CHILDREN REFERRED WITH LENNOX-GASTAUT SYNDROME IN THE WESTERN CAPE OF SOUTH AFRICA

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DECLARATION

I Robert Sebunya hereby declare that all the work in this dissertation is original unless otherwise acknowledged. This work has not been presented to any university or higher institution for an academic award, publication or otherwise. Whereas information from previous literature has been cited, it been appropriately referenced.

Robert Sebunya 10/03/2021

Signed by candidate

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List of Abbreviations, figures.

ASMs; Anti-seizures medications

EE; Epileptic encephalopathy

EOEE; Early onset epileptic encephalopathy

ESS; epileptic spasm syndrome

LGS; Lennox Gastaut Syndrome

GTCs; generalized tonic –clonic seizure

MAE; myoclonic Atonic seizures

KD; Ketogenic diet

HIE; Hypoxic ischemic encephalopathy

ILAE; International League Against Epilepsy

LRS; Low resource setting

RCWMCH; Red Cross War Memorial Children`s Hospital.

Figures; 1; LGS and the other epileptic syndrome.

Figure ;2; The typical EEG finding in one of our LGS cohort.

Table 1;Cohort with epileptic spasms. Table 2; Cohort Clinical demographics

Table 3; EEG findings of the cohort. Table 4;Cohort management and outcome

Table5; Cohort associated comorbidities

ABSTRACT

Introduction: Lennox-Gastaut Syndrome (LGS) is one of the most common refractory epilepsies of childhood with significant morbidity and mortality. However there is paucity of data of this syndrome in resource limited settings (RLS)

Objective: We sought to delineate the phenomenology, diagnosis, aetiologies, management and outcomes of children diagnosed with LGS in the Western Cape Province of South Africa. And to further identify early clinical markers differentiating LGS from other types of epilepsy.

Methods: This retrospective observational cohort study included all children between 1 to < 18 years of age in the neurology database with a referral label of LGS between 2000-2018. The group were critiqued for those who met the diagnostic criteria of LGS. Then were categorized into those with confirmed LGS and remainder were not- LGS. Data of the social demographics, age of seizure onset, etiology, preceding epileptic spasms, and semiology of epilepsy types, management interventions were reviewed to identify key diagnostic indicators to permit early and targeted interventions for children with this epilepsy syndrome.

Results; Of 2551 children managed with epilepsy, 110 were suspected at presentation to have LGS of these 66 records were available for assessment**.** The median (IQR) age in months at presentation was 35(16.0-54.5) with a slight male (37/66) predominance. 43(65%) met the criteria LGS and 23(35%) were not-LGS. 34(52%) had no identifiable cause for their epilepsy whilst a structural and metabolic cause were identified in 25(38%) and 3(5%) respectively. Moderate or severe cognitive impairment was associated with LGS (*OR* 2.59, $p = 0.02$ and *OR* =3.15, $p = 0.01$) and so were tonic seizures (OR=4.03, p=0.04). The most common diagnoses in the not-LGS group were other types of DEE not meeting the LGS criteria (15%) and un-categorised epileptic syndromes 11%.

Conclusion; Over third of the children in this cohort were erroneously referred with LGS early in their course. This has implications on their management and prognostic counselling..
Identification of indicators such as tonic seizures and moderate or severe intellectual/cognitive impairment are useful early markers which support a diagnosis of LGS and could be viable for use in our setting.

ACKNOWLEDGEMENTS AND CONTRIBUTIONS

I would like to thank Professor Jo Wilmshurst for her invaluable guidance and support rendered throughout this project. I am profoundly indebted to her.

Special thanks good out to Richard Burman (RB) and Helishia Dirks (HD) for their immense contribution towards this project.

RS; Conceived the ideal, developed the proposal, collected the data and analyzed, plus writing of the draft manuscript. JMW; Supervised the whole project development, with major inputs from its conception to writing of the manuscripts. HD; Neurophysiologist, with RS looked at the EEGs that met the diagnostic criteria of LGS and also helped to collect some data. RB assisted with data analysis inclusive of the statistical screens and provided comment on the Manuscript.

Sincere gratitude goes out to the Red Cross War Memorial Children`s Hospital Department of Paediatric Neurology: Dr Alvin Ndondo, Dr Gillian Riordan who are part of the team of attending neurologists. Rotating neurology registrars and my fellow colleagues the past and present; Drs Raga, Oshi, Oyieke, Hammond, Mekki, Ackermann, Kija who managed these patients. The nurses, neurophysiologists and administrative staff that manage the unit. The medical record staffs, and the caregiver plus their children who gave permission for their data to be used.

CHAPTER 1

Introduction and literature review

Lennox Gastaut Syndrome (LGS) is one of the most severe developmental and epileptic encephalopathies (DEE) of childhood onset (1-3). It is characterized by multiple intractable seizures namely; tonic seizures which are the hallmark seizure type, atypical absences are common but subtle, and myoclonic, focal, atonic seizures as well (2, 4). Secondly, a characteristic abnormal electroencephalographic (EEG) recording of a slow spike and wave (SSW) at < 3Hz frequency occurring during wakefulness or a paroxysmal fast rhythm of 10-20Hz occurring during non-rapid eye movement (NREM) sleep (2, 5). Thirdly the psychomotor delay with behavioral dysfunction which may not be present at the onset of the epilepsy (6).

Onset of this epileptic syndrome ranges from early childhood between 18 months and 8 years of age, with most presenting between 3-5years (2, 6-8). Onset after the first decade is unusual(6). This condition persists through adolescence and adulthood (9). The aetiology of LGS is variable (2, 7) with no biological marker. However the majority of children have an underlying cause such as structural brain abnormalities in the form of neuromigration disorders (cortical dysplasia, heterotopias, polymicrogyria)(2, 5, 7); post-infectious causes such as meningitis, encephalitis, prior intraventricular haemorrhage (IVH) following premature births and insults due to hypoxic ischaemic encephalopathy (3), and neonatal infection especially meningitis. A small number occur de novo(10), with increasing recognition of genetic causes (11). Progressive metabolic disorders also occur but are not common(2). A proportion of children have a prior history of other epileptic disorders such as epileptic spasms, reported in 13%- 20% (1, 8, 12).

The diagnosis and management of this electroclinical syndrome is challenging. Other epileptic syndromes can present with similar clinical phenomenology (3, 13), as stated there is no biological marker and patients may not have the characteristic triad at the onset(13). Delayed or lack of diagnosis impacts on the management and subsequent quality of life (QOL) of patients (13).

A Cochrane review found that the optimal antiseizure medication (ASM) recommendations for LGS is uncertain (10). Expert opinion supported sodium valproate and other adjuvant ASMs such as clobazam, lamotrigine and topiramate (14). The use of cannabinoid agents are being explored as possible adjuvant interventions (15, 16). Non-pharmacological treatment interventions such as the ketogenic diet (KD) and other alternative diet regimens such as the modified Atkins and low glycemic treatment (17) have resulted in variable outcomes, similarly

surgical intervention in lesional LGS cases (18). Neuromodulation techniques such as vagus nerve stimulation (VNS) are also among the treatment options with limited data (19).

Rationale/Motivation

Despite sub-Saharan Africa having the greatest burden of epilepsy(20) there is limited data of this electroclinical epileptic syndrome in our setting. Available literature is from high income countries (HICs) (21, 22). We sought to explore the phenotype of children presenting to the Red Cross War Memorial Children`s Hospital (RCWMCH), with the referral label of LGS, and to understand the key features which supported a subsequent diagnosis of LGS. We further aimed to ascertain if children diagnosed with LGS truly complied with the diagnostic criteria or would be better placed under other categories in line with the ILAE epilepsy classification terminology (23). Additionally, we wanted to understand the possible aetiology and explore effective management pathways especially with regard to optimal ASMs in a low resource setting.

METHODS.

This was a retrospective observational study of children and adolescents in the child neurology service who were being managed under the referral diagnostic label of LGS. Children between 1-<18 years of age who attended the epilepsy clinic between 2000-2018 were identified through a neurology registry. The criteria for diagnosis of LGS was multiple seizure types, a specific interictal EEG pattern of slow spike and wave of <3Hz in awake state or paroxysmal fast rhythm(>10Hz) during sleep plus cognitive impairment when present(2) were recorded.

All study participants were managed at the RCWMCH which services a predominantly low income socioeconomically challenged population. All patients were evaluated for aetiology, seizures, frequency and therapeutic modalities. Additional clinical and demographic data were obtained from the medical records. Development delay (children <5 year old) were recorded and documented according to the Molteno Adapted Development Scale as per the standard practice in the neurodevelopment clinic(24). Intellectual disability (children >5years was still based on the Molteno Adapted Development scale assessment. Developmental quotient or intellectual quotient (IQ) below 70 was classified as cognitively impaired. It was mild (50-70), moderate (35-50) and severely impaired/delayed if less than 35(24). All study participants had baseline EEGs performed and repeated when clinically indicated (e.g. concern of sub-clinical status, change in seizure semiology). As part of standard care video electroencephalography (vEEG) monitoring telemetry was ideally performed where capacity allowed. Pharmacoresistant/drug resistant epilepsy was defined in accordance with the consensus proposal by the International League Against Epilepsy (ILAE) Commission task force(25). Management intervention spanned from third generation ASMs, to the non-pharmacological treatment options including dietary

therapies such as Ketogenic diet (KD), epilepsy surgery and neuro modulation (vagal nerve stimulation). Neuroimaging, using either computed tomography (CT) or magnetic resonance imaging (MRI), metabolic and karyotyping are performed when indicated for the diagnosis and management. Genetic testing services for children with epilepsy is largely restricted to karyotyping or targeted syndromic diagnoses. Testing for some specific mutation such as *SCN1A* mutations is only available through collaborative research projects(26) and otherwise was not routinely available at the time of the study. Good response to the KD was taken as having 50% reduction in the seizure frequency. However the assessment included when patients failed the diet despite a trial because of poor tolerability and cost.

Settings: The study was carried out at the RCWMCH in the Western Cape of South Africa, which is the only stand- alone tertiary hospital in sub-Saharan Africa dedicated entirely to child healthcare. This tertiary hospital is the academic paediatric training platform for the University of Cape Town and runs nationally accredited sub-speciality training, inclusive of child neurology. It is government funded and serves a provincial population of over 1.7 million children below 14 years of age(27). The neurology service is unique compared to international units in that it cares for children aged 0-12 completed years at first consultation across all levels of care, primary to quaternary. Children may remain in service until 16 year of age or older, prior to transfer to adult services. Capacity to manage children with epilepsy at primary level centers within the Western Cape is very limited. As such direct referral to the neurology service from primary care centres is common.

Additionally the department serves as a quaternary epilepsy service for other South African provinces. It handles a wide range of neurological diseases common to children from resource-poor countries and functions as the sub-Saharan referral centre for complex epilepsy diseases. A dedicated epilepsy service is supported by specialists in paediatric neurology, with on-site neurophysiology and neuroimaging facilities. The service has some 1800 clinic visits a year of children specifically with paediatric epilepsy.

Inclusion criteria

Children referred with the diagnostic label of LGS

Children with complete clinical records and investigations inclusive of neuroimaging and electrophysiology.

Exclusion criteria

Children with inadequate data

Data assessment: Children who met the inclusion criteria were further delineated inclusive of demographics, seizure semiology, co-morbidities, investigations, management and preceeding risk factors. Children were allocated into 2 groups. Those who met the diagnostic criteria for

LGS and those who did not (non-LGS group). The non-LGS group were further delineated where possible into other epilepsy categories or syndromes. The two groups were compared for key features present at the time of referral which would increase the likelihood of differentiating between children subsequently confirmed to have LGS and those not.

Data management: Data was captured using REDcap database . Data was processed through R statistical programming language (**R** Core Team (2013). **R**: A language and environment for statistical computing. **R** Foundation for Statistical Computing, Vienna, Austria. URL http://www.**R**-project.org/.). Categorical data was first processed into frequency tables for descriptive statistics. To test for the significance of associations between variables and different groups, categorical data was then processed into cross-tabulations and the Fisher's Exact Test performed. To quantify the measure of association between variables and diagnosis, odds ratios were computed using a multinomial logistic regression model designed using only those variables previously shown to have a significant association with diagnosis. Continuous data was first tested for normality (using Shapiro-Wilk test) and then appropriate measures of central tendency are described. Code and data can be made available with publication (will upload data and code onto online repository and supply link in publication.

Ethical considerations

Ethical approval was attained from the RCWMCH Research committee plus the University of Cape Town Faculty of Health Science Human Research and Ethics Committee. Ref 612/2018

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CHAPTER TWO: PUBLICATION READY MANUSCRIPT

CHILDREN REFERRED WITH LENNOX-GASTAUT SYNDROME IN THE WESTERN CAPE OF SOUTH AFRICA

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Declarations of interest; none

ABSTRACT

Purpose; To delineate the phenomenology, diagnosis, aetiologies and identify early clinical markers differentiating LGS from other types of epilepsies in the Western Cape Province of South Africa.

Methods; This retrospective observational cohort study included all children between 1 to < 18 years of age in the neurology database with a referral label of LGS between 2000-2018. The group were critiqued for those who met the diagnostic criteria of LGS. Then were categorized into those with confirmed LGS and remainder were not- LGS. Data of the social demographics, age of seizure onset, etiology, preceding history of epileptic spasms, and semiology of epilepsy types, management interventions were reviewed to identify key diagnostic indicators to permit early and targeted interventions for children with this epilepsy syndrome.

Results; Of 2551 children managed with epilepsy, 110 were suspected at presentation to have LGS of these 66 records were available for assessment**.** The median (IQR) age in months at presentation was 35(16.0-54.5) with a slight male (37/66) predominance. 43(65%) met the criteria LGS and 23(35%) were not-LGS. 34(52%) had no identifiable cause for their epilepsy whilst a structural and metabolic cause were identified in 25(38%) and 3(5%) respectively. Moderate or severe cognitive impairment was associated with LGS (*OR* 2.59, $p = 0.02$ and *OR* =3.15, $p = 0.01$) and so were tonic seizures (OR=4.03, p=0.04). The most common diagnoses in the not-LGS group were other types of DEE not meeting the LGS criteria (15%) and uncategorised epileptic syndromes 11%.

Conclusion; Over a third of our cohort were erroneously diagnosed with LGS early in their course. This has implications for their management and prognostic counselling and calls for continued diagnostic label re-evaluation on follow-up. Identifying tonic seizures and moderate or severe intellectual/cognitive impairment are useful early markers which support a diagnosis of LGS and are viable for use in our setting.

Key words; Lennox Gastaut Syndrome, Diagnosis, Children Sub-Saharan Africa.

1. Introduction

Lennox Gastaut Syndrome (LGS) is one of the most severe developmental and epileptic encephalopathies (DEE) of childhood onset (1-3). It is characterized by multiple intractable seizures namely; tonic seizures which are the hallmark seizure type, atypical absences which are common but subtle, and myoclonic, focal, atonic seizures as well (2, 4). Secondly, a characteristic abnormal electroencephalographic (EEG) recording of a slow spike and wave (SSW) at < 3Hz frequency occurring during wakefulness or a paroxysmal fast rhythm of 10-20Hz occurring during non-rapid eye movement (NREM) sleep(2, 5). Thirdly the psychomotor delay with behavioral dysfunction which may not be present at the onset of the epilepsy(6).

Onset of this epileptic syndrome ranges from early childhood between 18 months and 8 years of age, with most presenting between 3-5years(2, 6-8). Onset after the first decade is unusual (6). This condition persists through adolescence and adulthood (9). The aetiology of LGS is variable (2, 7) with no biological marker. However the majority of children have an underlying cause such as structural brain abnormalities in the form of neuromigration disorders (cortical dysplasia, heterotopias, polymicrogyria)(2, 5, 7); post-infectious causes such as meningitis, encephalitis, prior intraventricular haemorrhage(IVH) following premature births and insults due to hypoxic ischaemic encephalopathy(7), and neonatal infection especially meningitis. A small number occur de novo(10) and there is increasing recognition of genetic causes(11). Progressive metabolic disorders also occur but are not common(2). A proportion of children have a prior history of other epileptic disorders such as epileptic spasms evident in 13%- 20% of reports (1, 8, 12).

The diagnosis and management of this electroclinical syndrome is challenging and prognosis is poor (3, 14(8, 9).) Other epileptic syndromes can present with similar clinical phenomenology(2, 3, 13), as stated there is no biological marker and not all patients display the characteristic triad at the onset(13). Delayed or lack of diagnosis impacts on the management and subsequent quality of life (QOL)(6, 9).

A Cochrane review found that the optimal antiseizure medication (ASM) recommendations for LGS is uncertain (10). Expert opinion supported use of sodium valproate and other adjuvant ASMs such as clobazam, lamotrigine and topiramate(28). The use of cannabinoid agents are currently being explored as possible adjuvant interventions(15, 16). Non-pharmacological treatment interventions such as the ketogenic diet (KD) and other alternative diet regimens such as the modified Atkins and low glycemic treatment (17) have variable outcomes, similarly surgical intervention in lesional LGS cases(18). Neuromodulation techniques like vagus nerve stimulation(VNS) are also among the treatment options(29) explored with variable outcomes.

Despite sub-Saharan Africa having the greatest burden of epilepsy (2, 20, 30, 31) there is limited data of this electroclinical epileptic syndrome in our setting. Available literature is from high income countries (HICs)(2, 22). We sought to explore the phenotype, of children presenting to

the Red Cross War Memorial Children`s Hospital (RCWMCH), with the referral label of LGS, and to understand the key features which supported a subsequent diagnosis of LGS. RCWMCH is the largest children's hospital in sub-Saharan Africa with a dedicated epilepsy service. We further aimed to ascertain if children diagnosed with LGS truly complied with the diagnostic criteria or would be better placed under other categories in line with the ILAE epilepsy categorization terminology(23). Additionally, to understand the possible aetiology and early clinical markers that could help differentiate between LGS and other epilepsies.

2. Methods

2.1Context

This was a retrospective observational study of children and adolescents in the child neurology service who presented with the referral diagnostic label of LGS from lower health facilities by general physcians. Children between 1-<18 years of age who attended the epilepsy clinic between 2000-2018 were identified through a neurology registry. All study participants were managed at the RCWMCH which services a predominantly low income socioeconomically challenged population. All patients were evaluated for aetiology, seizures, frequency and therapeutic modalities. Additional clinical and demographic data were obtained from the medical records. Development delay (children <5 year old) were recorded and documented according to the Molteno Adapted Development Scale as per the standard practice in the neurodevelopment clinic(24). Intellectual disability (children >5years was still based on the Molteno Adapted Development scale assessment. Developmental quotient or intellectual quotient (IQ) below 70 was classified as cognitively impaired. It was mild (50-70), moderate (35-50) and severely impaired/delayed if less than 35(24). All study participants had baseline EEGs performed and repeated when clinically indicated (e.g. concern of sub-clinical status, change in seizure semiology). As part of standard care video electroencephalography (vEEG) monitoring telemetry was ideally performed where capacity allowed. Pharmacoresistant/drug resistant epilepsy was defined in accordance with the consensus proposal by the International League Against Epilepsy (ILAE) Commission task force(25). Management intervention spanned from third generation ASMs, to the non-pharmacological treatment options including dietary therapies such as Ketogenic diet (KD), epilepsy surgery and neuro modulation (vagus nerve stimulation). Neuroimaging, using either computed tomography (CT) or magnetic resonance imaging (MRI), metabolic and karyotyping are performed when indicated for the diagnosis and management. Genetic testing services for children with epilepsy is largely restricted to karyotyping or targeted syndromic diagnoses. Testing for some specific mutation such as *SCN1A* mutations is only available through collaborative research projects(26) and otherwise was not routinely available at the time of the study. Good response to the KD was taken as having 50% reduction in the seizure frequency. However the assessment included when patients failed the diet despite a trial because of poor tolerability and cost

The study was carried out at the RCWMCH in the Western Cape of South Africa, which is the only stand- alone tertiary hospital in sub-Saharan Africa dedicated entirely to child healthcare. This tertiary hospital is the academic paediatric training platform for the University of Cape Town and runs nationally accredited sub-speciality training programs, inclusive of child neurology. It is government funded and serves a provincial population of over 1.7 million children below 14 years of age (27) .The neurology service is unique compared to international units in that it cares for children aged 0-12 completed years at first consultation across all levels of care, primary to quaternary. Children may remain in service until 16 year of age or older, prior to transfer to adult services. Capacity to manage children with epilepsy at primary level centers within the Western Cape is very limited. As such direct referral to the neurology service from primary care centres is common.

Additionally the department serves as a quaternary epilepsy service for other South African provinces. It handles a wide range of neurological diseases common to children from resource-poor countries and functions as the sub-Saharan referral centre for complex epilepsy diseases. A dedicated epilepsy service is supported by specialists in paediatric neurology, with on-site neurophysiology and neuroimaging facilities. The service has over 1800 clinic visits a year of children with epilepsy.

2.2 Inclusion criteria

Children referred with the diagnostic label of LGS

Children with complete clinical records and investigations inclusive of neuroimaging and electrophysiology.

2.3 Exclusion criteria

Children with inadequate data

2.4 Data assessment:

Children who met the inclusion criteria were critiqued for the diagnosis of LGS; multiple seizure types, a specific interictal EEG pattern of slow spike and wave of <3Hz in awake state (**figure1)**or paroxysmal fast rhythm(>10Hz) during sleep plus cognitive impairment when present. They were further delineated inclusive of demographics, seizure semiology, co-morbidities, investigations, management and preceeding risk factors. Children were allocated into 2 groups. Those who met the diagnostic criteria for LGS and those who did not (non-LGS group). The non-LGS group were further delineated where possible into other epilepsy categories or syndromes. The two groups were compared for key features present at the time of referral which would increase the likelihood of differentiating between children subsequently confirmed to have LGS and those not.

2.5 Data management:

Data was captured using REDcap database then was processed through R statistical programming language (**R** Core Team (2013). **R**: A language and environment for statistical computing. **R** Foundation for Statistical Computing, Vienna, Austria. URL http://www.**R**-project.org/.). Categorical data was first processed into frequency tables for descriptive statistics. To test for the significance of associations between variables and different groups, categorical data was then processed into cross-tabulations and the Fisher's Exact Test performed. To quantify the measure of association between variables and diagnosis, odds ratios were computed using a multinomial logistic regression model designed using only those variables previously shown to have a significant association with diagnosis. Continuous data was first tested for normality (using Shapiro-Wilk test) and then appropriate measures of central tendency are described. Code and data can be made available with publication (will upload data and code onto online repository and supply link in publication).

Ethical approval was attained from the RCWMCH Research committee plus the University of Cape Town Faculty of Health Science Human Research and Ethics Committee. Ref 612/2018

Results

The neurology registry recorded 110 children referred with a diagnosis of LGS. Of these 44 were excluded due to inadequate data. The remaining 66 patients were included for full analysis. The overall median (IQR) age in months at first seizure presentation of the cohort was 35 months with an interquartile range 16-54.5 months.

43/66 (65%) fulfilled the diagnostic criteria of LGS whilst the remaining 23 (35%) had other types of epilepsy (Table 1).

Half of the study participants were of indigenous black African ancestry (33/66). Generalized tonic clonic seizures 28/66 (42%) were the most common initial seizure type at presentation. As the children became older other seizure types evolved namely; myoclonic (61%), tonic (56%) and atonic (55%) as the most prevalent types. A large proportion 34 (52%) of the cohort had no identifiable cause for their epilepsy. Only, 25(38%) had a structural cause, with migrational disorders (12/25) closely followed by HIE (9/25) being the most common structural abnormalities identified. Three patients had a metabolic cause of their epilepsy namely: nonketotic hyperglycinemia, mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS), and Glutaric aciduria type 1

The most common epilepsy syndromes that were erroneously labelled as LGS, were other types of developmental and epileptic encephalopathies excluding MAE (15%), followed by uncategorized syndromes (11%) and MAE (9%) as illustrated in figure 1. Of the DEEs/EE, early onset epileptic encephalopathy (EOEE) was seen in seven patients. Epileptic encephalopathy during slow-wave sleep (ESES) was observed in one patient in table 2 below.

Figure 2: Pie chart showing how original diagnosis of LGS misdiagnoses other paediatric epilepsy syndromes

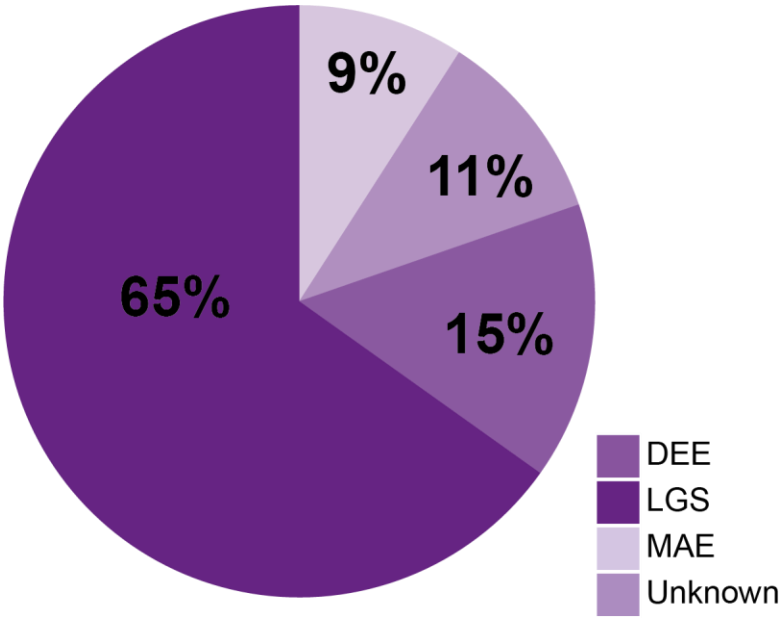
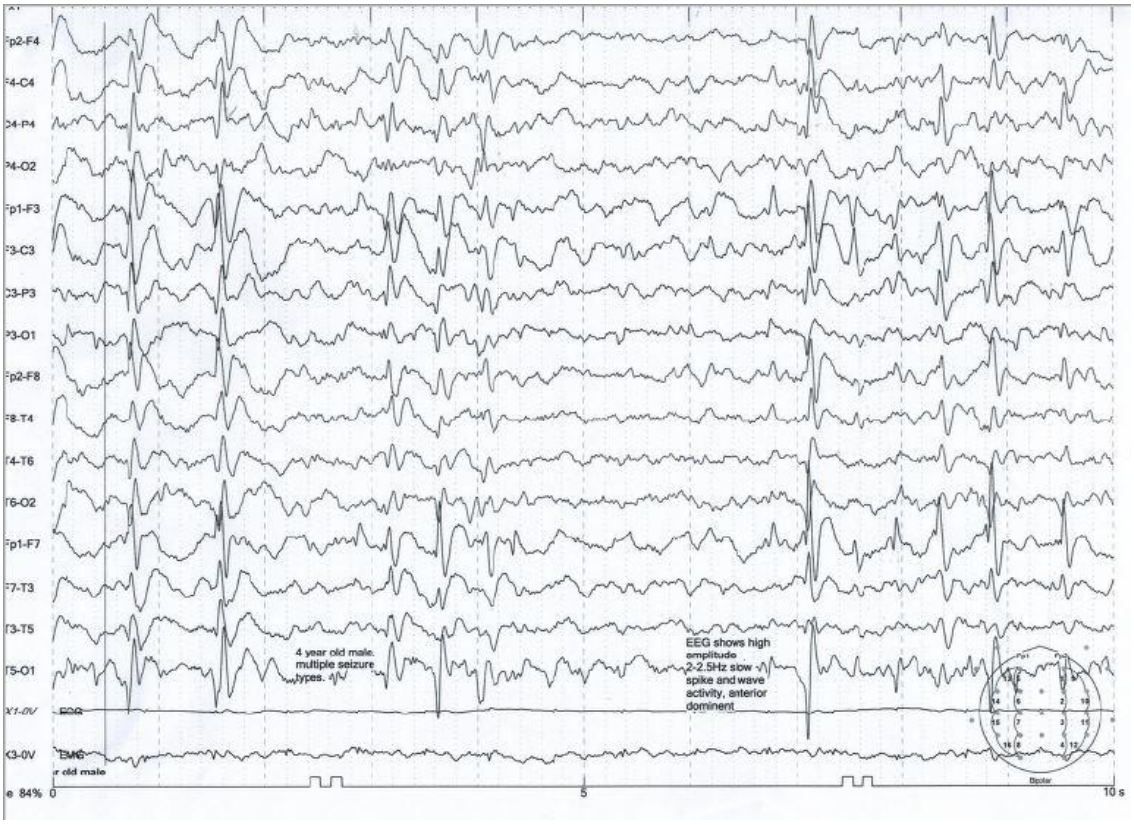


Figure 1: Below is an EEG epoch of a 4 year old boy who presented with multiple seizures including tonic, myoclonic, drops and absences. Interictal EEG revealed 2-2.5 Hz generalized slow spike and wave complex, compatible with LGS.



Thirty percent (13/43) (30%) of our LGS study participants had a history of epileptic spasms as opposed to n=3 (13%) in the not-LGS group. However this did not reach significance as a risk factor in developing LGS compared to the children in the not-LGS group. Table 1.

Table 1 study participants with epileptic spasms

Table 1: Epileptic spasms				
	Total (*n* = 66)	**LGS** (*n* = 43)	**Not LGS** (*n* = 23)	***p-value***
Epileptic spasms	16 (24%)	13 (30%)	3 (13%)	0.14

Since the epileptic spasms were not a marker of being diagnosed with LGS amongst our cohort, we excluded them in analysis before comparing clinical features between the LGS and non-LGS groups

Table 2: Clinical and Demographic Data				
	Total (*n* = 66)	**LGS** (*n* = 30)	**Not LGS** (*n* = 20)	***p***
Sex				0.78
Female	29 (44%)	12 (40%)	9 (45%)	
Male	37 (56%)	18 (60%)	11 (55%)	
Ancestry				0.73
African	33 (50%)	14 (47%)	9 (45%)	
European	5 (8%)	1 (3%)	2 (10%)	
Mixed	28 (42%)	15 (50%)	9 (45%)	
Age of seizure onset				0.57
Child	39 (59%)	23 (77%)	16 (80%)	
Infant	24 (36%)	6 (20%)	2 (10%)	
Neonate	3 (5%)	1 (3%)	2 (10%)	
Epilepsy Syndrome				
Lennox-Gastaut syndrome (LGS)	43 (65%)	30 (100%)		
Myoclonic astatic epilepsy (MAE)	6 (9%)		6 (30%)	
Developmental and epileptic encephalopathy (DEE) – not LGS or MAE	10 (15%)		6 (30%)	
Early-onset epileptic encephalopathy (EOEE)			3	
Epileptic encephalopathy	1 (2%)		1 (1%)	
Electric status epilepticus during slow-wave sleep (ESES)			1	
Unknown epilepsy syndrome	7 (11%)		7 (35%)	
Semiology of first seizure (excluding epileptic spasms)				0.07
Generalised tonic-clonic seizure (GTCS)	28 (42%)	15 (50%)	9 (45%)	
Tonic	11 (17%)	6 (20%)	0 (0%)	
Focal	9 (14%)	2 (7%)	6 (30%)	
Myoclonic	7 (11%)	1 (3%)	2 (10%)	
Convulsive status epilepticus (CSE, excluding febrile status	5 (8%)	3 (10%)	2 (10%)	

epilepticus)				
Atonic	3 (5%)	1 (3%)	1 (5%)	
Febrile status epilepticus (FSE)	2 (3%)	2 (7%)	0 (0%)	
Unknown	1 (2%)	0 (0%)	0 (0%)	
Semiology history (after first seizure)				
Atypical absence	12 (18%)	6 (20%)	4 (20%)	>0.99
Atonic	36 (55%)	15 (50%)	12 (60%)	0.57
Clonic	2 (3%)	1 (3%)	1 (5%)	>0.99
CSE	2 (3%)	1 (3%)	1 (5%)	>0.99
Focal	4 (6%)	10 (33%)	6 (30%)	>0.99
Febrile	19 (29%)	3 (10%)	1 (5%)	0.64
GTCS	36 (55%)	17 (57%)	15 (75%)	0.24
Myoclonic	40 (61%)	23 (77%)	12 (60%)	0.23
NCSE	6 (9%)	6 (20%)	0 (0%)	0.07
Tonic	**37 (56%)**	**19 (63%)**	**6 (30%)**	**0.04**
Number of different seizure types				0.81
One	8 (12%)	2 (7%)	2 (10%)	
Two	13 (21%)	4 (13%)	4 (20%)	
Three	30 (45%)	15 (50%)	11 (55%)	
Four	10 (15%)	6 (20%)	2 (10%)	
Five	4 (6%)	3 (10%)	1 (5%)	
Provoked	10 (15%)	6 (20%)	4 (20%)	>0.99
Aetiology				0.16
Autoimmune	0 (0%)	0 (0%)	0 (0%)	
Genetic	1 (2%)	0 (0%)	1 (5%)	
Infectious	3 (5%)	1 (3%)	0 (0%)	
Metabolic	3 (5%)	1 (3%)	0 (0%)	
Structural	25 (38%)	14 (47%)	5 (25%)	
Unknown	34 (52%)	14 (47%)	14 (70%)	
Structural pathology	*n* = 25	*n* = 14	*n* = 5	>0.99
Malformation of cortical development.	12 (48%)	6 (43%)	2 (40%)	
HIE	9 (36%)	5 (36%)	2 (40%)	
Vascular	4 (16%)	3 (21%)	1 (20%)	

HIE= hypoxic Ischemic encephalopathy

All the patients had an electroencephalogram done (98%) and or telemetry sessions (n=13) where the seizure semiology had been difficult to a certain (Table 3). The commonest abnormality recorded was interictal discharges with background slowing. Most discharges were generalized and some multifocal. **Figure 1** illustrates the typical findings in one of the cohort with LGS.

Table 3: EEG Findings of the Different Groups				
	Total (*n* = 66)	**LGS** (*n* = 30)	**Not LGS** (*n* = 20)	***p***
Outpatient EEG				0.26
One	55 (83%)	27 (90%)	16 (80%)	
2 or More	10 (15%)	2 (7%)	4 (20%)	
Telemetry sessions				0.43
One	10 (15%)	4 (13%)	3 (15%)	
2 or More	3 (5%)	0 (0%)	2 (10%)	
EEG features				
Burst suppression	1 (2%)	0 (0%)	0 (0%)	>0.99
Continuous spikes	6 (9%)	4 (13%)	2 (10%)	>0.99
Electrodecremental changes	3 (5%)	1 (3%)	1 (5%)	>0.99
Interictal discharges (IEDs)	53 (80%)	23 (77%)	15 (75%)	>0.99
Low amplitude fast activity	10 (15%)	4 (13%)	1 (5%)	0.64
Paroxysmal activity	3 (5%)	1 (3%)	1 (5%)	>0.99
Polyspikes	19 (29%)	8 (27%)	6 (30%)	>0.99
Slowing	51 (77%)	26 (87%)	13 (65%)	0.09
Suppression	8 (12%)	2 (7%)	2 (10%)	>0.99
Discharge source	(*n* = 66)	(*n* = 23)	(*n* = 15)	0.65
Focal	8 (15%)	4 (17%)	3 (20%)	
Generalised	32 (60%)	13 (57%)	10 (67%)	
Multifocal	13 (25%)	6 (26%)	2 (13%)	

Most of our cohort had intractable (65%) seizures, with only 35% having seizure control. The majority had daily seizures despite receiving three ASMs and trialed with more than four ASMs. Sodium valaproate, lamotrigine and clobazam were the most commonly used ASMs. Eight study participants were managed on a KD. Two had a good response but 3 had inadequate trials as illustrated in **table 4**. Epilepsy surgery was performed on two study participants with seizure

reduction in one whilst the other despite also having placement of a VNS device had no noticeable seizure reduction. ***Seizure control for the total group was documented as absence of convulsive seizures per the caretaker account.***

Table 4: Management of the Different Groups				
	Total (*n* = 66)	**LGS** (*n* = 30)	**Not LGS** (*n* = 20)	***p***
Seizure control				0.31
Controlled	23 (35%)	8 (27%)	11 (55%)	
Intractable	43 (65%)	22 (73%)	9 (45%)	
Seizure frequency	(*n* = 43)	(*n* = 22)	(*n* = 9)	0.53
Daily	20 (46%)	8 (36%)	5 (56%)	
Monthly	8 (19%)	7 (32%)	1 (11%)	
Weekly	15 (35%)	7 (32%)	3 (33%)	
Anti-seizure medications (ASMs) tried				
Two	10 (15%)	4 (13%)	2 (10%)	0.76
Three	21 (32%)	8 (27%)	9 (45%)	
Four or more	35 (53%)	18 (60%)	9 (45%)	
Number of ASMs maintained on				0.75
One	8 (12%)	3 (10%)	4 (20%)	
Two	19 (29%)	8 (27%)	6 (30%)	
Three	31 (47%)	15 (50%)	8 (40%)	
Four	8 (12%)	4 (13%)	2 (10%)	
ASMs used				
Carbamazepine	3 (5%)	1 (3%)	0 (0%)	>0.99
Clobazam	31 (47%)	15 (50%)	11 (55%)	0.78
Clonazepam	1 (2%)	0 (0%)	0 (0%)	>0.99
Diazepam	1 (2%)	0 (0%)	0 (0%)	
Lamotrigine	35 (55%)	17 (57%)	11 (55%)	>0.99
Levetiracetam	17 (26%)	7 (23%)	5 (25%)	>0.99
Phenobarbital	8 (12%)	2 (7%)	2 (10%)	>0.99
Topiramate	15 (23%)	11 (37%)	3 (15%)	0.12
Valproate	59 (89%)	26 (87%)	17 (85%)	>0.99
Ketogenic diet	8 (12%)	4 (13%)	2 (7%)	
Response to ketogenic diet	(*n* = 8)	(*n* = 4)	(*n* = 2)	0.73
Good (>50% reduction in seizure	2 (25%)	1 (25%)	1 (50%)	

burden)				
Partial (<50% reduction in seizure burden)	1 (13%)	0 (0%)	1 (50%)	
Inadequate trial	3 (38%)	1 (25%)	0 (0%)	
No benefit	2 (25%)	2 (50%)	0 (0%)	
Epilepsy surgery	2 (3%)	0 (0%)	1 (5%)	0.4
Outcome post-surgery (ILAE outcome scale)	(*n* = 2)		(*n* = 1)	
Class 3 (1 to 3 seizure days per year; ± auras)	1 (50%)			
Class 5 (<50% reduction of baseline seizure days)	1 (50%)		1 (100%)	
Vagal Nerve Stimulator (VNS) implanted	1 (2%)			
Response to VNS	(*n* = 1)			
No benefit	1 (100%)			

2 epilepsy surgery patients (1 had corpus Callosotomy, patient 2 had focal dysplasia. ***Seizure control for the total group was documented as absence of convulsive seizures per the caretaker account.***

The commonest comorbidities of our cohort was cognitive impairment, with many of the study participants having moderate cognitive impairment. Having severe or moderate cognitive impairment was associated with a diagnosis of LGS as opposed to the not-LGS group. Frequent hospital admission occurred in 45% of our cohort with the majority occurring in the LGS group as illustrated in table 5.

Table 5: Comorbidities of Different Groups

	Total (*n* = 66)	**LGS** (*n* = 30)	**Not LGS** (*n* = 20)	***p***
Adverse events to ASMs				0.46
None	38 (58%)	17 (57%)	11 (55%)	
Drowsiness	8 (12%)	2 (7%)	3 (15%)	
Hepatotoxicity	2 (3%)	2 (7%)	0 (0%)	
Hyperactivity	7 (11%)	4 (13%)	1 (5%)	
Hypersensitivity	2 (3%)	0 (0%)	2 (10%)	
Psychosis	6 (9%)	3 (10%)	3 (15%)	
Weight gain	2 (3%)	1 (3%)	0 (0%)	

Weight loss	1 (2%)	1 (3%)	0 (0%)	
Cognitive impairment				
Mild	8 (12%)	1 (3%)	7 (35%)	0.07
Moderate	**37 (56%)**	**19 (63%)**	**10 (50%)**	**0.02**
Severe	**21 (32%)**	**10 (33%)**	**3 (15%)**	**0.01**
Frequent hospital admissions	30 (45%)	17 (57%)	6 (30%)	0.09
Traumatic injuries from seizures	7 (11%)	3 (10%)	3 (15%)	0.67

Cognitive impairment = development or intellectual quotient (IQ) if below 70, Mild if DQ/IQ is 70-50, Moderate (50-35) and severe if < 35. Frequent hospital admission = >1 admission in a month

Children with moderate cognitive impairment were more likely to fall into the LGS group compared to those with mild cognitive impairment (*OR* 2.59, *95% CI* 0.004-0.51, *p* =0.02). Similarly, patients with severe cognitive impairment were more likely to fall into the LGS group compared to those with mild cognitive impairment (*OR* 3.15, *95% CI* 0.002-0.37, *p* =0.01).

Discussion

This study is one of the few describing LGS in a sub-Saharan African context to date. It was undertaken with the intention of describing the diagnosis, phenomenology, aetiology, management and identification of early clinical markers and treatment outcomes of children referred with a diagnosis of LGS in the Western Cape Province of South Africa. All the study participants had comparable management and as such diagnostic labels may not have been adequately revisited during clinic follow-ups. Although the sample size was small identification of early indicators to enhance the probability of a diagnosis of LGS, permitting targeted therapy for this group and focused re-assessment for the not-LGS group is viable in our resource limited setting. Our study also was limited by its intrinsic limitations of retrospective study design. Secondly, not all our study participants had vEEG,with a possibility of having missed some seizures especially the subtle tonic seizures and atypical absences. Thirdly, our study population comprised mostly the socio- economically disadvantaged patients which could have introduced some form of bias, with interrupted clinic attendance, patient attrition and often presentation delays. However this could reflect the true picture of a RLS.

Only 65% of children complied with the diagnostic criteria of LGS. The rest were better placed under other diagnostic categories in-line with the International League Against Epilepsy (ILAE). This finding is consistent with the review by Arzimanoglou at al (13)which highlighted that many childhood epileptic syndromes mimic LGS and as such this misdiagnosis is not unusual and further supported in other reports (4, 13). The developmental and epileptic encephalopathy syndromes that did not meet the LGS criteria were, possibly labeled LGS due to having multiple intractable seizures and the cognitive impairment, which characterized them(32, 33).The same could be true for the unknown epileptic syndromes. The lack of genetic testing in our clinical setting is a limitation to diagnosis, precision therapy and prognostic counselling. Esterhuizen et al highlighted for the need for genetic testing in Africa(34).

Myoclonic atonic epilepsy (MAE) is potentially misdiagnosed for LGS as noted in previous studies (3, 13). MAE as well as LGS presents with multiple seizure types namely; myoclonic, atypical absences, atonic and even generalized tonic clonic seizures, there is also overlap in the age of presentation between 3-5years with LGS. However myoclonic atonic seizures are the hallmark seizure type(3, 35). EEG can have a normal background at seizure onset as well as a monomorphic biparietal theta rhythm. As seizures become established interictal clusters or generalized polyspike and wave at 3-6Hz often occur(35). As such the interictal EEG can be useful to differentiate from the typical slow spike and wave (SSW) complexes at < 3Hz or paroxysmal fast rhythms of >10Hz during NREM sleep of LGS. In the African setting access to EEG is often very limited(36).

One of our patients had a continuous spike and wave during slow wave sleep (CSWS) which is an epileptic encephalopathy with neurocognitive regression, there are few seizures at the onset and the child has a typical EEG pattern of electrical status epilepticus during sleep(37). Again without access to EEG this condition would be challenging to diagnose. So for many of the children the multiple seizures types and neurocognitive impairment could have led to the misdiagnosis of LGS.

Structural brain abnormalities such as malformations of cortical development, brain insults from traumatic brain injury, HIE and vascular pathology were some of the identifiable causes. The presence of HIE as a cause reflects to the need for improvement of newborn care in our RLS. Although the numbers were too small to compare in this cohort, structural causes common

aetiologies (1, 5, 7) and as such reaffirm the critical role of neuroimaging whilst investigating the causes of LGS. Other reports(1, 7, 38), found no apparent cause (unknown) in some 25%, but our in cohort this was 47% which could have reflected our limitations with lack of access to genetic studies in the government setting as well as more complex metabolic screens (39, 40). Various de novo mutations in the synaptic transmission genes are described as causes of DEE with LGS phenotype, these include *DNM1*, *STXBP1*, and *GABRB3*(39).

In our study over 73% of our LGS patients had pharmacoresistant seizures as opposed to the 45% of the not-LGS group. This finding is not surprising(5, 41). Sodium valproate, lamotrigine and clobazam were the most prescribed ASMs. This combination is supported by expert opinion recommendations (10, 14). The use of sodium valproate was the standard ASM in the management of LGS spectrum in consensus report (28) and supported by a Cochrane review(10). Recommendations supporting the withdrawal of valproate(42, 43) in females of child bearing age could compromise the care of children who have achieved acceptable seizure control. In the Africa setting converting to agents such as levetiracetam is not viable for many sectors and children are more likely to be prescribed to phenobarbital instead. However with regard to other ASMs as adjunctive therapy, no one drug is reported to be more effective over the other (10). One patient with LGS had a good response with seizure reduction greater than 50% whilst on KD and ASMs. The efficacy of the KD in LGS has been reported by Lemmon et al(17) with 44% seizure freedom at 12 months. As such, it is used as one of the non-pharmacological treatment modalities in our centre when feasible.

In this study, intellectual/cognitive impairment and tonic seizures were markers of the child with LGS. This finding is consistent with reports describing this DEE (2, 44) and all our LGS patients had a degree of cognitive impairment. The majority of our cohort were referred from secondary and primary level health care settings by general physicians with inevitable delays in reaching tertiary levels of care as many children were from poor socioeconomic backgrounds. This could have contributed to the cognitive impairment that was seen in all our study participants. However owing to the retrospective nature of the study, a prospective comparative study could help prove this. Berg et al reported cognitive impairment in children with LGS at 84% as opposed to 11% in other epilepsies(45), and other studies report between 20-60%(1, 44). However the intellectual and behavior impairment may not be evident at presentation, but becomes apparent over time,

usually by 5 years of age in 75%-95% (5, 6, 45). Having tonic seizures had a high likehood of being diagnosed with LGS. This finding is very consistent with the available literature of tonic seizures and this seizure type being the wholemark seizure type in LGS(2, 3, 44). However a small proportion of our LGS cohort seemed had no tonic seizures which could be missing leading, but had strong markers of LGS. This finding could have resulted from the observer description, as such missing the tonic seizure component. Furthermore, the inability to perform telemetry on the entire cohort could have resulted in missing some of tonic seizures. It is noteworthy that the majority of our LGS cohort had GTCs as their index seizures at presentation and the tonic seizures plus other seizure types evolved as the disease progressed. Presentation with GTCS was also common in the not LGS group further compounding early differentiation. Approximately 30% of our LGS cohort had preceding epileptic spasms syndrome (ESS). However this finding was not statistically significant. This may have been compounded by small numbers or reflected the presence of children with other types of DEE also suffering EES as part of their syndrome. Different studies have reported varying rates, Berg et al noted 13%(45) had preceeding EES, whilst Ohtahara and Ohtsuka reported 20%(5, 7). The variance in incidence may reflect lag in access to care as reflected by the lower rate reported by Berg and colleagues, potentially as a result of improved care of children with ESS.

Conclusion

Our findings are largely similar to the available literature on LGS despite the small sample size. Over a third of the children in this cohort were erroneously labelled with a diagnosis of LGS early in their course. This has implications on their management and prognostic counselling. Reports from other centres have highlighted the challenges of differentiating between LGS and other epilepsy syndromes. As such continuously critiquing of diagnostic label where an alternate one is possible is of upmost importance.

Identifying the indictors of cognitive impairment, and tonic seizures could be useful early clinical markers which support a diagnosis of LGS, and viable for use in our setting.

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RS; Conceived the ideal, developed the proposal, collected the data and analyzed, plus writing of the draft manuscript. JMW; Supervised the whole project development, with major inputs from its conception to writing of the manuscripts. HD; Neurophysiologist, with RS looked at the EEGs that met the diagnostic criteria of LGS and also helped to collect some data. RB assisted with data analysis inclusive of the statistical screens and provided comment on the Manuscript.

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Disclosure of conflict of interest

The authors declare no conflict of interest and confirm that we have read the journal`s position on issues related to the ethics of publication and affirm this report is consistent with the guidelines.

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Appendix;

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 October 2018

HREC REF: 612/2018

Prof J Wilmshurst
Paediatric Neurology
Room 514, ICH Building
Red Cross War Memorial Children's Hospital

Dear Prof Wilmshurst

PROJECT TITLE: CHILDREN WITH LENNOX-GASTAUT SYNDROME IN THE WESTERN CAPE OF SOUTH AFRICA: AETIOLOGY, DIAGNOSIS, AND OUTCOMES (MPhil Candidate - Dr R Sebunya)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 04 October 2018.

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

Approval is granted for one year until the 30 October 2019.

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)

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.

The HREC acknowledge that the student, Dr Robert Sebunya will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

DATA EXTRACTION TOOL

Children with Lennox Gastaut Syndrome in the western Cape of South Africa.

Study number…….

A.**Demographics**

i) Sex/ Gender……Date of birth…… Date of enrolment in epilepsy clinic……Current Age……..

ii)Physical Location……..

iii) Rural area……. Urban……

iv)Ancestry: African…… Mixed race/Coloured…..Indian…..,,European……Others……...

v) NOK; Mother… father ….. Sibling…… grand…… other…….

vi) Level of education of education of care caregiver: primary…….. secondarily…… ……. University…….

vii) Social Economic Settings levels. H1……H2…….. H3.....

B. (i)Presence of tonic seizures especially at night, plus other seizure types YES…….NO…….

(ii) EEG findings of generalised slow-spike; YES……..NO……..

(iii) Level of Cognition /behavioural impairment mild…. Moderate….Severe…..

C. Does this child have true LGS? Yes…….. No……. ……

D. If No (in b(iii) above what was the labelled or current diagnosis?

MAE……. Dravet……. Epileptic Encephalopathy……. LKS……

Others (mention) E.g EOEE……..

IF C above is Yes (True LGS) then we proceed to E.

E Seizure History

i) Age of first seizure onset…….....

ii) If in Infancy was it Status Epilepticus at presentation? YES……..NO…….

iii) If Yes in ii above What was the time duration from the Status Epilepticus to occurrence of other seizure types.

1-2 months…… 3-6months……. 6-1year……1-2years…….

iv) Level of Development: Normal…… Static ……...
Regression…….

v) **Initial** type of seizure at enrolment into the epilepsy clinic.
Tonic,…….Myclonic…….Atonic……..…Abscence……..Atypical absence…….infantile spams……... GTC…….

vi) Seizure semiology:(Status Epilepticus,onset/ awake/asleep, aura, evolution and cessation)……
……
……
……
……

vii)**Curren**t: Most prevalent seizure type……..

viii) **Other** occurring seizure types. Tonic…….. Myoclonic……atonic ……..Atypical absence……Drop attacks…… EEG subclinical status…….

Xi). Average number of seizures per month (if possible) <5,…… >5…… uncountable…….

F) **Atiology**

i) Structural brain anomalies**: Yes…….. No…….. IF YES which imaging modality MRI…….. CT……**

Migrational disorders……

IVH/ PVL/ strokes……

Post infectious…….

Traumatic brain injury……..

ii) Metabolic cause… Yes……No……

iii) Genetic studies Yes……...unknown…….

iv) No identifiable cause……..

G) Electroencephalographic finding/ telemetry findings (Date done, age and Circumstances)

……
……
……
……
……
……..

H) Seizure control

i) Intractable yes…… No……..

If yes in H above how many seizure episodes occur in a day…… Week…… Month……..

I)Treatment

i) Anti-epileptic drug treatment (AED).

Initial AEDs……..

Current regimen (AED)…….

Number of AEDs …….

ii) Other non-pharmacological treatment modalities.

a)Ketogenic diet……Yes …….No……..

If yes what is the response in seizure control/ frequency
Poor……good……

ii)Epilepy surgery…Yes ……NO…….……

iii) If yes what procedure was done……..

Response In terms of seizure control; Poor……Good……

iv) Vagal nerve stimulation device(VNS) Yes…….. NO……..

V) if yes what was the response Good…… Poor……

J) **Related co-commodities**

i) Behaviour: Normal…….. Abnormal……

ii) Development delay: Yes…… No……

iii)If yes what was the score. Profound…… severe…… moderate ……... and mild

iv) Neuroregression: Yes….. …… No…….

Physical disabilities: Normocephalic…….. Microcephaly……. Macrocephaly…….

v) CP spastic Yes……,.. No…….. Dyskinetic……

vi) Other motor disabilities Yes,,,…….. No…….

vii) Schooling; Yes……No…….

If placed which type of school. Mainstream…….. Special school…….

Epilepsy related hospital admissions in numbers;

1 Monthly……

2.monthly…….

3 or more……

Referral centre for epilepsy management.

Primary……..

Secondary…….

Tertiary…….

Private ……..

3.Journal instructions

SEIZURE - EUROPEAN JOURNAL OF EPILEPSY

Types of articles

Seizure - European Journal of Epilepsy publishes the following types of article:

1.1 Peer-reviewed articles

a. Full reviews.

Seizure welcomes comprehensive reviews on all subjects relating to epilepsy and other seizure disorders. Authors planning/proposing are invited to discuss their ideas with Editor-in-Chief prior to submission. Full reviews should be preceded by an abstract. Full reviews should not exceed 7,000 words, include no more than 6 figures or tables and 150 references.

B. Full-length original research articles.

The body of the text of these articles should be limited in length to 4,000 words, and there should be a maximum of 6 figures or tables. Additional figures, tables and other material (such as associated videos) can be submitted as online only Supporting Information (see section 'preparation of manuscripts' for further details). Full length research articles should be preceded by an abstract. The body of the text of the article should be clearly structured into **1) Introduction, 2) Methods 3) Results, 4) Discussion, 5) Conclusion and 6) References**.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid
abbreviations and formulae where possible.

• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s)
of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author**.**

• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Correct author name format

To prevent confusion please ensure that all author names are listed in the following format; first (Christian) name first and the last name (Surname/Family) last. This is specified because Spain, China and some other countries often write them differently and this causes confusion with databases like MEDLINE.

Highlights

Highlights are mandatory for this journal as they help increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.
Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Article structure

Subdivision - unnumbered sections
Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross referencing text: refer to the subsection by heading as opposed to simply 'the text'.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.
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Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise. Results should usually be presented in graphic or tabular form, rather than discursively. There should be no duplication in text, tables and figures. Experimental conclusions should normally be based on adequate numbers of observations with statistical analysis of variance and the significance of differences. The number of individual values represented by a mean should be indicated.

Discussion
This should explore the significance of the results of the work, not repeat them. Avoid extensive citations and discussion of published literature. Speculative discussion is not discouraged, but the speculation should be based on the data presented and identified as such. In most cases a discussion of the limitations is appropriate and should be included in this section of the manuscript.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented

separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself. Abstracts for regular articles and short communications should be structured, using the subheadings purpose, methods, results, conclusion. For reviews, the abstract does not need to follow this structure. They should be no longer than 250 words. Case reports (Clinical Letters) do not need to be preceded by an abstract.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using British spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted
for publication.

Reference formatting

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/ book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged.

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text