
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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his Thesis/Dissertation/Research Report.

Article 1: Title: An audit of CT brain findings in adults with new-onset seizures in a resource restricted setting in South Africa

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Dedication

In memory of my mother, Zanele Zandile Mabaso, 1964-2004

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List of abbreviations and terminology

CECT	Contrast enhanced computed tomography
CHBAH	Chris Hani Baragwanath Academic Hospital
CSF	Cerebrospinal fluid
CTB	Computed tomography of the brain
ED	Emergency Department
EEC	Electroencephalogram
FBL	Focal brain lesion
GCS	Glasgow coma scale
HIV	Human immunodeficiency syndrome
ICH	Intracerebral haemorrhage
LP	Lumbar puncture
MRI	Magnetic Resonance Imaging
NECT	Non-enhance computed tomography
NHLS	National laboratory services
NIC	No identified cause
PACS	Picture archive and communication system
TBM	Tuberculous meningitis
WHO	World Health Organization

Chapter 1: Article for publication

The following PDF insert is an article submitted published in the SA Journal of Radiology

An audit of CT brain findings in adults with new-onset seizures in a resource restricted setting in South Africa

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Background: Globally, adults presenting with seizures account for 1% – 2% of visits to emergency departments (EDs), of which 25% are new-onset seizures. Neuroimaging is essential as part of the initial workup. Multiple studies have demonstrated abnormal CT brain (CTB) findings in these patients.

Objectives: To review the CTB findings in adults presenting with new-onset seizures in a resource restricted setting.

Method: A retrospective review of 531 CTBs was conducted at a tertiary hospital in Gauteng on adults presenting to the ED with new-onset seizures.

Results: The mean age of the patients was 45.6 ± 17.1 years, and the male to female ratio was 1.2:1. Generalised and focal seizure types were almost equally represented. Of the total 531 patients, 168 (31.6%) were HIV positive. The CTB findings were abnormal in 257 (48.4%) patients, albeit vascular pathology accounted for 21.9%. Infective pathology accounted for 14.1% with a statistically significant association with HIV ($p = 0.003$). Trauma related pathology was 2.4%, whilst neoplastic pathology was seen in 3.0%. Other causes included congenital pathology, calcifications, atrophy and gliosis. Clinical factors associated with abnormal CTB findings were age ≥ 40 years, HIV infection, hypertension, focal seizures, low Glasgow Coma Scale (GCS), raised cerebrospinal fluid (CSF) protein and presence of lymphocytes.

Conclusion: A high yield of abnormal CTB findings was noted in adult patients who presented with new-onset seizures, supporting the use of urgent CTB in patients with certain clinical risk factors. Patients without these risk factors can be scanned within 24–48 h in a resource restricted setting.

Keywords: new-onset; first-onset; adult-onset; seizure; CT findings.

Introduction

Globally, adults presenting with seizures account for up to 2% of visits to medical emergency departments (EDs)^{1,2,3,4} and of these, 25% are new-onset seizures.^{1,5} It is estimated that 5% – 10% of the population will experience a seizure in their lifetime.^{3,6,7}

According to Gavvala and Schuele,⁵ seizures represent ‘a transient occurrence of signs and symptoms due to excessive neuronal activity in the brain’. They may be classified simply as focal (affecting a single cerebral hemisphere), generalised (affecting both hemispheres) or unknown^{1,5}. In a clinical setting, seizures are defined in a specific manner. Gavvala and Schuele⁵ described them as follows: unprovoked seizure, occurring without precipitating factors; acute asymptomatic seizure, occurring in close temporal relationship with a transient brain insult; focal seizure, affecting one part of cerebral hemisphere; generalised seizure, distributed in both cerebral hemispheres; and epilepsy, an enduring predisposition to generate seizures.

The estimated incidence rate of adult-onset seizures is 81.7 per 100 000 per year in developing countries compared to 45.0 per 100 000 per year in developed countries, as reported by Ba-Diop et al.⁸ The incidence rate of new-onset adult seizures is higher in HIV positive populations.⁹ Another study noted that the majority of patients that were severely immunosuppressed had an underlying, identifiable intracranial abnormality,¹⁰ confirming the predisposition of patients with advanced HIV to opportunistic infections as a cause of new-onset seizures.

Patients with new-onset seizures require imaging as part of their clinical workup.¹ Multiple international studies have demonstrated varying degrees of abnormal CT brain (CTB) findings,^{3,5,7} however, the urgency or optimal timing of imaging has not yet been determined. Computed tomography is the initial imaging of choice, being the most practical, especially in the emergency

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setting and for those requiring follow-up imaging to monitor disease progression.^{6,7} Magnetic resonance imaging (MRI) may be utilised as supplementary imaging, where CTB findings are inconclusive or for further characterisation.^{3,5}

The purpose of this study was to determine the underlying CTB findings in adults with new-onset seizures and to identify specific risk factors, if any, that may contribute to the urgency or timing of imaging.

Research methods and design

A retrospective cross-sectional study of 531 adult patients was conducted, reviewing the CTB findings in cases with new-onset seizures at a tertiary hospital in Gauteng, South Africa, between 01 January 2016 and 31 December 2018. Patients with missing data, illegible reports, those presenting with acute trauma, repeat scans for patients with a known diagnosis and CTB findings not reviewed by a consultant radiologist were excluded from the study.

Clinical information including patient age, sex, type of seizure (generalised, focal or status epilepticus) and co-morbidities (including HIV status) were accessed and recorded from the hospital picture archiving and communication system (PACS). Relevant laboratory results were accessed from the National Health Laboratory Services (NHLS) and relevant clinical data were recorded and tabulated using an anonymous data collection sheet.

Categorical variables were expressed as numbers and percentages and compared with the chi-square test. Continuous variables with a normal distribution were expressed as means and standard deviation (s.d.). The median and interquartile ranges (IQR) were used for continuous variables with a non-normal distribution. The one-way analysis of variance (ANOVA) was used to compare normally distributed continuous variables and the Kruskal-Wallis rank test was used to compare medians for non-normal data. Differences between groups were considered statistically significant at $p < 0.05$. All analyses were conducted using STATA MP version 13.0 (StataCorp, Texas).

Ethical considerations

The study was approved by Human Research Ethics Committee of the University of the Witwatersrand, certificate number M190609. Participant consent was not required as this was a retrospective record review and to maintain strict anonymity, no personally identifiable information was recorded.

Results

Of the included 531 patients, 285 (53.7%) were male. The ages ranged from 18 to 95 years with a mean age of 45.6 years (s.d.: ± 17.1) and a median age of 44 years (IQR: 32–59 years). Demographic data and major abnormal findings are presented in Table 1.

Clinical and laboratory data

There were 94 (17.7%) focal seizures, 95 (17.9%) generalised seizures and 14 (2.6%) cases of status epilepticus; 328 (61.8%) were undocumented. The Glasgow Coma Scale (GCS) was documented in 104 patients with a median GCS of 13 (IQR: 9–14). The GCS was < 8 in 16 (15.4%) patients, between 9 and 12 in 29 (27.9%) patients and between 13 and 15 in 59 (56.7%) patients. Abnormal CTB findings were more frequent in patients with a GCS ≤ 12 ($p = 0.175$).

A total of 168 (31.6%) patients were HIV positive, while 225 (42.4%) had undocumented HIV statuses. There was a significantly high prevalence of HIV in the 30–49 years age group ($p < 0.001$). The CD4 count was documented in 124 HIV positive patients with a median CD4 count of 229 cells/ μL (IQR: 52 cells/ μL – 430 cells/ μL); 48.4% were below 200 cells/ μL .

Hypertension was present in 78 (14.7%) patients. There was a statistically significant prevalence of hypertension above the age of 49 years ($p < 0.001$). Diabetes mellitus was documented in 23 (4.3%) patients and was significantly prevalent above the age of 59 years ($p = 0.001$). There were 16 (3.0%) patients with chronic kidney disease and 42 (7.9%) with other co-morbidities including 18 (3.3%) cases of tuberculosis, 11 (2.1%) cases of known primary malignancy, 4 (0.8%) cases of eclampsia, 6 (1.1%) cases of systemic lupus erythematosus and 3 (0.6%) cases of liver disease.

Laboratory data included renal function, full blood count and cerebrospinal fluid (CSF) analysis. A high prevalence of abnormal CTB findings was seen in patients with a white cell count above $10.0 \times 10^9/\text{L}$ ($p = 0.011$). Abnormal CTB findings were also more prevalent in patients with a CSF protein above 0.45 g/L ($p = 0.033$); CSF lymphocytosis was significantly associated with abnormal CTB findings ($p = 0.004$).

CT brain findings

The CTB findings were abnormal in 48.4% of the cases. The aetiologies of the abnormal CTB findings are presented in Table 2. Of the 116 vascular cases, 60 (51.7%) had infarcts, 12 (10.3%) intracerebral haemorrhages and 3 (2.6%) vascular malformations. There were 41 (35.4%) cases of vascular pathologies related to white matter changes, of which most were suggestive of chronic small vessel ischemic disease and posterior reversible encephalopathy syndrome. Selected images of vascular related pathology are demonstrated in Figure 1.

TABLE 1: Demographic data of patients presenting with new-onset seizures.

Characteristics	All patients (n = 531)	HIV positive (n = 168)	Abnormal CTB (n = 257)	Major categories of abnormal CTB	
				Vascular (n = 116)	Infective (n = 75)
%	100.0	31.6	48.4	21.9	14.1
Mean age (years)	45.6	42.4	51.3	59.6	41.0
Median age (years)	44.0	41.0	50.0	62.0	40.0
M: F (male: female)	1.2: 1	1: 1.2	1.4: 1	1: 1.1	1.8: 1

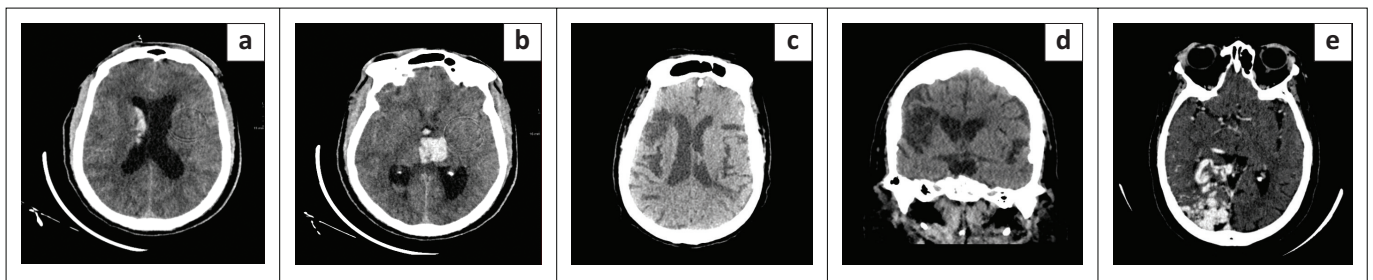
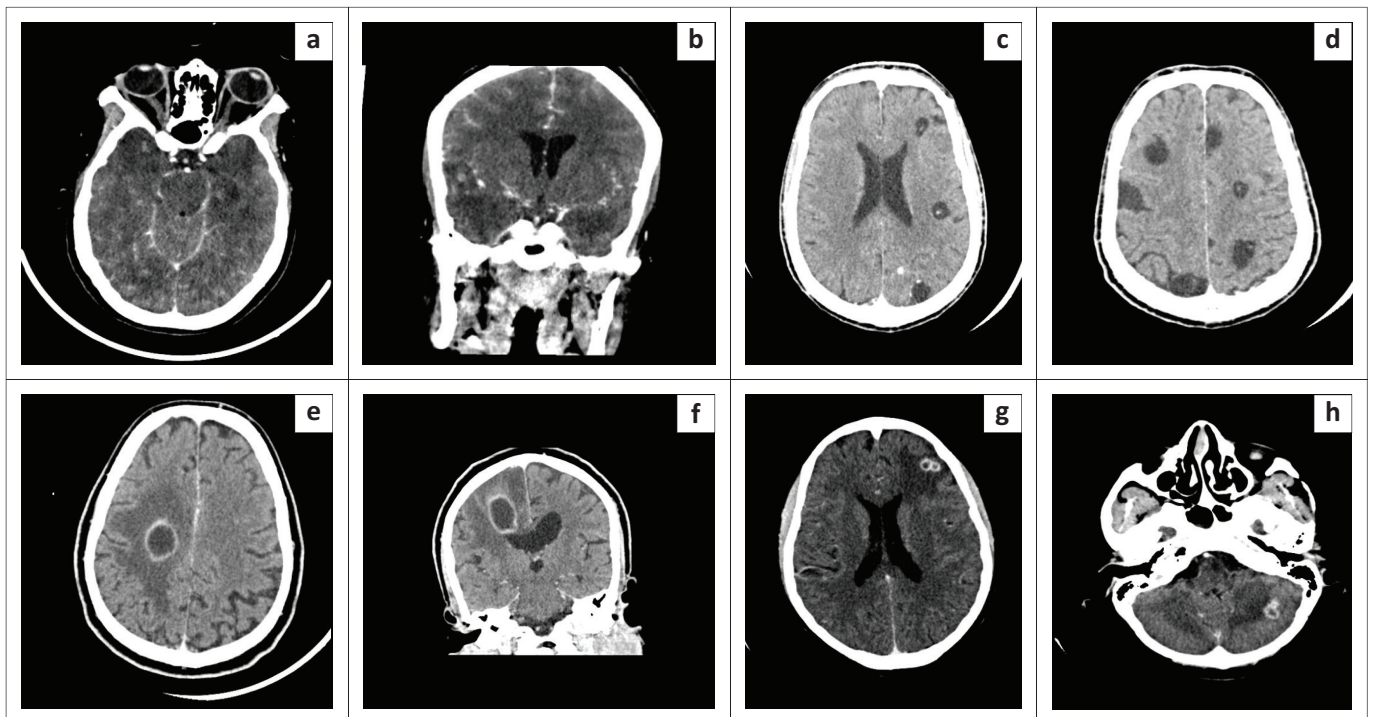
CTB, CT brain; HIV, human immunodeficiency virus.

TABLE 2: Proportions of abnormal CTB findings and cause categories in patients with new-onset seizures.

Neuroimaging findings	Frequency (n = 531)	Percentage
CTB findings:		
Normal CTB findings	274	51.6
Abnormal CTB findings	257	48.4
Pathology categories:		
Vascular	116	21.9
Infective	75	14.1
Neoplastic	16	3.0
Trauma	13	2.4
Congenital	5	0.9
Other	32	6.0

CTB, CT brain.

Seven (9.3%) of the 75 infective cases had features suggestive of meningitis, 6 (8.0%) pyogenic abscesses, 14 (18.7%) neurocysticercosis and 3 (4.0%) toxoplasmosis. The other cases were attributable to tuberculosis, cryptococcosis and miscellaneous infective white matter disease disorders. Of the tuberculosis cases, 7 (9.3%) had tuberculous meningitis, whilst 12 (16.0%) were attributable to tuberculomas and tuberculous abscesses. There were 26 (34.7%) cases of white matter changes related to infection, of which herpes encephalitis was seen in 6 (8.0%) patients, cerebritis in 5 (6.7%) cases, suspected HIV encephalopathy in 9 (12%) cases and progressive multifocal leukoencephalopathy in 6 (8.0%) cases. Selected images of infective pathology are shown in Figure 2.

**FIGURE 1:** Vascular pathology as a cause of adult-onset seizures. (a and b) Hypertensive intraparenchymal haemorrhage in a 56-year-old male with newly diagnosed hypertension. Axial non-enhanced CT (NECT): Left thalamic haemorrhage with minimal surrounding oedema. Associated intraventricular blood. (c and d) Chronic right middle cerebral artery territory infarction in an adult patient with index episode of seizures. Axial and coronal NECT: Right MCA territory wedge-shaped hypodensity with mild right lateral ventricular ex vacuo dilatation. (e) Right occipital lobe arteriovenous malformation in a 53-year-old female with no background medical history. Axial contrast enhanced CT (CECT): 'Bag of worms' appearance of draining and feeding vessels in the right occipital lobe.**FIGURE 2:** Infective pathology as a cause of adult-onset seizures. (a and b) Herpes Simplex (HSV) encephalitis in a young immunocompromised female patient. Axial NECT: Bilateral anterior temporal lobe oedema with hyperdense foci in keeping with microhaemorrhages. (c and d) Neurocysticercosis in a 47-year-old male with newly diagnosed HIV. Axial - contrast enhanced CT (CECT): Multiple bilateral non-enhancing round CSF density cystic intra-axial lesions of varying sizes with central hyperdense scolices (dot sign). (e and f) HIV positive patient on tuberculosis treatment. Coronal and axial CECT: Large right frontal lobe ring-enhancing lesion adjacent to the right lateral ventricle. Surrounding vasogenic oedema with associated mass effect. A differential diagnosis of a pyogenic or a tuberculous abscess was given. (g and h) A 53-year-old HIV positive male patient. CD4 = 26 cells/ μ L. Axial CECT: Multiple ring-enhancing lesions with vasogenic oedema in the cerebellum and corticomedullary junction of cerebrum. A differential of toxoplasmosis and tuberculomas was given.

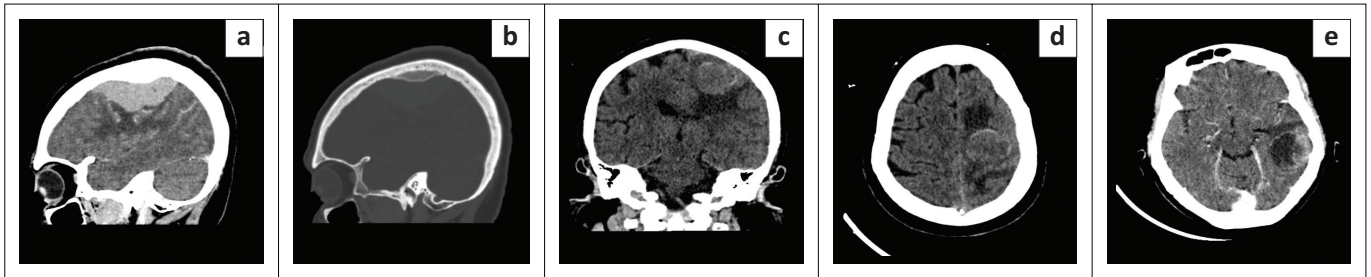


FIGURE 3: Neoplastic pathology as a cause of adult-onset seizures. (a and b) Meningioma in a 64-year-old female with worsening of left arm weakness and new-onset seizures. Sagittal contrast enhanced CT (CECT). (brain and bone window): Large right frontal avidly enhancing extra-axial mass with associated hyperostosis of the adjacent skull inner table as well as mass effect and oedema of the adjacent parenchyma. (c and d) Left frontal lobe mass in a 59-year-old female who presented with new-onset seizures. Axial and coronal non-contrast CT (NCCT): Large left frontal lobe solid round intra-axial heterogeneously hyperdense mass with surrounding vasogenic oedema and mass effect on the frontal horn of the left lateral ventricle. A differential diagnosis of metastases or lymphoma was given. e: Metastasis from endometroid adenocarcinoma of the endometrium. 69-year-old female with endometroid adenocarcinoma of the endometrium who presented with first onset seizures. Axial CECT: Large ring-enhancing solid-cystic intra-axial mass in the left temporal lobe corticomedullary junction with surrounding oedema.

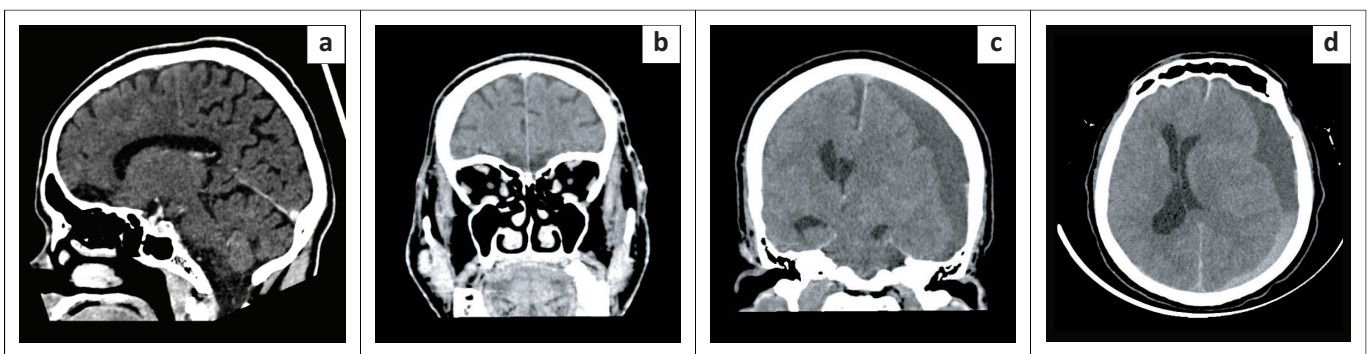


FIGURE 4: Trauma related pathology as a cause of adult-onset seizures. (a and b) Bilateral rectus gyri gliosis in a 49-year-old male with new-onset seizures. Sagittal and coronal contrast enhanced CT (CECT): Hypodensities of bilateral rectus gyri consistent with gliosis. (c and d) Left acute subdural hematoma in a 72-year-old male with new-onset seizures and confusion. Axial and coronal non-enhanced CT (NECT): Large left mixed density subdural hematoma with a haematocrit level. Associated subfalcine and uncus herniation with right lateral ventricle entrapment hydrocephalus.

Neoplastic pathologies were seen in 16 (3.0%) of the patients, of which 9 were primary central nervous system (CNS) neoplasms whilst 7 were secondary CNS neoplasms. Selected images of neoplastic pathology are shown in Figure 3. The CT findings in neoplastic or infective cases were diagnosed largely on clinical and imaging work up and treated accordingly. Not all cases had histological or microbiological confirmation at the time of the study.

A total of 13 (2.4%) traumatic pathologies were recorded. These were subdural hematoma and old depressed fractures with underlying encephalomalacia. Selected images of trauma related pathology are shown in Figure 4.

Of the 5 (0.9%) cases with congenital pathology, frontoethmoidal encephalocele accounted for 2 cases, with the other 3 cases being arachnoid cyst, schizencephaly and Dandy-Walker malformation. A total of 32 (6.0%) unclassified abnormal CTB findings were recorded, 5 cases of calcifications, 5 of atrophy and 22 of gliosis.

Associations with various CTB abnormalities

Cerebral oedema was present in 40 cases, midline shift in 26 cases, hydrocephalus in 32 cases and herniation in 10 cases. Extra-axial collections were seen in 8 cases associated with

TABLE 3: CTB abnormality in patients with new-onset seizures characterised by site of involvement.

Pathology of abnormal CTB	Site of involvement (n = 531)											
	Frontal lobe		Parietal lobe		Temporal lobe		Occipital lobe		Cerebellum and brainstem		Basal ganglia	
	n	%	n	%	n	%	n	%	n	%	n	%
Vascular	56	10.6	70	13.2	53	10.0	33	6.2	3	0.6	45	8.5
Infective	34	6.4	42	7.0	19	3.6	17	3.2	11	2.1	10	1.9
Neoplastic	5	0.9	4	0.8	5	0.9	4	0.8	1	0.2	1	0.2
Trauma	11	2.1	8	1.5	6	1.1	1	0.2	1	0.2	10	1.9

CTB, CT brain.

infective pathologies. Venous sinus thrombosis was noted in 2 cases associated with infection. Infarction was present in 12 cases associated with infective pathology. There was higher parietal lobe involvement with vascular and infective pathologies. The basal ganglia were more involved with vascular pathology, whilst extra-axial involvement was seen more in infective and traumatic pathologies. This data is presented in Table 3.

The mean age for vascular pathology was 59.6 years and for infective causes, 41.0 years (Table 1). Patients with focal seizures had a high prevalence of abnormal CTB findings ($p = 0.560$). Of the patients with neoplastic pathologies that had a recorded seizure type, 50% had focal seizures. The relationship between various pathology categories and seizure type is shown in Table 4.

TABLE 4: Relationship between seizure type and abnormal CTB categories.

Seizure type	Causes of abnormal CTB (<i>n</i> = 531)											
	Vascular		Infective		Neoplastic		Trauma		Congenital		Other	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Focal	28	5.3	12	2.3	8	1.5	3	0.6	2	0.4	4	0.8
Generalised	18	3.4	21	4.0	2	0.4	4	0.8	1	0.2	3	0.6
Status epilepticus	3	0.6	2	0.4	0	0	1	0.2	1	0.2	0	0
Undocumented	67	12.6	40	7.5	6	1.1	5	0.9	1	0.2	25	5.7

CTB, CT brain.

A large proportion of HIV positive patients had a higher prevalence of infective causes on abnormal CTB imaging ($p=0.003$). There were more infarcts, intracerebral haemorrhages, chronic small vessel ischemic white matter disease and posterior reversible encephalopathy syndrome in patients with hypertension.

Discussion

Relating to demographics, this study demonstrated a gender distribution that was similar to other studies with a male to female ratio of 1.2:1. A study by Zarmehri et al. also consisted of more males, accounting for 62% of their study population.¹¹ In contrast, in a retrospective study performed in South Africa by Smith et al, their study sample consisted of more females, accounting for 61.2%.⁷ Another study by Kaur et al. had 65% male subjects.¹²

The mean age for abnormal CT brain findings in this study was 51.3 years. In the study by Smith et al.,⁷ the common age of presentation of new-onset seizures was between 31 and 40 years. In another study by Zarmehri et al., their study population had a mean age of 39.78 ± 17 years.¹¹ Additionally, this study revealed that elderly patients had more abnormal CTB findings. More vascular pathologies were seen in older patients and more infective pathologies in younger and HIV infected patients. Kaur et al. showed that 68.1% of patients aged below 40 years had idiopathic seizures.¹² This observation suggests that older patients require CTB imaging more urgently than HIV negative younger patients.

Clinically, Smith et al. found that generalised seizures were the commonest seizure type, representing 86.7% of their patients.⁷ A high prevalence of generalised seizures were also reported by Kaur et al. at 59%.¹² In contrast, this study showed that focal and generalised seizures were almost equally represented when the seizure type was documented. There was a high prevalence of abnormal CTB scans in patients with focal seizures, but this was not statistically significant ($p = 0.560$). Yang et al. demonstrated similar findings in children, but no comparable study was found in adults.¹³

The GCS value was recorded in 104 (19.6%) patients. Although there was a high number of abnormal CTB scans seen in patients with $GCS \leq 12$ (29/45 [64.4%]), this number was not statistically significant ($p = 0.175$). Despite the lack of statistical significance, this observation is similar to international literature. Wang et al. demonstrated that altered level of consciousness is a strong predictor of abnormal

CTB findings.¹⁴ In another study by Moolla et al. that looked at adult-onset seizures in HIV positive patients, GCS less than 15 was found to predict space occupying lesions and cerebral oedema.⁹ The lack of statistical significance in this study may be attributable to the low proportion of recorded levels of consciousness.

The HIV prevalence of 31.6% in this study was higher than the 2018 Statistics South Africa report, which estimated the prevalence of HIV at 13.1%. The age group commonly affected by HIV in our study was similar to the 2018 Statistics South Africa report which states that 15–49-year-old patients are predominantly affected.¹⁵ There was a statistically significant relationship between HIV and infective pathology accounting for abnormal CTB findings ($p = 0.003$), owing to vulnerability to opportunistic intracranial infections in this group. In a study by Sinha et al., the majority of HIV infected patients had opportunistic central nervous system infections, ranging from tuberculosis, cryptococcosis, toxoplasmosis and HIV encephalitis.¹⁶ The infections demonstrated in this study included pyogenic abscesses, neurocysticercosis, toxoplasmosis, tuberculosis and cryptococcosis.

The other common comorbidities included diabetes mellitus, hypertension and chronic kidney disease, all of which were common in older patients. However, only hypertension showed a statistically significant relationship with abnormal CTB findings ($p = 0.012$), including infarcts, intracerebral haemorrhages, chronic small vessel ischemic white matter disease and posterior encephalopathy syndrome. This could be explained by an increased risk of stroke and other intracranial complications associated with hypertension. Hesdorffer et al.¹⁷ found that severe uncontrolled hypertension increased the risk of unprovoked seizures and they postulated the mechanism to be that of epileptogenic white matter changes caused by hypertension. Hypertension related central nervous system complications such as intracerebral haemorrhage, subarachnoid haemorrhage and posterior reversible syndrome increase the likelihood of abnormal CTB findings.¹⁸

There was a significant association between a high white cell count (above $10.0 \times 10^9/L$) and abnormal CTB findings ($p = 0.011$). This may be related to infective pathologies but we found no supporting literature in this regard. A study by Khalili et al. found that a raised white cell count has a low positive predictive value and low specificity for bacterial meningitis.¹⁹ Elevated CSF protein (above 0.45 g/L) was significantly associated with abnormal CTB findings ($p = 0.033$) in this study, although this is a retrospective association since lumbar puncture is usually performed after CTB imaging. Zisimopoulou et al. found a correlation between abnormal CSF protein and unprovoked first episodes of seizure, thought to be related to disruption of the blood brain barrier.²⁰ No studies have looked at the direct correlation between abnormal CSF protein and CTB findings. The presence of high CSF lymphocytes showed a statistically significant correlation with abnormal CTB findings ($p = 0.004$). This is supported by the findings in

the study by Zisimopoulou et al., where a high CSF cell count correlated with abnormal CTB findings in 71 patients.²⁰

There were 48.4% abnormal CTB findings in this study. According to the literature, abnormal CTB findings range from 10% to 68.9%,^{5,6,21} most likely underlined by the demographic differences in patients studied as suggested by Adams et al.² Additionally, this study did not differentiate between CTBs performed with or without intravenous iodinated contrast as no significant impact was anticipated. Studied literature indicated that administration of intravenous contrast does little to change the sensitivity of CTB findings.^{1,22,23,24}

Vascular pathology accounted for 21.9% of abnormal CTB findings. These results are similar to a South African study by Smith et al., where vascular pathology contributed a larger proportion of CTB abnormalities, with infarcts accounting for 25% and intracerebral haemorrhage 12.5%.⁷ Similarly, Kaur et al. showed that stroke was the most common cause of abnormal CTB findings in India, accounting for 23%.¹² Vascular causes of abnormal CTB were more likely in the patients over 60 years and included ischemic infarction, chronic small vessel white matter disease and intracerebral haemorrhage. This finding confirms that age is a major risk factor for cerebral vascular disease. Yousufuddin and Young noted that 'aging is the most robust non-modifiable risk factor for stroke, which doubles every 10 years after age 55 years'.²⁵ Similarly, Kaur et al., demonstrated that 95.6% of seizures above the age of 40 years were secondary to stroke.¹² This study also showed a high occurrence of vascular pathology in the parietal lobe, which is likely due to a higher incidence of stroke in the MCA distribution. This finding is supported by Ng et al., who found that MCA territory infarcts accounted for 50.8% of all ischemic strokes.²⁶

Infective pathology constituted 14.1% of abnormal CTB findings and was seen in younger patients and the HIV infected. In the literature, the range of infective pathology ranged between 5.2% and 11.5%.^{7,12} There was a high frequency of infective pathology in the parietal lobe, likely due to a higher incidence of haematogenous sources of cerebral infection, which is also likely to involve the middle cerebral arterial territory. A review article by Patel et al. reported that hematogenous spread accounted for 9% – 43% of cerebral abscesses.²⁷

Neoplastic pathology contributed 3.0% to the abnormal CTB findings, occurring in older patients with a mean age of 57.6 years. This is slightly different from the international literature, where neoplastic pathology contributed 8% – 14.8% of abnormal CTB findings.^{11,12} Focal seizures were seen in 50% of cases with neoplastic pathology but there was poor documentation of seizure type and statistical significance was not reached.

The fourth common cause of abnormal CTB finding was trauma related pathology, contributing 2.4%. These were largely subdural hematomas and old depressed fractures with underlying encephalomalacia. There was a high frequency of

traumatic pathology in the frontal lobe. Frontal lobe pathology is more likely to present with seizures, behavioural and personality changes, whilst other areas of brain involvement will have additional focal neurological deficits.²⁸

Congenital pathology as abnormal CTB finding in this study was an unexpected finding in patients over the age of 18 years who were unlikely to have their first seizure as adults. It is possible that patients may have been unconscious around the time of the seizure event and were unable to provide a history of previous seizures or there was a lack of thorough history taking. On the other hand, this may be due to loss to follow-up or caregivers seeking alternative opinion in a different health centre. The case of an arachnoid cyst in this study was likely an incidental finding and not the cause of the seizure, as arachnoid cysts are usually asymptomatic.²⁹

Cerebral oedema, midline shift and hydrocephalus were the associated findings predominantly seen with infective and neoplastic pathologies. These findings guide the need for urgent medical or neurosurgical intervention. CTB is an ideal imaging modality for the emergent identification of these associated findings due to its ease of access and relatively low cost.³⁰ This study did not investigate the follow-up management of the patients with these associated CTB findings.

Study limitations

This retrospective study was limited by poor documentation of seizure type by the referring clinicians. As a result, *p*-values were calculated on smaller sample sizes and likely underestimate the power of our findings and the ability to investigate for predictors of abnormal CTB findings.

Conclusion

A high yield of CTB imaging in adult new-onset seizures was demonstrated, with vascular and infective pathologies being the most common. Age $\geq$ 40 years, HIV infection, hypertension, focal seizures, low GCS, raised CSF protein and lymphocytes were identified as predictors of an abnormal CTB, and patients with these risk factors should be scanned urgently for prompt detection of medical and neurosurgical emergencies. Other patients without these risk factors, can be imaged as soon as possible within 24–48 h in resource restricted settings.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contribution

S.H.M. was the principal investigator responsible for literature review, data collection and preparation of the manuscript. S.L. and D.B.N. were responsible for the research conception and supervisory roles.

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Data availability

The data that support the findings of this study are available from the corresponding author, S.M.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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Chapter 2: Protocol with extended literature review

1. Rationale

Seizures are common in medical emergency departments, representing 0.24 -2 % of the visits (1). Of these 25 % are new-onset seizures (1, 2). It is estimated that 5 -10% of the population will experience a seizure in their lifetime (3-5).

According to Tranvinh et al, patients with new-onset seizures require imaging as part of their clinical workup (1). Multiple international studies have been done demonstrating a varying degree of abnormal CT brain (CTB) findings in these patients (2, 3, 5). According to Ba-Diop et al, new-onset seizure incidence in developing country adult population is likely higher (6), but, imaging studies of adult epilepsy are lacking in the South African population (5).

Therefore, this study aims to determine the underlying CTB findings in adults with new-onset seizures and to compare these findings with the international literature.

2. Introduction

2.1 Definition

According to Gavvala et al, seizures are “a transient occurrence of signs and symptoms” which may be focal or generalised. They develop due to excessive amounts of “or synchronous neuronal activity within the brain”, this can affect a single cerebral hemisphere (resulting in focal seizures) or both hemispheres (causing generalised seizures). This may or may not result in an altered level of consciousness (2).

2.2 Types and classification of seizures

There are many different ways of classifying seizures, the three major groups are focal onset, generalised onset or unknown (1).

There are specific definitions for a seizure that help in the evaluation and management of patients with seizures as described by Gavvala et al. These include (2):

- “Unprovoked: occurring in the absence of precipitating factors and may be caused by pre-existing brain injury or progressive central nervous system disorder.
- Acute symptomatic seizures: a seizure with a close temporal association with transient brain insult presumed to be an acute manifestation of the insult. These include metabolic derangements, drug withdrawal or acute head injury.
- Focal seizure: initial onset within one part of the cerebral hemisphere.
- Generalised seizures: Initial activity is consistent with rapidly engaging network distributing in bilateral cerebral hemispheres.
- Epilepsy: a disorder of the brain characterized by an enduring predisposition to generate epileptic seizure. It has been defined as 2 or more unprovoked seizures occurring more than 24 hours apart or unprovoked seizure and high risk (at least 60 %) of recurrent unprovoked seizures over the next 10 years”.

2.3 Worldwide epidemiology of seizures

According to the literature, the incidence of new-onset seizures in adults is 29 -39 per 100 000 per year. According to the literature, 0.24% -2% of visits to the Emergency Department (ED) is due to new onset seizure (1-3).

According to Hauser, males are affected more than females, but this is largely influenced by the epidemiologic characteristics of the underlying neurologic disease (7).

2.4 Seizures in the developing world

Ba-Diop et al, reports that the incidence rate of adult-onset seizures in developing countries to be much higher than that in developed countries. According to Ba-Diop et al, the estimated incidence rate is 81.7 per 100 000 per year in developing countries compared to 45.0 per 100 000 per year in developed countries (6). Thus, an assumption can be made that the incidence rate in developing countries is much higher due to the prevalence of other factors, such as HIV and other communicable diseases. This kind of data is not available in the literature for South Africa.

According to WHO (World Health Organisation) (8), other factors have been cited to contribute to higher incidence rates in the developing countries. Some of these factors include poor perinatal history, high incidence of head trauma and high impact of infectious diseases.

2.5 Impact of HIV on new-onset adult seizures

According to Moolla et al, the incidence rate of new-onset adult seizures is higher in the HIV positive population (9). In a study done by Modi et al, the majority of patients in this subgroup were severely immunosuppressed and a large percentage (75%) demonstrated underlying identifiable intracranial pathology (10), thus, confirming the predisposition of patients with advanced HIV to opportunistic infections resulting in new-onset seizures.

New onset seizures associated with HIV are clinically categorized according to four different mechanisms (10). There are:

- Focal brain lesions
- Meningitis
- Metabolic derangements
- No identified cause other than HIV.

However, in a study performed by Smith et al, HIV positive patients contributed 16 per cent of the sample but HIV status did not seem to influence their diagnostic workup or the abnormal yield of the investigations (5).

2.6 Clinical factors to be considered

Many other risk factors have been identified to be associated with an epileptic seizure, these include (2):

- patient age
- family history
- “excessive sleep deprivation”
- “use of alcohol or illicit drugs and”
- other metabolic derangements

Many differential diagnoses must be kept in mind in patients with seizures. The most common includes (2-5):

- paroxysmal neurological disorder
- psychogenic non-epileptic seizure
- syncope

This underlines the importance of history and clinical examination in the diagnosis of seizures.

The medical impact of seizures is 2-fold. Firstly, on the “patient’s life” resulting in a serious change in lifestyle, work, ability to drive and emotional impact, which will then limit the degree of autonomy of the affected individual (1, 11). Secondly, the medical burden on the health care system as this will result in an increasing number of visits to the emergency department, as has been alluded to by Faizi et al (12).

2.7 Neuroimaging work up and findings

The diagnosis of seizures and epilepsy are largely made on clinical grounds. Neuroimaging is vital in the workup of new-onset seizures, as serious underlying conditions can be detected and timeously treated. For this reason, patients with new-onset seizures should receive neuroimaging as part of their workup, however, there is still debate as to the timing and type of imaging (1, 2).

CTB is the initial imaging tool of choice. It is the most practical method of first-line imaging, especially in cases in the emergency setting and those requiring follow up imaging to monitoring progression (4, 5). MRI may be utilized as a second line where CTB findings were inconclusive or confirmation of CTB findings are required (2, 3).

Emergency neuroimaging is strongly indicated when serious intracranial lesions are suspected or when new neurological deficits are present such as (2):

- persistent altered mental state
- recent head trauma or
- prolonged headaches.

In a retrospective study by Kotisaari et al also identified clinical factors associated with critical imaging findings on NCCT (13). These included:

- headaches
- focal motor sign
- history of malignancy
- altered mental state
- age

Other common underlying causes that may result in seizures are (5, 14):

- Stroke
- Neoplastic lesions
- Post-traumatic lesions
- Infection/sepsis

- Birth injury.

Studies have shown that a significant number of adults with new-onset seizures had abnormal CTB findings (3, 5). In addition to this, adults with a predisposing history, abnormal clinical features and/or neurological examination were more likely to have an abnormality on imaging.

These factors are therefore positive predictors of abnormal CTB findings (2, 15).

This confirms the important role that neuroimaging plays in evaluating patients with new onset seizures.

Table 1 compares the different studies that investigated the role of neuroimaging.

Table 1. Comparison of similar studies of imaging findings of adult onset seizures

Reference	Study design	NCCT or CECT	Number of CTB	No. (%) of abnormal CTB	No. (%) of significant CT findings and description	Clinical findings
Modi et al (10)	Prospective	Not specified	Not specified	Not specified	21 (57%) had FBL 6 (16%) had meningitis 10 (27%) were NIC	Generalized 25 (65%) Focal 8 (24%) Status 4 (11%). Mean CD4 count 238.
Ho et al (14)	Prospective	49% CECT	954	476 (49.90%)	Stroke 93 (32%), post traumatic 64 (22%), neoplastic 54 (18%), mesial temporal sclerosis 17 (6%), Malformation of cortical development 14 (5%), cavernoma 10 (3%), other vascular malformations 10 (3%), perinatal insult 8 (3%), other 25 (8%)	Not specified
Smith et al (5)	Prospective cross-sectional	Not specified	169	96 (56.8%)	Infarct 24 (25%), TBM 5 (5.2%), ICH 12 (12.5%), Atrophy 12 (12.5%), Neurocysticercosis 11(11.5%), Calcifications 7 (7.3%), metastases 6 (6.3%), Other 19 (19.8%).	80% received full renal and electrolyte screen, blood glucose and full haematological screen. 76.1% had normal CSF findings. 8 % had EEG. 53 (16 %) were HIV positive.
Moolla et al (9)	Retrospective	Not specified	132	55%	Space Occupying Lesion 23 %, Cerebral oedema 13 %, other 24%	Generalized 74%, focal 16%, Abnormal LP 17%.

Breen et al (16)	Prospective descriptive	Not specified	26 (17%)	1 (4%) abnormal, 5 (19%) report unavailable.	Previous stroke	“Alcohol excess 25 (26%), sleep deprivation 16(16%), head injury 11(11%), drug misuse 9 (9%), alcohol withdrawal 5 (5%), prescription drugs 3 (3%)”.
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Zarmerhi et al (17)	Retrospective, descriptive analytical study.	Not specified	100	27 (27%)	Non-specific senile changes in 11 (40.7%), Encephalomalacia in 3 (11.1%), acute infarct in 5 (18.5%), lacunar infarct in 3 (11.1%), mass-like lesion in 4 (14.8%) and cerebral venous thrombosis in 1 (3.7%)	Not specified.
Kaur et al (18)	Prospective crosssectional study	Not specified	100	70 (70%)	Infarct (18%), brain tumours (8%), Gliosis (7%). Ring enhancing lesion (5%), haemorrhage (5%) and cortical atrophy (5%).	Generalised seizures 59, Simple partial seizure 16, Complex partial seizure 15, Status epilepticus 17.

Kotisaari et al (13)	Retrospective registry based study	280 NCCT +CECT. 136 NNCT only	416	220 (53%)	Acute intracranial haemorrhage ²³ (5.5%), Tumour with severe secondary findings 16 (3.8%), Acute ischemia 6 (1.4%), Subacute/chronic SDH with mass effect with mass effect 2 (0.5%), Diffuse cerebral oedema 1 (0.2%), Encephalitis 1 (0.2%).	These were associated with critical findings on NCCT: Headaches, Focal motor signs, history of malignancy, altered mental state and age.
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FBL- Focal brain lesion; NIC- No identified cause; EEG- electroencephalogram

NCCT- Non-contrast computed tomography. CECT – contrast enhanced computed tomography.

3. Aim

The study aims to review CTB findings in adult patients with new onset seizures.

4. Study Objectives

- To investigate clinical and CTB findings in adults with new-onset seizures.
- To measure the associations between the clinical findings and CT brain findings.

5. Methods

5.1. Research paradigm

The study is a retrospective cross-sectional study reviewing the CTB findings in adult-onset seizures.

5.2. Sample

The study population will include adults (> 18 years of age) who presented with new onset seizures to ED at Chris Hani Baragwanath Academic Hospital (CHBAH) in between 01 January 2016 - 31 December 2018.

5.2.1. Inclusion criteria

All patients above 18 years of age with new-onset seizures and had a CTB done at the time of presentation.

5.2.2. Exclusion criteria

- Missing reports.
- CT findings not reviewed by a radiology consultant.

5.3. Materials and Methods

Emergency Department register will be accessed, and cases of new-onset seizures will be recorded.

This will be an audit and data collection will continue according to the inclusion and exclusion criteria for patients imaged for new onset seizures between the period of 01/01/2016 to 31/12/2019.

Clinical information regarding the presenting signs and symptoms will be accessed from the Picture Archiving and Communication System (PACS). Clinical data will be recorded, and this will include patient age, sex, type of seizure (generalised or focal or status epilepticus), HIV status and CD4 count.

Relevant laboratory results will be accessed from the National Health Laboratory Services (NHLS), these will include renal and electrolyte screen, full blood count and cerebrospinal fluid analysis.

CTB findings, as well as relevant clinical data, will be reviewed and tabulated. Comparison between the clinical data and CTB findings will be made.

5.4. Data collection

Clinical information and CTB reports will be collected from the radiology department PACS. All this data will be collected using an anonymous data collection sheet. (Appendix A)

5.5. Reliability and validity

5.5.1 Reliability

The CTB reports will be used. Several radiologists were reading these cases at the time. This could impact on the reliability of the reports, as there is a spectrum of experience present in the doctors working in these departments at the time.

5.5.2. Validity

Although MRI is considered the gold standard for imaging patients with seizures, CTB imaging is regarded as a very accurate method of assessing the presence of underlying intracranial pathology, especially in a resource-restricted environment.

5.6. Bias

Due to different levels of experience of the admitting physicians, observations are likely to differ and present bias because the diagnoses of seizures are largely dependent on the clinical history.

6. Data analysis and statistics

The data will be presented as frequencies and percentages.

The likelihood ratio test will be used to determine the most significant clinical and imaging features.

Chi-test and Fisher's exact will be used to compare categorical variables. STATA version 16 will be used for data analysis. 95 % confidence interval will be calculated for all data.

7. Ethics

The application for the study has been approved by the Human Research Ethics Committee of University of the Witwatersrand.

CEO permission has been obtained from Chris Hani Baragwanath Academic Hospital.

7.1. Consent forms

Participant consent will not be required as this is a retrospective record review only

7.2. Data safety

Backups of the raw data and analysis will be made on to an external device and kept separate to protect against data loss.

No personally identifiable information will be documented in the data collection sheet to maintain strict anonymity.

8. Timing

Month of the Year	Jan-Mar	Apr-Jun	July-Aug	Sept-Nov	Dec	Jan 2020	Feb 2020	Mar 2020	Apr 2020
Literature search	x								
Reading literature	x								
Summarising literature	x								
Preparing Protocol		x							
Protocol Assessment		x							
Ethics application		x							
Collecting data			x	x	x				
Data analysis				x	x				
Writing up a thesis						x	x		
Submit: marking								x	
Writing up paper									X

9. Budget

This will be a low-cost project. No funding will be required.

Photocopy and printing costs will be paid for by the primary investigator.

Photocopying and printing	R 500
Travel expenses to present results and printing of the poster.	R 6000

10. Anticipated problems

There may be missing laboratory findings for some of the participants. These participants will not be excluded from the study, but they will be discussed separately.

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Appendices: Data collection sheet

DATA COLLECTION SHEET				
Study Number:			Date of CT	
Gender: M / F				Age:
Clinical Findings				
Seizure Type	Focal	Generalised	Status	Unknown
Glasgow Coma Scale:				
RVD	YES	NO	UNKNOWN	CD4 COUNT:
Comorbidities	Hypertension	Diabetes mellitus	Other:	
Laboratory findings				
Renal function	Sodium: Potassium:	Urea:	Creatinine	
Full blood count	White cell count: Haemoglobin:	Platelets:	Other:	
Finger prick glucose				
CSF Analysis	Cells: CLAT:	Glucose: Protein:	Other:	
CT Findings				
Normal	YES	NO		
Cause				
Vascular	Infarct	Intracerebral Other:	vascular	
		haemorrhage	malformation	

	Site Size: Number of lesions: Complications: Additional description:				
Infective	Meningitis	Pyogenic abscess	Neurocysticercosis	Toxoplasmosis	Other:
	Site: Size: Number of lesions: Complications:				
Neoplastic	Primary	Metastasis			
	Site: Size: Number of lesions: Complications:				
Trauma	Gliosis	Surface collections			
	Further description:				
Congenital					
	Further description:				
Other					
	Further description:				

Chapter 3: Appendices

Appendix A: Ethic clearance certificate



R14/49 Dr SH Mabaso

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M190609

NAME: Dr SH Mabaso
(Principal Investigator)
DEPARTMENT: School of Clinical Medicine
Department of Radiation Sciences
Division of Radiology
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: An audit of CTB findings in adults with new-onset seizures
in a resonance restricted setting in South Africa

DATE CONSIDERED: 2019/06/28

DECISION: Approved unconditionally

CONDITIONS: Change of study title noted on 27/11/2019

SUPERVISOR: Drs D Bhana-Nathoo and S Lucas

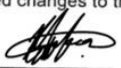
APPROVED BY: 
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2019/07/01

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 on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. I **agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

30/11/2019
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix B: Turnitin report

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Appendix C: Note on reference style

Please note that the referencing in this thesis is a modification of the Vancouver Referencing style, done according to the Faculty of Health Sciences Style Guide as set out by the Wits Health Sciences Library.

The information on this WHSL Vancouver Citation Style Guide for Theses, Dissertations and Research Reports is available from <http://libguides.wits.ac.za/whsl-vancouver> updated on 8 August 2017.