SEIZURE CONTROL IN CHILDREN ON FOLLOW-UP AT KENYATTA NATIONAL HOSPITAL PAEDIATRIC NEUROLOGY CLINIC

A dissertation submitted in part fulfilment for the degree of Master of Medicine (Paediatrics and Child health), University of Nairobi.

Dr. Judith A. Amolo

M.B.Ch.B. (U.O.N.)

DECLARATION

I declare that this dissertation is my original work and has not been presented for a degree in any other university.

Signed _____ Date 14/10/2011

Dr. Judith A. Amolo

M.B.Ch.B. (U. O. N.)

This thesis has been submitted for examination with our approval as the university supervisors.

Prof. Ruth Nduati

M.B. Ch.B. M. Med (Paediatrics), MPH

Associate Professor, Chairman, Department of Paediatrics and Child Health

University of Nairobi

Signed _____ Date 17/10/2011

Dr. Donald Oyatsi

M.B.Ch.B, M.Med (Paediatrics), Dip Neurology (London)

Lecturer, Department of Paediatrics and Child Health

University of Nairobi

Signed _____ Date 17.10.2011

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to:

- First and foremost, my supervisors Prof. Ruth Nduati and Dr. Donald Oyatsi for their guidance, support, patience and valuable comments criticism throughout the study.

- All the children and their caregivers for their willingness to participate and patience during the study period.

- The staff of the KNH Paediatric Neurology Clinic for their cooperation during the course of the study period.

- My family for their support and encouragement.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AED – Anti-epileptic drug

CNS – Central Nervous System

EEG – Electroencephalogram

ILAE - International League against Epilepsy

IQR – Inter-quartile Range

KNH – Kenyatta National Hospital

R - Pearson correlation

WHO – World Health Organisation

DEFINITIONS

Epilepsy has been defined as two or more unprovoked seizures on different days in the year.

Idiopathic epilepsy refers to epilepsy with a presumed genetic basis that is not the result of some other brain abnormality.

Symptomatic epilepsy refers to epilepsy without an immediate cause in a patient with an identifiable prior brain injury such as major head trauma, birth trauma, congenital malformations, CNS infection or a static encephalopathy such as cerebral palsy or mental retardation that is known to be associated with increased risk of seizures

Cryptogenic epilepsy refers to epilepsy resulting from a probable underlying cause that is yet to be identified. The International League against epilepsy has recently renamed it probably symptomatic epilepsy.

Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Daily seizures refer to one or more seizures occurring daily.

Weekly seizures refer to one or more seizures per week occurring less than six days in a week.

Monthly seizures refer to one or more seizures per month but less than one seizure per week.

Good control refers to no seizures during the past 6 months while receiving the same antiepileptic drug or while not taking any medication.

Partial control refers to more than 50 % reduction in pre-treatment seizure frequency during the past 6 months.

Poor control refers to less than 50 % reduction in baseline pre-treatment frequency or intractable seizures during the past 6 months.

Favourable early response to antiepileptic drugs is defined as a 75 to 100 % reduction in the frequency of seizures within three months after the initiation of treatment.

Remission of epilepsy is defined as a seizure-free period of 5 or more consecutive years.

Refractory seizures refers to when seizures are so frequent or severe that they limit the patient's ability to live life fully according to his or her wishes or necessitate the use of medications that, although effective, produce adverse effects.

Seizure Freedom - Freedom from all types of seizures for 12 months or three times the pre-intervention interseizure interval, whichever is longer.

Febrile seizure refers to a seizure associated with an elevated temperature in a child younger than six years of age with no CNS infection or inflammation, no acute systemic metabolic abnormality and no history of previous afebrile seizures.

Simple febrile seizures are characterized by seizures that last less than 15 minutes, have no focal features, and, if they occur in a series, the total duration is less than 30 minutes.

Atypical febrile seizures last more than 15 minutes, have focal features or postictal paresis, and occur in a series with a total duration greater than 30 minutes

Cerebral palsy refers to a chronic non-progressive cerebral disorder in young children that results in impaired motor function.

Primary caregiver refers to the caretaker who is primary responsible for the child's physical, social and financial well-being.

ABSTRACT

Background: Recent studies in both developed and developing countries have shown that after 2 to 5 years of successful treatment with anti-epileptic drugs, drugs can be withdrawn in about 70% of children without relapses.

Objective: To determine prevalence of poorly controlled epilepsy and factors associated with poor seizure control among children on follow up at the Kenyatta National Hospital paediatric neurology clinic.

Results: Two hundred and four children were recruited into the study. The median age of was 5 years (IQR; 8 months to 12 years). Up to 14.7% (30) of children recruited into the study were poorly controlled. Partial seizures were associated with a higher risk of poorly controlled epilepsy, OR=14.3[(95% CI, 5.3, 37.3), p <0.05]. A family history of epilepsy was also associated with a significantly increased risk of poor seizure control, OR=5[(95% CI, OR 1.4, 17.3), p <0.05]. The odds of having cerebral palsy among children with poorly controlled epilepsy was OR=12.3 [(95% CI, 4.3, 35.5), p<0.05]

Conclusions: The prevalence of poorly controlled epilepsy was 14.7%. Partial seizures, increased number of pre-treatment seizures, family history of epilepsy and cerebral palsy independently predict the risk of poor seizure control.

Recommendations: Children at risk of intractable epilepsy should be identifying early in the course of their presentation so that they can be followed up closely and their caregivers better prepared to cope with their child's condition.

1. BACKGROUND AND LITERATURE REVIEW

Epilepsy is a chronic neurological disorder that affects people of all ages. It is defined by occurrence of two or more unprovoked seizures. It is characterized by recurrent seizures which are physical reactions to sudden, usually brief, excessive electrical discharges in a group of brain cells. Seizures can vary from the brief lapses of attention or muscle jerks, to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day. [1] Epilepsy is characterised by its episodic and chronic nature. The unpredictability of seizure recurrence is a constant threat to the patient with epilepsy and his or her family. [2] This condition has serious physical, psychological, social and economic consequences for the concerned persons and their families. [3]

According to the World Health Organisation around 50 million people worldwide have epilepsy with nearly 90% of the people with epilepsy found in developing regions. [1] The estimated number of children with epilepsy worldwide is 10.5 million. [4] In developed countries, annual new cases are 40 to 70 per 100,000 people in the general population. In developing countries, this figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage such as birth asphyxia, accidental injuries and CNS infections. [1]

In recent systematic reviews the lifetime prevalence rates for active epilepsy varied from 5.2 to 74.4 per 1,000 person years in sub-Saharan Africa. [5] Data from developing countries notably Africa is incomplete. Kaamugisha et al found a prevalence of 18.2 per 1000 in a study population of 2960 with 64.8% under the age of 20 years. [6] A three phase community screening survey of 151,408 individuals in Kilifi District showed overall prevalence of active convulsive epilepsy to be 4·5 per 1000 in a population of 153,291. Generalised tonic clonic seizures were found to be the predominant type occurring in 70.4% of subjects. [7]

In 1981, The International League against Epilepsy developed an international classification of epileptic seizures. This classification is still widely accepted. The diagnosis of epilepsy involves determining the cause, the type of seizures and epileptic syndrome. Of these three, the type of seizure has the most important influence on therapy. The medical history and EEG define the epileptic syndrome and the type of seizure but must be interpreted cautiously so that diagnostic errors are not made. Focal epileptiform activity (spikes and sharp waves) or slowing of activity on the EEG supports a diagnosis of partial epilepsy, and generalized

spike-and wave discharges with a frequency of 3 Hz or greater strongly suggest primary generalized epilepsy.

Aetiology and risk factors for epilepsy

Several causes and risks factors for epilepsy have been identified. The causes of epilepsy can be classified into 3 general aetiological groups; idiopathic, symptomatic or cryptogenic. [1, 3] Idiopathic epilepsy accounts for 60 per cent of cases. It is the threshold, which determines the susceptibility of individual brain cells to generate seizures in response to epileptogenic perturbations. They are usually benign and often remit spontaneously or after uninterrupted pharmacological treatment with anti-epileptic drugs. [3]

Symptomatic epilepsy is related to a specific epileptogenic abnormality, which could be an acquired lesion of the brain, congenital malformations of the brain or genetic disorders. These epilepsies are very common in developing countries, where they are responsible for the difference in terms of prevalence and prognosis. Risk factors are dominated by perinatal insults, head trauma, and intracranial infection. Their control requires, in addition to anti-epileptic drugs, specific care of the aetiology (medical and/or neurosurgical). [3] Cryptogenic epilepsy is presumed to be due to an underlying but unidentified focal abnormality on the basis of clinical information and study results. [3]

Table 1: Reported causes of seizures and epilepsy in regards to the age of onset in sub-Saharan Africa [3]

0 – 4 months	**4 months – 2 years**	**2 – 10 years**
Neonatal asphyxia	Sequel of previous causes	Sequel of previous causes
Perinatal trauma	Infections	Idiopathic generalized epilepsy
Infections	Vascular causes	Infections
Cerebral malformations	Inborn errors of metabolism	Post-traumatic epilepsy
Subdural haematomas	West syndrome	Intoxication
Hypoglycaemia		Lennox-Gastaut syndrome
Hypocalcaemia		Inborn errors of metabolism
Inborn errors of metabolism		Primary tumours

Infections that can cause epilepsy include encephalo-meningitis (HIV, bacterial, viral), septicaemia, malaria, other parasites (toxoplasmosis, neurocysticercosis, amoebiasis,

trypanosomiasis, nematodosis, trematodosis) and possibly onchocerciasis. [3, 8] A study in Kilifi, Kenya identified history of febrile seizures, family history of seizures, birth difficulties and neonatal insults to be significantly associated with development of lifetime epilepsy. [9] Two to five per cent of all children below the age of 5 years experience febrile seizures. Atypical febrile seizures are associated with a higher risk for epilepsy. The factors which predict subsequent development of epilepsy among children with febrile seizures include: low Apgar score; neurological abnormalities before first febrile seizure; focal, recurrent or prolonged seizures; postictal paralysis, and family history of epilepsy. Febrile seizures and epilepsy should be considered independent outcomes of a common antecedent. [10]

Seizure Control

According to the World Health Organisation recent studies in both developed and developing countries have shown that up to 70% of newly diagnosed children and adults with epilepsy can be successfully treated (i.e. their seizures completely controlled) with anti-epileptic drugs and drugs withdrawn after 2 to 5 years without relapses. [1] Several anti-epileptic drugs are available for the control of seizures in children with epilepsy. In developing countries, choice of anti-epileptic drugs is influenced to a considerable extent by cost and availability. [11] The most prescribed anti-epileptic drugs in Africa are phenobarbital and phenytoin. These two drugs are the cheapest and are prescribed in 65% to 85% of treated epileptic patients. Carbamazepine is the third cheapest drug, and is prescribed in only 5 to 20% of reported treated cases. Sodium Valproate is prescribed in 5 to 15%, but is less widely available and the annual costs are also much higher than those of the aforementioned drugs. [3]

Although the prognosis for the majority of patients is good up to 30 % do not have remission despite appropriate therapy with antiepileptic drugs; the results are substantial deleterious effects on individual's health and quality of life and a heavy burden on society. [12] Despite state-of-the-art medical management with modern anti-epileptic drugs, most of these patients continue to have drug-resistant epilepsy with frequent debilitating seizures and severe consequences such as increased mortality. [13] Epilepsy increases a person's risk of premature death by about two to three times compared to the general population. [1]

Treatment with a single anti-epileptic drug has been the gold standard in epilepsy treatment for the past 20 years. However, up to one third of patients do not achieve sufficient seizure control with a single anti-epileptic drug. Usually a drug given as monotherapy is titrated to a maximally tolerated dose before the decision is made to try another drug. If two drugs have

thus been unsuccessful as monotherapy, the patient is given anti-epileptic drug polytherapy in an attempt to improve effectiveness. Effectiveness has been defined as a measure encompassing both efficacy (i.e., seizure control) and tolerability. A combination can improve effectiveness by improving efficacy, tolerability, or both. [14]

An epidemiological review of natural history of epilepsy found that prognosis of newly diagnosed epilepsy may be broadly classified into 3 groups reflecting the underlying neurobiological process. In the first group with an excellent prognosis where 20 to 30 % of patients lie, the condition enters long term remission after a variable period of time and level of activity. If treated this patients become seizure free on the first and second monotherapy often requiring no more than moderate doses which can be successfully withdrawn after a period of seizure freedom. It is therefore possible that among the 30% of newly diagnosed patients who are able to remain in remission after eventual drug withdrawal, the epileptogenic process has remitted spontaneously, regardless of treatment. [15, 16]

The primary aim of antiepileptic drug treatment, if indicated, in this group of patients is to suppress seizures until ‘‘spontaneous’’ remission occurs, as seizures themselves are not benign and may cause considerable morbidity or even mortality. Epilepsy syndromes that fall into this category include benign neonatal seizures, benign rolandic epilepsy, and childhood absence epilepsy. [17]

The 20–30% of patients comprising the second group remain seizure-free only with continuing antiepileptic drug treatment. Some may require more than one antiepileptic drug and multiple attempts may be needed to find the right combination for the individual patient. Continuing antiepileptic drug treatment is required to suppress seizure relapse. Examples of this group may include juvenile myoclonic epilepsy, and the bulk of the localisation related epilepsies. [15]

In the remaining 30–40% of patients, seizures recur in varying degrees of intensity and frequency despite antiepileptic drug treatment. Antiepileptic drug treatment can at best only ameliorate the severity or frequency of seizures. Conditions in this category include many symptomatic/cryptogenic localisation related epilepsies, progressive myoclonic epilepsies, and West syndrome. [15]

Recent outcome studies suggest that medical intractability may be predicted after failure of two antiepileptic drugs. Poor prognostic factors include a high initial seizure density,

symptomatic or cryptogenic aetiology, and presence of structural cerebral abnormalities, all of which can be identified early on. [15] Other unfavourable prognostic factors include an early onset of epilepsy, multiple types of seizures, complex febrile seizures or febrile status epilepticus, and generalized epileptiform activity on surface electroencephalography. [12]

A study in Finland found 67% of patients achieved terminal remission while 33% were found to be antiepileptic drug resistant. Up to 31% of these patients were free of seizures within the first year of treatment. Medication was discontinued in 91% within 4 years. The most important predictors of being seizure-free for at least five years were a rapid response to therapy and a diagnosis of idiopathic seizures. [17] A study by Schimdt found that those patients who are seizure-free at 6 months have a 90% chance of being seizure-free at 12 months, whereas those not seizure-free at 6 months have only a 45% chance of being seizure-free at 12 months. The main conclusion is that response at 6 months is an excellent predictor of response at 12 months. [18]

In a study of 1,017 children in South Africa acceptable seizure control was maintained with a single standard antiepileptic drug in 65% of cases. In children on two anti-epileptic drugs 29% achieved good seizure control while 19% of cases in children on three anti-epileptic drugs achieved control. In this study 43% of these children had historic, clinical and radiological evidence to suggest that epilepsy was symptomatic of underlying brain damage or defect. Best seizure control was achieved in children with granulomata and poor control observed in those who had suffered damage as a result of metabolic derangement in early infancy. [19]

A study in Glasgow, Scotland among 525 patients found 63% remained seizure-free during antiepileptic-drug treatment or after treatment was stopped. Among previously untreated patients, 47% became seizure-free during treatment with their first anti-epileptic drug and 14 % became seizure-free during treatment with a second or third drug. The prevalence of persistent seizures was higher in patients with symptomatic or cryptogenic epilepsy than in those with idiopathic epilepsy and in patients who had had more than 20 seizures before starting treatment than in those who had had fewer. [12]

A study by Mativo in KNH, in the adult epilepsy population found that 60.9% were well controlled compared to 39.1% who were poorly controlled. In a community based study in Kenya, 249 untreated patients completed a treatment programme with either carbamazepine or phenobarbital monotherapy for 12 months. Although 53% of the patients had had recurrent

seizures for over five years and 68% had had more than 10 seizures in the year before recruitment, altogether 53% were seizure-free in the last six months of treatment. This is one of the few studies where there was no association between good seizure control and either the duration of epilepsy or the total number of lifetime seizures in this cohort. [16]

When people with epilepsy continue to have frequent seizures despite multiple drug therapy, epilepsy surgery may be indicated. In many parts of the world, epilepsy centres are performing surgery routinely with good results in those selected from the 25% of people with epilepsy who do not benefit from drug therapy and who are candidates for such operations. Other alternatives to surgery are vagus nerve stimulation and use of a ketogenic diet especially in children with drug-resistant epilepsy. Although it is expensive and difficult to tolerate, reduction in seizures frequency have been reported with the ketogenic diet. [3]

2. STUDY JUSTIFICATION AND UTILITY

Epilepsy is one of the most common neurological disorders in sub-Saharan Africa. The main disturbance, seizures appear episodically but they can impair the quality of life and can absolutely change the whole lifestyle of a patient and his family. Recent studies have shown that seizures can be controlled in 60 to 70% of persons with epilepsy using anti-epileptic drug therapy. Several factors including the rapid response to a single anti-epileptic drug, aetiology of the seizure, seizure frequency, age at onset, caregiver perceptions have been shown to influence seizure control in children.

Local studies on the level of seizure control and factors associated with poor seizure control in children with epilepsy on follow-up at KNH paediatric neurology clinic are few. The study evaluated the level of control achieved with various anti-epileptic drugs and factors associated with poor seizure control.

3. STUDY OBJECTIVES

Primary Objective

- To determine prevalence of poorly controlled epilepsy among children on follow up at KNH paediatric neurology clinic.

Secondary Objectives

- To determine the correlates of poor epileptic seizure control in children.

4. STUDY METHODOLOGY

4.1.Study Design

A hospital based descriptive cross-sectional study was carried out.

4.2.Study Area

The study was carried out in the KNH paediatric neurology clinic. KNH serves as a teaching hospital for the University of Nairobi and is a National Referral Hospital for the whole country. It is also the provincial hospital for Nairobi and serves approximately two million people in Nairobi. According to the 2009 KNH medical records 2,262 children with neurological problems were seen in the paediatric neurology clinic. It was purposively chosen because it is one of the few centres in Nairobi with paediatric neurologists where majority of children with epilepsy are eventually referred after diagnosis. It also serves as a referral centre for rural areas of the country where children with poorly controlled epilepsy are referred for further specialised treatment. This may create a bias in that children residing in rural areas are found to have poorly controlled epilepsy. Due to limited time and resources only KNH was chosen for the study. The clinic is run every Tuesday afternoon. Paediatric neurologists are available every week to review children with various neurological conditions including epilepsy.

4.3.Study Population

The study population comprised of children less than 12 years with a confirmed diagnosis of epilepsy and a history of continuous use of antiepileptic drugs for at least 6 months. Epilepsy has been defined as two or more unprovoked seizures on different days in the year.

4.4.Inclusion Criteria

- Children aged less than 12 years with a physician diagnosis of epilepsy.
- Children whose parents/ guardians gave informed consent.

4.5.Exclusion Criteria

- Children on treatment for less than 6 months

4.6.Operational Definitions

Epilepsy has been defined as two or more unprovoked seizures on different days in the year.

Good seizure control refers to no seizures during the past 6 months while receiving the same antiepileptic drug or while not taking any medication.

Partial seizure control refers to more than 50% reduction in pre-treatment seizure frequency during the past 6 months.

Poor seizure control refers to less than 50% reduction in baseline pre-treatment frequency or intractable seizures during the past 6 months.

4.7.Sample Size Determination

According to the 2009 KNH medical records 2,262 children with neurological problems were seen in the paediatric neurology clinic. [20] Of these 60% were old patients. Sample size was determined by the formula for sampling proportions for a finite population. [21]

$$n = \frac{Z^2 N\, p\,(1-p)}{d^2\,(N-1) + z^2\, p(1-p)} = \frac{1.96^2 \times 678 \times 0.3(1-0.3)}{0.05^2(769-1) + 1.96^2 \times 0.3(1-0.3)} = 219 \text{ children}$$

- n is the required sample size
- N is the population size. Among the 2,262 children with neurological problems seen in the paediatric neurology clinic 60% were old patients. Based on a study in Ghana it was estimated that 51.5 % of old patients were on follow-up for epilepsy therefore 678 was used in this study. [22]
- p is the population proportions – 30% of patients with uncontrolled epilepsy
- z is the Normal Standard Deviation taken with a confidence level of 95%, Confidence Interval is set to 1.96
- d refers to the margin of error in this case 0.05

4.8.Data Collection

Data for the study was collected between June 2010 and January 2011. KNH paediatric neurology clinic is held weekly on Tuesday afternoon. The interviewer visited the KNH paediatric neurology during the morning preceding the clinic and examined files of patients booked for clinic. Potential study participants were selected by screening patient files for diagnosis of any seizure disorder. Patients were then recruited while waiting for their routine check-up.

The principal investigator approached identified patients to determine if they met eligibility criteria for the study. The interviewer introduced herself and explained to the potential study participants the purpose and methods of the study. Informed voluntary verbal and written consent using a predesigned consent form was sought from the parent. The interviewees were

assured of confidentiality of the data and requested to answer questions truthfully. All children who were eligible and met the inclusion criteria were recruited by consecutive sampling until the minimal sample size was reached.

Data was collected using a structured pre-tested questionnaire. The questionnaire was administered by the principal investigator or her research assistants who will filled out responses. The questionnaire assessed the following:

- Child's and parent's socio-demographic data (age, gender, residence, religion, education level, income)
- Clinical profile including age at onset, age at diagnosis, initial seizure frequency and duration, type of seizures, aetiology and risk factors
- Antiepileptic drug treatment and level of adherence
- Current level of seizure frequency and duration

4.9.Data Management and Analysis

Data was coded, cleaned, verified and analysed using SPSS (Statistical Package for Social Sciences) computer version 17.0 and Microsoft Excel 2007.

Categorical data assessed included patient's age, gender and residence, caregiver's marital status, level of education and occupation, type of seizures, aetiology and risk factors associated with seizures, antiepileptic drug treatment, level of seizure control, caregiver's perception on epilepsy and level of control. Quantitative or continuous data included patient's and caregiver's age, age at diagnosis of epilepsy, age at onset of seizures, duration of treatment with antiepileptic drugs, seizure frequency and seizure duration.

Prevalence of epilepsy was determined by simple proportion. Children with good seizure control were compared to those with poor control for socio-demographic and clinical characteristics to determine the univariate correlates of poor control. Categorical data was tabulated. Mean, median and standard deviation was used to summarise the data. Statistical testing was done using Chi square test for categorical variables and for continuous data comparisons of means and medians was be done using Student's t test and Mann Whitney U test respectively. Tests of associations were performed using Chi-square test for categorical variables. Logistic regression analysis with inclusion of variables found to be significant was carried out to determine independent determinants of poor epilepsy control. Data is presented using pie charts, histograms and tables.

4.10. Ethical considerations

- Approval to carry out the study was sought and received from KNH Ethics and Research Committee.
- Informed verbal and written consent to participate in the study was obtained from the parent or guardian accompanying the child to the clinic after explanation of the study and voluntary nature of participation. Caregivers were informed that refusal to participate in the study would not affect treatment of their child.
- Confidentiality was maintained.
- Any information pertinent to the management of the child discovered during the interview was communicated to the attending physician.
- No child suffered delayed treatment as a result of the study.
- Study participants did not incur any extra cost as a result of the study.

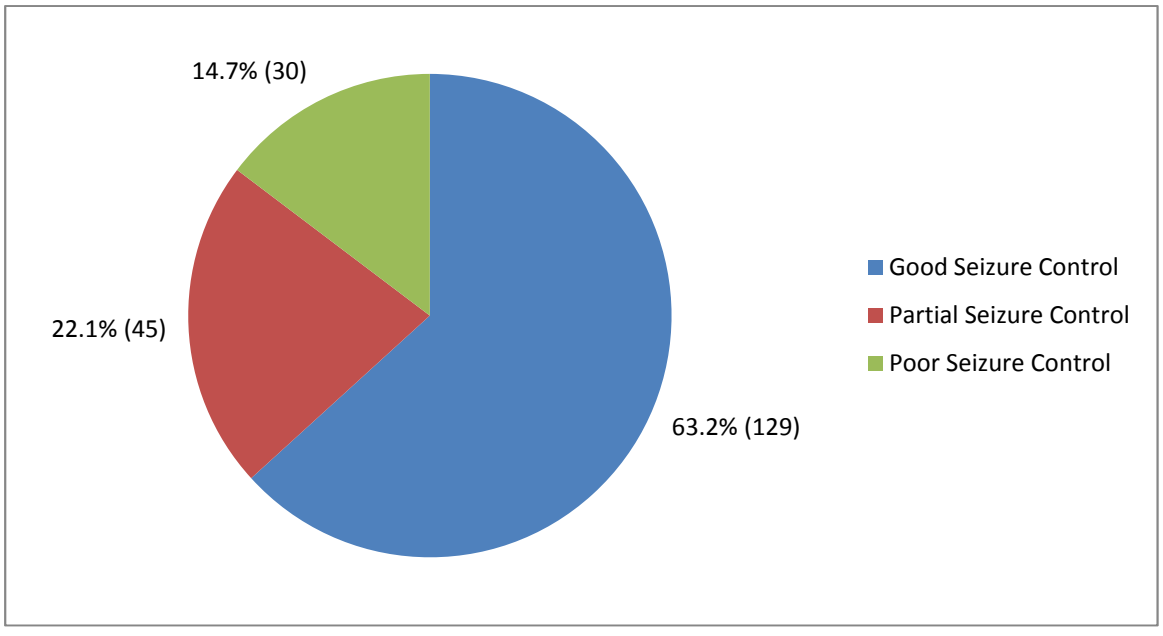
5. RESULTS

A total of 204 children on follow-up at the Paediatric Neurology clinic were recruited into the study. The median duration of follow-up of children in this study was 2 years. This chapter presents results of the demographic characteristics of both children with epilepsy and their caregivers as well as seizure and clinical characteristics seen in children with epilepsy. Information on anti-epileptic drug treatment is also provided. Correlation of the above factors with level of seizure control is also given. Children with good seizure control were compared to children with poor seizure control to determine factors associated with poor seizure control. Children who were partially controlled were excluded in the analysis as the aim of the study was to correlate factors associated with poor seizure control when compared with children who were well controlled.

5.1.Level of Seizure Control

Up to 63.2% (129) of the children recruited into the study were well controlled. At least 22.1% (45) were partially controlled while 14.7% (30) were poorly controlled.

Figure 1: Level of Seizure Control



At least 63.2% (129) of the children recruited had no seizures in the last 6 months during the study while 16.2% (33) of children had more than 11 seizures. Up to 20.6% (42) had 1 to 10 seizures in the last 6 months of follow-up. The mean duration of freedom from seizures was

12 months. At least 34.8% (71) and 13.2% (27) of children had a seizure free period of 7 months to 1 year and, 1 to 2 years respectively. Children who were seizure free for more than 1 year accounted for 15.2% (31) of patients recruited.

Table 2: Level of seizure control and duration of follow-up and treatment

Variable	**Level of Control**	
	Poorly Controlled (N=30)	**Well Controlled (N=129)**
Median duration of follow-up (months)	36 (6-132)	24 (7-120)
Median duration of treatment (months)	42 (10-132)	36 (8-132)

5.2. Socio-demographic characteristics of study population

Table 3 presents the socio-demographic characteristics of the children and their caretakers. The median age of the children recruited into the study was 5 years with a range from 8 months to 12 years. Children less than one year accounted for 2% (4) of the study population, 43% (87) aged 1 – 4 years, 35% (72) between 5- 8 years and 20% (41) were 9 – 12 years. There were slightly more males than females 54.9% (112) versus 45.1 % (92). Overall 79.9% (163) of the children resided in an urban area.

Table 3: Socio-demographic characteristics of the study population

Characteristics	**N = 204 (%)**
Children	
Age distribution	
Less than 1 year	4 (2.0%)
1–4 years	87 (42.6%)
5- 8 years	72 (35.3%)
9- 12 years	41 (20.1%)
Sex	
Male	112 (54.9%)
Female	92 (45.1%)
Residence	
Urban	163 (79.9%)
Rural	41 (20.1%)

Primary caregivers	
Age distribution	
20 – 30 years	106 (52.0%)
30-40 years	88 (43.1%)
41 – 50 years	10 (4.9%)
Marital status	
Currently single	23 (11.3%)
Currently married	181 (88.7%)
Level of education	
Any primary education	18 (8.8%)
Any secondary education	152 (74.5%)
Post-secondary education	34 (16.7%)
Occupation	
Salaried formal employment	30 (14.7%)
Informal employment	85 (41.7%)
Self-employment	27 (13.2%)
Unemployed	62 (30.4%)

The median age of the primary caregivers was 30 years with a range of 21 to 47 years, 52% (106) were aged 21 to 30 years, 43.1% (88) between 31 and 40 years and 4.9% (10) aged between 41 and 50 years. Only 11% (23) of the care providers were currently single. All care-givers were literate with 74.5% (152) having secondary education, 16.7% (34) post-secondary education and 8.8% (18) having primary education. Up to 41.7% (85) of the caregivers were in informal employment, 14.7% (30) on salaried jobs, 13.2% (27) on self-employment and 30.4% (62) unemployed.

5.3.Relationship between level of seizure control and socio-demographic characteristics of study population

The thirty children who were poorly controlled were compared to the one hundred and twenty nine with good control. An equal proportion of children with poorly controlled and well controlled epilepsy were under 5 years of age at 53.3% (16) vs. 53.5% (69) while 20 (66.7%) of poorly controlled children were male as compared to 65(50.4%) of well controlled children. The odds of a male child having poorly controlled epilepsy was OR = 2[95%, 0.9,

4.5], p >0.05 a statistically non-significant difference. A higher proportion of poorly controlled children with epilepsy were living in rural areas as compared to well controlled children at 14(46.7%) of 30 compared to 16 (12.4%) of 129. Children residing in rural areas were more likely to have poorly controlled epilepsy, OR= 6.2[95%, 2.6, 14.9)] p <0.05, a statistically significant association.

An almost equal proportion of children with poorly controlled epilepsy had caregivers who were currently single 10.0% (3) as compared to well controlled children 11.6% (15). The association between marital status of primary caregiver and poor seizure control was not statistically significant, p >0.05. The proportion of primary caregivers of children with poorly controlled epilepsy educated until primary level was 13.3 % (4) compared to 7.0% (9) among well controlled children. A slightly higher proportion of caregivers of children with well controlled epilepsy had secondary education at 76.7% (99) compared to 70.0% (21) among poorly controlled children. An equal proportion of primary caregivers of children with poorly controlled epilepsy had post-secondary education as compared caregivers of well controlled children at 16.7 % (5) compared to 16.3% (21). There was no significant association between level of education and poor seizure control, p >0.05.

Compared to salaried employment, care takers in informal employment, self-employment and unemployed had a 4-6 fold increased likelihood of having a child with poorly controlled epilepsy, OR= 4.3[95%, 0.8, 30.1), OR=5[95%, 0.7, 35.9] and OR= 6.3[95%, 1.0, 4.0] respectively. The increased likelihood was not significant, p >0.05.

Table 4: Socio-demographic characteristics and level of seizure control

	Level of Control		**OR (CI 95%)**	**P Value**
	Poorly Controlled (N=30)	**Well Controlled (N=129)**		
Age of Child				
Less than 5 years	16 (53.3%)	69 (53.5%)	1.0	
6 to 12 years	14 (46.7%)	60 (46.5%)	1.0 (0.4-2.4)	0.988
Sex of child				
Male	20 (66.7%)	65 (50.4%)	2.0 (0.8-4.9)	0.107
Female	10 (33.3%)	64 (49.6%)	1.0	

Residence				
Rural	14 (46.7%)	16 (12.4%)	6.2 (2.3-16.5)	0.000
Urban	16 (53.3%)	113 (87.6%)	1.0	
Caregiver Marital Status				
Currently Married	27 (90.0%)	114 (88.4%)	1.2 (0.3-5.6)	0.800
Currently Single	3 (10.0%)	15 (11.6%)	1.0	
Caregiver Education level				
Primary	4 (13.3%)	9 (7.0%)	1.9 (0.3-11.0)	0.420
Secondary	21 (70.0%)	99 (76.7%)	0.9 (0.3-3.1)	0.834
Post-secondary	5 (16.7%)	21 (16.3%)	1.0	
Caregiver Occupation				
Salaried formal	1 (3.3%)	20(15.5%)	1.0	
Informal employment	14 (46.6%)	58(45.0%)	4.8 (0.6-104.6)	0.107
Self-employment	4 (13.3%)	16(12.4%)	5.0 (0.4-130.1)	0.136
Unemployed	11 (36.7%)	35(27.1%)	6.3 (0.7-139.8)	0.058

5.4.Primary caregiver expectations on epilepsy

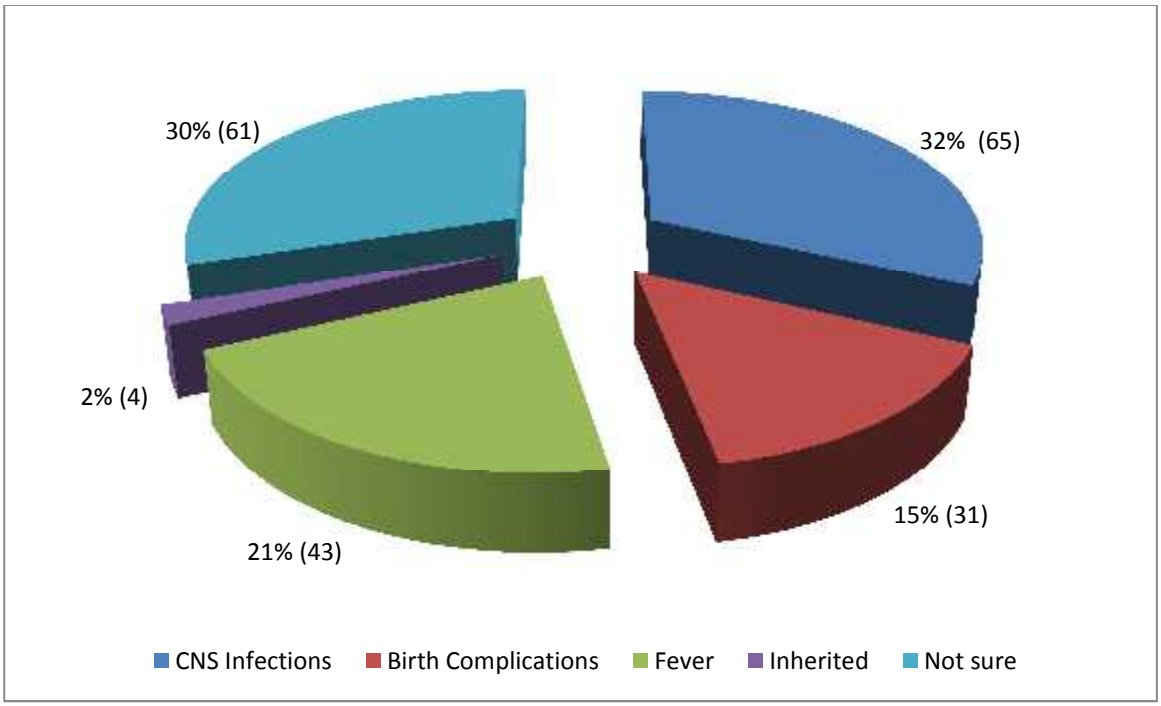
5.4.1. Expectations from anti-epileptic drugs

About 94.1% (192) of primary caregivers expected eventual cure from epilepsy following anti-epileptic drug use. One primary caregiver had sought herbal treatment for their child's epilepsy while thirty two primary givers had sought religious intervention as a means to seizure control. Up to 20.6% (42) of caregivers expected their children would be able to fully participate in school and social events. Only about 4.4% (9) of parents were not sure what to expect from anti-epileptic drug use.

5.4.2. Perceived cause of epilepsy

Primary caregivers has a wide range of perceived causes of their children's epilepsy ranging from central nervous system infections 31.9% (65), birth complications 15.2% (31), fever 21.1% (43) and inherited conditions 2% (4). At least 29.9% (61) were not sure what may have caused the seizures. Figure 2 below shows the perceived causes of epilepsy among primary caregivers.

Figure 2: Perceived Cause of Epilepsy



5.5.Seizure Characteristics

Table 5 presents characteristics of the seizures experienced by the study population. The median age of onset of seizures in children was 1 year with a range of 1 day to 10 years. The age at onset was before 2 months for 14.7% (30) children, between 3 and 6 months for 10.8% (22), 6 months and 5 years of age for 68.6% (140) and, 5.9 % (12) in the period 6 to 10 years of age.

The majority of children were classified as having generalised seizures accounting for 78.9% (161), while partial seizures and unclassified seizures accounted for 20.1% (41) and 1.0% (2) of the study population. In this population seizure treatment was initiated relatively soon after onset of the seizures with 55.4% (113) of the children having less than 5 seizures at initiation of therapy, 16.7% (34) had 6-10 seizures while 5.4% (11) range of 11-20 seizures and only 22.5% (46) had experienced more than 20 seizures at initiation of therapy. Before treatment onset 27.5% (56) of the children had daily seizures, 13.7% (28) weekly seizures, 34.3% (70) monthly and the remainder 24.5% (50) seizures more than one month apart. Duration of seizures varied with 95.6% (195) of the children reporting initial seizures lasting less than 5 minutes and 4.4 %(9) prolonged duration in excess of five minutes.

Table 5: Seizure Characteristics

Variable	N = 204 (%)
Age at onset of seizures	
Less than 2 months	30 (14.7%)
3 – 6 months	22 (10.8%)
6 months - 5 years	140 (68.6%)
6 - 12 years	12 (5.9%)
Type of seizure	
Generalised	161 (78.9%)
Partial	41 (20.1%)
Unclassified	2 (1.0%)
Number of seizures before initiation of treatment	
< 5	113 (55.4%)
6-10	34 (16.7%)
11-20	11 (5.4%)
>21	46 (22.5%)
Frequency of Seizures	
Daily	56 (27.5%)
Weekly	28 (13.7%)
Monthly	70 (34.3%)
>1 Monthly	50 (24.5%)
Duration of seizure	
≤ 5 minutes	195 (95.6%)
>5 minutes	9 (4.4%)

5.6. Relationship between level of seizure control and seizure characteristics of study population

A higher proportion of study participants with poorly controlled epilepsy had their first seizure before the age of 2 months as compared to well controlled children at 46.7% compared to 3.9%. Study participants who had their first seizure before 2 months of age were 4.2 [95% CI, 0.4, 54.1] times more likely to have poorly controlled epilepsy. This was

however not statistically significant p >0.05. A much higher proportion of children with well controlled epilepsy (93.8%) had their first seizure between 3 months and 5 years of age as compared to poorly controlled children (46.7%). There was a statistical difference between these two groups, p <0.05. An almost similar number of well controlled (2.3%) and poorly controlled (6.7%) children had their first seizure between 6 and 12 years of age.

Among children who were well controlled a higher proportion had less than 10 seizures at initiation of treatment as compared to poorly controlled children at 89.9% (116) compared to 6.7% (2). An almost similar proportion of well controlled children had 11 to 20 seizures at initiation of treatment as compared to poorly controlled children at 4.7% (6) and 10.0% (3) respectively. Children with more than 21 seizures at initiation of treatment had a 200 fold increased chance of poorly controlled epilepsy compared to well controlled children at 83.3% (25) versus 5.4% (7), OR=207[(95% CI, 35.7, 1603.7), p=0.000]. Among children with 11-20 seizures at initiation of therapy the odds of having poorly controlled epilepsy was OR=29[(95% CI, 3.1, 324.7), p=0.000]. More than 11 pre-treatment seizures had a significant association with poor seizure control, p <0.05.

A higher proportion of children with well controlled epilepsy had generalised seizures at 91.5% (118) as compared to poorly controlled children at 42.9% (12). Partial seizures were associated with a higher risk of poorly controlled epilepsy, OR=14.3[(95% CI, 5.5, 37.3)] which was a statistically significant association, p <0.05. An equal proportion of children with poorly controlled and well controlled epilepsy had seizure duration of less than five minutes at 66.7% (20) and 65.9% (85) respectively. One third (10) of children with poorly controlled epilepsy had seizure duration of more than five minutes as compared to well controlled children at 30.2% (44). Duration of seizure was not statistically significant when associated with poor seizure control (p >0.05).

Table 6: Seizure characteristics and level of seizure control

Variable	Level of Control		OR (95% CI)	P value
	Poorly Controlled (N=30)	Well Controlled (N=129)		
Age at onset of seizures				
<2 months	14 (46.7%)	5(3.9%)	4.2 (0.4-54.1)	0.155
3 months – 5 years	14 (46.7%)	121 (93.8%)	0.2 (0.0-1.6)	0.041
6 – 12 years	2 (6.7%)	3 (2.3%)	1.0	
Number of pre-treatment seizures				
< 10	2 (6.7%)	116 (89.9%)	1.0	
11-20	3 (10.0%)	6 (4.7%)	29.0 (3.1-324.7)	0.000
>21	25 (83.3%)	7 (5.4%)	207.1 (35.7-1603.7)	0.000
Type of seizure				
Partial	16 (57.1%)	11 (8.5%)	14.3 (4.9-42.8)	0.000
Generalised	12 (42.9%)	118 (91.5%)	1.0	
Duration of seizure (minutes)				
Less than 5 minutes	20 (66.7%)	85 (65.9%)	1.0	
More than 5 minutes	10 (33.3%)	44 (30.2%)	1.0 (0.4-2.6)	0.936

5.7.Clinical Characteristics of Children with Epilepsy

Family history of epilepsy was uncommon in this study population. Only 12 children had a family history of epilepsy of whom 2 (1%) had a first degree relative suffering from epilepsy while 10 children (4.9%) reported seizures in second degree relatives. A history of febrile convulsions was reported in 55 children (27%). At least 18.1% (37) of the study population had a history of perinatal complications. Cerebral palsy and delayed milestones were seen in 20.6% (42) and 25% (51) of the recruited children respectively. Among the children with delayed milestones 82.4% (42) had cerebral palsy. CNS infections including cerebral malaria and meningitis prior to the onset of seizures were reported in 11.3% (23) of the children. None of the study participants had a history of major head injury.

Table 7: Clinical Characteristics of children with Epilepsy

Characteristics	**N = 204 (%)**
Family history of epilepsy	
None	192 (94.1%)
First degree relative	2 (1.0%)
Second degree relative	10 (4.9%)
History of febrile convulsions	55 (27.0%)
Perinatal Complications	37 (18.1%)
Cerebral Palsy	42 (20.6%)
Delayed Milestones	51 (25.0%)
CNS Infections	23 (11.3%)
Head Injury	0 (0%)

5.8. Relationship between level of seizure control and clinical characteristics of the study population

A higher proportion of children with poor seizure control had a family history of epilepsy compared to well controlled children, 16.7% (5) versus 3.9% (5), a significantly increased risk OR=5 [(95% CI, 1.1, 21.8), p=0.01]. Febrile convulsions occurred in 38% (49) of well controlled children. None of the children with poorly controlled epilepsy gave a history of febrile convulsions as compared to 38% (49) of children with well controlled epilepsy. At least 36.7% (11) of poorly controlled children had reported perinatal complications as compared to 10.9% (14) of well controlled children. This difference was significant with children with poor seizure control having a more than fourfold increased likelihood of reporting perinatal complications, OR= 4.8 [(95% CI, 1.7, 13.3), p=0.000].

Prevalence of cerebral palsy was noted in 53.3% (16) of children with poorly controlled epilepsy compared to 8.5% (11) of well controlled children. The odds of having cerebral palsy among children with poorly controlled epilepsy was OR=12.3 [(95% CI, 4.3, 35.5), p=0.000] a significantly increased risk. Delayed or regressed milestones were seen in 60.0% (18) of well controlled children compared to 12.4% (16) of poorly controlled children, OR=10.6 [(95% CI, 4.0, 28.9), p=0.000] a statistically increased risk.

Previous history of CNS infections was reported in a higher proportion of children with poorly controlled epilepsy as compared to well controlled children, 20% (6) versus 8.5% (11). CNS infections were associated with a higher risk of poorly controlled epilepsy OR=2.7 [(95% CI, 0.8, 8.9), p=0.067] an important statistical trend.

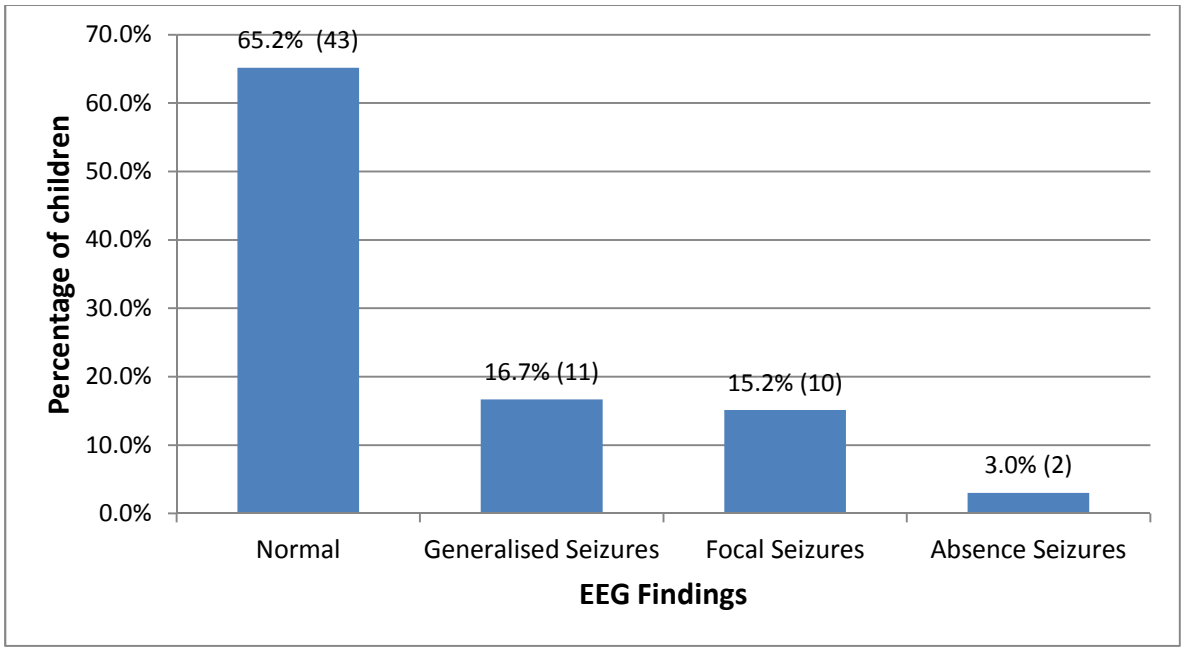
Table 8: Clinical characteristics and level of seizure control

Variable	Level of Control		OR (95% CI)	P Value
	Poorly Controlled (N=30)	Well Controlled (N=129)		
Family history of epilepsy	5 (16.7%)	5 (3.9%)	5.0 (1.1-21.8)	0.009
Perinatal Complications	11 (36.7%)	14 (10.9%)	4.8 (1.7-13.3)	0.000
Cerebral Palsy	16 (53.3%)	11 (8.5%)	12.3 (4.3-35.5)	0.000
CNS Infections	6 (20.0%)	11 (8.5%)	2.7 (0.8-8.9)	0.067
Delayed Milestones	18 (60.0%)	16 (12.4%)	10.6 (4.0-28.9)	0.000
Febrile convulsions	0 (0%)	49 (38.0%)	-	-

5.9.Electroencephalography (EEG) And Computerised Tomography (CT Scan) Head Findings

Although EEG and CT scans are available, only 32.4% (66) of the study population had an EEG reading while 46.1% (94) had CT Scans of the Head. Of the study population 45.1% (92) children did not have an EEG or CT scan done. Among the 66 children with EEG evaluation 43 (65.2%) had a normal EEG, 11 (16.7%) generalised seizures, 10 (15.2%) focal seizures and 2 (3%) absence seizures as shown in figure 3.

Figure 3: EEG Findings



Among the 94 study participants with CT scans, 66 (70.2%) showed a normal CT scan, 22 (23.4%) brain atrophy and 1 (1.1%) a brain infarct. CT scans showing both brain atrophy and hydrocephalus were seen in 4 participants (4.3%) while 1(1.1%) showed a brain infarct and brain atrophy as shown in figure 4.

Figure 4: CT scan (Head) Findings

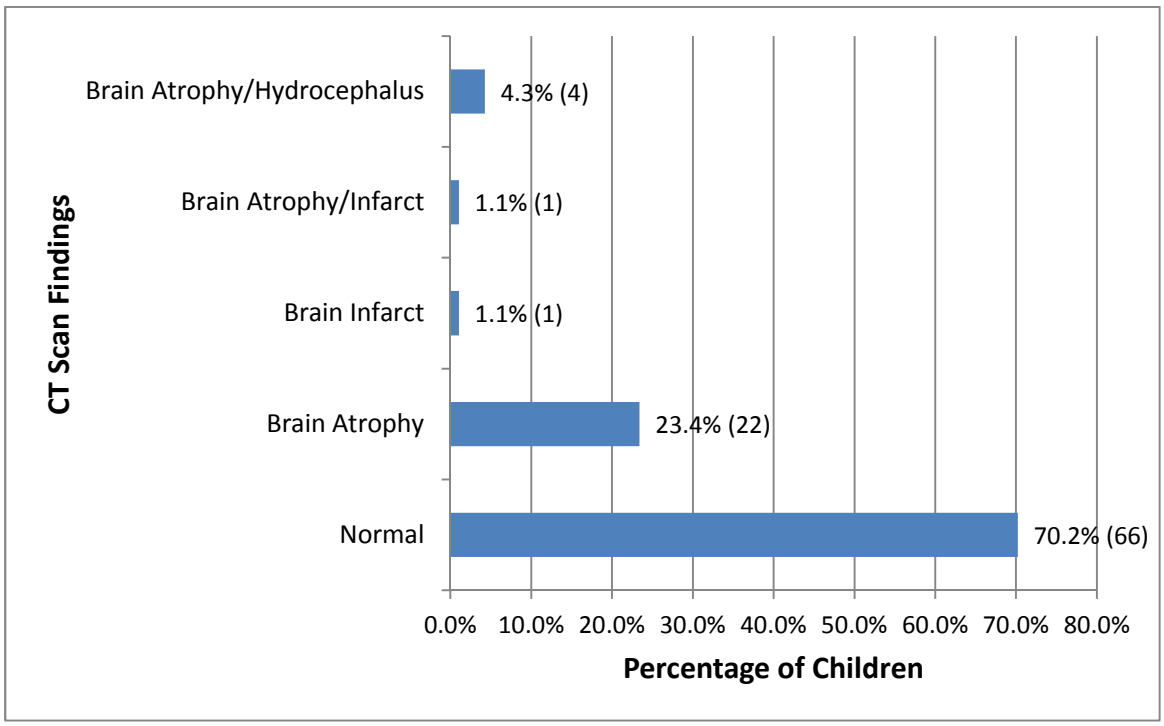


Table 9 below is cross-tabulation of EEG and CT scan findings. Among the children with a normal EEG finding 30 (69.8%) had a normal CT scan, 2 (4.7%) had an abnormal CT scan while 11 (25.6%) did not have a CT scan available. At least 13 (56.5%) of children with epileptiform discharges on EEG had a normal CT scan finding while 3 (13%) had an abnormal CT scan. A total of 92 patients (66.7%) did not have EEG or CT examination. Only 48 patients (23.5%) had both EEG and CT scan.

Table 9: Comparison of EEG and CT scan findings

		EEG Findings		
		Normal (N=43)	**Epileptiform discharges (N=23)**	**Not available (N=138)**
CT Scan Findings	Normal	30 (69.8%)	13 (56.5%)	23 (16.7%)
	Abnormal	2 (4.7%)	3 (13.0%)	23 (16.7%)
	Not available	11 (25.6%)	7 (30.4%)	92 (66.7%)

5.10. Relationship between level of seizure control and EEG & CT Scan head findings

At least 53.3% (8) of poorly controlled children had epileptiform discharges on EEG as compared to 46.7 % (7) who had normal EEG findings. Up to 34.9% (15) of well controlled children had epileptiform discharges on EEG while 65.1% (28) had normal EEG findings. There was a higher risk of poor seizure control with epileptiform seizures at OR= 2.1 [95% CI, 0.6, 8.3]. This was however not statistically significant, p=0.208. At least 45.5% (10) of poorly controlled children had abnormal CT scan findings as compared to 54.5 % (12) who had normal scans. Abnormal CT scan findings included brain atrophy, brain infarcts and hydrocephalus. Only 22% (11) of well controlled children had abnormal CT scans while 78% (39) had normal scans. There was also a higher risk of poor seizure control with abnormal CT scans OR=3.0 [(95% CI, 0.9, 9.9), p=0.044] which was statistically significant.

Table 10: EEG & CT Scan head findings versus level of seizure control

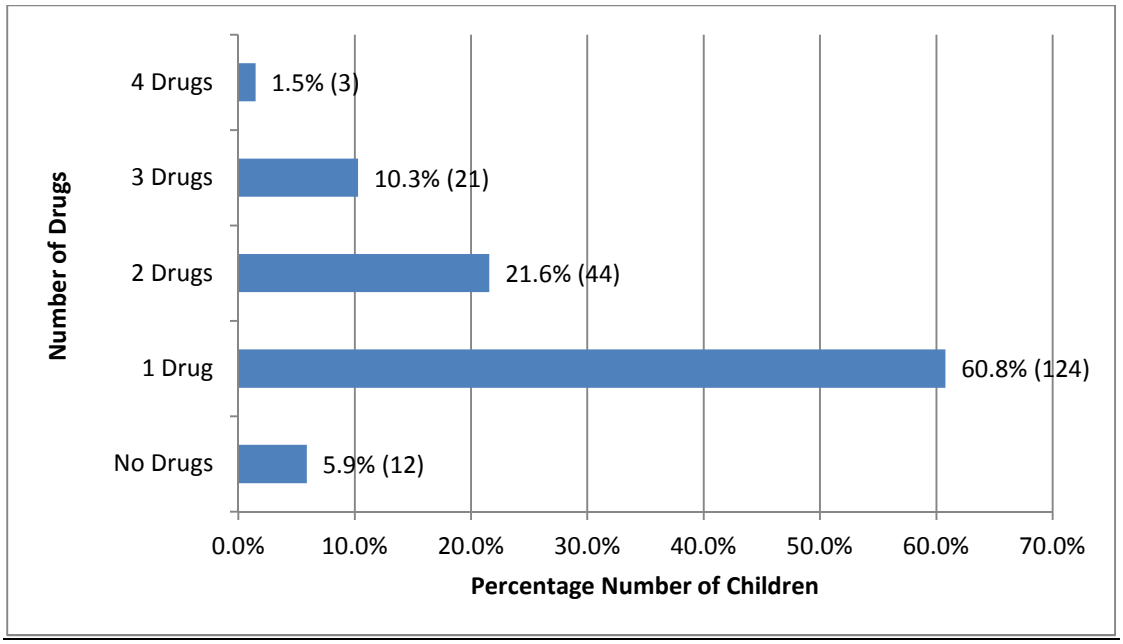
	Level of Control		OR (CI 95%)	P Value
	Poorly Controlled	Well Controlled		
EEG Findings	**N=15**	**N=43**		
Epileptiform discharges	8 (53.3%)	15 (34.9%)	2.1 (0.6-8.3)	0.208
Normal	7 (46.7%)	28 (65.1%)	1	
CT Scan Findings	**N=22**	**N=50**		
Abnormal	10 (45.5%)	11 (22%)	3.0 (0.9-9.9)	0.044
Normal	12 (54.5%)	39 (78%)	1	

5.11. Anti-Epileptic Drugs

5.11.1. Anti-Epileptic Drugs in Use for Seizure Control

The study population consisted of 192 children (94.1%) who were currently on anti-epileptic drug treatment. Twelve patients (5.9%) were at the time of the study not on any drug treatment. One hundred and twenty four children (60.8%) were on one anti-epileptic drug. Forty four children (21.6%) were on two drugs while twenty one children (10.3%) were on three drugs. Only three children accounting for 1.5% of the study population were on four drugs. The median duration of treatment with anti-epileptic drugs was 36 months.

Figure 5: Number of anti-epileptic drugs child currently taking



Among the patients who were currently using anti-epileptic drugs 89(43.6%) were on monotherapy with phenobarbital, 22(10.8%) with sodium valproate while 12 (5.9%) were on carbamazepine alone. Only one patient (0.5) was on monotherapy with topiramate. Of the patients on 2 drugs 26 (12.7%) were on phenobarbital and carbamazepine, 7 (3.4%) were on phenobarbital and sodium valproate, 5 (2.5%) were on carbamazepine and valproate, 4 (2.0%) were on carbamazepine and clonazepam while 2 (1.0%) were on valproate and clonazepam. Table 12 shown below summarises the anti-epileptic drugs which the study children were currently taking.

Table 11: Current anti-epileptic drugs in use by the study children

Anti-epileptic Drugs Currently prescribed	**N=204 (%)**
None	12 (5.9%)
Monotherapy	
Phenobarbital	89 (43.6%)
Valproate	22 (10.8%)
Carbamazepine	12 (5.9%)
Topiramate	1 (0.5%)
Polytherapy	
2 Drugs	
Phenobarbital/Carbamazepine	26 (12.7%)
Phenobarbital/Valproate	7 (3.4%)
Carbamazepine/Valproate	5 (2.5%)
Carbamazepine/Clonazepam	4 (2.0%)
Valproate/Clonazepam	2 (1.0%)
3 Drugs	
Phenobarbital/ Valproate/Carbamazepine	1 (0.5%)
Phenobarbital/Phenytoin/Valproate	2 (1.0%)
Phenytoin/Valproate/Carbamazepine	8 (3.9%)
Phenobarbital/Carbamazepine/Clonazepam	5 (2.5%)
Lamotrigine/Valproate/Carbamazepine	1 (0.5%)
Valproate/Carbamazepine/Clonazepam	4 (2.0%)

4 Drugs	
Phenobarbital/Valproate/Carbamazepine/Clonazepam	1 (0.5%)
Valproate/Carbamazepine/Clonazepam/Topiramate	1 (0.5%)
Clonazepam/Carbamazepine/Lamotrigine/Topiramate	1 (0.5%)

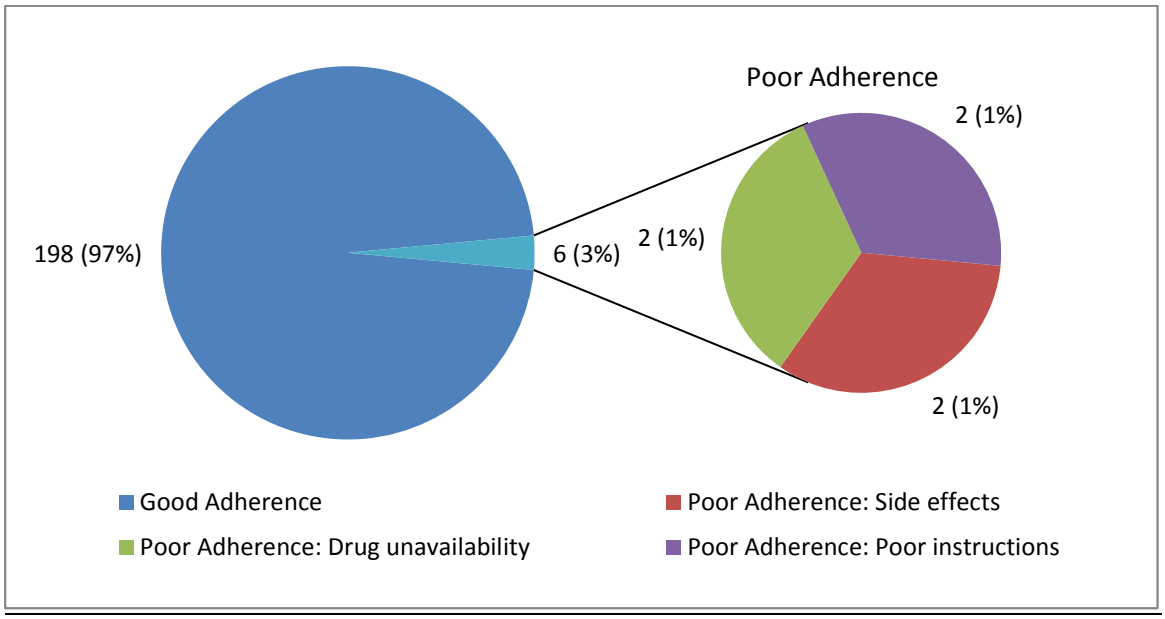
5.11.2. First Line Anti-epileptic Drugs

Out of the two hundred and four children started on anti-epileptic drugs monotherapy with phenobarbital accounted for 179 (87.7%) of first anti-epileptic drug prescribed, followed by monotherapy with carbamazepine 10 (4.9%) and then sodium valproate 9 (4.4%). Another 3 children (1.5%) had received a combination of phenobarbital and clonazepam while 2 (1.0%) had received phenobarbital and carbamazepine. Only one primary caregiver was not sure of which anti-epileptic drug was prescribed first.

5.12. Adherence to Anti-Epileptic Drugs

Out of the 186 patients on anti-epileptic drugs only 3% were non-adherent. Reasons for non-adherence included poor instructions on how long drug should be taken (1%), unavailability of drugs in their locality (1%) and perceived side-effects (1%).

Figure 6: Adherence to Anti-epileptic Drugs



5.13. Number of anti-epileptic drugs and level of seizure control

Only 9.3% (12) of children with well controlled seizures were not on any anti-epileptic drugs. Five children who accounted for 16.7% of poorly controlled children were on one drug compared to a higher proportion of well controlled children at 69.8% (90) who were also on one drug. Almost 30% (9) of poorly controlled children were on two drugs as compared to 18.6% (24) of well controlled children. A higher proportion of poorly controlled children were on three or four drugs at 53.3% (16) compared to 2.3% (3) of well controlled children.

Table 12: Number of anti-epileptic drugs and level of seizure control

Variable	**Level of Control**	
	Poorly Controlled (N=30)	**Well Controlled (N=129)**
Number of anti-epileptic drugs		
None	0 (0%)	12 (9.3%)
One	5 (16.7%)	90 (69.8%)
Two	9 (30.0%)	24 (18.6%)
Three/Four	16 (53.3%)	3 (2.3%)

5.14. Multivariate Analysis

Logistic regression analysis was performed to determine the factors independently associated with poor control of seizures. The variables used in the model included residence, age at onset of seizures, type of seizure, number of seizures at initiation of treatment, family history of epilepsy and cerebral palsy. Perinatal complications and delayed milestones were eliminated from the model because of their strong correlation with cerebral palsy (r= 0.633 & 0.867 respectively). Also, frequency of seizures and number of drugs were eliminated due to their correlation with number of seizures at initiation of therapy (r=0.745 & 0.609 respectively). The model showed that partial seizures, increased number of seizures prior to initiation of therapy, family history of epilepsy and cerebral palsy independently predict the risk of poor seizure control. Table 14 below shows the independent predictors of poor seizure control.

Table 13: Analysis of independent predictors of poor seizure control

Variable	OR (95% CI)	P value
Residence		
Rural	0.7 (0.1 -6.0)	0.70
Age at onset of seizures		
<2 months	0.2 (0.0-100.3)	0.62
3 – 12 months	0.0 (0.0-9.7)	0.19
1 – 5 years	0.1 (0.0-33.9)	0.44
6 – 12 years	1.0	
Type of seizure		
Partial	14.8 (1.6-133.9)	0.02
Number of seizures at initiation of therapy		
>=11	149.4 (12.2-1831.2)	<0.001
Family history of epilepsy	72.9 (2.2-2455.5)	0.02
Cerebral palsy	26.7 (1.2-614.0)	0.04

6. DISCUSSION

In spite of several advances in treatment of epilepsy a significant number of children do not respond well to anti-epileptic drugs and continue to have seizures. In this study it was found that the prevalence of poorly controlled epilepsy was 14.7% compared to 63.2% who had well controlled epilepsy. This concurs with several studies where up to 70% of newly diagnosed children and adults with epilepsy can be successfully treated with anti-epileptic drugs. Up to 30% of patients do not go into remission despite appropriate therapy with anti-epileptic drugs. Majority of children in this study were seizure free for 6 to 12 months with fewer children with longer seizure free periods seen in the clinic. This can be attributed to discharge by from the paediatric neurology clinic once seizures are controlled. A large number of children are discharged from the clinic once seizures have been controlled while some children default their clinic appointments once they feel their seizures are well controlled. There are also a number of children in the clinic who had been seizure free for a long period of time but due to breakthrough seizures after drug withdrawal were no longer classified as well controlled altering the results of this study. [1, 13, 23, 24]

Consensus is still on-going on the definition of good or adequate seizure control. The ILEA has established a task force to categorise outcome of both therapeutic and non-therapeutic intervention of epilepsy. Broadly the outcome categories include seizure free, treatment failure and undetermined. [25] For this study a seizure free duration of at least 6 months with treatment duration of at least 6 months was considered. A study by Schimdt found that those patients who are seizure-free at 6 months have a 90% chance of being seizure-free at 12 months, whereas those not seizure-free at 6 months have only a 45% chance of being seizure-free at 12 months. The main conclusion is that response at 6 months is an excellent predictor of response at 12 months. [18] The median duration of follow-up in this study was 2 years with a median duration of treatment with anti-epileptic drugs for 3 years. This disparity is mainly because many children had been started on treatment prior to referral to the neurology clinic.

Children residing in rural areas were found to have a higher risk of poor seizure control. This could be attributed to the referral of poorly controlled patients to KNH, the main referral hospital while well controlled children continued follow-up in the rural area. In this study there was also an increased risk of poor level of seizure control in children who had their first seizure before 2 months of age. Increasing age at onset of seizures was associated with a better prognosis. Age at onset of seizures was however not an independent factor for poor

seizure control. Kwong et al also observed age at onset was significant on univariate analysis but not on multivariate analysis. [26]

Concerning the number of pre-treatment seizures and timing of initiation of treatment this study found a significant association between number of pre-treatment seizures and poor level of seizure control. In this study an increased number of pre-treatment seizures was an independent predictor of poor seizure control. Many previous studies reported a high number of pre-treatment seizures as a predictor of poorly controlled epilepsy. [12, 27, 28] Camfield et al reported less than 20 seizures before initiation of treatment was a significant predictor of seizure remission. [29] A study by Musicco et al however showed that treatment of the first tonic clonic seizure did not improve the prognosis of epilepsy. [30] Partial type of seizure was found to be an important independent predictor of poor seizure control. Some studies have found that partial seizures were associated with lower remission rates as compared to generalised seizures. [23, 31, 32] Berg et al however found that delayed remission may be observed in children with focal seizures. [33]

A family history of epilepsy was also a found to be an independent predictor of poor seizure control in this study. Majority of the study population however did not give a family history of epilepsy. Perinatal complications, cerebral palsy and delayed or regressed milestones were found to increase the risk of poor seizure control. Cerebral palsy was an independent predictor of poor seizure control in this study. Gururaj et al found that the overall outcome of seizures in children with cerebral palsy was poor needing prolonged course of polytherapy with a higher incidence of refractory seizures. [34] It is likely the presence of the cerebral palsy enhances the severity of the underlying CNS abnormality rather than directly alter the outcome. Presence of a CNS infection was associated with a higher risk of poor seizure control though this was not an important predictor of poor level of seizure control. CNS infections included in this study were meningitis and cerebral malaria though in many cases this was a clinical diagnosis without supportive investigations. Febrile convulsions were not associated with poor seizure control in this study. Data from studies of children with febrile seizures indicate that 2 to 10% of children who have febrile seizures will subsequently develop epilepsy. A study by Berg et al found no association between febrile seizures and intractable epilepsy. [35] Camfield et al on the other hand noted prolonged febrile seizures were associated with intractable epilepsy. [36] No history of febrile convulsions was given in any of the poorly controlled children.

Rapid response to the first monotherapy was a good predictor to good seizure control. Majority of children in this study had good response to the first anti-epileptic drug. The most commonly prescribed anti-epileptic drug for monotherapy was phenobarbital (43.6%) followed by valproate (10.8%) then carbamazepine (5.9%). This is similar to several studies in Africa where phenobarbital and phenytoin (65 – 85%) were commonly prescribed followed by carbamazepine (5 – 20%) then valproate (5 – 15%). In a South African study acceptable seizure control was maintained with a single standard antiepileptic drug in 65% of cases. In children on two anti-epileptic drugs 29% achieved good seizure control while 19% of cases in children on three anti-epileptic drugs achieved good seizure control. Only six per cent were not on any drug treatment following drug withdrawal after good seizure control. [19] Various studies show that anti-epileptic drugs can be withdrawn after 2 to 5 years in 70% of children. [1] The low number of the study population not on any anti-epileptic drug treatment could be accounted for discharge from the clinic with instructions to only come back in case of a problem.

Many children in this study did not have an EEG or CT scan done as part of investigations into their epilepsy. The high cost of these investigations was observed as a factor leading to unavailability of these tests for most patients. This study did not reveal a significant correlation between poor seizure control and EEG findings. Ohtsuka et al also found no correlation between abnormal EEG findings and development of intractable seizures. [37]

Majority of primary caregivers expected eventual cure from epilepsy following anti-epileptic drug use. Primary caregivers has a wide range of perceived causes of their children's epilepsy ranging from central nervous system infections, birth complications, fever and inherited conditions with almost one third not sure what caused their child's epilepsy. This is similar to a study done in rural Kenya where birth complications, fever, malaria, congenital transmission where among perceived causes of epilepsy. [38] This could be due to limited sub-optimal counselling or health education given at the initiation of treatment or at diagnosis time.

7. STUDY LIMITATIONS

This study was a cross-sectional study on level of seizure control therefore it was difficult to determine causal relationships associated with poor seizure control. This study was also retrospective in nature and was subject to recall bias. Almost half the children in this study did not have a standard panel of investigations including a CT scan or EEG therefore making it difficult to assess relationship between poor seizure control and investigation findings. This study was also a hospital based study as compared to a community based study making it biased towards children who may have good or poor seizure control. Due to end-user fees charged at the hospital, caregivers who cannot afford the fees were also eliminated from the study therefore creating a bias towards caregivers with higher socio-economic status than the general population which may have affected the results. Lack of universal consensus among several studies on definition of a child with poor and good seizure control was also a challenge in this study.

8. RECOMMENDATIONS

Children with partial seizures, increased number of pre-treatment seizures, cerebral palsy and a family history of epilepsy are at risk of intractable epilepsy therefore identifying this children early in the course of their presentation may be useful in designing effective multi-displinary treatment modalities. They can be followed up closely and their caregivers better prepared to cope with their child's condition.

Health education and counseling of caregivers of children with epilepsy is recommended to give them a better understanding of their children's epilepsy.

A long-term prospective study on the factors predictive of poor seizure control including causal relationships is recommended. This study should be a hospital based study as well expanded into a community based study. A follow-up study on socio-economic burden and quality of life of children with epilepsy is recommended to find out how poor seizure control and epilepsy in general affects the lives of children with epilepsy.

9. CONCLUSIONS

The prevalence of poorly controlled was 14.7%. Partial seizures, increased number of pre-treatment seizures, family history of epilepsy and cerebral palsy independently predict the risk of poor seizure control. Majority of caregivers in this study expected eventual cure from epilepsy for their children after taking anti-epileptic drugs. Primary caregivers had a wide range of perceived causes of their children's epilepsy ranging from central nervous system infections, birth complications, fever and inherited conditions with almost one third not sure what caused their child's epilepsy.

REFERENCES

1. WHO factsheet no. 999 Updated, January 2009

2. **Ronen G, Streiner D and Rosenbaum P.** Health- Related quality of life in children with epilepsy: Moving beyond 'seizure control with minimal adverse effects'. *Health Qual Life Outcomes.* 2003; 1: 36.

3. Epilepsy in the WHO African Region: Bridging the Gap 'Global Campaign against Epilepsy'. World Health Organization, 2004.

4. **Guerrini R.** Epilepsy in children. *The Lancet.* 2006; 367: 499-524.

5. **Preux PM and Druet-Cabanac M.** Epidemiology and aetiology of epilepsy in sub-Saharan Africa. *Lancet Neurol.* 2005; 4: 21-31.

6. **Kaamugisha J and Feksi AT.** Determining the prevalence of epilepsy in the semi-urban population of Nakuru, Kenya, comparing two independent methods not apparently used before in epilepsy studies. *Neuroepidemiology.* 1988; 7: 115-121.

7. **Edwards T, Scott AG, Munyoki G, et al.** Active Convulsive epilepsy in a rural district of Kenya: A study of prevalence and possible risk factors. *The Lancet Neurol.* 2008; 7: 50-56.

8. **Cansu A, Serdaroğlu A, Yüksel D, et al.** Prevalence of some risk factors in children with epilepsy compared to their controls. *Seizure.* 2007; 16: 338-344.

9. **Mung'ala-Odera V, White S, Meehan R, et al.** Prevalence, incidence and risk factors of epilepsy in older children in rural Kenya. *Seizure.* 2008; 17; 396-404.

10. **Sridharan R.** Epidemiology of Epilepsy. *Current Science.* 2002; 82: 6.

11. **De Bittencourt PRM, Adamolekum B, Bharucha N, et al.** Epilepsy in the Tropics: II. Clinical Presentations, Pathophysiology, Immunologic Diagnosis, Economics, and Therapy. *Epilepsia.* 1996; 37: 1128-1137.

12. **Kwan P and Brodie MJ.** Early identification of refractory epilepsy. *N Engl J Med.* 2000; 342: 314-319.

13. **Sillanpää M and Schmidt D.** Natural History of Treated Childhood-Onset Epilepsy: Prospective, Long-Term Population-Based Study. *Brain.* 2006; 129: 617–624.

14. **Deckers CL, Czuczwar SJ, Hekster YA, et al.** Selection of Antiepileptic Drug Polytherapy Based on Mechanisms of Action: The Evidence Reviewed. *Epilepsia.* 2000; 41: 1364-1374.

15. **Kwan P and Sander J.** The natural history of epilepsy: An epidemiological view. *J Neurol Neurosurg Psychiatry.* 2004; 75: 1376-1381.

16. **Feksi AT, Kaamugisha J, Sander JWAS, Shorvon SD and Gatiti S.** Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. *The Lancet.* 1991; 337: 406-409.

17. **Sillanpää M, Jalava M, Kaleva O and Shinnar S.** Long-term prognosis of seizures with onset in childhood. *N Engl J Med.* 1998; 338: 1715-1722.

18. **Schmidt D.** How reliable is early treatment response in predicting long-term seizure outcome? *Epilepsy Behav.* 2007; 10: 588-594.

19. **Leary PM, Riordan G, Schlegel B and Morris S.** Childhood Secondary(Symptomatic) Epilepsy, Seizure Control and Intellectual Handicap in a Nontropical Region of South Africa. *Epilepsia.* 1999; 40: 1110-1113.

20. **Kenyatta National Hospital Medical Records.**

21. **Wayne Daniel.** *Biostatistics, A foundation for analysis in health sciences.* Willey.

22. **Commey JO.** Neurodevelopmental problems in Ghanaian children: Part 1 Convulsive disorder. *West African Journal of Medicine.* 1995; 14:189-193.

23. **Annegers JF, Hauser WA and Elveback LR.** Remission of Seizures and Relapse in Patients with Epilepsy. *Epilepsia.* 1979; 20: 729–37.

24. **Cockerell OC, Sander JW, Hart YM, Shorvon SD and Johnson AL.** Remission of epilepsy: Results from the National General Practice Study of Epilepsy. *The Lancet.* 1995; 346: 140–144.

25. **Kwan P, Arzimanoglou A, Berg AT, et al,.** Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2010; 51: 1069–1077.

26. **Kwong K, Sung W, Wong S and Kwan T.** Early predictors of medical intractability in childhood epilepsy. *Pediatr Neurol.* 2003; 29: 46-52.

27. **Casetta I, Granieri E, Monetti VC, et al.** Early predictors of intractability in childhood epilepsy: A community-based case-control study in Copparo, Italy. *Acta Neurol Scand.* 1999; 99: 329–33.

28. **Sillanpaa M and Schmidt D.** Early Seizure Frequency and Aetiology Predict Longterm Medical Outcome in Childhood-onset Epilepsy. *Brain.* 2009; 132: 989-998.

29. **Camfield C, Camfield P, Gordon K, Smith B and Dooley J.** Outcome of childhood epilepsy: A population-based study with a simple scoring system for those treated with medication. *The Journal of Pediatrics.* 1993; 122: 861–868.

30. **Musicco M, Beghi E, Solari A, Viani F, First Seizure Trial Group (FIRST Group).** Treatment of first tonic clonic seizure does not improve prognosis of epilepsy. *Neurology.* 1997; 49: 991-998.

31. **MacDonald BK, Johnson AL, Goodridge DM, Cockerell OC, Sander JW and Shorvon SD.** Factors predicting prognosis of epilespy after presentation with seizures. *Ann Neurology.* 2000; 48: 833-841.

32. **Del Felice A, Beghi E, Boero G, et al.** Early versus late remission in a cohort of patients with newly diagnosed epilepsy. *Epilepsia.* 2010; 51: 37–42.

33. **Berg AT, Vickrey BG, Testa FM, et al.** How long does it take for epilepsy to become intractable? A prospective investigation. *Ann Neurol.* 2006; 60: 73–79.

34. **Gururaj AK, Sztriha L Brner A, Dawodu A and Eapen V.** Epilepsy in children with cerebral palsy. *Seizure.* 2003; 12: 110-114.

35. **Berg AT, Levy SR, Novotny EJ and Shinnar S.** Predictors of intractable epilepsy in childhood: A case-control study. *Epilepsia.* 1996; 37: 24-30.

36. **Camfield P, Camfield C, Gordon K and Dooley JM.** What types of epilepsy are preceded by febrile seizures? A population-based study of children. *Devl Med Child Neurol.* 1994; 36: 887-892.

37. **Ohtsuka Y, Yoshinaga H, Kobayashi K, et al.** Predictors and underlying causes of medically intractable localization-related epilepsy in childhood. *Pediatr Neurol.* 2001; 24: 209-13.

38. **El Sharkawy G, Newton C and Hartley S.** Attitudes and practices of families and healthcare personnel toward children with epilepsy in Kilifi, Kenya. *Epilepsy Behav* 2006; 8:201–212.

APPENDICES

APPENDIX 1: QUESTIONNAIRE

Study Identification Number_____

Participant details

1) Age of the patient (years) _____

2) Sex of the patient
    1. Male
    2. Female

3) Residence
    1. Urban
    2. Rural

4) Age at onset of seizures

Years _____ Months (if less than 1yr) _____

5) Duration of treatment with antiepileptic drugs

Years _____ Months (if less than 1yr) _____

6) Duration of follow-up in neurology clinic

Years _____ Months (if less than 1yr) _____

Primary Caregiver Socio-demographic Data

7) Age of primary caregiver (years)
    1. 20 - 30
    2. 30 – 40
    3. 40 – 50
    4. >50

8) Marital status
    1. Never married
    2. Married
    3. Separated
    4. Widowed

9) Level of education

1. No formal education
2. Primary education
3. Secondary education
4. Tertiary education

10) Occupation of mother

1. Salaried formal employment
2. Informal employment
3. Self employment
4. Unemployed

Seizure and Clinical Characteristics prior to antiepileptic drug treatment

11) How often did your child get seizures prior to antiepileptic drug treatment?

1. Daily
2. Weekly
3. Monthly
4. Other _____

12) How many seizures did your child experience prior to treatment?

_____

13) How long does a seizure episode last in your child?

1. Less than 5 minutes
2. 5 to 10 minutes
3. 10 to 30 minutes
4. More than 30 minutes

14) Does your child have generalized or partial seizures?

1. Partial
2. Generalized
3. Not sure

15) When was your child's last convulsion?

1. Less than 1 month ago
2. _____ months ago

3. _____ years ago

16) How many seizures did your child experience in the last 6 months?

_____

17) Does any other member of your family have a history of epilepsy?

1. None
2. First Degree Relative
3. Second Degree Relative
4. Third Degree Relative

18) Has your child ever had a major head injury?

1. Yes
2. No

When? (Age in years/months)_____

19) History of febrile seizures?

1. Yes
2. No

20) History of complications during delivery or shortly after birth?

1. Yes
2. No

If yes specify_____

21) History of CNS infection prior to onset of seizures?

1. Yes
2. No

Specify_____

22) History of cerebral palsy?

1. Yes
2. No

23) Did your child have delayed developmental milestones/Regression of milestones?

Social smile - 1 – 2 months

Head support – 3 – 4 months

Sitting unsupported – 6 – 8 months

Walking – 12 to 18 months

One/two words – 12 months

1. Yes
2. No

24) Previous Electroencephalogram findings

1. Normal
2. Generalised epileptiform spikes
3. Focal epileptiform spikes
4. Not available/not done
5. Other _____

25) CT Scan findings

1. Normal
2. Brain atrophy
3. Brain infarct
4. Hydrocephalus
5. Not available/not done
6. Other_____

Antiepileptic Drug Use

1. Phenobarbital
2. Phenytoin
3. Sodium valproate
4. Carbamazepine
5. Clonazepam
6. Topiramate
7. Lamotrigine

26) How many antiepileptic drugs does your currently child take?

None 1 2 3 4

27) Number of AEDs given at onset of therapy?

None 1 2 3 4

28) Which antiepileptic drug(s) does your child currently take?

1 2 3 4

Other _____

If not on initial antiepileptic drug(s)

29) Specify 1st antiepileptic drug(s)

1 2 3 4

Other _____

30) Specify 2nd antiepileptic drug(s)

1 2 3 4

Other _____

31) Specify 3rd antiepileptic drug(s)

1 2 3 4

Other _____

32) Reasons of change of antiepileptic drug(s)

1. Side effects
2. Poor seizure control
3. Non-availability of antiepileptic drug(s)
4. High cost of drugs
5. Other_____

33) Has your child missed any doses of antiepileptic drugs over the past 1 month?

1. Yes
2. No

34) How many days has medication been missed?_____

35) If more than 6 days have been missed over past month what led to the missed medication?

1. High cost of drugs
2. High number of drugs

3. Side effects/Fear of side effects
4. Perceived lack of effect of antiepileptic drugs
5. Forgetfulness
6. Reduced seizure frequency
7. Stopped by doctor
8. Other _____

36) Have you experience any side effects from the anti-epileptic drugs?

1. Yes
2. No

If yes specify_____

37) Have you used any alternative treatment methods for your child's epilepsy?

1. Yes
2. No

In what form?

i) Herbs
ii) Religious Intervention
iii) Acupuncture
iv) Other_____

38) Are you still using any alternative treatment methods?

1. Yes
2. No

If yes specify_____

<u>Caregiver's perceptions on epilepsy and level of control</u>

39) Did you know about epilepsy before your child was diagnosed with epilepsy?

1. Yes
2. No

40) Where did you learn about epilepsy?

1. Health care worker
2. Media – Print, Radio, Television

3. Outreach campaign
4. Friends and relatives
5. Other_____

41) What is the cause of your child's epilepsy?

1. Central nervous system infection – malaria, meningitis
2. Birth complications
3. Head injury
4. Inherited
5. Fever
6. Emotional stress
7. Religious
8. Witchcraft
9. Not sure/Don't know
10. Other_____

42) How can your child's epilepsy be controlled?

1. Antiepileptic drugs
2. Religious intervention
3. Cultural practices/rituals
4. Herbs
5. Other_____

43) Expectations from antiepileptic drug therapy?

1. Complete cure from seizures
2. Reduction in seizure frequency
3. No effect
4. Not sure
5. Other _____

APPENDIX 2: CONSENT FORM FOR PARTICIPATION IN THE STUDY

Study Identification Number:_____

Date:_____

Study title

Seizure control in children with epilepsy on follow-up at Kenyatta National Hospital (KNH)

Investigator's statement

I am a postgraduate student at the University of Nairobi – Department of Paediatrics. I am asking you and your child to participate in a research study. The purpose of this consent form is to give you information you will need to help you decide whether to participate in the study. Please read this form carefully. You are free to ask any questions about the study. The investigator will be available to answer any questions that arise during the study and afterwards.

Brief description of Study

Epilepsy is one of the most common chronic neurological disorders affecting children in sub-Saharan Africa. The study aims to assess the level of seizure control in children on follow-up at KNH paediatric neurology clinic and factors that affect seizure control.

Your participation in this study will help us identify how well we are able to achieve seizure control with the various antiepileptic drugs. It will also help us identify factors that lead to poor seizure control. The results of this study will help health workers in this facility and beyond to improve care given to all children with epilepsy. It will also provide you with information on the current level of seizure control of your child and the steps you can take to improve seizure control.

All the information obtained will be held in strict confidentiality. Any information that may identify you or your child will not be published or discussed with any unauthorised persons. We will however discuss overall findings regarding all children who participated in the study without revealing you or your child's identity. No invasive procedures will be done on your child as part of the study. Your participation in this study is purely voluntary and there is no monetary gain. It will not cost you financially to participate in this study. You are free to withdraw from the study if you so wish without any penalty.

If you have any questions about the study or your participation in the study you can contact the principal investigator, Dr. Amolo Judith, 0721 272210.

If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC) by calling 2726300 Ext. 44355

I confirm I have explained to the parent/caregiver all relevant information about the study as indicated above.

Interviewer's Signature .....Date.....

I confirm the above study has been explained to me. I agree to have my child and l participate in the study. I have had a chance to ask questions about the research, to which satisfactory answers have been given. I understand l can withdraw from the study at any time without any penalty.

Guardian's Signature_____Date_____

APPENDIX 3: BUDGET AND TIMELINES

Category	Remarks	Units	Unit Cost (KShs)	Total (KShs)
Proposal Development	Printing drafts	1000 pages	5	5,000
	Proposal Copies	10 copies	300	3,000
Data Collection	Pens	10	10	100
	Research assistants			10, 000
Data Analysis	Statistician	1		20,000
Thesis Write Up	Computer Services			5,000
	Printing drafts	1000 pages	5	5,000
	Printing Thesis	5 copies	500	2, 500
Total				50,100

Number	Activity	Estimated Time
1	Proposal Development and Presentation	Jan to Feb 2010
2	Submission of proposal for ethical approval	March 2010
3	Pretesting and seeking permission	May to June 2010
4	Data Collection	July to January 2011
5	Data Analysis	Jan to Feb 2011
6	Thesis writing	March 2011
7	Thesis submission	April 2011