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CT brain findings and common co-morbid disease in patients presenting with first time seizures

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2021
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CT BRAIN FINDINGS AND COMMON CO-MORBID DISEASE IN PATIENTS PRESENTING WITH FIRST TIME SEIZURES

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology

Johannesburg, 2021

Declaration

I, Cwengile Gagela, declare that this research report is my own work. It is being submitted for the degree of MMed (Rad D) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR CWENGILE GAGELA

On this … July 2021

Dedication

To my family and friends:

Thank you for your unyielding love, support and encouragement.

Abstract

INTRODUCTION: A significant number of patients attend to the Emergency Department due to the occurrence of a seizure event[3–5]. Seizure events can constitute up to 1% of all emergency department (ED) visits, with a quarter of these first time seizures[6]. Neuroimaging is key in the evaluation of patients with first time seizures[10], and due to wider availability and quick acquisition time, computed tomography (CT) is routinely utilised. The expense associated with radiological imaging is significant[9] and places a burden on constrained healthcare rescources[12]. Moreover, there is high mortality associated with acute symptomatic seizures from CNS infections, stroke and traumatic brain injury[2,7,13] , necessitating determination of the prevalence of these diseases.

AIM: The aim of the study was determining the CT scan findings of patients presenting with first time seizures.

METHOD: The study was a retrospective analysis of CT brain scans done in patients with first time seizures at Helen Joseph Hospital in Johannesburg, from January 2015 – December 2015. Associated co-morbid disease was also documented and analysed.

RESULTS: About 313 CT brain scans were included in the study, with the average patient age being 44 years and 56% of the scans having abnormal findings. CNS infections (15% or 47 cases) were the most prevalent cause of radiological abnormality, followed by cerebrovascular accidents (CVA) (11% or 33 cases) and lastly Traumatic Brain Injury (TBI) (4% or 14 cases). The most prevalent co-morbid disease was retroviral disease (RVD), (27% of patients), hypertensive disease (16%) and acute head injury (10.5%). We also found a strong association between patient age and abnormal CT scan findings, with the average age of patients with abnormal scans being 49 years and those with normal scans 38 years (p-value: 0.001). Furthermore, we found that the older patients were likely to present with CVA or neoplastic brain disease, and that overall , the patients with CVA were on average 52 years old (p-value 0.001).

CONCLUSIONS: We established that CNS infections were the most common finding in first time seizure patients and that underlying HIV infection was the most common associated co-morbid disease, thus firmly establishing the leading role of infectious disease in seizure presentation. CVA's were the third most common radiological finding and co-morbid hypertension the second most common disease, reflecting the effect of non-communicable disease in the South African population. Lastly, despite the endemic prevalence of trauma in South Africa, traumatic brain injury did not feature as highly in the causes of first-time seizure presentation (6th overall). The 8% prevalence we found is within the 4-9% prevalence in most international studies[3,6,29]

Acknowledgements

To God and those who call themselves my ancestors, thank you for giving me the strength to finish this study.

In addition, I would like to acknowledge and thank my friends and family, who have a played a huge role in my academic accomplishments

Lastly, to my research supervisor, Dr N Mabandla, I will forever be grateful for your guidance in completing this study.

Table of Contents

Declaration ..... *ii*
Dedication ..... *iii*
Abstract ..... *iv*
Acknowledgements ..... *v*
List of Figures ..... *vii*
List of Tables ..... *viii*
Nomenclature ..... *ix*
Abbreviations ..... *ix*
1. Introduction *1*

1.1. Motivation and Rationale **1**
1.2. Literature Review **2**
1.2.1. Provoked or Acute Symptomatic Seizures 2
1.2.2. Unprovoked Seizures and Epilepsy 4

1.3. Medical Evaluation of Seizures **5**
1.4. Radiological Evaluation of Seizures **6**
1.4.1. Computed Tomography 7
1.4.2. Magnetic Resonance Imaging 9

1.5. Aims and Objectives **9**
1.5.1. Aims 9
1.5.2. Objectives 9

2. Materials and Methods *9*

2.1. Study Design **9**
2.2. Study Setting and Sampling **10**
2.3. Inclusion Criteria **10**
2.4. Exclusion Criteria **10**
2.5. Data Collection **10**
2.6. Data Analysis **11**
2.7. Bias **12**
2.8. Ethics **12**

3. Results *13*

3.1. Objective 1: Demographics **13**
3.2. Objective 2: Proportion of Normal vs Abnormal Findings **14**
3.3. Objective 3: Prevalent Radiological Findings **16**
3.4. Objective 4: Prevalent Co-morbid Disease **19**

4. Discussion *21*

4.1. Results in Context **21**
4.2. Limitations of the Study **22**
4.3. Future Applications **22**
5. Conclusion **23**

6. References *24*

List of Figures

Figure 1: Gender of Participants **14**

Figure 2: Race of Participants **14**

Figure 3: Gender Aggregated by Race **14**

Figure 4: Normal vs Abnormal Scans **14**

Figure 5: Normal vs Abnormal Scans by Gender **15**

Figure 6: Normal vs Abnormal Scans by Race **15**

Figure 7: Prevalent Radiological Findings **16**

Figure 8: Other Radiological Findings **17**

Figure 9: Categories of All Abnormal Findings **17**

Figure 10: Mean Age of Normal vs Abnormal Findings **18**

Figure 11: Mean Age by all Radiological Findings **18**

List of Tables

Table 1: Imaging Guidelines for New-onset Seizures **6**

Table 2: Comparison of Relevant Studies / Research **8**

Table 3: Classification of CT Findings **10**

Table 4: Classification of Co-Morbid Disease **11**

Table 5: Demographics of Participants **13**

Table 6: Prevalent Co-morbid Disease **19**

Table 7: Results in Context **21**

Nomenclature

Seizure	an uncontrolled discharge of neurons, originating from any part of the cerebral hemisphere[1]
Acute Symptomatic Seizures	seizures occurring at or closely associated to a time of brain or systemic insult[2]
Unprovoked Seizures	seizures occurring in the absence of precipitating factors[2]
Epilepsy	recurrent unprovoked seizures beyond neonatal life[2]
Status Epilepticus	seizures lasting more than 30 minutes or intermittently without regaining consciousness[2]

Abbreviations

CT	Computed Tomography Scan
MRI	Magnetic Resonance Imaging
CNS	Central Nervous System
CVA	Cerebrovascular Accident
HAND	HIV Associated Neurocognitive Disorder
TBI	Traumatic Brain Injury
ED	Emergency Department
EEG	Electroencephalogram

1. Introduction

Throughout the world a significant number of patients attend to the Emergency Department due to the occurrence of a seizure event[3–5]. In one study conducted in the United States of America (USA), seizure presentation accounted for up to 1% of all emergency department (ED) visits, and up to a quarter of these were first time seizures[6].

Generally, seizures are classified as either provoked (acute symptomatic) or unprovoked, based on the presence or absence of underlying precipitating factors respectively[2,7]. The incidence of provoked seizures is slightly lower than unprovoked seizures at 29-39 vs. 23-61/ 100 000 per annum[2]. Provoked seizures however have a higher mortality, but a lower risk of recurring into epilepsy than unprovoked seizures[8,9].

Neuroimaging is key in the evaluation of patients with first time seizures[10], and due to wider availability and quick acquisition time, computed tomography (CT) is more routinely utilised than magnetic resonance imaging (MRI)[11]. The expense associated with these radiological procedures is significant[9] and places a burden on healthcare finances[12]. For purposes of equitable resource allocation, the prevalence and scope of neuroimaging findings in patients with first time seizures requires on-going research.

Furthermore the high mortality associated with acute symptomatic seizures due to CNS infections, stroke and traumatic brain injury[2,7,13] necessitates the radiological determination of the prevalence of such conditions in these patients. This is particularly important in the South African context of high HIV/AIDS, non-communicable and trauma related disease[14].

1.1. Motivation and Rationale

Research data on first time seizures specifically is poorly developed in South Africa, but Smith et al (2013) conducted a study that included 309 adult non-trauma patients presenting with first time seizures in six hospitals in the Western Cape[10].

Among other findings it highlighted deficiencies in the medical imaging capabilities of the public sector. For example, it found that although CT scan imaging was intended for 218 patients (70.6%), only 169 patients (54,6%) actually received it. Importantly, 96 (56.8%) of those imaged had abnormalities. Although that was already 31% of the total population with CT scan abnormalities, it remains unknown what the actual prevalence of disease would have been if more patients were scanned.

Also, the study showed that there was considerable inconsistency in the management of these patients, with patient investigation variations from doctor to doctor and centre to centre[10], impacting the quality of patient care.

Generally the imaging of these patients poses a major economic burden[15], requiring a prudent allocation of resources. Also the significant morbidity and mortality associated with acute symptomatic seizures related to CNS infections, traumatic brain injury and stroke[13,16] warrants development of careful management guidelines for these patients. Considering the high prevalence of HIV/AIDS, trauma and lifestyle related diseases in South Africa[14], locally developed research is therefore important in developing these guidelines and for the purposes of resource allocation.

1.2. Literature Review

1.2.1. Provoked or Acute Symptomatic Seizures

Acute symptomatic or provoked seizures are seizures occurring at the time of, or in close temporal association with a documented brain insult[2,7]. Furthermore there is typically a pathophysiological causal and correlative explanation between the brain insult and the seizure[7,8]. This correlation is also typically demonstrated in terms of the severity of the insult, with more severe events resulting in more severe and higher incidence of seizures[7,8].

Unlike epilepsy and unprovoked seizures, acute symptomatic seizures have no predilection for recurrence[17]. While there is an increased cumulative risk for future development of epilepsy with this type of seizures, it is lower if the underlying condition does not recur[7]. Clinical and pathophysiological evidence suggests that prognosis of acute symptomatic / provoked seizures is thus much better than in unprovoked seizures[13].

By definition epilepsy is also not included in the definition of acute symptomatic / provoked seizures[17]. People with epilepsy can however develop this type of seizure related to a specific brain insult[13,17]. It however remains unestablished whether epileptic patients are any significantly more susceptible to developing acute symptomatic / provoked seizures compared to the general population.

Globally CNS infections are an important cause of acute symptomatic seizures[7,18]. In Sub-Saharan African countries these constitute about 26% of causes of first time seizures[19,20], whereas in developed countries this is much lower. In turn, about a third of CNS infections result in seizures[20]. These can occur beyond a week post infection in a patient with persistently abnormal clinical and laboratory findings.

On neuroimaging the causative infectious disease is typically identifiable, particularly in neurocysticercosis, TB and other common infections or infestations. Underlying chronic diseases like HIV/AIDS influence the frequency of some of the above-mentioned pathological entities. Specific studies have established a prevalence of new onset seizures of 3-11% in HIV infected communities[21–24]. Whilst the direct effect of the HI virus has been cited[22,23], most of these seizures are caused by HIV/AIDS related opportunistic infections, inflammatory disease and neoplasia[10,11,22,23]. Smith et al (2013)[10] established TB meningitis in 5.2% of Western Cape patients presenting to the ED over a six month period.

Hypertension is a common non-communicable disease and is directly linked to up to 62% of strokes or cerebrovascular accidents (CVA)[25] according to the World Health Organisation (WHO). In the USA, some studies established a 15% incidence of seizures in CVA patients[3,5]. Acute strokes may present with early (<7-14 days) or late (>14 days) seizures and a status epilepticus[26]. Early seizures and the subsequent risk of epilepsy is higher in severe ischemic and hemorrhagic strokes as well as in patients with cortical involvement [26].

Eclampsia is an important cause of seizures and may be associated with posterior reversible encephalopathy (PRES)[27]. This reversible condition typically presents in the context of pregnancy related hypertension, but also in patients with renal and autoimmune diseases and organ transplant[28].

Traumatic brain injury (TBI) is an important risk factor for seizures, and contributes to 4-9% of subsequent epilepsy[29]. These can occur early, i.e. less than a week post trauma or up to a month in cases of infection and complications[18]. Presentation beyond this period is typically related to permanent structural brain damage. There is a high mortality[13] and a 1,5 times higher risk of epilepsy in TBI seizures[18]. The most important risk factors for seizures are brain contusions, subdural haemorrhages, skull fractures, more than one day loss of consciousness or amnesia and patients older than 65 years[18].

Accordingly factors primarily related to acute symptomatic seizures[7] can be broadly divided into the following pathological classes:

1) Infectious / Infestation Conditions
    - TB, Viral, Bacterial, Neurocysticercosis, Malaria
2) Inflammatory Disease
    - Demyelinating diseases e.g., multiple sclerosis, ADEM
3) Cerebrovascular Disease
    - Haemorrhage, Infarcts, PRES
4) Structural Anomalies
    - Acute Head Trauma, Prior Surgery
5) Metabolic Disease

- Electrolyte Disorders, Uraemia, Hypoxaemia, Hypoglycaemia and Hyperglycaemia

6) Neoplastic Disease
   - Primary and Metastatic
7) Psychogenic
   - Factitious, Somatoform and Conversion Disorders

1.2.2. Unprovoked Seizures and Epilepsy

Unprovoked seizures occur in the absence of a precipitating neurological or systemic event or illness during a 24 hr period[2,13] . They are typically related to either a once off and now static brain injury (remote symptomatic) or a progressing injury (progressive symptomatic)[2]. The incidence is lower than provoked seizures, at 23-61 / 100 000.

Unprovoked seizures may be once-off or recurrent, and there is a significant and demonstrable cumulative increase in the risk of subsequent seizures following an episode of an unprovoked seizure. This recurrence manifests in up to 50% of cases in the first year[2,8,13]. After a second seizure the risk of a third seizure is 70% and more than 75% after the third[2,7,13]. The risk of development into epilepsy is higher in unprovoked seizures[2,13]than it is in provoked symptomatic seizures[7,13].

Although up to 10% of the world population develops a first time seizure in their lifetime, only 2% go on to develop epilepsy with or without structural brain disease[11,12]. Whilst in the developed world, the lifetime prevalence of epilepsy is 5,8 per 1000 people, it is up to 15,4 per 1000 in some rural communities of the developing world[12]. The estimated prevalence in South Africa is 7 per 1000[30]. Furthermore Wagner et al (2013) demonstrated that the prevalence of diagnosed epilepsy in rural KwaZulu Natal, South Africa is 7 per 1000[30].

Roughly 50 million people in the world live with epilepsy and up to 2,4 million people are diagnosed with the disease annually[31], making it one of the most prevalent illnesses worldwide. Nearly 3% of all people in the world will be diagnosed with epilepsy by the age of 74 years[32], with the age adjusted incidence of newly diagnosed disease of about 44 per 100 000 person years[1].

About 10% (5 million) of the 50 million people with epilepsy live in Sub-Saharan Africa[31]. In this geographical area, the prevalence of epilepsy has two modal values, 11.5 per 1000 (20 – 29-year-olds) and 8.2 per 1000 (40 -49-year-olds). The lowest prevalence is 3.1 per 1000 in people over the age 60 years[33].

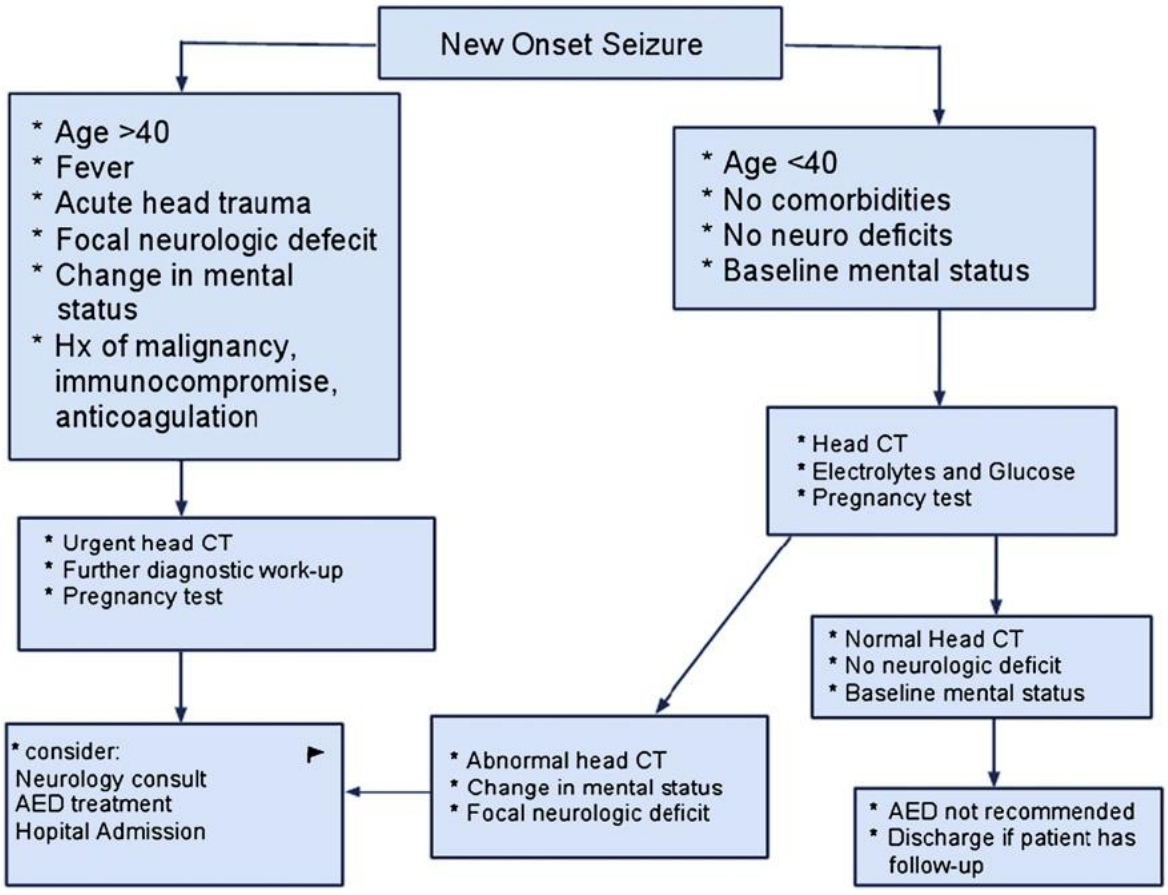
Socioeconomic factors and poor access to healthcare have a bearing on the prevalence of diagnosed lifetime epilepsy[12]. For example, the prevalence is 15.4 and 10.3 per 1000 in rural

and urban communities of the developing world, whereas it is a uniformly low 5.8 per 1000 persons in developed countries[12].

1.3. Medical Evaluation of Seizures

Untreated acute symptomatic seizures lead to high mortality[13], and for this reason the primary aim of medical workup in these patients is establishing the presence or absence of most precipitating diseases. In their study, Jagoda and Gupta (2011)[34] devised the following flowchart for managing patients with new onset seizures presenting in the Emergency Department. It is a practical, clinical history and neurological status-based guideline typically used in most ED rooms.

Flowchart for Management of Seizures in the ED



(source : http://dx.doi.org/10.1016/j.emc.2010.08.004)

Hypoglycaemia and electrolyte imbalances are an important cause of seizures, especially in the elderly and chronically ill patients[1,2]. As such, upon arrival in the ED these patients routinely require blood biochemical analysis including glucose, sodium, calcium, and magnesium[1].

Toxicology is also indicated particularly in patients with status epilepticus or persistent post-ictal confusion. Barring a contraindication, further evaluation with a lumbar puncture is crucial in all patients, particularly if haemorrhagic, infective or inflammatory disease is suspected[16,22].

Specialised neurological assessment consists of a standard 21-lead, 30-minute recording electroencephalogram (EEG), which may determine the presence of an epileptic focus. However this may be falsely negative (sensitivity 50% to 60%)[1] and a 24-hour EEG may be necessary to establish a diagnosis.

1.4. Radiological Evaluation of Seizures

Neuroimaging is key in establishing the presence or absence of brain lesions in the assessment of adult new onset seizures. The radiological evaluation is typically confined to computed tomography (CT) with or without contrast enhancement and magnetic resonance imaging (MRI) with spectroscopy[11,35].

Table 1: Imaging Guidelines for New-onset Seizures
(adopted from the American College of Radiology)[35]

	CT	**MRI**
Non-traumatic: 18-40 years old	Acceptable	Preferable
> 40 years old	Acceptable	Preferable
Seizure with focal neurological deficit	Acceptable	Preferable Recommended if normal CT
Trauma related: Acute[18]	Recommended	Useful in minor trauma
Late[18]	Acceptable	Preferable
Alcohol/ Toxin related	Acceptable	Preferable Recommended if normal CT

In the absence of trauma, in younger adult patients the main considerations include infectious diseases, and as such a contrasted scan should be done. This is unlike in the older patients where tumours and haemorrhagic strokes are more common, necessitating a non-contrasted scan prior the contrast enhanced sequence[2,11,35]. In trauma patients, non-contrasted CT brain is the gold standard of imaging[16,35] because it also allows assessment for fractures.

Functional and metabolic imaging with nuclear medicine studies such as fluor-deoxy-D-glucose / positron emission tomography (FDG/PET), single photon emission computed tomography (SPECT)[35] can also be acquired for further treatment and surgical planning.

1.4.1. Computed Tomography

Many studies recommend urgent CT brain imaging for patients presenting with first time seizures[10,11,16,34,35]. Patients with additional focal neurologic deficits, head trauma, history of HIV or malignancy and the elderly are at higher risk of having abnormalities on imaging and emergency CT significantly alters their management[35].

The notable advantages of CT include its quick acquisition time and good contrast imaging, even in non-contrasted studies[35]. Furthermore, compared to other imaging modalities such as MRI, CT is cheaper and thus more widely accessible[10,16,35]. It is also more sensitive in detecting and characterizing calcifications than other modalities.

The major disadvantage of CT imaging is ionising radiation, particularly in the paediatric population[16,35]. The energy deposited in the brain (organ absorbed dose) during a head CT scan increases from about 30 mGy in new-borns to 40 mGy in adults. Patients weighing less than 20 kg receive body organ absorbed doses of 7 mGy, which is a factor of 2 less than for average sized (70-kg) adults. This is significant radiation exposure with significant risk of radiation induced disease such as neoplasia in the longterm[16,35]. CT is also less sensitive than MRI in detecting seizure-triggering lesions, particularly those associated with neurodevelopmental anomalies[6].

The estimated lifetime risk of death from radiation-induced malignancy caused by a single CT of the head at one year of age is 0.07 percent[16]. In adults head CT effective doses are 0.9 mSv, four times less than those for the neonate[36], comparable to that delivered by normal environmental factors[36].

CT imaging of patients presenting with first time seizures is well researched in international literature as stipulated. A selection of studies performed in Finland by Kotisaari et al (2017)[3], the Middle East by Pathan et al (2014)[4] and in South Africa by Smith et al (2013)[10] was reviewed and the salient findings tabulated below.

Table 2: Comparison of Relevant Studies / Research							
Reference	**Study Design**	**Non-Contrast CT or Contrast CT**	**No. of Exams**	**Mean Age**	**No (%) Abnormal Exams**	**CT Descriptions / Diagnosis: No (%)**	**Co-Morbid Illness**
Kotisaari[3]	Retrospective	136 NCCT / 280 CCT	416	47	220 (53)	Emergent findings only: - ICH: 23 (5.5) - Tumour: 16 (3.8) - Ischaemia: 6 (1.4)	Hx of CVA 63 (15) Cancer 30 (7.2) Head Injury 6 (1.4)
Pathan[4]	Retrospective	Unspecified	436	35.3	154 (35)	Neurocysticercosis: 40 (9.2) Calcific lesions: 26 (6) Ill-defined: 21 (4.8) Old CVA: 18 (4.1) Mets & Neoplasia: 15 (3.4)	Unspecified
Smith[10]	Prospective	Unspecified	169	-	96 (57%)	Infarct: 24 (25) ICH: 12 (12.5) Atrophy: 12 (12.5) Mets: 6 (6.3) TB meningitis: 5 (5.2)	HIV: Positive: 49 (16) Negative: 53 (17.2)

Two of the studies were retrospective and one was prospective. Whilst Smith at al (2013) was a smaller study, it was South African based and thus offers invaluable locally relevant insights. The average age of patients in both Kotisaari (2017) and Pathan (2014) was below 50 years. This was not stipulated in Smith (2013).

In Kotisaari (2017)[3] patients were disaggregated according to whether intravenous contrast was administered or not, and about two thirds of the patients had contrasted studies. The yield of abnormal scans between these studies was 35-57%, and is well within the range of 35-56% abnormal scans in other similar international studies[3,4,10,19,37].

Only emergent findings were reported in Kotisaari (2017)[3] and there was no significant yield of CNS infections. These findings were similar to Pathan (2014), although CNS infestations with neurocysticercosis were a prominent finding in that study.

In Smith (2013)[10], brain atrophy, which could be interpreted as a similar finding to encephalopathy, also featured in 12.5% of the cases[10]. Also 16% of the patients in this study were HIV positive, meaning HIV related encephalopathy (HAND) is a plausible underlying cause of the seizure presentation. Only 17% were HIV negative and the status of 67% of participants was unknown[10]. These findings were not borne out by the other studies.

The aggregate total of infarcts and ICH was 37.5% in Smith (2013)[10]. It is however unclear if these were acute events of CVA or sequalae of pre-existing brain pathology. In Kotisaari (2017)[3] the total aggregate of CVAs was 6.9%, and these were 'emergent' and thus acute events. In Pathan (2014)[4] only old CVAs (4.1%) were reported. In a USA-based study Sethuram (2019)[5] found that about 15% of CVA patients develop seizures, and 80% of these happen within 48 hrs.

1.4.2. Magnetic Resonance Imaging

Although CT imaging is more readily available and utilised in the Emergency Department setting, MRI has a crucial role in imaging first time seizures. Significant abnormalities have been established on subsequent MRI in patients with focal neurological deficits and normal CT[34]. It has also been demonstrated to have a 20-60% yield in patients with intractable seizures[6].

A major advantage of MRI is the lack of ionising radiation and superior soft tissue resolution. Furthermore, MRI spectroscopy provides valuable metabolic and functional information on activity of the seizure related pathophysiology[11,35]. It is established as the preferred modality in a non-emergency setting, particularly for older patients or those with focal neurological symptoms[35]. In trauma patients MRI may be utilised in late seizures, where subdural haematoma is suspected[13,35] or in minor trauma to exclude subarachnoid haemorrhage[35].

The main disadvantage of MRI is cost[16,35], and thus poor accessibility, as well as the long image acquisition times. Its use in patients presenting with first time seizures has not been widely studied.

1.5. Aims and Objectives

1.5.1. Aims

The aim of the study was determining the CT scan findings of patients presenting with first time seizures

1.5.2. Objectives

- To describe the demographic characteristics of the study participants
- To determine the proportion of abnormal CT brain scans.
- To establish the prevalence of CNS infections, traumatic brain injury and CVA
- To document the most common underlying comorbid diseases.

2. Materials and Methods

2.1. Study Design

The study was a secondary analysis of CT brain scans done in patients with first time seizures at Helen Joseph Hospital in Johannesburg, from January 2015 – December 2015

2.2. Study Setting and Sampling

The study population was patients who presented with first time seizures at the Radiology Department at Helen Joseph Hospital between 1 January and 31 December 2015. The study was conducted at the Helen Joseph Academic Hospital, Johannesburg (part of the Wits University Academic Hospital Complex), which is equipped with a 16 Slice Phillips Brilliance MDCT Scan, Eindhoven, The Netherlands.

The CT scan indication and consistency with the research inclusion criteria was verified using CT scan request forms and patient files where necessary. The local NHLS laboratory was also utilised to confirm patients' HIV statuses where warranted. A retrospective descriptive analysis of the final CT reports was conducted and the findings recorded utilising an excel spreadsheet constructed based on the categories below.

2.3.Inclusion Criteria

- Adult (18 years and older) patients who had a CT brain for first time seizures.

2.4.Exclusion Criteria

- Known epileptic patients
- Patients on treatment for seizures

2.5.Data Collection

CT findings will be classified into the following radiological categories

Table 3: Classification of CT Findings

Finding	Description
TBI	fracture
	contusions / DAI
	extra/subdural, subarachnoid bleed
Neoplasm	intra-axial
	extra-axial
CVA	infarct
	bleed
Infection / Demyelination	meningitis
	empyema
	abscess
	granuloma
	cysts
	demyelination
Other	
Normal	

If one category of the CT findings represents more than 50% of the sampled records, we created a binary outcome to compare that category to the remaining categories.

The patients' underlying disease

Table 4: Classification of Co-Morbid Disease

Co-Morbid Disease	
HIV/AIDS	Positive Negative Unknown
Blood Pressure	Normal Elevated
Other	

2.6. Data Analysis

- To describe the demographic characteristics of the study participants
- To determine the proportion of abnormal CT brain scans.
- To establish the prevalence of CNS infections, traumatic brain injury and CVA
- To document the most common underlying comorbid diseases in patients with seizures.

Microsoft Excel was used to capture data and STATA software, version 13.0 (StataCorp, College Station, Texas) was used for data management and analysis. Sociodemographic characteristics of patients included sex, age and race.

In order to increase the reliability of the study, two radiologists read the scans and Kappa test was used to calculate inter-rater agreement between the two radiologists. Only scans read by the two radiologists were included into the study. To enhance internal as well as external validity of the study, we took care of the confounding variables and a relatively large sample was used. A standardized data collection sheet (see annexe) will be used to extract data from the medical records. Extracted data will be captured on an excel spreadsheet and imported into Stata for further data management and data analysis.

To describe the study population, we used descriptive statistics. Frequency tables and proportions were used to describe categorical variables. Means and standard deviations (or median and interquartile range) were used to describe continuous variables depending on the underlying distribution of the variable.

To determine the proportion of abnormal CT scans, and document the common co-morbidities we used frequency tables and proportions. To determine the prevalence of CNS infections, traumatic brain injury and CVA, we used frequency and proportions.

Pie charts and bar graphs were also used to portray distributions of the sociodemographic characteristics. To document sociodemographic differences in CNS infections, traumatic brain injury and CVA we used Pearson Chi-Square for categorical variables, and one-way Anova for continuous variables.

2.7. Bias

Bias in the study was potentially be created by

- Helen Joseph being a busy academic hospital, with many patient CT scan requests based on a doubtful or limited clinical information.
- the actual occurrence of seizures may have been doubtful in some instances
- the relatively quick availability of a CT scan within the premises potentially drove the number of unwarranted requests.
- there was variability in the seniority of the requesting professionals.

These factors were mitigated by:

- the extended period of data collection.
- the multiple sources of CT scan requests (Wards, Clinics, Emergency Dept.)

2.8. Ethics

Ethical clearance for the study was sought and granted by the Human Research Ethics Committee of Wits University, Johannesburg prior the commencement of data collection. Although we had access to the medical records, the patients were anonymised during the data collection and no personal identifiers were used. Each file was assigned a number and no attempt was made to link patient records to personal identifiers.

In this retrospective study, patient investigations were collected anonymously for statistical purposes. As such, patient consent was not relevant., and data was also collected anonymously by allocating a random number code to each patient. The key to this code was only available to the primary investigator and supervisor.

3. Results

3.1. Objective 1: Demographics

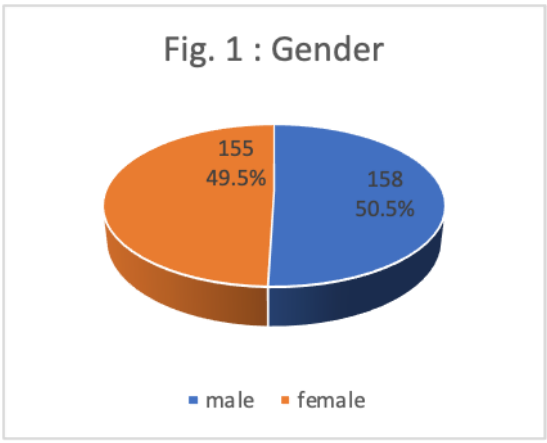
There were 313 CT brain scans that were considered meeting the selection criteria, and that were included in the study. These were CT scans conducted in patients presenting with first time seizures during the period of 01 January 2015 to 31 December 2015 at Helen Joseph Hospital.

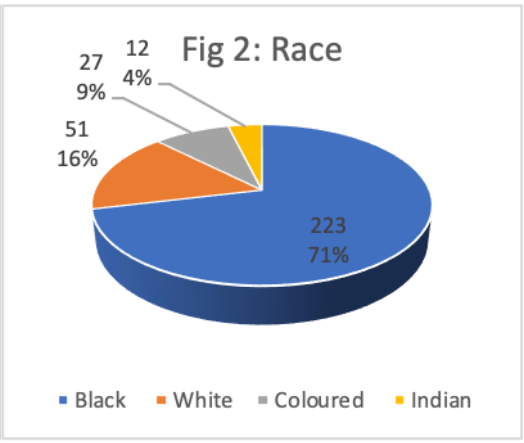
Table 1 below represents the demographics of the study participants. It demonstrates that the average patient age was 44 years (with a standard deviation of 16 years around the average age). The 95% confidence interval (CI) age range of these patients was 42-46 years. Of the 313 patients included in the study, 158 (50.5%) were males, and 155 (49.5) females.

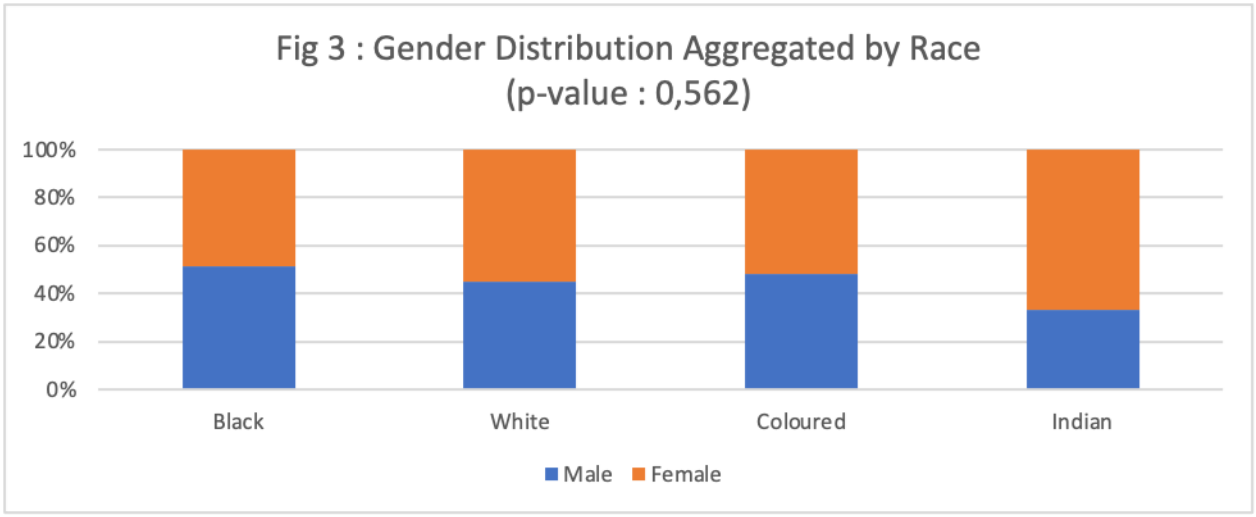
Table 5 : Demographics of Participants

Age (mean, sd)	(44, 16)
Gender	**Frequency (%)**
Male	158 (50.5)
Female	155 (49.5)
Ethnicity	
Black	223 (71)
White	51 (16)
Coloured	27 (9)
Indians	12 (4)

Figures 1 and 2 below show the gender and racial distribution of the patients, and Fig 3 describes the gender distribution disaggregated by race. The majority of patients were black, followed by those from the white, the coloured and lastly the Indian communities. In the black cohort, the number of patients presenting with first time seizures was evenly distributed between females (51.6%) and males (48.4%). In the coloured patients, male patients (52%) were more prevalent compared to their female counterparts (48 %). The difference was slightly pronounced in the white patients, with females representing 45% and males (55%). Although it was a far smaller sample, in the Indian community 67% of the patients were male with only 33% female. These distribution differences were not statistically significant, and had a Pearson Chi-square test p-value of 0.562.

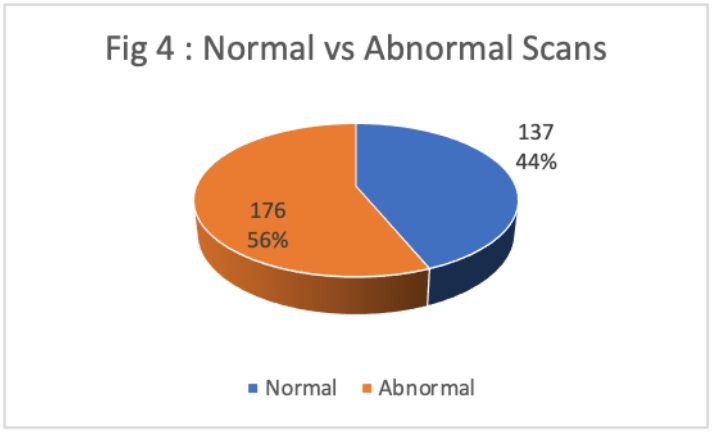




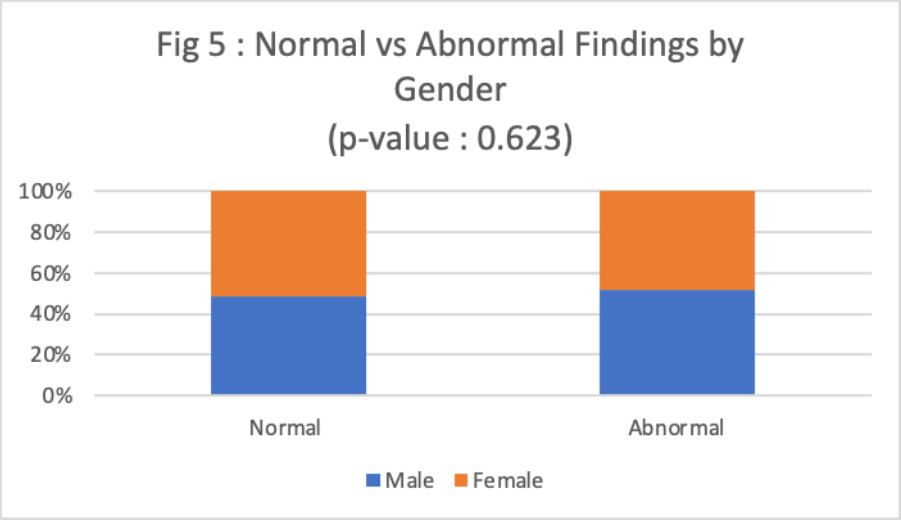


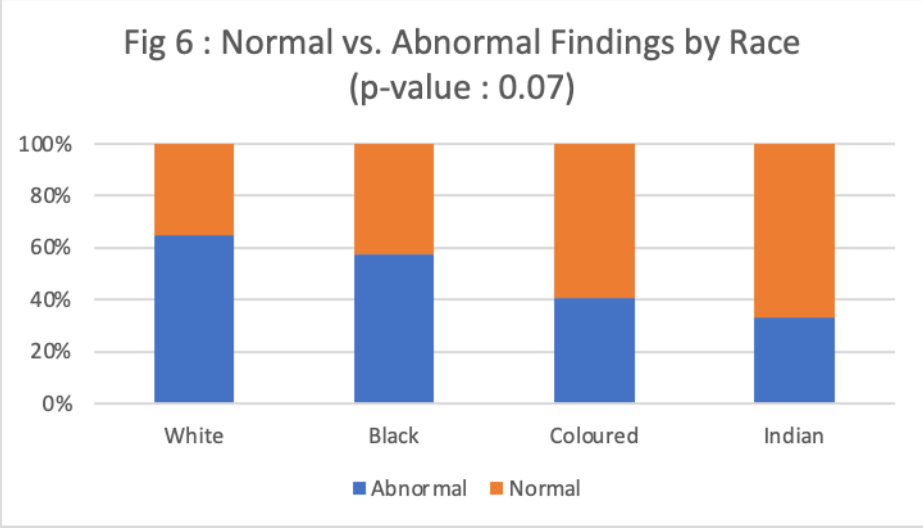
3.2. Objective 2: Proportion of Normal vs Abnormal Findings

We also determined the proportion of normal vs abnormal CT brain scans, and our study revealed that 44% of the CT scans were normal, while the remaining 56% were abnormal, demonstrated in Fig 4 below.



There was no statistically significant difference (Chi - Square test p-value: 0.623) in the distribution of normal vs. abnormal scans across the gender divide, as depicted in Fig 5 below. We however found a marginally significant difference (p-value 0.07) in the distribution of abnormal CT scans across the racial classification, as shown in Fig 6. The highest prevalence of abnormal CT findings was in the white patient cohort (65%), followed by the black patients (57%), the coloured patients (41%), while the Indians patients had the lowest proportion of abnormal CT brain scan findings of 33%.



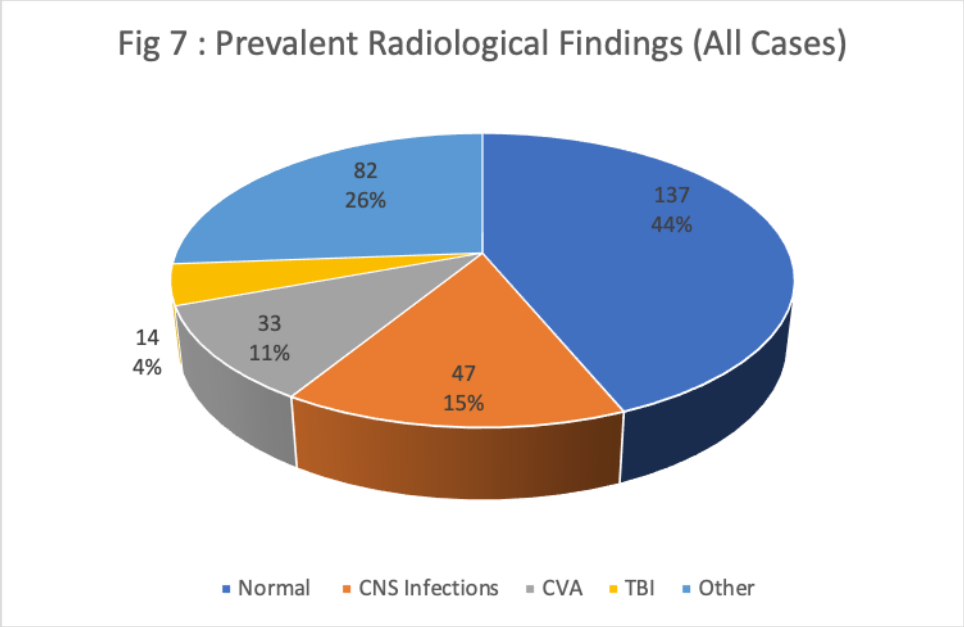


3.3. Objective 3: Prevalent Radiological Findings

As stipulated, of the 313 cases reviewed 137 (44%) were normal, and 176 (56%) had abnormal findings. In line with our literature review and study objectives, we sought to document the occurrence of the most lethal disease entities in these patients, and as such our findings were further classified into CNS Infections, CVA and Traumatic Brain injury (TBI). Radiological findings not fitting into any of these classes were separately categorised under 'other' findings.

As demonstrated in Fig. 7 below, the prevalence of CNS infection was 15%, representing 47 cases (this included cases of infective granuloma, meningitis, infective cysts, empyema and brain abscesses). There were 33 cases of CVA representing a prevalence of about 11% of all cases, and these included 22 cases of infarcts and 11 cases of bleeds. The prevalence of Acute Traumatic Brain Injury (TBI) was 4%, representing 14 cases (including 6 contusions / DAI, 6 intracranial haemorrhages and 2 fractures).

The 'other findings' category was significant in that it constituted 26% of the total study population (82 cases). As demonstrated in Fig 8, this included encephalopathy (39 cases), encephalomalacia (18 cases), neoplasia (14 cases), congenital anomalies (7) and vasculopathy (4).



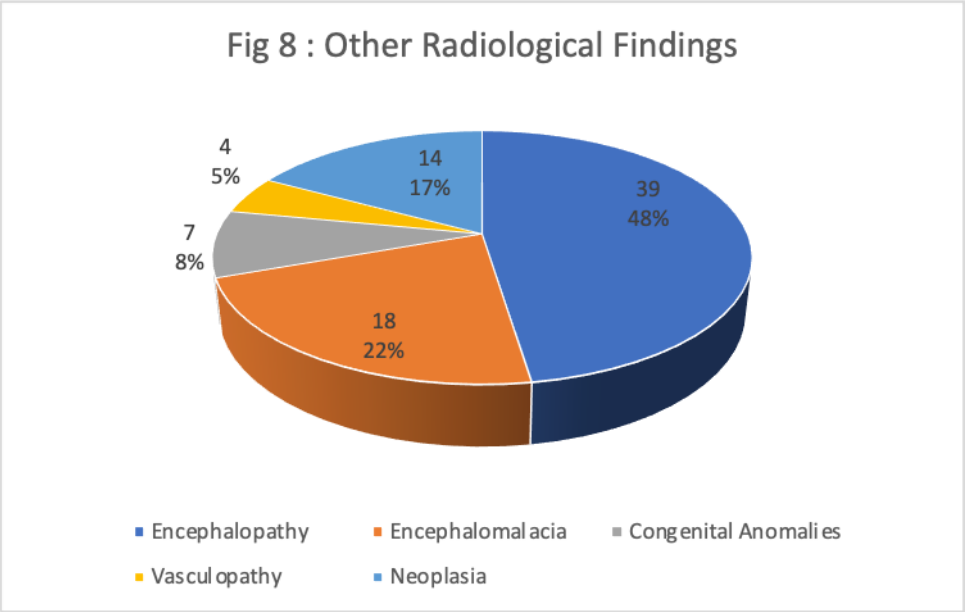
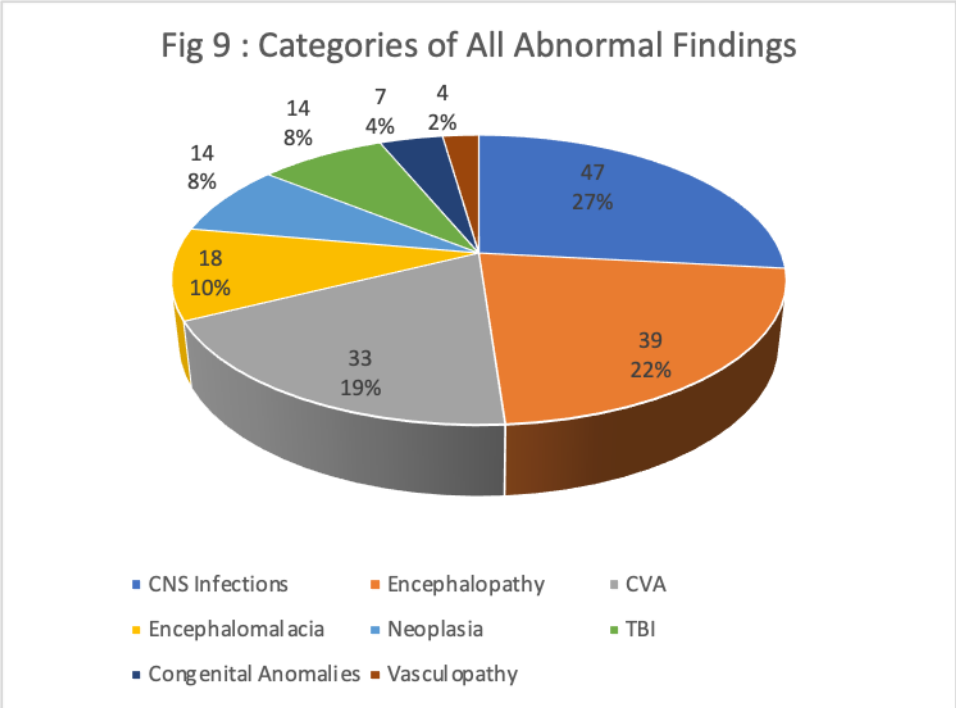
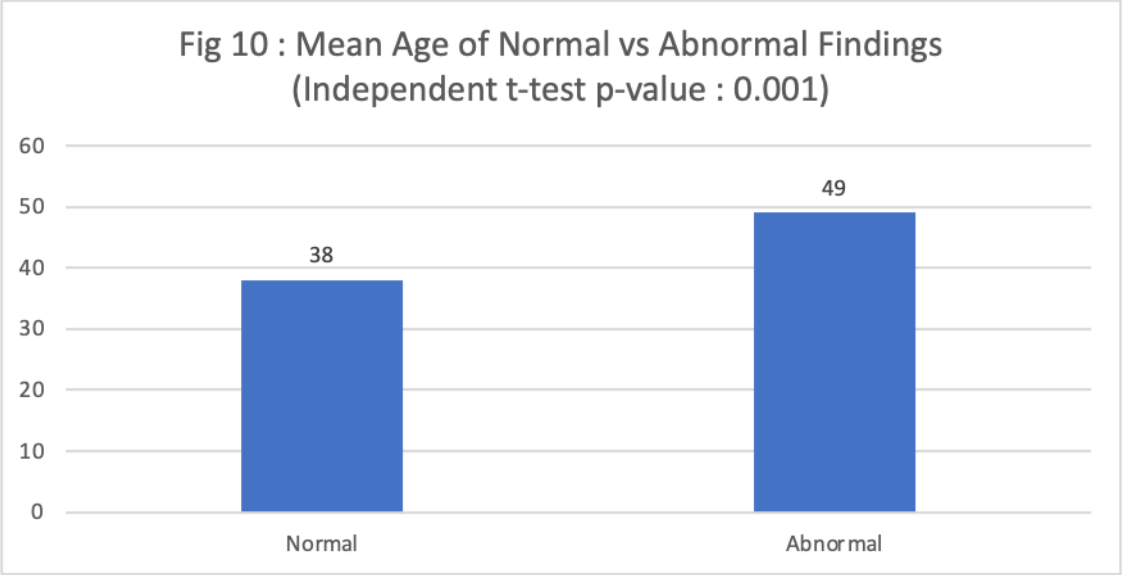


Fig 9 below demonstrates the categories and the prevalence of the different radiological diseases in the entire population studied. The frequency of diseases classified under 'other' radiological findings above is underpinned because encephalopathy, for example, is the second most common abnormality in the entire study population.

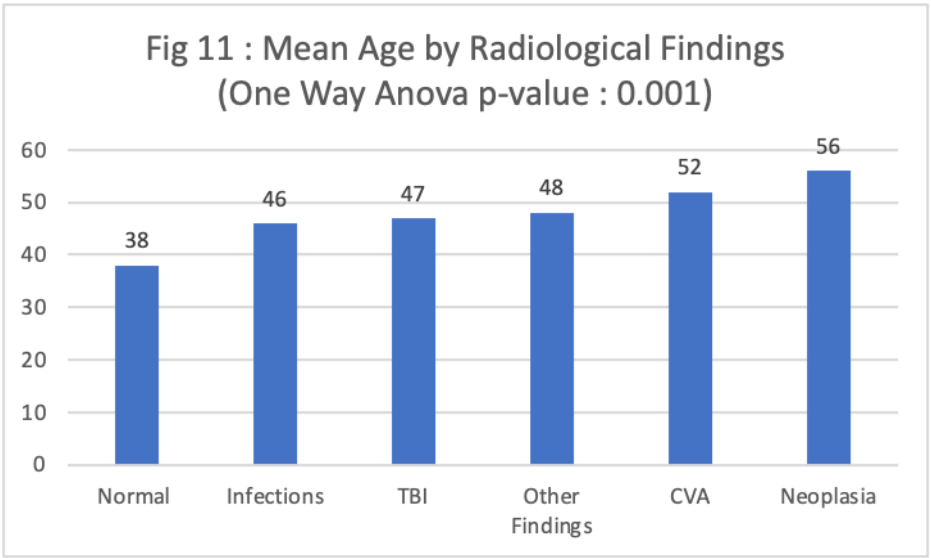


Although this study did not specifically seek to investigate the association between radiological findings of the CT brain scans and the sociodemographic variables, we explored the potential underlying associations. We found strongly significant evidence that the age of patients significantly differed between patients with normal vs. abnormal findings. For instance, as

shown in figure 10 below, patients with abnormal CT findings were on average relatively older (49 years old), compared to those with normal CT brain scans (38 years old), p-value: 0.001.



Since age proved to be statistically significantly associated with a normal vs. abnormal CT brain scan, we used analysis of variance (Anova) to document age differences across the pathological classes. For the purposes of this analysis, neoplastic disease was aggregated separately (outside the 'other' findings category). We found that on average patients above 50 years of age were likely to present with CVA or neoplastic brain disease whereas those younger than 40 years of age were likely to have normal CT brains. Furthermore, we found that patients with CVA were on average 52 years old (p-value 0.001).



3.4. Objective 4: Prevalent Co-morbid Disease

The medical illness or events associated with the seizure were tabulated from using the clinical history provided upon requisition of the scan. The most prevalent of these was retroviral disease (RVD) (about 27% of patients), hypertensive disease (16% of patients) and acute head injury (10.5% of patients).

Table 6 : Prevalent Co-morbid Disease

Co-Morbid Illness / Medical Hx	Frequency (%)		Co-Morbid Illness / Medical Hx	Frequency (%)
RVD			**Hypertension**	
No	229 (73.16)		No	263 (84.03)
Yes	84 (26.84)		Yes	50 (15.97)
Acute Head Injury			**TB**	
No	280 (89.46)		No	293 (93.61)
Yes	33 (10.54)		Yes	20 (6.39)
Diabetes Mellitus			**Known Cancer**	
No	297 (94.89)		No	300 (95.85)
Yes	16 (5.11)		Yes	13 (4.15)
Previous Head Injury			**Previous CVA**	
No	302 (96.49)		No	303 (96.81)
Yes	11 (3.51)		Yes	10 (3.19)
Chronic Renal Disease			**Psychosis Psychiatry**	
No	303 (96.81)		No	304 (97.12)
Yes	10 (3.19)		Yes	9 (2.88)
Hyponatraemia			**Alcohol Abuse**	
No	306 (97.76)		No	306 (97.76)
Yes	7 (2.24)		Yes	7 (2.24)
Acute Renal Failure			**Hypothyroidism**	
No	309 (98.72)		No	309 (98.72)
Yes	4 (1.28)		Yes	4 (1.28)
Meningitis			**Cushing Disease**	
No	310 (99.04)		No	312 (99.68)

Yes	3 (0.96)		Yes	1 (0.32)
Fever			**Pneumonia**	
No	312 (99.68)		No	312 (99.68)
Yes	1 (0.32)		Yes	1 (0.32)

4. Discussion

4.1. Results in Context

Table 7: Results in Context

Reference	Study Design	Non-Contrast CT or Contrast CT	No. of Exams	Mean Age	No (%) Abnormal Exams	CT Descriptions / Diagnosis: No (%)	Co-Morbid Illness
Kotisaari[3]	Retrospective	136 NCCT / 280 CCT	416	47	220 (53)	Emergent findings only: - ICH: 23 (5.5) - Tumour: 16 (3.8) - Ischaemia: 6 (1.4)	Hx of CVA 63 (15) Cancer 30 (7.2) Head Injury 6 (1.4)
Pathan[4]	Retrospective	Unspecified	436	35.3	154 (35)	Neurocysticercosis: 40 (9.2) Calcific lesions: 26 (6) Ill-defined: 21 (4.8) Old CVA: 18 (4.1) Mets & Neoplasia: 15 (3.4)	Unspecified
Smith[10]	Prospective	Unspecified	169	-	96 (57%)	Infarct: 24 (25) ICH: 12 (12.5) Atrophy: 12 (12.5) Mets: 6 (6.3) TB meningitis: 5 (5.2)	HIV: Positive: 49 (16) Negative: 53 (17.2)
This Study	Retrospective	94 NCCT / 219 CCT	313	44	176 (56%)	CNS Infections: 47 (27) Encephalopathy: 39 (22) CVA: 33 (19) Encephalomalacia: 18 (10) Neoplasia: 14 (8) TBI: 14 (8)	Retroviral Disease: 84 (27) Hypertension: 50 (16) Head Injury: 33 (10.5)

The average age of our study population was similar to that in Kotisaari et al (2017)[3] and slightly older than in Pathan et al (2014). We demonstrated a statistically significant association bewtwen advancing age and CVA patients presenting with seizures and this correlates with findings in Kotisaari (2017). Whilst Smith at al (2013) was a smaller study than ours, it was South African based and thus offered invaluable locally relevant insights and comparisons.

Our study disaggregated scans according to whether intravenous contrast was administered or not, similar to Kotisaari (2017)[3]. In this regard about 70% of our patients had contrast, about 2% more than in Kotisaari (2017).

The yield of abnormal scans was 56% in our study, and this is slightly higher than all our comparative studies, but similar to local findings by Smith (2013)[10]. It is however noteworthy that many similar international studies yield 35-56% abnormal scans[3,4,10,19,37].

The top three most common radiological findings in our studies were CNS infections (27%), Encephalopathy (22%) and CVA (19%). These findings are dissimilar to Smith (2013) with respect to the prevalence of infections. Since that study was unclear on the number of scans in

which intravenous contrast was used, it remains unclear if this had a bearing on the detection of infections or not. In Kotisaari (2017) only emergent findings were reported and there was no significant yield of CNS infections. These findings were similar to Pathan (2014), although CNS infestations with neurocysticercosis were a prominent finding in that case.

Unexplained encephalopathy was the second most common (22%) finding in our study. In Smith (2013), brain atrophy also featured in 12.5% of the cases, and could be interpreted as a similar finding to encephalopathy. These findings were not borne out by the other studies. In our study retroviral disease (RVD) was the most common co-morbid disease (27%) and although not specifically corelated to these patients, HIV related encephalopathy (HAND) is a plausible contributing factor for further exploration. In Smith (2013), 16% of the patients were HIV positive, 17% negative and the status of the rest was unknown.

CVA constituted 19% of findings in our study. This constituted both acute ischaemic and haemorrhagic strokes (ICH), and excluded post CVA brain sequalae like encephalomalacia, which was classified separately. In Smith (2013) the aggregate total of infarcts and ICH was 37.5%. It is however unclear if these were acute of events of sequalae. In Kotisaari (2017) the total aggregate of CVAs was 6.9%, and these were 'emergent' and thus acute events. In Pathan (2014) only old CVAs (4.1%) were reported. According to Sethuram (2019) in the US about 15% of CVA patients develop seizures[5], and 80% of these happen within 48 hrs. Our study demonstrated this.

4.2. Limitations of the Study

- The description of a seizure episode mainly relied on eye-witness accounts and was elucidated from radiological referral forms.
- The high demand of radiological examinations delays and limits access to CT scan examination. As a result it sometimes took more than 24 hours for patients to actually get scanned, and this mirrors findings in Smith (2013) that only about 55% of the patients in need of radiological imaging actually received it[10].
- HIV infection was the leading co-morbid disease however only 37% of the patients had a known status (27% positive and 10% negative).

4.3. Future Applications

- The role of MRI in first time seizures needs to be explored.
- Further exploration of imaging findings and subsequent mortality.

5. Conclusion

Seizures are an important source of morbidity and mortality worldwide and radiological examination plays a crucial role in the initial and subsequent evaluation of patients presenting with seizure episodes.

The utility of CT imaging in single episode first time seizures remains an interesting area of research particularly for purposes of resource allocation. Juxtaposed to this is the uniquely South African high prevalence of non-communicable disease, communicable disease and trauma.

In this retrospective study we aimed to establish the common radiological findings in patients with first time seizures, and what the common associated (and possibly causative) co-morbid diseases were.

We established that CNS infections were the most common finding in these patients, followed by encephalopathy. We also established that underlying HIV infection was the most common associated co-morbid disease, thus firmly establishing the leading role of infectious disease in seizure presentation.

CVA's were the third most common radiological finding and co-morbid hypertension the second most common disease. This reflects the prevalence and the effects of non-communicable disease in the South African population.

Lastly, whilst there is still an endemic prevalence of trauma in South Africa, it is noteworthy that traumatic brain injury did not feature as highly in the causes of first-time seizure presentation (6th overall). The 8% prevalence we found is within the 4-9% prevalence in most international studies[3,6,29], and reaffirms the high impact infectious and non-communicable diseases have on seizure prevalence.

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Data Collection Sheet

Study ID

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Demographics

Sex	Male (0), Female (1)
Age	In years
Race	Black (1), White (2), Coloured (3), Indian (4)
Education	Primary (1), Secondary (2), Tertiary (3)
Income	In SA Rand
Place	Urban (0), rural (1)
Employment Status	Employed (0), unemployed (1)
Coverage (health insurance)	Yes (1) / no (0)
Marital Status	Married or in union (1), unmarried or divorced or single (0)
Number of alive children	Count
Family history of epilepsy	No (0) / yes (1)

Finding	**Description**	**Description code**
TBI (1)	fracture	1
	contusions / DAI	2
	extra/subdural, subarachnoid bleed	3
Neoplasm (2)	intra-axial	4
	extra-axial	5
CVA (3)	infarct	6
	bleed	7
Infection / Demyelination (4)	meningitis	8
	empyema	9
	abscess	10
	granuloma	11
	cysts	12
	demyelination	13
Other (5)		14
Normal (6)		15