Clinical characteristics of children with epilepsy managed at a tertiary hospital in Africa: a retrospective study

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Abstract

Background: Most children with epilepsy reside in resource-limited regions such as sub-Saharan Africa, where the majority of studies have been conducted in rural areas with limited investigations. Medical records from children with epilepsy seen at an urban hospital in Kenya were examined to provide a comprehensive description of epilepsy in children from this hospital.

Methods: A retrospective observational study was conducted which involved reviewing medical records of 426 epilepsy patients (260 males and 166 females) aged 0 - 18 years, seen in Nairobi, Kenya between February 2011 and December 2014.

Results: The most frequent age at presentation; documented in 29% was in infancy. Generalized seizures due to structural brain abnormalities were the most common form of epilepsy (28%). Lennox-Gastaut Syndrome was the most common electroclinical syndrome (7%). Focal seizures and focal seizures with loss of awareness were identified in 12% of the population. There were no cases of childhood absence epilepsy in this group. Brain atrophy was the most common MRI finding, occurring in a fifth of the population (20%), while cystic encephalomalacia occurred in 13%. Half (50%) of all EEG recordings performed for this cohort were abnormal. Generalized seizures due to structural brain abnormalities and Lennox-Gastaut Syndrome (LGS) were significant predictors of a treatment history of three or more AEDs. At the conclusion of the review period, 16% of the patients had not visited the clinic for more than 12 months and were considered to be lost to follow-up.

Conclusion: The highest frequency of epilepsy cases was documented in children less than one year of age. Generalized seizures due to structural abnormalities and Lennox-Gastaut syndrome were the most common seizure type and syndrome. Improvement of public awareness of different types of seizures in children may increase identification of children with childhood absence epilepsy.

Background

The has identified epilepsy as presenting a significant burden as measured by Disability-adjusted life years (DALY) [1]. Epilepsy affects approximately 50-70 million people worldwide [1-3] and up to 80% of those affected reside in low and middle-income countries (LMIC), such as those comprising the majority of Sub-Saharan Africa(SSA) [2][3][4].

According to studies in five SSA countries, the prevalence

of active convulsive epilepsy ranges from 7.0 - 14.8 per 1000 people [5]. Consistent with the global trend, the highest incidence of epilepsy in Africa occurs in the paediatric population [6]. The high prevalence of paediatric epilepsy in SSA is attributed to preventable risk factors including: poor perinatal care, endemic infectious diseases and head injury [6][7]. Factors contributing to the high epilepsy treatment gap in SSA include limitations in accessing adequate diagnostic and treatment services as well as negative cultural and social beliefs regarding epilepsy [3][4][6][8].

Following the 2010 proposal, Revised terminology and concepts for organization of seizures and epilepsies produced by the International League Against Epilepsy(ILAE) Commission on Classification and Terminology [9], Scheffer et al. proposed an organization of epilepsy diagnosis based on electroclinical syndrome and aetiology [10]. An electroclinical syndrome is a presentation of epilepsy that demonstrates specific outcomes, clinical and electroencephalogram(EEG) characteristics [9][10]. In resource-limited settings, various challenges present limitations for delineating epilepsy according to electroclinical syndrome and aetiology. Recent population and hospital-based studies conducted in Africa providing descriptions of epilepsy in children based on these electro-clinical syndromes or syndrome-associated outcomes are sparse to non-existent [6][10][11][12]. This paper describes the static and dynamic demographic characteristics of the patient population and seizure onset; electroclinical syndromes and seizure types; structural and electrophysiological brain abnormalities; types and number of anti-seizure medications(ASM) administered; co-morbidities and patient attrition rates.

Methods

Paediatric neurologists and local medical personnel practicing in low-resource settings face multiple challenges. Access to neuroimaging and specialised neurophysiological testing, such as electroencephalography(EEG), is typically concentrated in single centres, usually located in larger cities.

This was a retrospective observational study based on a review of the medical records of children and adolescents (aged 0 - 18 years) with epilepsy who were seen at Aga Khan University Hospital, Nairobi, Kenya between 2011 and 2014. The hospital is an urban academic institution which functions as a primary referral hospital for clients in the vicinity and also acts as a tertiary university hospital with facilities for EEG and neuroimaging. The hospital further provides supportive funding for patients without capacity to pay for such services. Approximately 10% of patients seen at the paediatric neurology clinic were sponsored by the hospital and another 10% had their medical costs supported by the National Hospital Insurance Fund (NHIF), Kenya's national health insurance scheme. It is estimated that 65% of patients seen at this facility are referrals from outside of the Aga Khan University hospital network of facilities.

The patient medical records examined consisted of physical files and as well as information stored on the hospital's electronic databases. Physical files of patients seen at the hospital during this period indicating a history of seizures or diagnosis of epilepsy were obtained from the medical records department using ICD-10 (International Classification of Diseases, Tenth Revision) codes utilized at the time of archiving. From these records, all patients diagnosed with epilepsy, according to the ILAE 2014 definition of epilepsy, were selected for inclusion in the study [13]. According to the ILAE, epilepsy is defined as two or more unprovoked seizures occurring at least 24 hours apart, or one unprovoked seizure with a probability of recurrence determined to be greater than 60% [13]. Based on this definition, the following patients were excluded from the study: patients presenting with typical simple febrile seizures only; patients with a single seizure episode without an epilepsy syndrome diagnosis or identifiable structural brain abnormality; those with a single provoked seizure in the context of fever or hypocalcemia, for example; as well as those with episodes of syncope only; or non-epileptic, psychogenic seizures solely.

Evaluation for co-morbidities such as attention deficity hyperactivity disorder(ADHD)and autism spectrum disorder(ASD) were made by the paediatric neurologist who assumed care for the children. Screening for these co-morbidities was done using National Institute for Children's Health Quality (NICHQ), Vanderbilt Assessment Scales for ADHD and the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM V) for ASD. Where other behavioural concerns were identified these children were evaluated by a child psychiatrist. Results of these evaluations were included in patient records. During regular clinic visits data on patient developmental progress was also included in the medical records.

Data on patient sex; age at seizure onset; electroclinical diagnosis; structural brain abnormalities; number and type of ASMs in treatment history; consistency of clinic follow-up and co-morbidities were extracted as previously documented in the patient's clinical notes. Further data was obtained from clinical notes and technical reports describing imaging and electrophysiological findings. The research assistant who collected and analysed the data was trained and supervised by the paediatric neurologist who assessed and managed the patients.

Electroclinical syndrome diagnoses were determined according to guidelines outlined in the Proposal for Revised Classification of Epilepsies and Epileptic Syndromes, by the Commission on Classification and Terminology of the ILAE [9][10]. Epilepsy that could not be classified as an electroclinical syndrome was described according to seizure type (i.e. generalized or focal) and cause (e.g. structural aetiology) [9].

Age at seizure onset was recorded in months and grouped into one of four periods of onset: i) neonatal - where onset of seizures occurred within the first 28 days of life; ii) infancy – where seizures commenced between 1 and 12 months of life; iii) childhood - where seizures began between 12 and 120 months (i.e. 1 - 10 years) of age; and iv)

adolescence - where onset of seizures occurred between 120 and 216 months of age (i.e. 10 years to 18 years). These groupings were based on WHO age classifications [14][15].

The findings of all EEG reports were counter-checked by the paediatric neurologist. Brain magnetic resonance imaging(MRI) and head computed tomography(CT) reports generated at both external hospitals and Aga Khan University Hospital were counter-checked by one neuroradiologist. Patients who had not visited the clinic for twelve months or longer were defined as being lost to follow-up.

This study was subjected to a full scientific and an expedited ethics review. The Aga Khan University Hospital Ethics Committee gave approval to conduct the study (reference number 2015/REC-27 (vl) dated 29th June 2015). Permission to access records from Aga Khan University Medical Records Department was granted from 30th June 2015 to 29th June 2016. As this was a retrospective review of medical records without direct patient contact, the Institutional Review Board(IRB) did not require patient consent to participate.

In analysing the data, patients were grouped primarily by electroclinical syndrome [9][10]. In cases where an electroclinical diagnosis could not be applied, patients were categorised according to seizure type and aetiology where known [9].

Variables including sex, age at seizure onset, use, results of investigations into structural and electrophysiological brain abnormalities, consistency of clinic follow up and co-morbidities were documented for all patients in the study group and these were analysed using descriptive statistics and presented in frequency tables and distributions.

Results

A total of 1,106 children were seen at the paediatric neurology clinic between February 2011 and December 2014. Among these were 576 children with a history of seizures, of whom only 426 had a diagnosis of epilepsy and were included in the study as shown in Table 1.

Sex and diagnosis frequency

The male: female ratio was 1.6:1 (260 males and 166 females), with males comprising 61% of the study population (Table 1). LGS was the most common electroclinical syndrome. Overall, of all the syndrome and seizure types, generalized seizures associated with structural brain abnormalities was the most frequent form of epilepsy.

Age at seizure onset

Fifty-six percent of patients 56.6% (N = 241) developed seizures between 1 and 10 years of age while 29% (N = 125) of patients developed seizures in infancy (between 1 and 12 months of age.) Fewer patients, 7.5% (N = 32), presented with seizures for the first time between 10 and 18 years. This data is shown in Table 2.

Structural and electrophysiological brain abnormalities

A total of 8.5% (N = 36) of patients had no investigation results available on file. The majority of the patients, 86.4% (N = 368) had a sleep EEG reported, while approximately half of the study population, 48.8% (N = 208) had a brain MRI scan with contrast. Reported findings from the brain MRI scans are summarized in Table 3. Ten children (4.8%) who had both brain MRI and head CT reports had their findings included in the brain MRI group. Four among these (0.9%) had both normal head CTs and brain MRIs while three children (1.4%) had delayed myelination on brain MRI. Two children (0.9%) had white matter hyperintensities and one child (0.4%) had polymicrogyria on brain MRI.

Among those who did not have brain MRI, 19.2% (N = 106) of patients had CT scans, of which 53.4% (N = 57) were abnormal. Brain atrophy and hydrocephalus were the most common abnormalities identified in 45.6% (N = 26) and (N = 10) 17.5% children respectively. A total of 47.2% (N = 50) had normal head CT reports. In this cohort 26.2% (N = 112) of children with epilepsy had no neuroimaging records.

A total of 557 EEG recordings were performed for the 426 patients in the study. Among these, 5.9% of all the EEG recordings (N = 33) demonstrated indeterminate findings, while 43.1% (N = 240) of these were normal and 50.1% (N = 284) were abnormal. Of the abnormal EEG recordings 56.7% (N = 161) showed generalized spike wave discharges, 25.3% (N = 72) showed focal spike wave discharges while 17.9% (N = 51) of abnormal EEG recordings showed slowing activity.

Anti-seizure medication use

Of the total patient population, 89.4% (N = 381) had been treated with one or more ASMs since onset of epilepsy while 10.6% (N = 45) of patients had not been on MRI treatment (Table 4). Among those on antiepileptic medication, 42.7% (N = 176) of patients been treated with one ASM, 24.2% (N = 100) with two ASMs, 17.4% (N = 72) with three ASMs and 9.2% (N = 38) with four or more ASMs serially. Table 4 summarizes types of ASMs that were utilized in this population in order of frequency. As illustrated above individual patients may have utilized more than one medication. Valproic acid was the most commonly used ASM with 69.4% usage amongst the study participants, followed by Carbamazepine and Clonazepam with 24.2% and 20.8% usage respectively. In contrast, Pregabalin and Gabapentin were the least used (each having been utilized by 0.3% of study participants).

Co-morbidities

Of the 426 children, 21.6% (N = 92) had psychiatric co-morbidities: Among these 10.1% (N = 43) had ADHD; 8.2% (N = 35) had ASD; 0.5% (N = 2) had mood disorders; 1.2% (N = 5) had a psychosomatic illness; and 1.6% (N = 7) had other behavioural concerns. Further, almost half of the patients with psychiatric co-morbidities 0.9% (N = 40) had focal seizures with loss of awareness. Various neurodevelopmental co-morbidities were observed in this study popu-

Table 1 Distribution of the Epilepsy diagnoses within the study sample, by sex

Diagnosis	Total N = 426 -100%	Male N = 260 -61%	Female N = 166 -39%	Proportion of Cohort %
Epilepsy syndromes				
Lennox-Gastaut syndrome(LGS)	29	18	11	6.8
Infantile spasms (West Syndrome)	22	12	10	5.2
Epilepsy with myoclonic astatic seizures(EMA)	5	4	1	1.2
Juvenile myoclonic epilepsy(JME)	5	1	4	1.2
Juvenile absence epilepsy(JAE)	3	2	1	0.7
Childhood epilepsy with centro-temporal spikes(CECTS)	2	2	0	0.5
Dravet syndrome	1	1	0	0.2
Seizure semiologies				
Generalized Seizures with structural brain abnormalities	117	76	41	27.5
Generalized Epilepsies of unknown cause	99	60	39	23.2
Focal Seizures	52	28	24	12.2
Focal seizures with loss of awareness	40	26	14	9.4
Febrile seizures plus	44	24	20	10.3
Genetic Epilepsy with febrile seizures plus	7	6	1	1.6

N represents the number of study participants

Table 2 Distribution of age at seizure onset

Diagnosis	Total	Neonatal < 28 days N	%	Infancy 1-12 months N	%	Childhood 12-120 months N	%	Adolescence 120-216 months N	%
Epilepsy syndromes									
	29	0	0	7	24.1	22	75.9	0	0
Infantile spasms (West Syndrome)	22	7	31.8	14	63.6	1	4.5	0	0
Epilepsy with myoclonic astatic seizures(EMA)	5	0	0	0	0	5	100	0	0
Juvenile myoclonic epilepsy(JME)	5	0	0	0	0	1	20	4	80
Juvenile absence epilepsy(JAE)	3	0	0	0	0	2	66.7	1	33.3
Childhood epilepsy with centro-temporal spikes(CECTS)	2	0	0	0	0	2	100	0	0
Dravet syndrome	1	0	0	1	100	0	0	0	0
Seizure semiologies									
Generalized seizures with structural brain abnormalities	117	18	15.4	54	50.9	37	34.9	8	7.5
Generalized epilepsies of unknown cause	99	0	0	19	19.2	68	68.7	12	12.1
Focal Seizures	52	3	5.8	16	30.8	31	59.6	2	3.8
Focal seizures with loss of awareness	40	0	0	5	12.5	32	80	3	7.5
Febrile seizures plus	44	0	0	8	18.2	34	77.3	2	4.5
Genetic epilepsy with febrile seizures plus	7	0	0	1	14.3	6	85.7	0	0
Total	426	28	6.6	125	29.3	241	56.6	32	7.5

N represents the number of study participants

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lation. These included developmental delay in 27.9% (N = 119) of patients; speech delay in 17.4% (N = 74); intellectual disability in 8.7% (N = 37); cerebral palsy in 15.3% (n = 65); and developmental milestone regression in 7.8% (N = 33) of patients. The greatest proportion of neurological co-morbidities was observed among patients with (N = 29), including developmental delay in 34.5% (N = 10) of patients, speech delay in 20.7% (N = 6), intellectual or learning disabilities in 27.6% (N = 8), and regression of milestones was in 24% (N = 7).

Attrition rates

At the conclusion of the review period, one patient had died and an additional 16.4% (N = 70) of study participants who had not visited the clinic for more than 12 months were considered to be lost to follow-up. In this group there were 60% (N = 42) males and 40% (N = 28) females. Among these, 41.5% (N = 29) were aged less than 24 months at initial presentation to the clinic. The diagnosis of patients lost to follow up is summarized in Table 5.

Discussion

In Africa preventable factors such as perinatal insults during complications of delivery, maternal and infant infections and trauma contribute to the high prevalence of epilepsy [16][17][18][19][20][21][22]. Limited access to quality healthcare care facilities and services further negatively impact prevention and management of epilepsy on the continent [19][23][24][25][26][27][28][29][30]. Epilepsy is associated with significant personal and social consequences including increased risk of injury, limited education, unemployment and social ostracism [31][32][33][34][35].

Infants in their first year of life accounted for the highest incidence of epilepsy overall and the highest proportion of paediatric patients presenting with generalized seizures due to structural brain abnormalities. These two observations may be related to the significant proportion of infants who had birth injury and various other congenital brain malformations. These findings are in keeping with a population study by Ellenberg et al showed that the highest incidence of non-febrile seizures occurred within the first year of life [36]. Targeted efforts to identify infants with epilepsy in the first year of life in this context would therefore be important in ameliorating morbidity associated with this condition.

Generalized epilepsy has been found to be the most common kind of epilepsy in many paediatric, and adult population studies [20][21][37]. This was found to be the case among patients in this cohort, a significant proportion of whom had generalized seizures due to structural abnormalities. This observation would be reflective of the fact that members of the cohort attended an urban medical facility where appropriate neuroimaging facilities were available. Data from various parts of rural Kenya regarding children with epilepsy indicate that generalized seizure are the most easily identifiable seizure presentations in the community [38][39]. Studies which reported higher prevalence of fo-

cal onset seizures also reported a higher incidence of acute symptomatic seizures in a malaria endemic area [40]. A multi-site population study in the country may help elucidate the distribution of epilepsy seizure types better.

Generalized epilepsy of unknown cause was the second most frequent type of epilepsy observed in this cohort. Other studies in Africa have also demonstrated that the cause of epilepsy can frequently be unknown [41][42][22]. Inability to determine the cause of epilepsy is largely due to financial and diagnostic limitations at the point of care [18]. Further, genetic and metabolic testing is not available locally and performance of these tests by overseas healthcare partners is associated with significant financial costs and time delays as has been our experience. This is particularly noteworthy when considering that Kenya's per capita GDP in 2016 was USD 1,410 [43], meaning that patients lacking medical insurance cover would struggle to access requisite tests such as the early infantile epileptic encephalopathy sequencing panel that costs USD 2000 on average.

Since generalized epilepsy of unknown cause was a frequent observation amongst patients in this cohort, as in other studies, and in light of potential benefits of determining the cause of epilepsy where possible, interventions to improve the quality of and access to local diagnostic facilities such as neuro-imaging, electroencephalography, metabolic and genetic testing would be beneficial to the management of epilepsy patients in sub-Saharan Africa.

Positive family history of febrile seizures in children who presented with atypical febrile seizures allowing a diagnosis of Genetic Epilepsy with febrile seizures plus was rarely determined in this cohort. This could be due to low rates of diagnosis of atypical febrile seizures in this setting or cultural reasons where families rarely discuss seizures in children openly due to associated stigma. Cultural reasons may also contribute to the predilection for more significantly male children presenting for care at this centre.

In this cohort we identified no children with childhood absence epilepsy(CAE) which being a common form of epilepsy, was an unexpected finding [40][44]. This is most likely due to under-recognition and lack of referral of such cases to the neurology teams. It is possible CAE is managed by paediatricians and being generally responsive to widely available first line ASMs, referral in such cases would not be required.

Critically, patients who are lost to follow-up are likely to remain untreated. Long-standing, untreated epilepsy has detrimental and enduring personal and social consequences, including impaired intellectual performance [31][32][33][34][35]. For these reasons, there is an urgent need to determine the reasons for defaulting on clinic follow-up [37]. Findings from these studies which may be applicable to other similar hospital settings would enable this institution to address these specific risk factors and potentially reduce the number of children with epilepsy who remain untreated.

Study limitations

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Table 3 Brain MRI findings in order of frequency

Brain findings	Total N = 208	Proportion of Cohort %
Normal	55	26.4
Brain atrophy	41	19.7
Cystic encephalomalacia	26	12.5
Mesial temporal sclerosis	20	9.6
White matter hyper intensities	16	7.7
Hydrocephalus	11	5.3
Benign enlargement of the subdural space	8	3.8
Periventricular leukomalacia	6	2.9
Agenesis of corpus callosum	6	2.9
Delayed myelination	4	1.9
Tuberous sclerosis complex (sub-ependymal nodules, harmatomas, calcifications)	3	1.5
Hemimegalencephaly	3	1.5
Meningeal enhancement	3	1.5
Holoprosencephaly	2	0.9
Schizencephaly	2	0.9
Lissencephaly	1	0.5
Polymicrogyria	1	0.5

N represents the number of study participants

Table 4 utilized in epilepsy management

Medication	N = 381	Proportion of cohort %
Valproic Acid	267	69.4
Phenobarbital	77	20
Clonazepam	80	20.8
Levetiracetam	46	11.9
Phenytoin	34	8.8
Vigabatrin	12	3.1
Carbamazepine	93	24.2
Lamotrigine	26	6.8
Topiramate	10	2.6
Pregabalin	1	0.3
Gabapentin	1	0.3
Clobazam	4	1

N represents the number of study participants

Findings presented here represent the context of an urban hospital and would be beneficial to the populations in similar contexts but would not be directly generalizable to most of the sub-Saharan African population who lack access to care and facilities of this nature. Cognitive, motor and behavioural outcomes for the different syndromes or seizure groups were not studied as this information was not measured in a standardised fashion for all the patients in the study population. This was a retrospective study and as such, missing data as well as other factors could impact on the quality of data generated. Future prospective studies in this area should make provision for two reviews of each laboratory investigation and plan to address inter-rater variance.

Conclusions

The study identified that males comprised the majority of paediatric epilepsy patients seen at this paediatric neurology service while LGS was the most common electroclinical syndrome. Generalized seizures associated with structural brain abnormalities were the most frequent form of epilepsy overall. Half of all EEGs performed displayed abnormalities including generalized spike wave discharges, focal spike wave discharges and slow background activity in decreasing occurrence respectively. Majority of patients had been treated with one ASM only, with valproic acid being most common utilized ASM. Psychiatric co-morbidities were more commonly identified in children with focal seizures while and those with Lennox Gastaut syndrome were more likely to present with developmental delay. The findings from this study hold significant relevance for the improved diagnosis and management of epilepsy among paediatric patients in urban SSA, including need for: greater preventive and diagnostic care predominantly targeting children in the 1 to 10 year age group; increased efforts to address patient attrition rates; and improvement of practitioner and public awareness of common forms of epilepsy to facilitate early detection and appropriate referral and management. This paper's contribution to existing research concerns its potential to address a dearth of recent studies conducted in sub-Saharan Africa describing electro-clinical syndromes or syndrome-associated outcomes among children in the region. Prospective studies may seek to explore precise relationships between specific syndromes and variable such as psychiatric and neuro-developmental co-morbidities and responses to anti-epileptic drugs.

Table 5 Diagnosis of patients lost to follow up

Diagnosis	N = 70	Proportion of cohort %
Focal seizures with loss of awareness	6	8.3
	5	7
Generalized epilepsies of unknown cause	39	55.7
Focal seizures	4	5.7
Epileptic spasms (West syndrome)	2	2.8
Generalized Seizures with structural brain abnormalities	4	5.6
	2	2.8
	1	1.4

N represents the number of study participants

Abbreviations

ADHD Attention deficity hyperactivity disorder

ASD Autism spectrum disorder

ASM Anti-seizure medication

CAE Childhood absence epilepsy

CECTS Childhood epilepsy with centro-temporal spikes

DALY Disability-adjusted life years

EEG Electroencephalogram

EMA Epilepsy with myoclonic astatis seizures

ILAE International League Against Epilepsy

JAE Juvenile absence epilepsy

JME Juvenile myoclonic epilepsy

LGS Lennox-Gastaut syndrome

LMIC Low and Middle Income Countries

MRI Magnetic resonance imaging

SSA Sub-Saharan Africa

WHO World Health Organization

Acknowledgements

Competing interests

Authors' contributions

PS designed the study. AB and SL analysed the patient data regarding the following variables: electroclinical syndromes, seizure types, patient gender, age at seizure onset, structural and electrophysiological brain abnormalities, medication history, co-morbidities, and other relevant medical and family history. KD, JW and CN were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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