Anterior Temporal Lobectomy: A Cross-sectional Observational Study of Potential Surgical Candidates at a Single Institute

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"We need more light about each other. Light creates understanding, understanding creates love, love creates patience, and patience creates unity"

Malcolm X

I remain eternally grateful for my sister Zakiyya, from whom the light shines within and I continually learn from.

Table of Contents

Declaration

I, Aayesha Jalaluddin Soni, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 16 November 2021

Abstract

Background: Epilepsy is a common neurological disorder, associated with serious cognitive, physical, and psychosocial burdens. Mesial temporal lobe epilepsy (mTLE) is the commonest form of focal epilepsy. It is often refractory to anti-epileptic drugs, and the most amenable to surgical treatment which can render patients seizure free. It is surprising, therefore, that surgery for mTLE remains widely under-utilised.

Objectives: The aim of this study was to establish the frequency of occurrence of patients with electroencephalographic epileptiform discharges consistent with mTLE attending a tertiary hospital in South Africa, and determine whether these patients may be candidates for anterior temporal lobectomy.

Methods: This was a cross-sectional observational study of all patients receiving scalp electroencephalograms (EEG) performed at the Groote Schuur Hospital Neurophysiology laboratory during the period January 1st 2017 to December 31st 2019. Where CT and MRI brain scans had been performed, these were assessed for corroborative evidence of mTLE.

Results: Over the three-year period, 4 342 EEGs were assessed. A total of 411 (11%) showed epileptiform discharges consistent with all epilepsy types. Of these, 327 (69%) were of focal onset and 108 (33% of all focal onset epilepsies) were consistent with mTLE. Of the patients with electroencephalographic features of mTLE, only 27 (25%) had had MRI brain scans performed according to an epilepsy surgery protocol. None of these patients had been considered for surgery.

Conclusion: Surgery, especially anterior temporal lobectomy, is widely acknowledged to be an efficacious and cost-effective intervention in patients with drug resistant mTLE. The findings of our study suggest that patients with mTLE in our setting are under-investigated for potential surgery; and that it is under-utilised. These findings are in line with similar studies in both well-resourced and resource-constrained countries. Our study also highlights the utility of EEG as a practical screening tool to identify potential surgical candidates, as well as the establishment of an EEG and MRI database to assist in recognising these patients.

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Format and Contributions

This thesis is presented in the Published/Publication-ready format. The findings of this research were published in a manuscript with the title "Anterior Temporal Lobectomy: A Cross-sectional Observational Study of Potential Surgical Candidates at a Single Institute" in the journal Surgical Neurology International (Citation: Soni A, Lee Pan E, Tucker L. Anterior temporal lobectomy: A cross-sectional observational study of potential surgical candidates at a single institute. *Surg Neurol Int* 2021;12:565. DOI: 10.25259/SNI_796_2021).

AJ Soni assisted with conceptualisation of the study, collected, and analysed the data and wrote the manuscript. E Lee Pan assisted with conceptualisation of study, and with reviewing and editing of the manuscript. L Tucker assisted with conceptualisation of study and with the analytical approach, revised and edited the manuscript.

List of Abbreviations

AEDs	Anti-epileptic drugs
ANOVA	Analysis of variance
CT	Computed tomography
EEG	Electroencephalogram
GSH	Groote Schuur Hospital
HS	Hippocampal sclerosis
ILAE	International League Against Epilepsy
MRI	Magnetic resonance imaging
mTLE	Mesial temporal lobe epilepsy
PACS	Picture Archiving and Communication System
RCT	Randomised controlled trial
SUDEP	Sudden unexpected death in epilepsy
TLE	Temporal lobe epilepsy

Chapter 1

Anterior Temporal Lobectomy: A Cross-sectional Observational Study of Potential Surgical Candidates at a Single Institute

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Conclusion: Surgery, especially anterior temporal lobectomy, is widely acknowledged to be an efficacious and cost-effective intervention in patients with drug resistant mTLE. The findings of

our study suggest that patients with mTLE in our setting are under-investigated for potential surgery; and that it is under-utilised. These findings are in line with similar studies in both well-resourced and resource-constrained countries. Our study also highlights the utility of EEG as a practical screening tool to identify potential surgical candidates, as well as the establishment of an EEG and MRI database to assist in recognising these patients.

Keywords: mesial temporal lobe epilepsy; anterior temporal lobectomy; EEG.

Introduction

Epilepsy is a common neurological disorder, which is estimated to affect at least 60 million people of all ages worldwide. [1] Despite numerous anti-epileptic drugs (AED) being available, up to 35% of patients remain refractory to medical management. [1] The International League Against Epilepsy (ILAE) defines drug-resistant/medically refractory epilepsy as 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom'.[2] Physical, cognitive and psychosocial burdens of poorly controlled epilepsy are significant and may include physical injury, sudden unexpected death in epilepsy (SUDEP), serious negative impact on employment, as well as severe depression and psychosis. [3]

In approximately 60% of patients with epilepsy, seizures have a focal onset.[4] In 2010, the ILAE recognised mesial temporal lobe epilepsy (mTLE) associated with hippocampal sclerosis (HS) as a discrete clinical syndrome.[5] mTLE is the most common form of human focal epilepsy and the most refractory to AEDs [6], but also the most amenable to surgical intervention. [7] Furthermore, diagnosing mTLE is generally straight-forward, being based on seizure semiology, the findings of non-invasive scalp electroencephalography (EEG) and brain magnetic resonance imaging (MRI).

The aim of this study was to determine the number of patients with anterior and/or middle temporal lobe epileptiform features on non-invasive electroencephalogram (EEG) consistent with mTLE referred to a South African, public sector tertiary hospital in Cape Town over a three-year period and determine what proportion of these patients had been appropriately

worked-up as potential candidates for epilepsy surgery. We suspected that patients are under-evaluated for surgical intervention; and that epilepsy surgery is under-utilised in our setting.

Methods

Study Population

This was a cross-sectional observational study of 4 342 consecutive EEGs performed on patients referred to the Groote Schuur Hospital (GSH) electrophysiological laboratory over a three-year period (1st January 2017- 31st December 2019). The study population included all adults (older than 13 years of age), who were referred for a scalp EEG. EEGs of younger persons, all recordings rendered illegible by severe persistent artefacts and duplicate patient EEGs were excluded.

Materials and Methods

All EEGs were performed in the neurophysiology laboratory or the wards of GSH. Nihon Kohden 21 channel digital EEG machines and software, and the international 10-20 electrode placement system are used along with 2 additional electrodes: FT9/T1 and FT10/T2 from the 10-10 system. All EEGs were performed by qualified technologists and recordings routinely lasted a minimum of 20 minutes, unless aborted earlier due to external medical or patient-related circumstances. Duplicate EEGs for the same patient were removed with the most abnormal report being used. Hyperventilation, intermittent photic stimulation and mental arousal procedures were routinely performed in the electrophysiology laboratory. All EEGs were performed on out-patients and in-hospital patients at GSH, or patients referred from the surrounding secondary and primary healthcare facilities. Reasons for referral included

unexplained losses of consciousness, suspected seizures, epilepsy, confusion, encephalopathy, dementia, and psychosis, amongst others.

Anonymised patient data relating to EEG and brain MRI findings for this study were recorded on a Microsoft Excel Sheet and stored on a password-protected laptop.

All EEGs performed during the study period were accessed and those reported by an attending specialist neurologist to show temporal lobe epileptiform activity were identified. The identified EEG traces were reviewed by a trainee neurologist experienced in EEG interpretation to confirm the presence and location of temporal epileptiform activity. These were then further classified as anterior and/or middle temporal, or posterior temporal lobe discharges. Hospital numbers of patients with anterior and/or middle temporal lobe epileptiform discharges were used on the GSH Picture Archiving and Communication System (PACS) to identify those patients in whom MRI or CT brain scanning had been performed, and whether mesial temporal sclerosis had been confirmed on an MRI using an epilepsy surgery protocol, which included axial and coronal T1-weighted, T2-weighted FLAIR, and T1-inversion recovery sequences. A trainee neurologist and specialist neurologist experienced in epilepsy management reviewed images of all MRI scans performed on patients with anterior and/or middle temporal epileptiform discharges to confirm radiological evidence of mesial temporal sclerosis and hippocampal atrophy. (Figure 1).

Ethics

Ethics clearance was granted by the University of Cape Town's Human Research Ethics Committee (HREC Reference number: 365/2020).

Statistical Analysis

Summary statistics are reported using frequencies and percentages for categorical responses and means with standard deviations for continuous measurement.

Results

The study sample included all EEGs performed at the GSH Neurophysiology laboratory over a three-year period between 1st January 2017 and 31st December 2019. A total of 4 342 EEGs were assessed, with 27 EEGs being excluded on the basis of duplication or illegibility. Of these, 411 (11%) showed evidence supporting epilepsy, of which 327 (69%) were focal and 144 (31%) generalised.

Temporal lobe epileptiform discharges were identified in 134 EEGs, which represented 41% of all EEGs with focal epileptiform discharges. Of all EEGs with focal temporal lobe discharges, 108 (81%) were in the anterior and/or middle temporal lobe, and 26 (19%) in the posterior temporal lobe.

Thus, anterior and/or middle temporal lobe discharges consistent with mTLE were identified in 108 (2%) of all EEGs, and 33% of EEGs with focal discharges, over the 3-year study period. (Figure 2) The mean age of patients with anterior and/or middle temporal lobe epileptiform discharges at the time of their EEG was 39,4 years, and 31% of these patients were in the 21–31-year age group. (Figure 3)

Appropriate MRI brain scanning according to an epilepsy surgery protocol had been performed in only 27 (25%) of the 108 patients with anterior and/or middle temporal lobe epileptiform discharges on EEG. Of these, 6 had MRI evidence of mesial temporal sclerosis ipsilateral to the

epileptiform discharge. All 6 of these patients had been diagnosed with drug-resistant epilepsy and were potential surgical candidates, but none had been subsequently worked up further or considered for epilepsy surgery. Table 1 summarises these findings with regards to the specific parameters assessed over each year.

Discussion

The prevalence of focal epilepsy is reported to be higher in Africa, Latin America and other low- and middle-income regions compared with high-income countries, with rural regions being especially affected. [8, 21, 22]

mTLE is the focus of this study because anterior temporal lobectomy is a highly effective and cost-efficient intervention in the management of drug-resistant seizures in patients with this condition, frequently rendering carefully chosen subjects seizure-free. Wiebe et al. have demonstrated superiority of surgery over medical therapy in terms of seizure control, quality of life, and the rates of employment or school attendance in patients with drug-resistant temporal lobe epilepsy. [9] Moreover, a recent systematic review and meta-analysis of TLE surgery found the overall rate of post-operative seizure freedom to be 72.4% in randomised controlled trials (RCT) conducted in adults, and 71.7% in prospective non-randomised adult cohorts, with increased seizure-freedom in cases in which mesial temporal sclerosis was clear on MRI. [5 ,9, 10] Numerous other reports and multi-centre analyses [10, 11, 12] also provide robust evidence for the efficacy and safety of epilepsy surgery. Furthermore, the risks of epilepsy surgery, and particularly anterior temporal lobectomy, are low. [13] Surgical complications, which occur at an estimated rate of 1–2%, include post-operative haematoma formation, hydrocephalus, CSF leakage, and procedure-related medical problems.[2]

Despite its efficacy and safety, epilepsy surgery remains under-utilised in both low- and high-income countries. [7] The reasons for this remain a matter of some debate. There appears to be a reluctance of primary physicians and even neurologists to refer their epilepsy patients for surgical intervention [14], which is often regarded as a "last resort". For example, the average interval between epilepsy onset and surgical intervention was 24 years in a large multi-center study involving 300 patients who had epilepsy surgery performed over a 5-year period [7]; and 18 years for 29 patients attending a Florida epilepsy centre in whom surgery was performed for mTLE over a 2-year period. [15] Thus, even in highly resourced settings, epilepsy surgery is often performed too late, leaving patients psychologically and socially disabled by years of uncontrolled seizures.[20] The delay in referral for epilepsy surgery may be explained, in part, by neurologists using an outdated or inappropriately conservative definition for drug-resistant epilepsy, as well as their failure to acknowledge the low risk and potential for excellent post-surgical outcomes of this intervention.[16] Interestingly, a study examining the social media imprint of epilepsy and surgery concluded that it is under-promoted by most social media accounts.[1]

The long-term costs of drug resistant epilepsy are well recognised. These include life-long multiple AED administration, recurrent hospital and intensive care admissions for seizure-related injuries and status epilepticus, as well as unemployment and the psycho-social burden on the patient and society. Therefore, the economic benefits of rendering a patient with drug resistant mTLE seizure-free are well established and accepted.[18, 19] Importantly, the cost-effectiveness of epilepsy surgery vs. medical management has also been established, especially in patients with mTLE. In a prospective cohort, Picot *et al* concluded that epilepsy surgery becomes cost-effective compared to medical treatment approximately 9-10 years after the surgery, and even

earlier if indirect costs are taken into count.[18] This finding is supported in a recent study by Sheikh *et al*, which concluded that even where the probability of a patient being a surgical candidate is low (e.g., 5%), surgical evaluation remains cost-effective.[19] In South Africa, ongoing poorly controlled epilepsy negatively impacts physical, mental and social health as well as economic prospects more seriously than most other chronic medical conditions. [3] This is a particular motivator for increasing the use of epilepsy in low- and middle- income countries.

Our study confirmed that most patients with temporal epileptiform discharges identified on EEGs performed at a large South African tertiary hospital were not adequately investigated with MRI brain scanning, long-term monitoring or neuropsychometric assessment to determine whether they were candidates for anterior temporal lobectomy. This is despite the fact that we have the resources and expertise to conduct all of the above, in addition to a competent and willing neurosurgical team to perform the surgery. It is significant that 31% (33) of patients identified with temporal lobe epileptiform activity in this study were between the ages of 21-31 years, and that epilepsy surgery, were it performed, would potentially render them seizure-free for the remainder of their lives.

In 62% of the patients with temporal lobe epileptiform activity, CT brain imaging (with and without contrast) was performed, rather than MRI. CT is a cheaper investigation and while effective in excluding tumours, parasitic infections, granulomas, hemorrhages and many other structural intracranial abnormalities, MRI is a pre-requisite for epilepsy surgery and the investigation of choice for identifying mesial temporal sclerosis, neuronal migration disorders and other subtle epileptogenic abnormalities which may be amenable to epilepsy surgery. MRI brain scans performed according to a standardised epilepsy surgery protocol were performed in

only 25% of the patients with anterior and/or middle temporal lobe epileptiform discharges in our study. To improve the efficacy of identifying candidates for epilepsy surgery, the application of an appropriate MRI protocol is vital. For example, an "essential 6" sequence protocol has recently been suggested for the detection of virtually all common epileptogenic lesion entities. [17]

Our study found that, over the three-year study period, 11% (411) of all EEGs showed epileptiform discharges, 69% (327) of which were focal in onset and significantly, a third of EEGs with focal discharges (108) (33%) were in the anterior and/or-middle temporal lobe consistent with mTLE, and thus were potential candidates for anterior temporal lobectomy.

The results of this study support the impression that patients with mTLE are under-investigated, and that epilepsy surgery is under-utilised in a tertiary healthcare centre in South African. Consideration should be given to increasing the use of surgery in low- and middle-income countries such as ours, where the expertise of a multi-disciplinary team are available and economic benefit is established. The study also demonstrates that standard scalp EEGs may be an effective way in which to identify potential epilepsy surgery candidates. These EEGs may be used as an initial tool to identify patients who should receive brain MRIs and be further worked up for potential surgery. A limitation to our study is that a standard 20-minute scalp EEG may not always identify interictal epileptiform discharges, and this could mean patients may be missed. Still, using non-invasive EEGs as an initial screening tool could offer resource constrained settings a stepwise protocol that could be implemented in patients with mTLE, in whom safe and cost-effective anterior temporal lobectomies may result in seizure freedom. A database of the epilepsy patients or radiological images of these patients did not exist in our

hospital prior to this study, which is another practical implementation which offers resource-constrained settings the platform to identify potential surgical candidates more readily.

Conclusion

Surgery in the form of anterior temporal lobectomy is a relatively straight forward, safe, and cost-effective intervention in carefully selected patients with drug resistant mTLE, and frequently results in seizure freedom. In line with the findings of similar studies in other low-, middle- and high-income countries, our study indicates that appropriate work up of these patients for possible neurosurgical intervention is lacking, and that epilepsy surgery is under-utilised. This is despite the infrastructure and expertise being available to investigate and assess these patients adequately and perform the procedure in some centres, such as ours. Our study also highlights the utility of an EEG as a practical screening tool to identify potential surgical candidates, as well as the benefit of the establishment of an EEG and MRI database to assist in recognising these patients. We encourage these measures to motivate increased surgeries in low- and middle-income countries especially.

Acknowledgements

None.

Conflict of Interest

None.

Author Contributions

AJ Soni was responsible for data collection and interpretation. EB Lee Pan, AJ Soni and LM Tucker supervised the study and contributed to the preparation and intellectual content of the manuscript.

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List of Figures and Tables

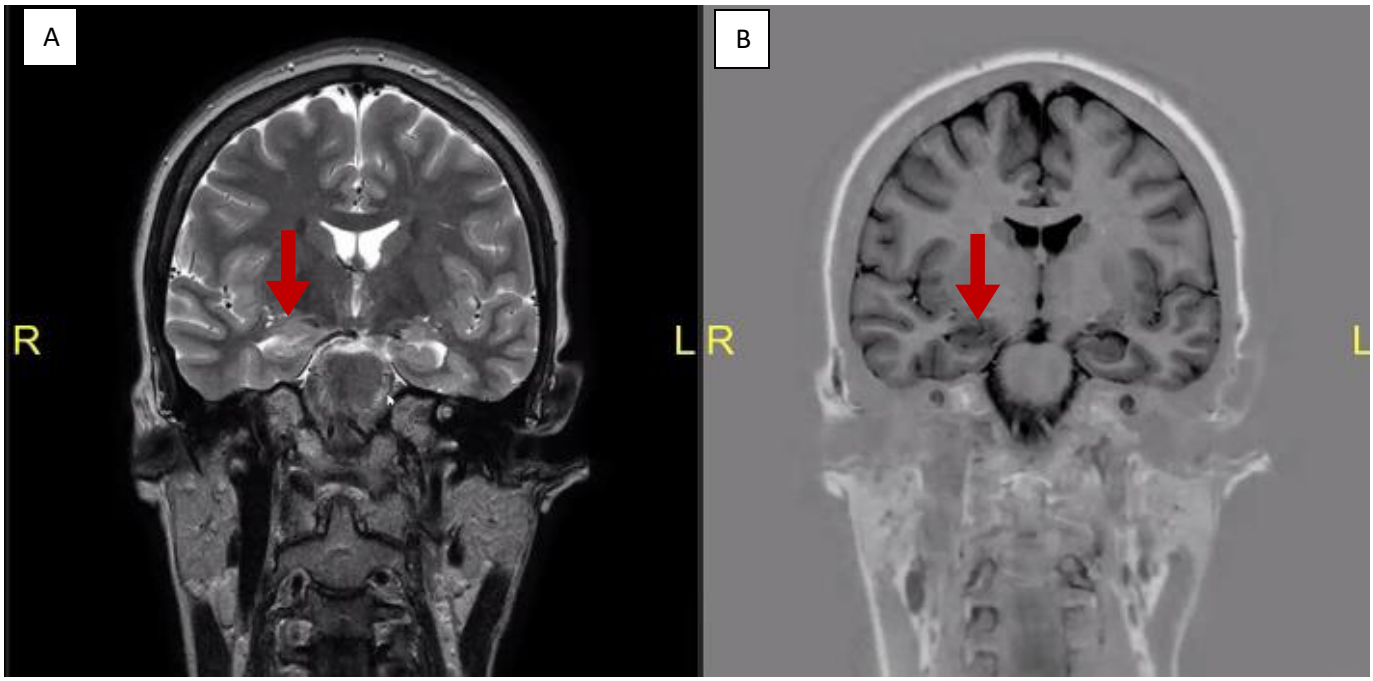

Figure 1: Coronal T2-weighted, and T1-weighted inversion recovery brain MRI (Panel A and B respectively) of a study participant showing evidence of right-sided hippocampal atrophy (indicated by arrows).

EEG Features		2017	2018	2019	Total
Normal or non-epileptiform abnormalities	Number (% of all EEGs)	1401 (91)	1282 (87)	1188 (90)	3871 (89)
Epileptiform (All: focal & generalised)	Number (% of all EEGs)	146 (9)	189 (13)	136 (10)	471 (11)
Epileptiform (generalised)	Number (% of all EEGs with epileptiform discharges)	53 (36)	56 (30)	35 (26)	144 (31)
Epileptiform (focal)	Number (% of all EEGs with epileptiform discharges)	93 (64)	133 (70)	101 (74)	327 (69)
Epileptiform (all temporal)	Number (% of all EEGs with focal epileptiform discharges)	46 (49)	41 (31)	47 (47)	134 (41)
Epileptiform (anterior/mid temporal)	Number (% of all EEGs)	37 (2)	33 (2)	38 (3)	108 (2)
MRI performed	Number (% of patients with ant/mid temporal discharges on EEG)	7 (25)	6 (19)	14 (29)	27 (25)
CT performed	Number (% of patients with ant/mid temporal discharges on EEG)	15 (54)	18 (56)	34 (71)	67 (62)
MRI features consistent with mTLE	Number (% of positive MRI result)	3 (43)	2 (33)	1 (7)	6 (22)
Total EEGs assessed		1547	1471	1324	4342

Table 1: Epileptiform discharges identified on EEG, and radiological imaging performed at a South African, public sector tertiary hospital over the three-year study period (1st Jan 2017 – 31st December 2019).

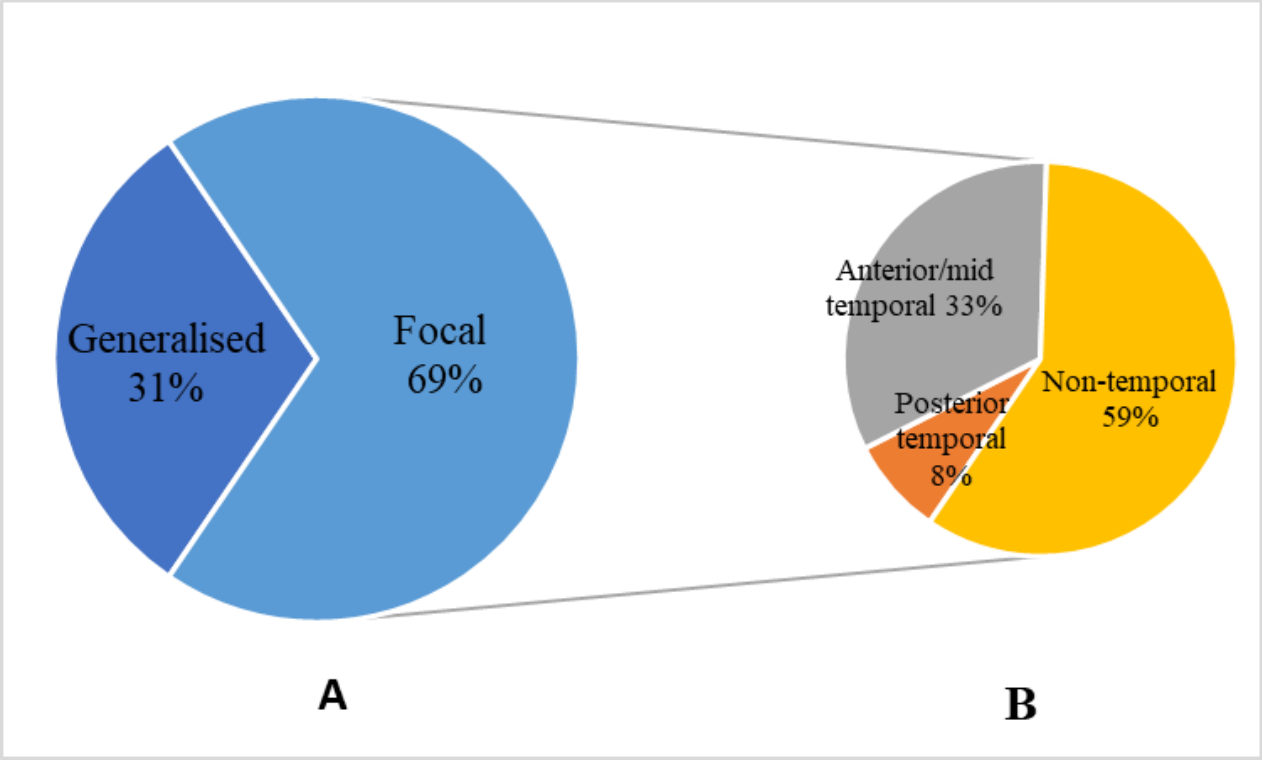

Figure 2: Pie charts representing (A) the proportion of focal vs. generalised epileptiform discharges, and (B) focal epileptiform discharges represented according to anatomical location.

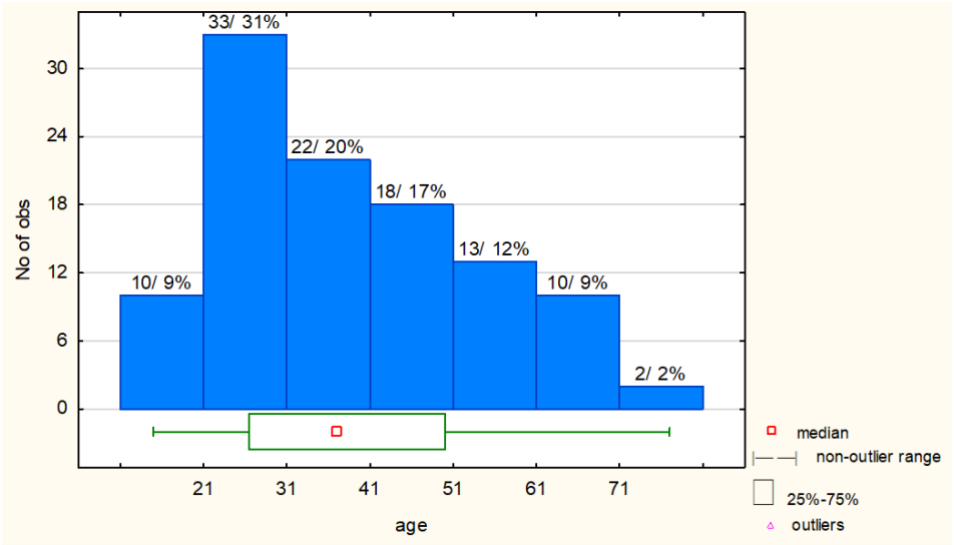

Figure 3: Histogram illustrating the age distribution of patients with anterior and/or middle temporal lobe epileptiform discharges on EEG consistent with a diagnosis of mTLE.

Appendices

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Original Article

Anterior temporal lobectomy: A cross-sectional observational study of potential surgical candidates at a single institute

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ABSTRACT

Background: Epilepsy is a common neurological disorder, associated with serious cognitive, physical, and psychosocial burdens. Mesial temporal lobe epilepsy (mTLE) is the commonest form of focal epilepsy. The aim of this study was to establish the incidence of patients with electroencephalographic epileptiform discharges consistent with mTLE attending a tertiary hospital in South Africa, and determine whether these patients may be candidates for anterior temporal lobectomy.

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Conclusion: Surgery, especially anterior temporal lobectomy, is widely acknowledged to be an efficacious and cost-effective intervention in patients with drug-resistant mTLE. The findings of our study suggest that patients with mTLE in our setting are under-investigated for potential surgery; and that it is under-utilized. These findings are in line with similar studies in both well-resourced and resource-constrained countries. Our study also highlights the utility of EEG as a practical screening tool to identify potential surgical candidates, as well as the establishment of an EEG and MRI database to assist in recognizing these patients.

Keywords: Anterior temporal lobectomy, Electroencephalogram, Mesial temporal lobe epilepsy

INTRODUCTION

Epilepsy is a common neurological disorder, which is estimated to affect at least 60 million people of all ages worldwide.[13] Despite numerous anti-epileptic drugs (AED) being available, up to 35% of patients remain refractory to medical management.[13] The International League Against Epilepsy (ILAE) defines drug-resistant/medically refractory epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or

in combination) to achieve sustained seizure freedom."[4] Physical, cognitive and psychosocial burdens of poorly controlled epilepsy are significant and may include physical injury, sudden unexpected death in epilepsy (SUDEP), serious negative impact on employment, as well as severe depression and psychosis.[12] SUDEP is a well-recognised, particularly negative consequence of mesial temporal lobe epilepsy (mTLE).

In approximately 60% of patients with epilepsy, seizures have a focal onset.[20] In 2010, the ILAE recognized mTLE associated with hippocampal sclerosis as a discrete clinical syndrome.[10] mTLE is the most common form of human focal epilepsy and the most refractory to AEDs,[17] but also the most amenable to surgical intervention.[6] Furthermore, diagnosing mTLE is generally straightforward, being based on seizure semiology, the findings of non-invasive scalp electroencephalography (EEG) and brain magnetic resonance imaging (MRI).

The aim of this study was to determine the number of patients with anterior and/or middle temporal lobe epileptiform features on non-invasive EEG consistent with mTLE referred to a South African, public sector tertiary hospital in Cape Town over a 3-year period and determine what proportion of these patients had been appropriately worked-up as potential candidates for epilepsy surgery. We suspected that patients are under-evaluated for surgical intervention; and that epilepsy surgery is under-utilised in our setting.

MATERIALS AND METHODS

Study population

This was a cross-sectional observational study of 4,342 consecutive EEGs performed on patients referred to the Groote Schuur Hospital (GSH) electrophysiological laboratory over a 3-year period (January 1, 2017-December 31, 2019). The study population included all adults (older than 13 years of age), who were referred for a scalp EEG. EEGs of younger persons, all recordings rendered illegible by severe persistent artefacts and duplicate patient EEGs were excluded.

Methods

All EEGs were performed in the neurophysiology laboratory or the wards of GSH. Nihon Kohden 21 channel digital EEG machines and software, and the international 10-20 electrode placement system are used along with 2 additional electrodes: FT9/T1 and FT10/T2 from the 10-10 system. All EEGs were performed by qualified technologists and recordings routinely lasted a minimum of 20 min, unless aborted earlier due to external medical or patient-related circumstances. Duplicate EEGs for the same patient were removed with the most abnormal report being used. Hyperventilation, intermittent photic stimulation, and mental arousal procedures were routinely performed in the electrophysiology laboratory. All EEGs were performed on out-patients and in-hospital patients at GSH, or patients referred from the surrounding secondary and primary healthcare facilities. Reasons for referral included unexplained losses of consciousness, suspected seizures, epilepsy, confusion, encephalopathy, dementia, and psychosis, among others.

Anonymised patient data relating to EEG and brain MRI findings for this study were recorded on a Microsoft Excel Sheet and stored on a password-protected laptop. All EEGs performed during the study period were accessed and those reported by an attending specialist neurologist to show temporal lobe epileptiform activity were identified. The identified EEG traces were reviewed by a trainee neurologist experienced in EEG interpretation to confirm the presence and location of temporal epileptiform activity. These were then further classified as anterior and/or middle temporal, or posterior temporal lobe discharges. Hospital numbers of patients with anterior and/or middle temporal lobe epileptiform discharges were used on the GSH Picture Archiving and Communication System to identify those patients in whom MRI or computed tomography (CT) brain scanning had been performed, and whether mesial temporal sclerosis had been confirmed on an MRI using an epilepsy surgery protocol, which included axial and coronal T1-weighted, T2-weighted FLAIR, and T1-inversion recovery sequences. A trainee neurologist and specialist neurologist experienced in epilepsy management reviewed images of all MRI brain scans performed on patients with anterior and/or middle temporal epileptiform discharges to confirm radiological evidence of mesial temporal sclerosis and hippocampal atrophy [Figure 1].

Ethics

Ethics clearance was granted by the University of Cape Town's Human Research Ethics Committee (HREC Reference number: 365/2020).

Statistical analysis

Summary statistics are reported using frequencies and percentages for categorical responses and means with standard deviations for continuous measurement. With regards to inferential statistics, this involved cross-tabulations, ANOVA and correlation analyses which were used as appropriate for the types of variables compared.

RESULTS

The study sample included all EEGs performed at the GSH Neurophysiology laboratory over a 3-year period between January 1, 2017, and December 31, 2019. A total of 4,342

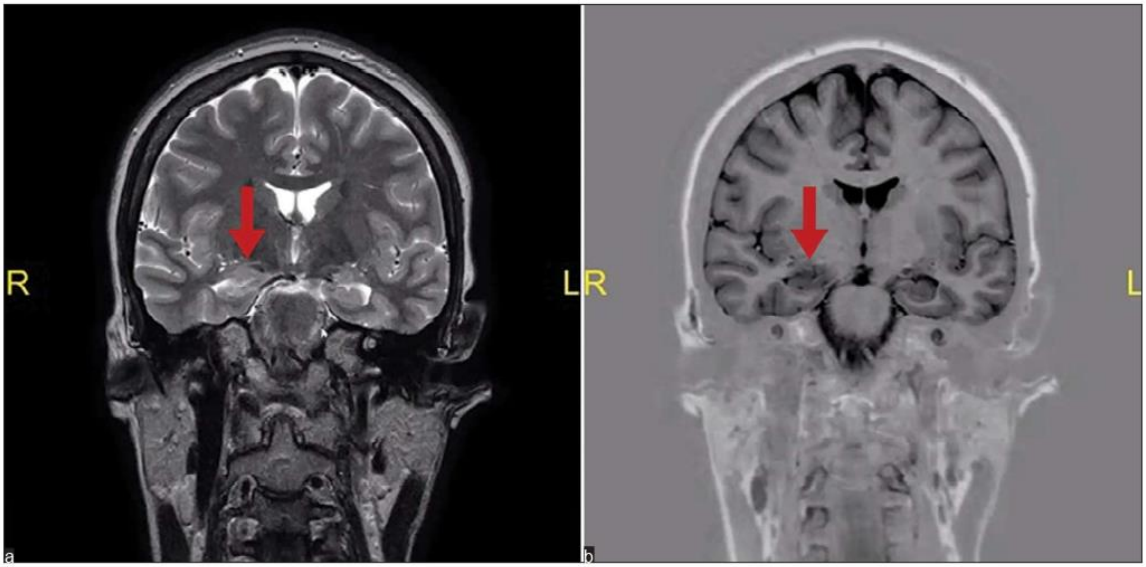

Figure 1: Coronal T2-weighted, and T1-weighted inversion recovery magnetic resonance imaging brain scan (Panel a and b respectively) of a study participant showing evidence of right-sided hippocampal atrophy (indicated by arrows).

EEGs were assessed, with 27 EEGs being excluded based on duplication or illegibility. Of these, 411 (11%) showed evidence supporting epilepsy, of which 327 (69%) were focal and 144 (31%) generalised.

Temporal lobe epileptiform discharges were identified in 134 EEGs, which represented 41% of all EEGs with focal epileptiform discharges. Of all EEGs with focal temporal lobe discharges, 108 (81%) were in the anterior and/or middle temporal lobe, and 26 (19%) in the posterior temporal lobe. Thus, anterior and/or middle temporal lobe discharges consistent with mTLE were identified in 108 (2%) of all EEGs, and 33% of EEGs with focal discharges, over the 3-year study period. [Figure 2] The mean age of patients with anterior and/or middle temporal lobe epileptiform discharges at the time of their EEG was 39.4 years, and 31% of these patients were in the 21–31-year age group [Figure 3].

Appropriate MRI of the brain scanning according to an epilepsy surgery protocol had been performed in only 27 (25%) of the 108 patients with anterior and/or middle temporal lobe epileptiform discharges on EEG. Of these, six had MRI evidence of mesial temporal sclerosis ipsilateral to the epileptiform discharge. All six of these patients had been diagnosed with drug-resistant epilepsy and were potential surgical candidates, but none had been subsequently worked up further or considered for epilepsy surgery. [Table 1] summarizes these findings with regards to the specific parameters assessed over each year.

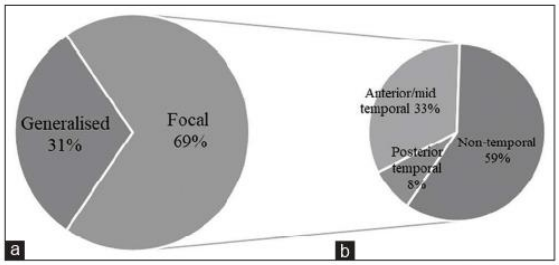

Figure 2: Histograms representing (a) the proportion of focal versus generalised epileptiform discharges, and (b) focal epileptiform discharges represented according to anatomical location.

DISCUSSION

The prevalence of focal epilepsy is reported to be higher in Africa, Latin America and other low- and middle-income regions compared with high-income countries, with rural regions being especially affected.[11,14,16]

mTLE is the focus of this study because anterior temporal lobectomy is a highly effective and cost-efficient intervention in the management of drug-resistant seizures in patients with this condition, frequently rendering carefully chosen subjects seizure-free. Wiebe *et al.* have demonstrated the superiority of surgery over medical therapy in terms of seizure control, quality of life, and the rates of employment or school attendance in patients with drug-resistant TLE.[22] Moreover, a recent systematic review and meta-analysis of TLE surgery found the overall rate of post-operative seizure freedom to be

Table 1: Epileptiform discharges identified on EEG and radiological imaging performed at a South African public sector tertiary hospital over the 3-year study period (January 1, 2017–December 31, 2019).

EEG Features		2017	2018	2019	Total
Normal or non-epileptiform abnormalities	Number (% of all EEGs)	1401 (91)	1282 (87)	1188 (90)	3871 (89)
Epileptiform (All: focal and generalised)	Number (% of all EEGs)	146 (9)	189 (13)	136 (10)	471 (11)
Epileptiform (generalised)	Number (% of all EEGs with epileptiform discharges)	53 (36)	56 (30)	35 (26)	144 (31)
Epileptiform (focal)	Number (% of all EEGs with epileptiform discharges)	93 (64)	133 (70)	101 (74)	327 (69)
Epileptiform (all temporal)	Number (% of all EEGs with focal epileptiform discharges)	46 (49)	41 (31)	47 (47)	134 (41)
Epileptiform (anterior/mid temporal)	Number (% of all EEGs)	37 (2)	33 (2)	38 (3)	108 (2)
MRI performed	Number (% of patients with ant/mid temporal discharges on EEG)	7 (25)	6 (19)	14 (29)	27 (25)
CT performed	Number (% of patients with ant/mid temporal discharges on EEG)	15 (54)	18 (56)	34 (71)	67 (62)
MRI features consistent with mTLE	Number (% of positive MRI result)	3 (43)	2 (33)	1 (7)	6 (22)
Total EEGs assessed		1547	1471	1324	4342

EEG: Electroencephalogram, CT: Computed tomography, mTLE: Mesial temporal lobe epilepsy

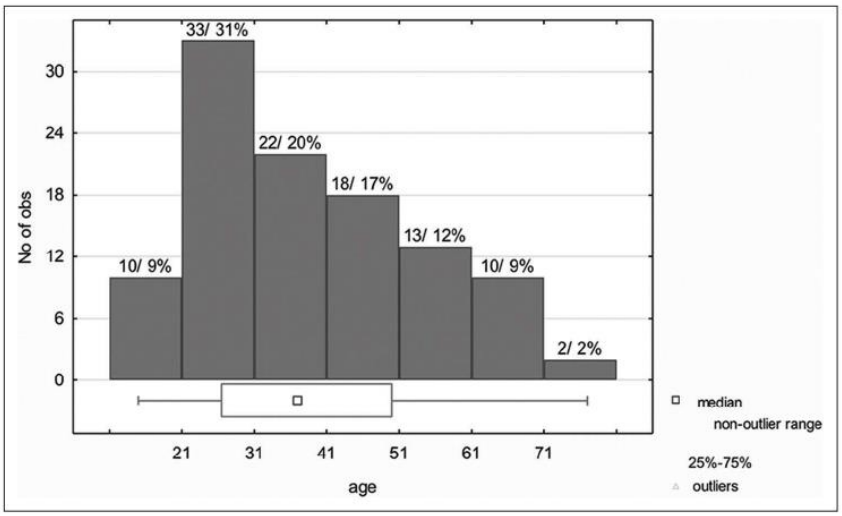

Figure 3: Histogram illustrating the age distribution of patients with anterior and/or middle temporal lobe epileptiform discharges on electroencephalogram consistent with a diagnosis of Mesial temporal lobe epilepsy.

72.4% in randomised controlled trials conducted in adults, and 71.7% in prospective non-randomized adult cohorts, with increased seizure-freedom in cases in which mesial temporal sclerosis was clear on MRI.[7,10,22] Numerous other reports and multi-centre analyses[1,7,9] also provide robust evidence for the efficacy and safety of epilepsy surgery. Furthermore, the risks of epilepsy surgery, and particularly anterior temporal lobectomy, are low.[3] Surgical complications, which occur at an estimated rate of 1–2%, include postoperative hematoma formation, hydrocephalus, cerebrospinal fluid leakage, and procedure-related medical problems.[4]

Despite its efficacy and safety, epilepsy surgery remains under-utilised in both low- and high-income countries.[6] The reasons for this remain a matter of some debate. There appears to be a reluctance of primary physicians and even neurologists to refer their epilepsy patients for surgical intervention,[5] which is often regarded as a "last resort". For example, the average interval between epilepsy onset and surgical intervention was 24 years in a large multi-center study involving 300 patients who had epilepsy surgery performed over a 5-year period;[6] and 18 years for 29 patients attending a Florida epilepsy centre in whom

surgery was performed for mTLE over a 2-year period.[2] Thus, even in highly resourced settings, epilepsy surgery is often performed too late, leaving patients psychologically and socially disabled by years of uncontrolled seizures.[19] The delay in referral for epilepsy surgery may be explained, in part, by neurologists using an outdated or inappropriately conservative definition for drug-resistant epilepsy, as well as their failure to acknowledge the low risk and potential for excellent post-surgical outcomes of this intervention.[8] Interestingly, a study examining the social media imprint of epilepsy and surgery concluded that it is under-promoted by most social media accounts.[13]

The long-term costs of drug-resistant epilepsy are well recognised. These include life-long multiple AED administration, recurrent hospital and intensive care admissions for seizure-related injuries and status epilepticus, as well as unemployment and the psycho-social burden on the patient and society. Therefore, the economic benefits of rendering a patient with drug-resistant mTLE seizure-free are well established and accepted.[15,18] Importantly, the cost-effectiveness of epilepsy surgery versus medical management has also been established, especially in patients with mTLE. In a prospective cohort, Picot *et al.* concluded that epilepsy surgery becomes cost-effective compared to medical treatment approximately 9–10 years after the surgery, and even earlier if indirect costs are taken into count.[15] This finding is supported in a recent study by Sheikh *et al.*, which concluded that even where the probability of a patient being a surgical candidate is low (e.g., 5%), surgical evaluation remains cost-effective.[18] In South Africa, ongoing poorly controlled epilepsy negatively impacts physical, mental and social health as well as economic prospects more seriously than most other chronic medical conditions.[12] This is a particular motivator for increasing the use of epilepsy in low- and middle-income countries.

Our study confirmed that most patients with temporal epileptiform discharges identified on EEGs performed at a large South African tertiary hospital were not adequately investigated with MRI brain scanning, long-term monitoring or neuropsychometric assessment to determine whether they were candidates for anterior temporal lobectomy. This is despite the fact that we have the resources and expertise to conduct all of the above, in addition to a competent and willing neurosurgical team to perform the surgery. It is significant that 31% (33) of patients identified with temporal lobe epileptiform activity in this study were between the ages of 21–31 years, and that epilepsy surgery, were it performed, would potentially render them seizure-free for the remainder of their lives.

In 62% of the patients with temporal lobe epileptiform activity, CT brain imaging (with and without contrast) was performed, rather than MRI. CT is a cheaper investigation and while effective in excluding tumors, parasitic infections, granulomas, haemorrhages and many other structural intracranial abnormalities, MRI is a prequisite for epilepsy surgery and the investigation of choice for identifying mesial temporal sclerosis, neuronal migration disorders and other subtle epileptogenic abnormalities which may be amenable to epilepsy surgery. MRI brain scans performed according to a standardised epilepsy surgery protocol were performed in only 25% of the patients with anterior and/or middle temporal lobe epileptiform discharges in our study. To improve the efficacy of identifying candidates for epilepsy surgery, the application of an appropriate MRI protocol is vital. For example, an "essential 6" sequence protocol has recently been suggested for the detection of virtually all common epileptogenic lesion entities.[21]

Our study found that, over the 3-year study period, 11% (411) of all EEGs showed epileptiform discharges, 69% (327) of which were focal in onset and significantly, a third of EEGs with focal discharges (108) (33%; $P = 0.00089$) were located in the anterior and/or-middle temporal lobe consistent with mTLE, and thus were potential candidates for anterior temporal lobectomy. A limitation to our study is that a standard 20-min scalp EEG may not always identify interictal epileptiform discharges, and this could mean patients may be missed. Another limitation is that patients were identified on an EEG database where the EEG had already been reported on, and this could have meant that patients with EEGs showing anterior-middle temporal epileptiform discharges could have been missed based on reporter abilities.

The results of this study support the impression that patients with mTLE are under-investigated, and that epilepsy surgery is under-utilised in a tertiary healthcare centre in South African. Consideration should be given to increasing the use of surgery in low- and middle-income countries such as ours, where the expertise of a multi-disciplinary team is available and economic benefits are established. The study also demonstrates that standard scalp EEGs may be an effective way in which to identify potential epilepsy surgery candidates. These EEGs may be used as an initial tool to identify patients who should receive brain MRIs and be further worked up for potential surgery. Still, using non-invasive EEGs as an initial screening tool could offer resource-constrained settings a stepwise protocol that could be implemented in patients with mTLE, in whom safe and cost-effective anterior temporal lobectomies may result in seizure freedom. A database of the epilepsy patients or radiological images of these patients did not exist in our hospital prior to this study, which is another practical implementation that offers resource-constrained settings the platform to identify potential surgical candidates more readily.

CONCLUSION

Surgery in the form of anterior temporal lobectomy is a relatively straightforward, safe, and cost-effective intervention

in carefully selected patients with drug-resistant mTLE, and frequently results in seizure freedom. In line with the findings of similar studies in other low-, middle- and high-income countries, our study indicates that appropriate work up of these patients for possible neurosurgical intervention is lacking, and that epilepsy surgery is under-utilised. This is despite the infrastructure and expertise being available to investigate and assess these patients adequately and perform the procedure in some centres, such as ours. Our study also highlights the utility of an EEG as a practical screening tool to identify potential surgical candidates, as well as the benefit of the establishment of an EEG and MRI database to assist in recognising these patients. We encourage these measures to motivate increased surgeries in low- and middle-income countries.

Author contributions

AJ Soni was responsible for data collection and interpretation. EB Lee Pan, AJ Soni and LM Tucker supervised the study and contributed to the preparation and intellectual content of the manuscript.

Declaration of patient consent

Patients' consent not required as patients' identities not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Research Proposal

Mesial Temporal Lobe Epilepsy Surgery: An Audit of the EEG and Imaging Findings of Patients at a Tertiary South African Hospital

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1. Introduction

Epilepsy is a common neurological disorder, which affects more than 60 million people of all ages worldwide. (1) It is characterized by recurrent, unprovoked seizure activity.

While there have been advances in the pharmacological treatment in recent years, refractory epilepsy persists in up to 35% of patients despite the availability of numerous anti-epileptic drugs (AED). (1) Furthermore, cognitive and psychosocial burdens of poorly controlled epilepsy are significant and may include severe depression and psychosis (2) . Epilepsy has a stronger impact on mental and social health than on physical health when compared with other chronic medical conditions such as hypertension, diabetes, and cardiovascular disease. (2) It remains a poorly understood condition and subject to stigmatization in many cultures.

Epilepsy is often classified as generalised or focal. While generalised epilepsy typically has an underlying genetic etiology, focal epilepsy is often associated with causative structural intracranial abnormalities. Seizures with a focal onset occur in 60% of patients with epilepsy. (3) Because the temporal lobe is the most epileptogenic region of the human brain, temporal lobe epilepsy (TLE) is the most common type of focal epilepsy. TLE is in fact a group of disorders that predominately involves dysregulation of hippocampal function and is thought to result from neuronal hyperexcitability secondary to dysfunctional neuronal suppression.

For the first time in 2010, The ILAE (International League Against Epilepsy) classification of epilepsy recognised mesial temporal lobe epilepsy (mTLE) associated with hippocampal sclerosis (HS), as a discrete clinical syndrome. MTLE was defined as a symptomatic focal epilepsy. Importantly, by definition, mTLE is causally related to a structural abnormality of the brain (HS) which may be amenable to surgical interventions which, in turn, frequently render the patient seizure-free. Consequently, patients with mTLE refractory to antiepileptic drugs (AEDs) are

commonly referred for epilepsy surgery, often in the form of temporal lobectomy. (4) Despite there now being consensus that epilepsy surgery, and especially anterior temporal lobectomy, is an effective intervention for mTLE, it is widely argued that this is misunderstood and hence under-utilised worldwide.

The focus of my study will be mTLE/HS and will include the determination of its prevalence in the patient population attending Groote Schuur Hospital (GSH), a tertiary hospital in Cape Town. One of the primary objectives will be to examine, retrospectively, the electroencephalogram (EEG) tracings of all patients with epilepsy referred for EEG to the neurophysiology laboratory at GSH. The aim would be to identify focal, epileptiform activity in the temporal lobe/s of patients with epilepsy which may suggest mTLE. Where such focal epileptiform activity is identified on an EEG, the patient's MRI brain scan, if performed, would be reviewed to confirm the diagnosis of mTLE. In this way I hope to estimate the number of patients with epilepsy sent for EEG studies at GSH who may be potential candidates for epilepsy surgery.

1.1. Clinical Features

Common clinical features of mTLE are well described and are reproducible in the majority of patients. Seizures in TLE may occur as focal-onset seizures with preserved awareness of self and surroundings and as focal onset seizures in which awareness is impaired. During focal onset with awareness seizures (previously known as simple partial seizures), patients commonly experience a variety of psychic, gustatory, olfactory, and autonomic symptoms. During focal onset with impaired awareness seizures (previously known as complex partial seizures), patients lose awareness and typically have a motionless stare accompanied by automatisms- stereotyped,

repetitive, involuntary movements such as lip smacking, chewing, picking at objects, scratching or gesturing. Up to two-thirds of patients with mTLE may have had a febrile seizure before developing focal seizures. (6) When prolonged, febrile seizures may induce hippocampal oedema which progresses to HS.

1.2. Diagnostic Studies

Typically, after taking a detailed history and examination, most patients presenting to our hospital with seizures or epilepsy, are referred for EEG. Furthermore, virtually every adult presenting with a recent first-time seizure or seizures have brain imaging (contrasted CT or MRI) performed to identify any causative structural intracranial abnormality.

1.2.1. Scalp Electroencephalogram

The scalp electroencephalogram (EEG) is a non-invasive test which may be useful in confirming the diagnosis of epilepsy and determining whether it is generalised or focal. It may also be helpful in localising an epileptogenic focus and confirming TLE. This is done by sampling electrical activity generated by cortical pyramidal cell neurons located at the gyral crests, through electrodes strategically placed on the patient's scalp. Any epileptiform discharges, recorded in this way between seizures (interictal) or during seizures (ictal) while the patient is connected to the EEG can then be interpreted. Depending on their character and distribution, epileptiform markers may represent biomarkers for TLE, and other forms of epilepsy and it is epileptiform discharges located in the temporal EEG leads which will be the subject of this study.

Scalp EEG typically detects only a small fraction of the inter-ictal epileptiform discharges (IEDs) originating in the mesial temporal structures. (7) Nevertheless, anterior temporal IEDs in the form of spikes or sharp waves may be identified in up to 90% of patients with mTLE(6). Mid-temporal epileptiform discharges occur less commonly in mTLE, although these should raise the possibility

of a larger, or extra-mesial temporal sclerosis. Importantly, approximately one-third of patients with mTLE have bilateral temporal IEDs, which become apparent with long-term EEG monitoring.

Where a patient with mTLE experiences a seizure during EEG, unilateral, regular, focal, evolving anterior temporal rhythmic theta or alpha activity (typically 5–9 Hz) is the hallmark. Risinger *et al* has reported that such a discharge correctly lateralised the seizure onset in 95% of the patients. (6) Inter-ictal epileptiform discharges (IED) are often associated with anterior temporal spikes or sharp waves with voltage that is typically maximal in the anterior temporal regions in 90% of patients with mTLE, as reported by Williamson et al. (6) Mid-temporal epileptiform discharges may occasionally occur in mTLE, but consistent mid-temporal EDs should increase the possibility of a larger, or extramesial temporal generator. Approximately one-third of patients have bilateral temporal IEDs, which become apparent with long-term EEG monitoring. mTLE may also be associated with slow waves that have localising value but are not necessarily specific for epilepsy. Spike frequency has therefore been believed to be a biomarker for patients with mTLE and predicts a worse surgical outcome by some by virtue of reflecting greater extra-hippocampal activity. (7) These would be the features we would be assessing in our patient population.

1.2.2. Magnetic Resonance Imaging

Complimenting an EEG in most cases is an MRI. The imaging that defines mTLE is hippocampal atrophy on T1 sequences and increased signal of the hippocampus on T2 and FLAIR images, in which case most studies deemed the findings as positive. (8)

An important study conducted in an Indian centre (9), coupled by another by Holmes et al., looked at a special subgroup of patients with MRI-negative medically refractory TLE and their

response to surgery. (10) This group of patients were selected by noninvasive means (scalp EEG only) for anterior temporal lobectomy and were recorded to have excellent postoperative seizure-free outcomes (success rates approaching 80%). The attributes of these patients are antecedent history of febrile seizures and strictly unilateral anterior temporal IEDs with concordant seizure origin. These studies are important preliminary reports for further studies as it demonstrates a cost-effective strategy to determine suitable ATL candidates. This is of special relevance in a developing country, as PET and SPECT are seldom readily available, and the cost of invasive monitoring limits its use as well. Whilst it highlights an interesting subgroup of patients, the focus of our study will be on establishing patients with positive MRI findings, correlating with EEG findings, in keeping with mTLE.

1.3. Surgery: Anterior Temporal Lobectomy

Having established what the clinical picture of patients with mTLE will look like, as well as highlighting the investigations that can be done to confirm the diagnosis, it would now be prudent to examine surgical management options of mTLE and its documented success rate.

Surgical treatment for epilepsy is arguably the most poorly utilised of all proven effective interventions in the field of medicine. (13) Failure in this regard is all the more unacceptable, given the documented magnitude of the global health burden represented by epilepsy. TLE responds very well to surgery with high rates of resulting seizure freedom and the risks of surgery being quite low. (11) The surgical procedure that our attention will be directed to currently being used for mTLE is an anterior temporal lobectomy (ATL).

mTLE with hippocampal sclerosis is the most common form of human epilepsy, the most refractory to AEDs(12), and the easiest to treat surgically. (13) It is also easily diagnosed, as

described above, non-invasively. However, when a surgical referral is considered for a patient with it it is usually viewed as a last resort. The average interval between onset of epilepsy and surgical intervention for more than 300 patients operated on in 5 years as part of a large multi-center study was 24 years(13), and for 29 patients operated in 2000 and 2001, at an epilepsy center in Florida, was 18 years. (14) Successful surgery is often too late to reverse the crippling psychological and social consequences of repeated epileptic seizures, already leaving patients disabled permanently.

An important reason for this aversive behaviour to surgery in epilepsy is largely driven by fear. Despite documented literature that the morbidity and mortality of disabling seizures far outweighs the morbidity and mortality of surgery(15), lack of information and knowledges still seems to drive the populations' perception- both in healthcare workers and patients. An interesting analysis study which looked at the social media imprint of epilepsy and surgery concluded that epilepsy surgery as a method of treatment is under-promoted by most social media accounts and that soon, surveying patient and public knowledge and perception of surgery will be important in building greater awareness. (1)

ATL consists of resection of the anterior temporal lobe, as well as a resection of the anterior mesial temporal structures including the anterior third of the hippocampus. Lateral temporal neocortex and mesial structures are removed at approximately 3 cm from the temporal pole within the dominant hemisphere, and up to 4.5 cm in the non-dominant hemisphere. (16) The ILAE reported that between 1980-1990, 2390 of 4426 (54%) epileptic patients undergoing surgery world-wide were subject to anterior temporal lobectomy (ATL), and 85% of these patients showed complete diminution or marked improvement of seizures. Conducting a randomised

controlled trial on the efficacy of this surgery had faced many obstacles, but there is one study that finally addressed the problem.

In their revolutionary trial, Wiebe et al. concluded that their results confirmed the superiority of surgery over medical therapy in terms of the control of seizures, the quality of life, and the rates of employment and school attendance among patients with poorly controlled temporal lobe epilepsy. (5) Further, the absolute benefit of surgery in terms of the rate of freedom from seizures was large (50% for seizures impairing awareness and 35% for all seizures) and precise. Their intention to treat analysis yielded a rate of freedom from seizures impairing awareness in the surgical group of 58%. This study provides robust evidence of the effectiveness and safety of surgery for patients with TLE from any cause and it was determined that surgery in this group of patients may preclude unnecessary disability and perhaps even death. (5)

There have been numerous other reports and multi-centre analyses which strongly supported the case for surgery in these patients. In one prospective longitudinal cohort follow up study, patients were followed for 8–18 years after mTLE/HS surgery. It was found that 62% were completely seizure free throughout the entire follow-up period, whereas 77% maintained an Engel class I outcome.(17) They concluded that their study demonstrated that mTLE/HS surgery prevents subsequent seizures for up to close to two decades.

A systematic review and meta-analysis of TLE surgery published last year shed some light on the paucity of level 1 evidence on the topic. The authors found an overall rate of seizure freedom of 72.4% for RCTs conducted in adults, which is remarkably similar to the overall rate of seizure freedom of 71.7% in prospective non-randomised cohorts. It was also postulated that perhaps the overall seizure-freedom rate is greater than 70% when accounting for the type of surgery and cases, with increased success in clear MRI-positive mTLE. The three RTCs evaluated included

the ROSE trial (18), the ERSET trial (19) and the trial mentioned above by Wiebe et al. Essentially, it was concluded that the evidence is over-whelming in favour of surgery for TLE and its success thereof, however, establishing this through randomised control trials is limited due to limitations in recruiting patients and methodological obstacles. (20)

1.4. Epilepsy Surgery in South Africa

In some areas – particularly in parts of Latin America and Africa – the prevalence of epilepsy appears higher than that reported in developed countries, with rural areas being especially affected. (16) Surgery programmes in developing countries, if they exist at all, usually exist as a result of individual efforts by physicians who were most likely trained abroad. (22) In Cape Town, where epilepsy services include two university-affiliated neurology departments (serving patients covered by the state) and a private epilepsy center, 250 epilepsy surgery procedures had been undertaken in 5 years (2000-2005), with most of these procedures being temporal lobectomies. (22) Less than 10% of individuals who might benefit from epilepsy surgery have undergone such procedures in the region, but outcomes have been good in those that have. It must be noted that there is a great paucity of literature with regards to epilepsy surgery in South Africa in general, and the study mentioned above published statistics not confined to mTLE/HS and ATL.

1.5. Summary

In short, mTLE is a common type of focal epilepsy that is relatively easy to diagnose with careful history taking, supported by characteristic findings on EEG and MRI brain scanning. mTLE remains refractive in a significant proportion of patients resulting in negative physical,

psychological, and social sequelae; and yet, in many instances it is amenable to epilepsy surgery which may result in seizure freedom with minimal risk. Anterior temporal lobectomy (ATL) is a well-recognised surgical intervention, which frequently renders appropriately chosen patients with mTLE seizure-free, in this way markedly improving their quality of life. Despite this, for a number of reasons, epilepsy surgery remains under-utilised as a treatment option.

My study examines the hypothesis that an EEG and, more specifically, epileptogenic waveforms occurring in temporal channels, may represent a useful tool to identify potential candidates for epilepsy surgery. I will retrospectively screen all EEGs performed on patients referred for EEG to a tertiary hospital, for temporal lobe epileptiform discharges. I will then determine if and what imaging has been performed for the patient. Where MRI brain scans have been performed on these patients, these will be examined for corresponding characteristics of hippocampal sclerosis to assist in identifying any patients who would be suitable potential surgical candidates.

2. Study Objectives

2.1 Primary Objectives

- To determine the percentage of all patients investigated with EEG who have electrographic features suggestive of temporal lobe epilepsy.

2.2 Secondary Objectives

- To determine the number of patients assessed at a tertiary hospital (GSH) for an EEG in whom temporal lobe epileptiform discharges were identified, and how many of these patients had MRI brain scanning performed according to an epilepsy surgery protocol.

- To determine how many patients with unilateral temporal lobe epileptiform discharges also have ipsilateral MRI findings consistent with a diagnosis of mTLE and are thus potential candidates for epilepsy surgery.

3. Methods

3.1. Research paradigm

This will be a quantitative audit which investigates EEGs from patients referred to the GSH electrophysiological laboratory over a certain time period.

3.2. Sample

The study population includes all adults (older than 13 years of age) who were referred for a scalp EEG to the neurophysiology laboratory of Groote Schuur Hospital (GSH).

3.2.1. Inclusion criteria

EEG studies performed on all patients referred for suspected or confirmed epilepsy, as well as other relevant intracranial pathologies, which were performed at the GSH neurophysiology laboratory, evaluated over each year starting with 2019, will be included.

3.2.2. Exclusion criteria

The following studies will be excluded:

- EEGs performed on subjects under the age of 13 years old.
- Tracings rendered illegible by artefact.

3.3. Materials and Methods

Nihon Kohden EEG machines and software, and the international 10:20 electrode placement system are used in the GSH neurophysiology laboratory. All EEGs are performed by qualified neuro-technologists and each patient is monitored for a minimum of 20 minutes.

Hyperventilation, intermittent photic stimulation and arousal procedure are routinely performed.

The GSH Neurophysiology laboratory receives referrals for EEG from within the hospital, as well as from the surrounding secondary and primary healthcare facilities as long as these are made by a medical doctor. Reasons for referral include seizures, epilepsy, confusion, encephalopathy, dementia and psychosis amongst other conditions.

All EEG traces performed during the study period, together with relevant information such as the subject's name, hospital number, gender, age, diagnosis and referring doctor are securely archived but can be easily accessed.

I will access records relating to all EEGs performed during the study period to identify those in which a temporal lobe abnormality has been reported. I will begin by evaluating the data captured from 2019 and depending on the number of positive results found progress annually backwards, up to a maximum of 5 years. After confirming that an epileptiform activity is present in these recordings, identifying data will be anonymised and recorded on a Microsoft Excel Sheet.

Once all EEGs with temporal epileptiform abnormalities have been identified, hospital numbers will be used on the GSH PACS system to identify those in whom MRI brain scanning has also been performed and whether or not this identified mesial temporal sclerosis. Irrespective of the attending radiologists report, all MRI scans will be scrutinised for evidence of mesial temporal sclerosis and hippocampal atrophy and this information will be anonymised and stored securely on the Excel document.

3.4. Data collection

The following data will be identified and recorded:

On EEG

- Any inter-ictal epileptiform waveforms of EEG occurring in one or both temporal lobes; in other words, waveforms which do not obviously represent seizure activity, but which are consistent with abnormal waveforms expected to be associated with TLE.
- Any ictal activity in one or both temporal lobes representing electrographic seizure activity.
- Focal slowing (TIRDA) or other focal, non-epileptiform EEG features, which might be consistent with focal, structural temporal lobe abnormalities.

On Brain Imaging

- Whether CT (contrasted/uncontrasted) and/or MRI (uncontrasted/contrasted) or neither, have been performed.
- Where MRI scanning has been performed, whether or not a special epilepsy surgery protocol had been followed.
- Whether or not brain imaging had identified a structural abnormality involving the mesial temporal lobes and asymmetry of the hippocampi consistent with mesial temporal sclerosis.

3.5. Reliability and validity

All EEG reports produced in our division are routinely checked by a specialist neurologist. Nevertheless, I will review the raw data of all EEG studies included in this study to confirm that temporal lobe abnormalities are present. Where there is any doubt, specialist neurologists (Drs Lee Pan & Tucker) who are competent at reading EEGs will be asked to review the relevant recordings.

With regards to MRI scanning results, I will be guided by the specialist radiology reports. However, I will personally review all original imaging and, where there is any doubt about the findings, seek the opinion of specialist radiologists as well as specialist neurologists with an interest in epilepsy .

Validity will be ensured by applying the ILAE definition of mTLE and its diagnostic features. The features on EEG and MRI that will be considered positive will be derived from the ILAE Commission Report. (23)

3.6. Bias

This study will be retrospective, and hospital based. It will be conducted in a Division of Neurology of a large tertiary hospital which receives many referrals, and caution will need to be exercised when translating prevalence of any findings to the general population.

4. Data analysis and statistics

Summary statistics will be reported using frequencies and percentages for categorical responses and means with standard deviations for continuous measurement. If the need arises for inferential statistics, this will typically involve cross tabulations, ANOVA or correlation analyses depending on the types of variables compared.

5. Ethics

Once my research has been approved by the Neurology Research Committee, ethics approval will be sought from HREC.

5.1. Data safety

Data will be anonymised by allocating a random number to each patient. The key to this code will only be available to me and my supervisors. Anonymised data will be entered into an Excel document which is suitably password-protected and stored on my laptop and not on any public domain. The data will be backed up from time to time. Suitably password-protected backup data

will be stored on my co-supervisors UCT computers. Access to all confidential study-related data will remain strictly limited to my co-supervisors and me. It will not be stored on any device besides my own and not on any public domain.

6. Timing

Month of the Year	May 2020	June	July	Aug	Sept-Nov	Dec-Feb 2021	March-July	Aug	Sep-Oct 2021
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol (divisional presentation)									
Protocol Assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis									
Submit: marking									
Writing up paper									

7. Budget

Printing of EEG reports	R 500, 00
Printing of MRI reports	R 500, 00
Transport	R 1000, 00
Total	**R 2000, 00**

All expenses will be borne personally.

There are no anticipated problems to my research study, including during the process of collecting and summating data and records.

8. Final Comment

This audit is being done with the intention of using the results translationally. Globally, including in South Africa, epilepsy surgery remains severely under-utilised and even considered as a treatment option. This is despite the evidence supporting its high success rate. By identifying the number of patients who have been investigated appropriately, compared to those who potentially could be further worked up and be potential surgical candidates, I am hoping to encourage an epilepsy surgery protocol and programme that is both efficient, resource-effective and widely implemented. This will hopefully include an increased frequency in appropriate imaging of a specified patient population, as well as the introduction of more regularly performed temporal lobectomies for patients within the state healthcare system.

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Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 July 2020

HREC REF: 365/2020

Dr E Lee Pan
Division of Neurology
E-8 NGSH
Email: eddy.leepan@uct.a.za
Student: aAjsoni008@gmail.com

Dear Dr Lee Pan

PROJECT TITLE: MESIAL TEMPORAL LOBE EPILEPSY SURGERY: AN AUDIT OF THE EEG AND IMAGING FINDINGS OF PATIENTS AT A TERTIARY SOUTH AFRICAN HOSPITAL (MASTERS STUDENT DR AAYESHA JALALUDDIN SONI)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Aayesha Jalaluddin Soni will also be involved in this study.

Please quote the HREC REF in all your correspondence.
Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Hospital Approval Letters

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
e-mail: Bernadette.Eick@westerncape.gov.za

Dr E. Lee Pan
MEDICINE - NEUROLOGY

E-mail: eddy.leepan@uct.ac.za / ajsoni008@gmail.com

Dear Dr Lee Pan,

RESEARCH PROJECT: Mesial Temporal Lobe Epilepsy Surgery: An Audit Of The EEG And Imaging Finding Of Patients At A Tertiary South African Hospital (Masters Student Dr Aayesha Soni)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 28 July 2020

C.C. Mr. L. Naidoo
Dr L. Booyens
Professor N. Ntusi

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : *Bernadette.Eick@westerncape.gov.za*

Dr Eddy Lee Pan
MEDICINE - NEUROLOGY

Email: eedy.leepan@uct.ac.za / ajsoni008@gmail.com

Dear Dr Lee Pan,

Study Closure: Mesial Temporal Lobe Epilepsy Surgery: An Audit Of The EEG And Imagining Finding Of Patients At A Tertiary South African Hospital (Masters Student Dr Aayesha Soni)

Congratulations on completing your research.

I would like to thank you for taking the time to fulfil my request in providing me with a report on completion of your research.

Yours sincerely

p.p. **DR BERNADETTE EICK**
CHIEF OPERATIONAL OFFICER
DATE:2 June 2021

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Instructions to Authors

Author Instructions

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- List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

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- Intermediate headings should be in italics, sentence case, left justified, 12 pt

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2.More than six authors
Cagin T, Wang G, Martin R, Zamanakos G, Vaidehi N, Mainz DT, et al. Multiscale modeling and simulation methods with applications to dendritic polymers. Computational and Theoretical Polymer Science. February 2001; 11: 345-356.
3. Organization as Author
Hypertension Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002; 40(5): 679-86.
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21st century heart solution may have a sting in the tail. BMJ. 2002; 325(7357): 184-5.
5. Journal article on the Internet
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm
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Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
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8. Author(s) and editor(s)
Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.
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As a minimum, the full URL should be given. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given.
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Reviewer Comments and Responses

September 20: (Reviewer 1) The authors reviewed all EEG and imaging at a single institution to understand the missed opportunities for surgery in patients with mesial temporal lobe epilepsy.

How many patients were operated for temporal lobe epilepsy in this time frame to help understand the scale of the missed diagnoses and surgical opportunity?

The authors should also include risk of death due to SUDEP and injury in medically intractable epilepsy as a major rational for surgery in mTLE, which achieves seizure freedom in most individuals thus eliminating this excess risk of mortality.

The authors could determine the possible number of mTLE patients who did not get the proper workup with an MRI. The scope of the challenge facing patients with drug resistant epilepsy to get the appropriate workup and treatment is even larger than reported.

September 20: (Reviewer 2) This paper fills an extremely important role in identifying and quantifying the patient cohort within a local epilepsy service, who would benefit from a simple but effective surgical procedure for a common adult epilepsy. The authors have diligently interrogated three years' worth of epilepsy clinic data to achieve this. Their observation of MRI brain (as an important biomarker for MTS) being performed for only 25% of relevant patients, highlights some of their acknowledged shortfalls in their system - something every honest audit should strive to do.

The excellent example set by Z Tahir and his team (Establishment of a comprehensive epilepsy center in Pakistan: initial experiences, results, and reflections, M Zubair Tahir, et al - Epilepsy Research and Treatment 2012, 2012: 547382) shows what is possible in terms of advancing epilepsy surgery in a resource constrained country.

The motivation shown by the authors will no doubt allow their institute to follow suit.

September 28: (Reviewer 1) Manuscript appears to be ready for publication.

September 28: (Reviewer 2) A relevant and necessary review of an extremely important area in neurology / neurosurgery - especially in the LMICs.

Aayesha Soni
University of Cape Town
36 Wessels Road, Kenilworth, CT

21 September 2021

Dear Respected Editor,

Thank you for your time and the time and effort of the reviewers for their feedback. In response to the points raised by the reviewers, please find my responses below:

1. Reviewer 1:
    a. There have been no operations performed yet. An epilepsy surgery clinic was initiated in September 2020, and we are planning on operating on our first patient before the end of the year.
    b. SUDEP is a major risk in refractory epilepsy. The reviewer's note has been added to the manuscript.
    c. This was calculated and was one of the findings in our conclusion.
2. Reviewer 2:
    a. Thank you for the comments and input.

I hope that this addresses all of the reviewers' concerns and look forward to hearing from you in the near future.

Thank you again for your time and consideration.

Sincerely,

Aayesha Soni