PREVALENCE, PATTERN AND FACTORS ASSOCIATED WITH COGNITIVE DYSFUNCTION IN CHILDREN WITH EPILEPSY ATTENDING THE PAEDIATRIC NEUROLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university or academic forum.

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LIST OF ABBREVIATIONS

AED antiepileptic drug

ADE adverse drug effects

BZ benzodiazepine

CBZ carbamazepine

EEG electroencephalogram

GTC generalized tonic clonic convulsions

ILAE International League Against Epilepsy

KNH Kenyatta National Hospital

MMSE Mini Mental State Examination

PLWE People Living With Epilepsy

VPA valproic acid

WHO World Health Organization

OPERATIONAL DEFINITION OF TERMS

Seizure transient occurrence of signs and symptoms due to an abnormal excessive neuronal activity

Epilepsy two unprovoked seizures more than 24 hours apart

Motor seizures involves body movements

Non motor seizures no visible body movements, presents as sensation, change in behaviour

Generalized seizure abnormal motor activity involving the whole body with impaired awareness

Focal seizure abnormal motor activity involving a part of the body usually a limb

Focal aware a person's awareness remains intact even if they are unable to walk and talk during seizure

Focal impaired awareness if awareness was affected during an on-going seizure activity

ABSTRACT

Background

Epilepsy is the fourth most common neurological disorder in the world. A vast majority of the children afflicted reside in sub-Saharan Africa. Children living with epilepsy have a higher risk of a broad range of cognitive disturbances and are predisposed to significant intellectual disability. Early diagnosis enables referral to rehabilitation programs and appropriate school placement. Optimal cognitive function in children is crucial for normal growth and development.

Primary objective

To determine the prevalence and pattern of cognitive dysfunction in children aged 7-13 years on treatment for epilepsy at the paediatric neurology clinic in Kenyatta National Hospital (KNH).

Methods

This was a cross-sectional study. It was conducted at KNH, paediatric neurology clinic. The participants were children aged 7-13 years with a diagnosis of epilepsy. Cognitive function was assessed using a standardized tool called the modified mini mental state examination tool. A questionnaire with seizure variables was administered to the caregiver.

Data analysis

A total of 177 children were recruited. The median age was 10years (IQ 8, 11).Majority (62.7%) was male. The most common type of epilepsy was generalised motor seizures (63.3%).Sodium valproate and phenobarbital were the most commonly prescribed anticonvulsant with majority of the children being on combination treatment. The mean age of onset of epilepsy was 1.33years (±0.47). The prevalence of cognitive dysfunction was 40.6%. Factors that were significantly associated with cognitive dysfunction included: Early age of onset (p=0.02), partial epilepsy (p=0.028), absent seizures (p=0.001), use of sodium valproate (p=0.03) and carbamazepine (p=<0.001) and high frequency of seizures (p=<0.001).

Conclusion

There is a high prevalence of cognitive dysfunction among children living with epilepsy at KNH.

Factors associated with cognitive dysfunction include: Early age of onset of epilepsy, partial or absent seizures, high frequency of convulsion and use of carbamazepine or sodium valproate.

CHAPTER ONE

BACKGROUND AND LITERATURE REVIEW

Epilepsy is the 4th most common neurological disorder worldwide as highlighted by the Epilepsy Foundation. An estimated 50 million people live with epilepsy globally (1). Approximately 80% of people living with epilepsy (PLWE) reside in third world countries (1). Children below 15 years comprise 25% of all PLWE (1). The incidence of epilepsy in children ranges from 41-187/100,000 with higher incidence in sub-Saharan Africa (2). Epilepsy is a chronic disorder and its clinical course is heralded by several comorbidities which could be neurological, physical or psychological. Cognitive dysfunction is a crucial neurological consequence of epilepsy.

The American Paediatric Neurological Association defines Cognitive dysfunction as loss of intellectual function, learning ability, memory, perception and problem solving skills of sufficient severity to interfere with daily function. Children living with epilepsy are at an increased risk for a broad range of cognitive disturbances and are predisposed to significant intellectual dysfunction (3).The impact of cognitive dysfunction associated with early onset epilepsy on the developing brain is important owing to its deleterious effects on neurodevelopmental, social outcomes and academic achievement (3).

Several studies have delineated the presence of cognitive disturbance in PLWE though local data is scanty (4)(5)(6).The consequences of cognitive dysfunction have an impact on day to day activities and the quality of life of PLWE (7)(8).Such impairments affect not only the children but also their family members and may be more deleterious for a patient than the seizures (3). Therefore it is vital to explore factors associated with cognitive impairment in epilepsy.

A myriad of factors have been shown to be associated with cognitive dysfunction in epilepsy. Three key aspects are clearly delineated: Structural abnormalities underlying the aetiology of epilepsy, seizure activity and the effects of antiepileptic drugs (AED) on the central nervous system (AED). Electro-physical dysfunction that leads to the convulsions can also result to learning difficulties, memory deficits and psychomotor regression (9)(10)(11).

Early age of onset of seizures has been documented to be one of the most vital predictor of cognitive impairment in children living with epilepsy (12). The risk of cognitive disturbance is

higher in those with more frequent convulsions, longer duration of epilepsy, abnormal electroencephalogram (EEG) and those with epilepsy attributable to underlying genetic disorder or structural abnormalities (12)(13)(14).

Anticonvulsants achieve control of seizure activity through inhibition of neuronal excitability generally improving the quality of life of PLWE but have several adverse effects. The cognitive effects of antiepileptic drugs (AED) are of special concern since they are iatrogenic and a modifiable aspect that can be altered by informed procurement and prescription practice (9).Since AEDs are the mainstay of treatment in epilepsy, clinicians should evaluate the patient's baseline cognitive condition and make an assessment of risk to benefit ratio before initiating treatment with an AED. This early assessment is crucial as the negative effects of AEDs on attention and memory might be additive over long-term (15).The underlying cerebral abnormalities and electro physical effects of the seizure activity interact with the detrimental side effects of AEDs resulting to even greater regression in neurodevelopment (16). Locally there is very scanty data on cognitive side effects of AED.

Highlighting the role of anticonvulsants in cognitive dysfunction will help clinicians in our setting to risk stratify patients and be vigilant of these adverse effects as they follow up patients in the outpatient clinic. Correct and prompt identification of cognitive impairment is necessary to provide early developmental interventions, appropriate schooling programs, vocational counselling, supportive work setting and a safe environment for promotion of independence across the lifespan in children with epilepsy.

1.1 Prevalence of cognitive dysfunction in epileptics

Epilepsy accounts for 10% of global neuropsychological burden (17). Epilepsy can be associated with abnormalities in cognition, psychiatric status and social adaptive behaviours now referred to as neurobehavioral comorbidities (18). In the absence of other chronic conditions, children living with epilepsy have a preponderance to cognitive deficits (3). Cognitive dysfunction associated with epilepsy of childhood onset is important as significant brain development is seen from prenatal life and continues into early childhood and adolescence ,making this a critical time for central nervous system development (19).

A study was carried out in Cairo, Egypt on forty, newly diagnosed, epileptic patients with their ages ranging between 7and 18 years old who were divided into 4 groups A, B, C and D (each

containing 10 patients). Each received one of the following antiepileptic drugs for 3 months, Group (A): received Carbamazepine (Tegretol) at dose of 10-20 mg/kg, Group (B): received sodium valproate (Depakine) at dose of 20-40 mg/kg, Group (C): received Lamotrigine (Lamictal) at dose of 3-5 mg/kg, Group (D): received Topiramate (Topiramate) at dose of 3-6mg/kg. All patients were evaluated for cognitive functions by Wechsler IQ before and three months after treatment. Parameters that were of significance in this study were assessed: Frequency of seizures, time of onset of epilepsy and EEG abnormality .The outcome indicated that there was a significant difference in each group between IQs before and after treatment. This point to the underlying seizure activity as a contributing factor to cognitive defects. Several other studies support this finding (14)(20).

Subnormal global cognitive function is seen in approximately one in every four children with epilepsy (12) .A national prospective study done in USA in 1984 that followed children with perinatal onset of convulsions to 7 years of age established 27% of children with epilepsy were mentally retarded (21). A population prevalence study in 10 year olds living with epilepsy in the USA in 1995 found that 30% had mental retardation (22) .Several other studies that highlight the burden cognitive impairment in epilepsy are summarised in the table below.

Table 1: Studies on Cognitive Function in Epilepsy

STUDY	AUTHOR	COUNTRY	TYPE OF STUDY	SAMPLE SIZE METHODS	OUTCOME
Global cognitive function in epileptic patients. (12)	Berg, Ann 2012	USA	Prospective longitudinal 10years	450 children Aged 1month-16 years Diagnosed with epilepsy. IQ assessed and correlation with cognitive function.	Subnormal global cognitive function in 26.4% of the study participants. Young age of onset of seizure and symptomatic epilepsy are independently associated with this outcome.
The impact of childhood epilepsy on neurocognitive and behavioural performance. (7)	Bailet, L 2000	USA	Prospective longitudinal 3 years	74 children with epilepsy. 23 normal controls 13 controls with migraine Aged 8-13 years Neurocognitive battery test done annually for 3 years.	Children with epilepsy scored significantly lower than controls in measures of intelligence , psychomotor speed, memory and academic performance.
Developmental reorganisation of the cognitive network in paediatric epilepsy. (23)	Camille Garcia-Ramos 2015)	USA	Case control 2 years	178 children aged 8-18 years 104 with new onset epilepsy 74 healthy age and gender matched controls.	Subjects with epilepsy showed significantly lower global integration as compared to healthy controls.

Cognitive function in Nigerian children with newly diagnosed epilepsy(24)	Ike Oluma 2016	Nigeria	Prospective study	40children aged 6-16 years Assessed with Wechsler's intelligence scoring (WISC-IV)	Preliminary report indicates 12.5% mild cognitive impairment 27.5% moderate cognitive impairment 2.5% severe cognitive impairment.
Seizure variables and cognitive performance in patients with epilepsy.(13)	Sunmonu Taofik 2008	Nigeria	Cross-sectional	41 adults with childhood onset epilepsy against 41 normal controls. Computer assisted cognitive test battery conducted.	Cognitive performance in those with epilepsy was significantly worse than controls. Duration of treatment and higher seizure frequency were associated with low scores in all domains.
Prevalence of emotional and behavioural problems in children with epilepsy.(5)	Sarah Karanja 2017	Kenya	Cross-sectional	Children with epilepsy aged 6-12 years Child behaviour checklist was used.	Prevalence of emotional and behavioural problems was 46.3%. Attention problems, depression and aggressive behaviour were leading causes.

1.2 Mechanisms of cognitive disturbance in epilepsy

There is a wide base of evidence that suggests that a broad lifespan perspective of cognition in epilepsy should include consideration of: a) neurobiological factors that antedate the first seizure and influence cognition, b) epilepsy-related factors that influence brain growth and cognitive development after epilepsy is diagnosed and treated, c) clinical epilepsy and other risk factors associated with poor cognitive prognosis in the context of chronic pharmacoresistant epilepsy, and d) the modifiable and non-modifiable risk factors that influence cognitive aging in the general population (25).

Several mechanisms have been linked to development of cognitive dysfunction in epilepsy. Neuroanatomical abnormalities have been noted way before evidence of the first seizure (26).These are linked to abnormal apoptosis, chanelopathies and improper dendritic networking in the central nervous system. With the onset of epilepsy, repetitive or prolonged seizure results to anoxia, lactic acidosis, and excessive neurotransmitter activity which may irreversibly damage the brain leading to cognitive impairment (3). Several other attributes are interrelated and contribute to cognitive impairment observed in epilepsy. These include: Type of seizure, time of onset of epilepsy, frequency of seizure activity and CNS adverse effects of antiepileptic drugs (24)(12).

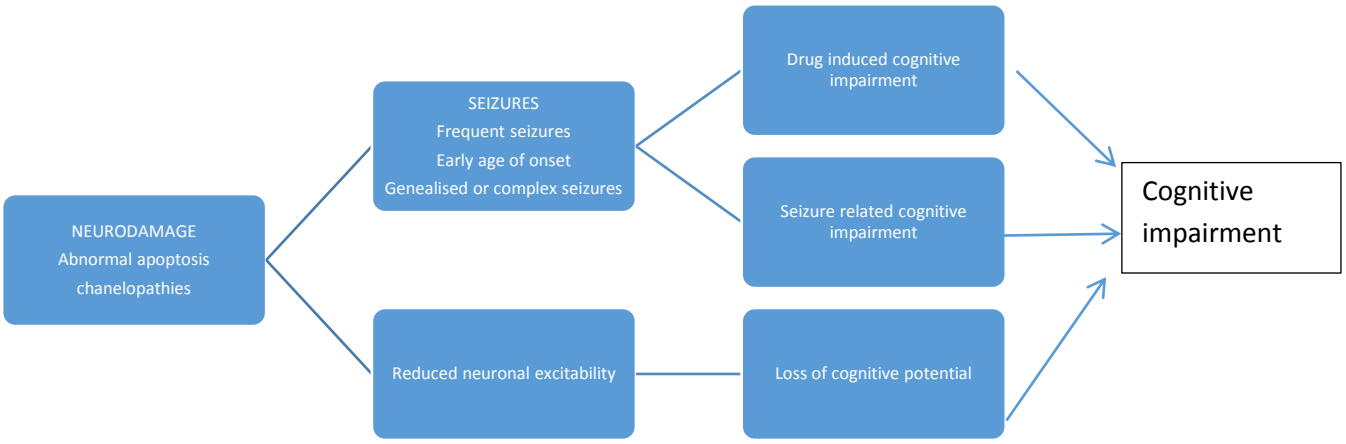


Figure 1: Conceptual framework

1.3 Factors associated with cognitive function in epilepsy

1.3.1 Age of onset of epilepsy

Epilepsy onset at an early age is associated with poor outcomes in cognitive function and higher neuropsychiatric morbidity (15)(13). Onset of epilepsy before five years of age with frequent seizures leads to interruption of brain development and long term impact on cognition through mitotic cell activity inhibition, reduced myelination, cell size and cell numbers (27).With early onset of seizure activity the delicate developing brain is exposed to more lifetime number of seizures and the resulting developmental defects are not compensated in later life (15).

A study done by Dikmens, M.C.G in 1975 sought to compare cognitive intellectual performance of individuals with a diagnosis of generalised motor seizures. Two groups of adults were studied; one group had an earlier age of onset of convulsions (0-5) years, the second group had a late onset of symptoms (17-50) years. Performance on the Wechsler intelligence scale was measured. Results indicated that subjects with earlier age of onset of generalised motor seizures got significantly lower scores than subjects with late onset epilepsy. The conclusion was that motor seizures that have an earlier onset are more likely to result in impairment of cognitive abilities in adult life than those with later onset (28).

The impact of time of onset of epilepsy on neuropsychological performance in children is further highlighted in a study by O'Leary Ds, Seidenberg. This study concluded that patients with early onset temporal lobe epilepsy had lower scores in neuropsychological measures compared with subjects who had late onset epilepsy and healthy controls. This conclusion is complemented by neuro-imaging studies on subjects with early onset epilepsy with findings of altered volumes of corpus callosum and atrophy of grey and white matter (25).

1.3.2 Type of epilepsy

Aetiologically, the epilepsies are classified into four groups: Idiopathic, symptomatic, cryptogenic and progressive (29). The idiopathic epilepsies which have a strong genetic predisposition, are associated with specific clinical characteristic and distinct electroencephalograph (EEG) findings (29). Symptomatic epilepsies are acquired conditions and the hallmark is an underlying structural abnormality of the brain. Cryptogenic epilepsy has no clear abnormality or risk factor identified but presents as symptomatic or acquired epileptic condition .The term progressive epilepsy is used when epilepsy is associated with an evolving neurological condition .The type of epilepsy can also be classified based on observed pattern of motor symptoms and awareness into either generalised or focal epilepsy. Long term cognitive outcomes in children differ depending on the type of epileptic syndrome (30).

Although a wide base of evidence indicates that benign focal epilepsies in childhood have no structural brain abnormalities and have a good prognosis in terms of seizure control, recent evidence suggests that benign focal epilepsy may be marred with impairment of global cognitive function, or difficulties with visual perception, attention, and deficits in memory (31). Specific cognitive impairments could originate in focal epilepsies in correlation with seizure focus.

Attention deficits and impairment of executive function are frequently described in frontal lobe epilepsy (32).Memory deficits almost always ensues in temporal lobe epilepsy particularly if caused by mesial temporal sclerosis and involvement of the limbic system (33)(34).

Generalized tonic clonic epilepsy and partial complex epilepsy have an increased risk of neurocognitive comorbidity (7) .Deficits in verbal attention, nonverbal attention, memory, execution of visual-motor tasks, and linguistic challenges have been described in absent seizures of childhood onset (35)(8)(26). Variable neurocognitive outcomes, ranging from normal cognitive development to cognitive delay are seen in myoclonic-astatic epilepsy (36).

1.3.3 Drugs

Anticonvulsants are the mainstay of therapy for different epileptic forms. Several guidelines are available based on response for the particular type of epilepsy diagnosed, individual susceptibility, tolerance, availability and also cost (reference). Antiepileptic drugs are a double-edged sword. They achieve control of seizure activity through inhibition of neuronal excitability, generally enhancing the quality of life of individuals living with epilepsy but have several adverse effects.

There are several anticonvulsants currently available in the market classified according to the mechanism of action. They are also broadly classified into the old generation and new generation antiepileptic drugs. Older AEDs (prior to1990), such as phenobarbital, can produce greater cognitive impairment. Case-control, studies on paediatric febrile convulsions have highlighted cognitive adverse effects of phenobarbital (37). However, carbamazepine, phenytoin, and valproic acid (VPA) are comparable in their cognitive effect (38). Topiramate, one of the new AED, is associated with significant memory and cognitive problems (39). The cognitive side effects of several anticonvulsants are dose-related and further worsened by polypharmacy (40). Oxcarbazepine (41), lamotrigine (42), and levetiracetam (43) are found to have no or few adverse effects on cognition. Use of a single effective drug has been shown to have better cognitive outcomes as compared to multiple drug regimens even when seizure control is achieved (15). There is evidence that drug-induced cognitive impairment has great impact on critical daily life function of patients with epilepsy (9)(44).

Several mechanisms have been proposed explaining the cognitive adverse effects of these drugs. Formation of free radicals, ischemia, apoptosis, folate and neuronal suppression are some of the postulated mechanisms (3). AEDs can be bio activated to free-radical reactive intermediates, which may adhere to key cellular macromolecules, resulting to destruction of deoxyribonucleic acid(DNA) and teratogenesis (45). Ischemia-induced embryopathy in animals is comparable to phenytoin-induced defects (46).

Ion channel modulators inhibit neuronal hyper excitability by inhibiting influx of particular ions in the neurons. Sodium ion channel blockers; commonly used antiepileptic drugs and include phenytoin, lamotrigine and carbamazepine. Calcium ion channel blockers include ethosuximide and gabapentin. Potassium ion channel blockers include retigabine. There are drugs that enhance GABA activity, which is an inhibitory neurotransmitter. They include benzodiazepine like clonazepam, tiagabine, vigabatrine and phenobarbital.

1.4 Diagnosis of cognitive dysfunction in childhood epilepsy

Cognitive assessment is an important component of diagnosing learning and behaviour problems in children with epilepsy. A thorough assessment will depend on functional information gleaned from careful clinical interviewing, observations of how the child performs, and finally, the results of psychiatric tests. Clinical assessment of children with epilepsy need to take into account the child's age and developmental level, and factors related to epilepsy. The underlying neuropathology may lead to different problems at different ages. In addition, not only will appropriate tests differ radically depending on the age of the child, but the child's age at testing and age at onset of epilepsy will also affect their performance on assessment and outcomes.

1.5 Mental state exam

The mini mental state examination (MMSE) was developed in 1975 by Folstein and Mchugh as a short quantitative assessment of cognitive impairment in adults. It is a brief questionnaire that has 30 points aggregated as five domains of cognition that are assessed. These include orientation, immediate and short-term memory, attention and calculation, language and praxis. One major challenge in the use of mini mental state examination tool is the low sensitivity in establishing mild cognitive impairment. Age and level of education, cause considerable bias in

MMSE scores rendering it a challenge to use in the paediatric population. These factors led to modification of the original mental state examination tool creating the modified mini mental state exam tool for the paediatric population.

In an attempt to develop a tool suitable for assessing cognitive function in children, Ouvrier et al modified the original mental state examination and adapted it for use in the paediatric population. The adapted version modified MMSE has several minor modifications incorporated from the mini-mental state examination and takes 5 to 10 minutes to administer. The modified version has an additional 5 points, making the total score 37, shortened the word to be spelt in assessment of language, repeated items for recall twice and created age adjusted cut-off points.

The findings of Ouvrier et al indicated that the MMSE could be used with children from the age of 4 to 12 years. The total that scores obtained is out of a maximum of 37. At the mental age of about 9 or 10 years, the score on the MMSE plateau as evidence suggests the child's performance on the test corresponds with normal adult performance. MMSE values below 27, in children above 10 years, suggested impaired cognitive functioning (15).

The modified MMSE was used to screen for poor cognitive function in two cohorts of children in India. One cohort had identified neurological illness of various aetiologies and the other cohort was of normal children. The MMSE identified children with poor outcomes with a sensitivity of 68% and specificity of 100% (47).

A population-based study carried out in Spain, aimed to analyse results of the modified MMSE and asses the usefulness of the instrument as a cognitive screening tool for children's development. The researchers also aimed to assess the relationship between MMSE scores and intelligent quotients of the children scores on the MMSE were found to correlate significantly either their chronological age and mental age (48).

One study in Australia compared all the available tools for assessing cognitive function in children. The modified mini mental status examination tool, the paediatric mini mental state exam tool and the school years screening test for evaluation of mental status (SYSTEMS). In the clinical study the modified MMSE revealed a sensitivity of 83%, specificity of 67%, positive predictive value of 52%, and likelihood ratio of 2.51. Paediatric Mini-Mental State Examination

results were better with a sensitivity of 83%, specificity of 81%, positive predictive value of 65%, and likelihood ratio of 4.37. The SYSTEMS results revealed a sensitivity of 83%, specificity of 76%, positive predictive value of 60%, and likelihood ratio of 3.46 (49).
The modified mini mental status examination tool has been chosen as the study tool because it is brief, has been used over years in the paediatric population to screen for cognitive impairment. It has been studied and validated in the black American, Canadian, Spanish, Indian and Australian populations and has acceptable sensitivity.

The modified mini mental state exam tool has been used in Kenya to assess cognitive function in youths suffering from depression.(6) It has also been used as a screening tool to identify cognitive dysfunction in diabetic children at Kenyatta national hospital.(50)

CHAPTER TWO

LITERATURE REVIEW

2.1 Statement of the Problem

Children living with epilepsy have a higher risk of a broad range of cognitive disturbances and are predisposed to significant intellectual disability. Optimal cognitive function in children is crucial for normal growth and development. It has a direct correlation with appropriate social interaction; academic achievement and quality of life of individuals living with epilepsy (15). Some of the factors that are attributed to cognitive dysfunction in epilepsy are modifiable factors like polypharmacy, high doses of antiepileptic drugs and the type of anticonvulsant drug in use.

Screening for cognitive dysfunction is not a routine undertaking by clinicians offering care to children living with epilepsy. The problem goes undiagnosed and unaddressed. Patients, caregivers and educators thus lack information pertaining to cognitive function and the effects on quality of life.

2.2 Justification of the Study

This study will highlight the burden of cognitive dysfunction among children living with epilepsy. Findings may be vital in advocating for cognitive function screening as part of treatment for children living with epilepsy. Prompt identification of cognitive impairment will enable provision of early developmental interventions, appropriate schooling programs and vocational counselling. This will promote independence across the lifespan of children with epilepsy. This study will provide data on factors associated with cognitive dysfunction. These data will be useful in filling the knowledge gap, and may be pivotal in influencing guidelines on the choice of anticonvulsants in paediatric clinical practice and procurement choices.

CHAPTER THREE

RESEARCH QUESTION

What is the prevalence, pattern and factors associated with cognitive dysfunction in children with epilepsy at Kenyatta National Hospital?

3. Objectives

3.1 Primary objective

i. To determine the prevalence and pattern of cognitive dysfunction in children aged 7-13 years on treatment for epilepsy at the paediatric neurology clinic in Kenyatta national hospital.

3.2 Specific objective

ii. To determine the factors associated with cognitive dysfunction in these children. Specifically, to determine whether the type of epilepsy, type and dose of anticonvulsant drug, seizure control and age of onset of epilepsy are associated with cognitive dysfunction.

CHAPTER FOUR

RESEARCH METHODOLOGY

4.1 Research Design

Descriptive cross-sectional hospital based study.

4.2 Population

4.2.1 Study Population

Children aged 7-13 years with a diagnosis of epilepsy attending the paediatric neurology clinic. This diagnosis of epilepsy was established from the medical file records by reviewing the clinicians' notes and a review of the electroencephalogram and brain scans. We further took collaborative history from the care givers.

4.2.2 Inclusion criteria

Diagnosis of epilepsy was based on the clinicians' notes, EEG and brain CT-scan and collaborative history.

Children aged 7-13 years.

4.2.3 Exclusion criteria

1. Children who had a convulsion 24hrs before administration of the questionnaire.
2. Children who had not started formal education were excluded from the study as the scores on the mini mental status tool are dependent on level of education.
3. Children whose parents failed to give consent.

4.3 Study period

The study period was conducted from October 2019 to November 2019.

4.4 Study site

The study was conducted at Kenyatta national hospital (KNH), which serves as one of the two national referral hospitals. It is situated in Nairobi, the capital centre of Kenya. KNH receives patients from across the country but majority of the patients come from within the capital and

nearby counties. It is also one of the county hospitals for Nairobi and serves approximately two million people in Nairobi. According to the 2018 KNH medical records, 2,262 children with neurological problems were reviewed in the outpatient clinic.

It was conducted at the paediatric neurology clinic which runs every Tuesday from 2.00pm to 5.00pm. This clinic is within the paediatric outpatient area. It is run by a consultant neurologist who is assisted by resident doctors from the department of paediatrics. All children aged 1 month to 13 years with neurological conditions that need a neurologist review and follow up are seen at this clinic. The clinic receives an average of 50 patients every clinic day, majority are children with a diagnosis of epilepsy. In this clinic all new patients are reviewed by the consultant neurologist, diagnosis is established and treatment commenced. The patients are seen regularly for prescription refill and review of medication.

4.5 Sampling design

The principal investigator reviewed the patients' medical records from 11.00am as the patients were awaiting review in the neurology clinic which commenced at 2.00 pm every Tuesday. All children who met the inclusion criteria were identified. The principal investigator introduced herself to the caregivers and potential study participants, explained the study procedure and sought consent. Eligible individuals were recruited by consecutive sampling until the desired sample size was achieved.

4.6 Study Tool

The modified mini mental state examination is a questionnaire that assesses the five domains of cognition. These domains include: i) orientation, ii) attention and concentration, iii) registration and sensory perception, iv) recall and v) language. It was administered in English and Swahili depending on the language that the child was most conversant with. The principal investigator and the research assistant familiarised themselves with the use of the modified MMSE downloadable user manual that is available online. A qualified psychiatrist familiar with the tool demonstrated how to administer and trained the research assistants.

The tool comprised of a series of standardised questions that assess orientation in place time and person. It involved asking the participants to state their name, date, place and time and for each

correct answer a mark is given, while zero is given for no response. Language domain was assessed by asking the participants to name five body parts that will be pointed out by the interviewer. A three-step command to fold a paper and give it to the interviewer was used for all study participants.

The total score is a maximum of 37. Orientation had 12 points in total, attention and concentration had a maximum score of seven, registration had three points, recall three points, and language had a total of 12 points. Standard age adjusted cut-offs were used to classify the score as either normal or cognitive impairment.

4.7 Sample size determination

The Cochran's formula for estimating sample size in prevalence studies was used with a finite population correction.

$$n = \frac{NZ^2P(1-p)}{d^2N - 1 + Z^2P(1-P)}$$

n = sample size

N = population of epileptic children attending clinic at KNH per month is estimated at 200, yielding a population of 400 for the study period.

P = Prevalence of cognitive dysfunction in children with epilepsy in a study by Berg etal (12) 27%

1-P = 1 minus the prevalence of cognitive dysfunction.

Z = Z statistic representing 95% level of confidence (1.96)

d = desired level of precision set to 5% (0.05)

$$n = \frac{400\ x\ 1.96^2 x\ 0.27(1-0.27)}{0.05^2 x 400 - 1 + 1.96^2 x 0.27(1-0.27)}$$

$$n = 171$$

4.8 Data Collection

Study participants were recruited from the paediatric neurology clinic. Children with a diagnosis of epilepsy were identified from the medical records. This was based on clinician notes, EEG findings and brain scans. The main researcher went through the potential participants medical file records to identify children that fit the inclusion criteria and also identify aspects that excluded the children from participating in the study. Consent was sought from caregivers of children that fit the inclusion criteria. In a private consultation room within the clinic, the main researcher explained to the caregiver the purpose of the study and sought consent to obtain medical records of their children and ask a series of questions to the children .We also informed them of the benefits of doing this study which included appropriate referral for neuro-rehabilitation for patients with moderate or severe cognitive dysfunction. Age appropriate assent was also sought from children in a language that they were conversant with.

A structured questionnaire was administered to capture the independent variables which included participants' demographic data like age, gender, level of education and the seizure variables that are linked to cognitive dysfunction in epilepsy which included time of onset of epilepsy, type of seizure disorder, remission status and type of anticonvulsants. The dependent variable was the cognitive function which was assessed using the modified MMSE tool.

Two research assistants who are clinicians in the field of psychiatry assisted in administering the mental state exam .The research assistants were trained by a qualified psychiatrist. A series of questions were administered to the children participating in the study then total scores were tallied and compared to age adjusted cut off points. The results were classified as either normal cognitive function or abnormal cognitive function.

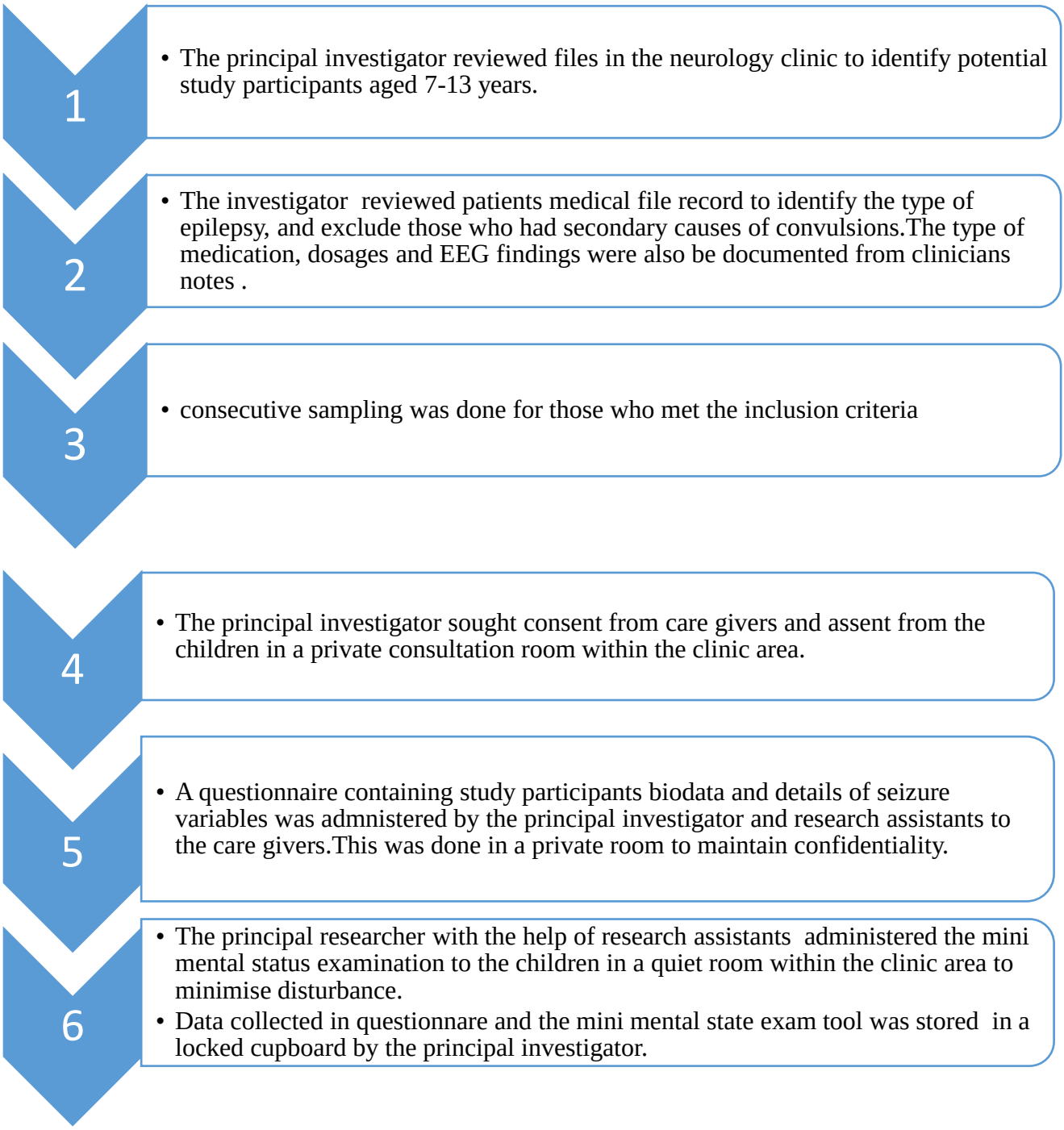
4.8.1 Data storage

Hard copy questionnaires and the filled out mental state exam were stored in folders under lock and key by the principle investigator. Data was coded then entered using SPSS version 24.. Electronic data was be saved in a laptop and protected by a password.

4.9 Data Analysis and Presentation

The first objective was answered by estimating the proportion of children that had cognitive impairment after administration of the mini mental status exam and providing a 95% confidence interval around this estimate. Continuous variables like age, age of onset of epilepsy, duration of treatment with anticonvulsants drugs, were summarized as medians with interquartile ranges. Categorical variables like level of education and gender were computed as proportions/percentages. Chi square test was used to determine association between cognitive dysfunction and seizure variables. In those variables that had a $p<0.05$ in univariate analysis, multivariate logistic regression was done to obtain adjusted odds ratios of association between cognitive function and some seizure variables like type of epilepsy, type of antiepileptic drugs, and frequency of seizure. These factors were included in the model apriori, and were informed by the literature.

4.10 Research Work Flow



4.11 Ethical Consideration

Ethical approval was obtained from Kenyatta National Hospital and University of Nairobi (KNH/UON) Ethics and Research Committee (ERC) before the study. The study was carried out based on the ethical standards set out in the ERC guidelines. (P27/07/2019)

At the end of every mini mental state assessment, the parents were be informed about the total score and were given a copy of the results. The interpretation and hardcopies of the results were filed in the medical records. The research assistants who are clinicians in psychology counselled the parents about the prognosis and rehabilitation options for children found to have cognitive dysfunction. Children found to have cognitive impairment were referred to the department of mental health which is headed by a child and adolescent psychiatrist for further assessment, counselling and rehabilitation.

5. RESULTS

A total of 177 children participated in the study. Majority of the participants were aged 9-12 years (67.8%).The median age was 10years (8, 11).A total of 111(62.7%) males were recruited, while 66 (37.3%) were female. All the participants had formal education with 120(67.8%) being in lower primary, 45(25.4%) in upper primary and 12 participants were in special school.

Table 2: Social-demographic characteristics of study participants

Demographic characteristics (n=177)	Frequency (n)	Percentage (%)
Age		
≤8	28	15.8
9-12	120	67.8
>12	29	16.4
Gender		
Male	111	62.7
Female	66	37.3
Education		
Lower (Grade 1-4)	120	67.8
Upper (Class 5-8)	45	25.4
Special school	12	6.8

The county of residence for majority of the participants was Nairobi County (59.3%).This was followed by Kiambu and Machakos County at 16.4% and 13% respectively. Figure 2 below describes the study subjects by place of residence.

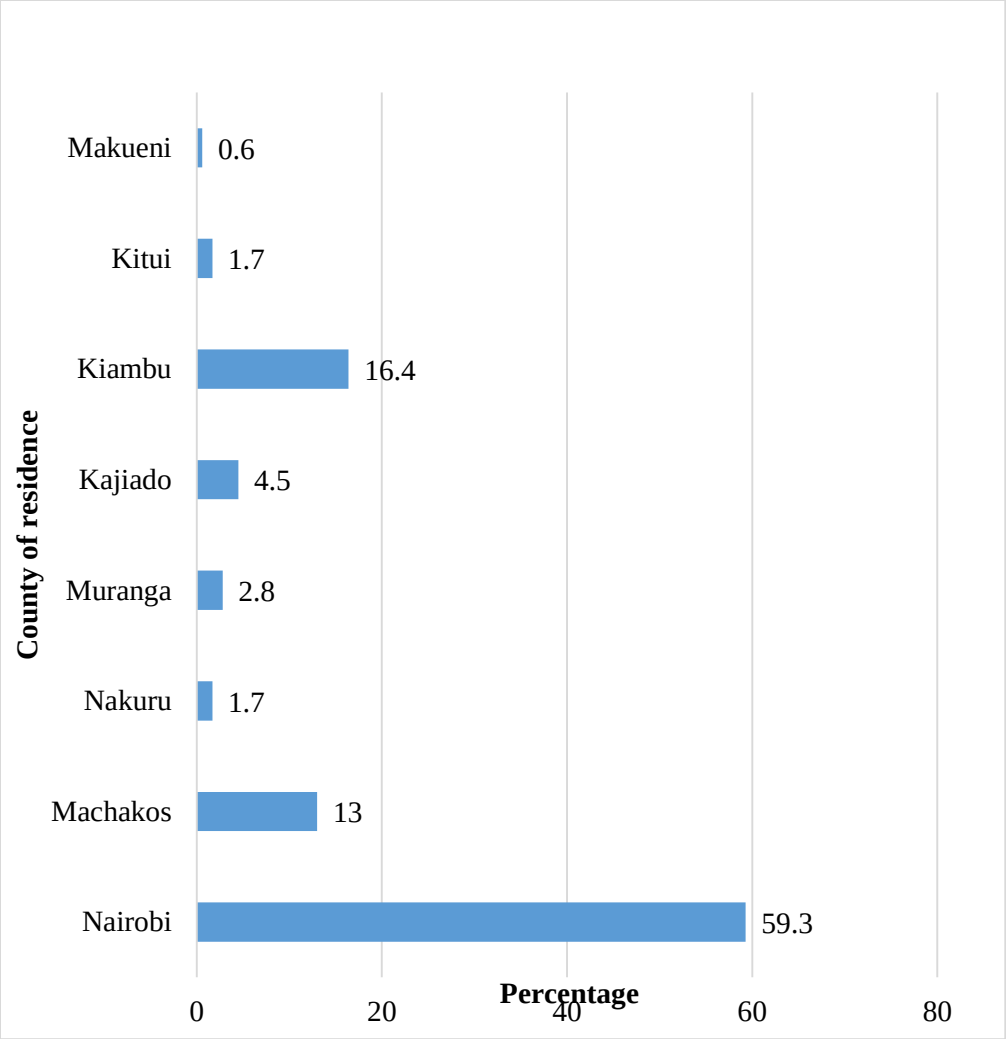


Figure 2: County of residence of the participants

Prevalence of cognitive dysfunction

An overall MMSE score was computed using cognitive performance data from the five sub-domains and applying age-specific cut-offs to classify overall cognitive function as normal or low MMSE scores. Among 177 total study participants, 72(40.7%) had cognitive dysfunction as seen below in figure 3.

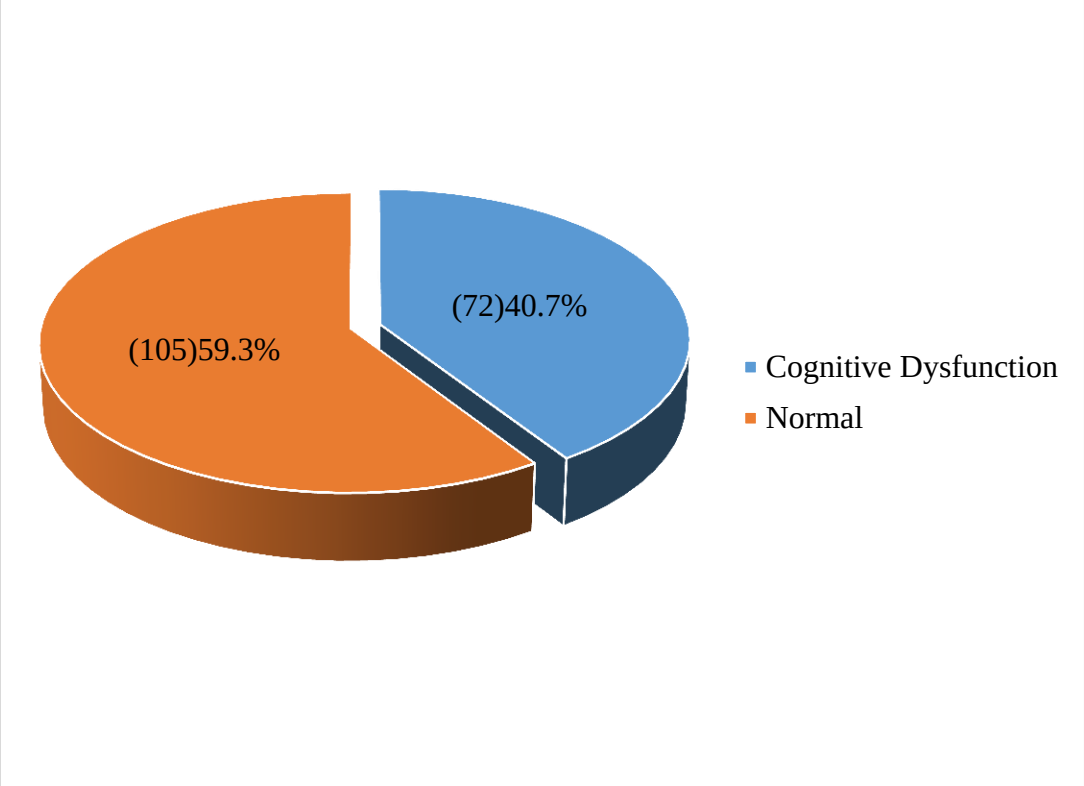


Figure 3: Proportion of children with cognitive dysfunction

Performance in the five sub-domains of the MMSE

The pattern of cognitive dysfunction is illustrated below in table 3.The mean score for orientation in children with cognitive dysfunction was 6.81(±2.47) compared to children who had normal cognitive function with a mean score of 11.15(±1.87).Registration had a maximum score of three. Those with cognitive dysfunction had a mean score of 2.19(±0.85) compared to those with normal cognition having a mean score of 2.96(±0.19).Those with cognitive dysfunction attained lower mean scores in attention 2.9(±1.26) compared to those with normal cognition who had a mean score of 5.53(±1.06).In the sub domain of recall, out of a maximum score of three, participants with cognitive dysfunction had a mean score of 1.74(±0.99) compared to 2.95(±0.21) in those with cognitive dysfunction. Children with cognitive dysfunction had lower mean score 7.82(±2.57) compared to those with normal cognition 11.62(±1.06).

Table 3: Mean scores in the five sub-domains

	Cognitive dysfunction n=72	**Normal n=105**
Domains(Total score)	**Mean score (SD)**	**Mean score (SD)**
Orientation(12)	6.81 (±2.47)	11.15 (±1.87)
Registration(3)	2.19 (±0.85)	2.96 (±0.19)
Attention(7)	2.9 (±1.26)	5.53 (±1.06)
Recall(3)	1.74 (±0.99)	2.95 (±0.21)
Language(12)	7.82 (±2.57)	11.62 (±1.06)

Association between cognitive dysfunction and type of epilepsy

The results from figure 4 reveal more than half 67.4 %(n=29) of those with focal motor seizure had cognitive dysfunction. Children with generalised non motor epilepsy performed dismally with almost half 45.5 %(n=10) attaining low MMSE scores. The proportion of children with generalised motor epilepsy who had cognitive dysfunction was less than the other two types of epilepsy 29.5 %(n=33).

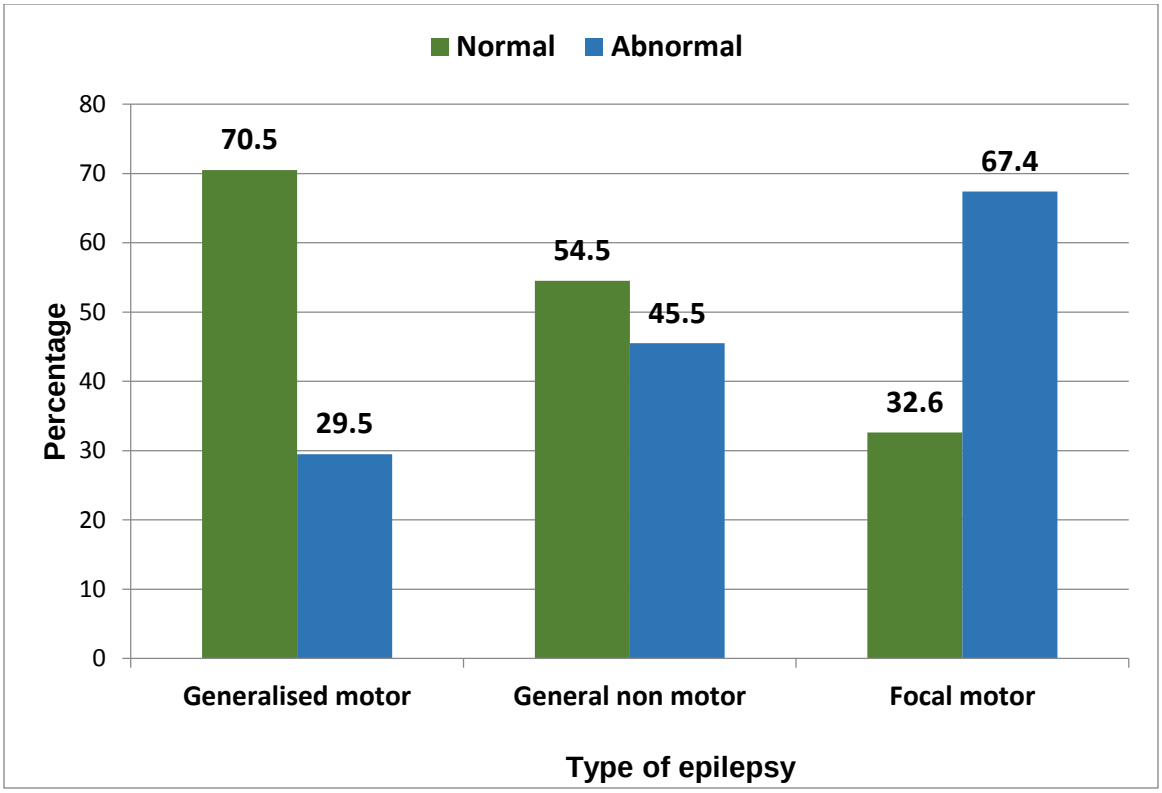


Figure 4: Relationship between cognitive dysfunction and type of epilepsy

Table 4: Association between cognitive dysfunction and the type of epilepsy

Type of epilepsy	Normal cognitive function N=105	Cognitive dysfunction N=72	OR(95%CI)	P-value
Focal motor	14(32.5%)	29(67.4%)	4.7(1.18-18.5)	0.028
Generalised non motor	12(54.5%)	10(45.5%)	5.0(1.94-12.98)	0.001
Generalised motor	79(70.5%)	33(29.5%)	1	

Children with focal motor epilepsy had a fourfold likelihood of having cognitive dysfunction compared to children with generalised motor epilepsy, OR=4.7(95%CI 1.18, 18.5) P=0.028. In children with generalised non motor epilepsy, the odds of having cognitive dysfunction was five folds higher compared to children with generalised motor epilepsy, OR=5(95%CI 1.94 12.98) p=0.001.

Association between type of anticonvulsant drug and cognitive dysfunction

Phenobarbital and sodium valproate were the most common anticonvulsants in use with 73 out of 177 participants on these medications. Carbamazepine and sodium valproate were significantly associated with cognitive dysfunction. Use of phenytoin, clonazepam and lamotrigine showed no significant association with cognitive disturbance. This is highlighted below in table 5.

Table 5: Relationship between the type of anticonvulsant and cognitive dysfunction

Treatment	n	Cognitive function		df	P
		Cognitive dysfunction	Normal		
Phenobarbital					
Yes	73 (41.2)	32 (44.4)	41 (39.0)	1	0.474
No	104 (58.8)	40 (55.6)	64 (61.0)		
Phenytoin					
Yes	19 (10.7)	7 (9.7)	12 (11.4)	1	0.719
No	158 (89.3)	65 (90.3)	93 (88.6)		
Carbamazepine					
Yes	62 (35.0)	39 (54.2)	23 (21.9)	1	<0.0001
No	115 (65.0)	33 (45.8)	82 (78.1)		
Sodium Valproate					
Yes	73 (41.2)	37 (51.4)	36 (34.3)	1	0.023
No	104 (58.8)	35 (48.6)	69 (65.7)		
Clonazepam					
Yes	3 (1.7)	2 (2.8)	1 (1.0)	1	0.355
No	174 (98.3)	70 (97.2)	104 (99.0)		
Lamotrigine					
Yes	5 (2.8)	1 (1.4)	4 (3.8)	1	0.34
No	172 (97.2)	71 (98.6)	101 (96.2)		

The likelihood of having cognitive dysfunction in children on carbamazepine OR=4.2(95%CI 2.19 8.11)p<0.0001 or sodium valproate OR=4.21(95% CI 1.10 3.74)p=0.023 was four folds higher than in children not on either of these two drugs. This is summarised in table 6 below.

Table 6: Drugs associated with cognitive dysfunction

Treatment	n (%)	Cognitive dysfunction	P	OR (95% CI)
Carbamazepine				
Yes	62 (35.0)	39 (54.2)	<0.0001	4.21 (2.19 - 8.11)
No	115 (65.0)	33 (45.8)		REF
Sodium Valproate				
Yes	73 (41.2)	37 (51.4)	0.023	4.21 (1.10 - 3.74)
No	104 (58.8)	35 (48.6)		REF

The results on table 7 show majority of the study participants were on a single drug regimen (63.7%).More than half (60.6%) of those on combination drug regimen had cognitive dysfunction. Being on combination drug regimen was significantly associated with cognitive dysfunction p<0.001.

Table 7: Relationship between the drug regimen and cognitive dysfunction

Treatment	n =171	Cognitive function		df	P
		Cognitive dysfunction	Normal		
Single drug	109 (63.7)	28 (39.4)	81 (81.0)	1	<0.001
Combination	62 (36.3)	43 (60.6)	19 (19.0)		

Association between frequencies of convulsions; age of onset of seizures and cognitive dysfunction

Majority of the participants had less than two convulsions in the last one year. For those with frequent convulsions, more than half of them 53.7 %(n=36) had cognitive dysfunction. Higher frequency of convulsions increased the likelihood of cognitive disturbance by approximately four folds OR=3.79(95%CI 1.94 7.40) p<0.001. Most of the participants 66.7 %(n=118) had an early age of onset of seizures, compared to 33.3% who had a later age of onset of the convulsions. The mean age of onset was 1.33years (±0.47) .Early age of onset of epilepsy increased the likelihood of cognitive dysfunction by three folds, OR=3.11(95%CI 1.54 6.26) p=0.002. These results are summarised below in table 8.

Table 8: Relationship between cognitive dysfunction and age of onset /frequency of seizures

Treatment	N (%)	Cognitive dysfunction N (%)	P	OR (95% CI)
Convulsions				
Frequent>2 convulsions/year	59 (35.8)	36 (53.7)	<0.001	3.79 (1.94 - 7.40)
Less frequent≤2 convulsions/year	106 (64.2)	31 (46.2)		REF
Age of onset of convulsions (Years)				
≤5 years Early onset	118 (66.7)	58 (80.6)	0.002	3.11 (1.54 - 6.26)
>5years Later onset	59 (33.3)	14 (19.4)		REF

Multivariate analysis

The results in table 9 below show multivariate logistic regression analysis of factors that were significantly associated with cognitive dysfunction on univariate analysis. In this model, frequent convulsions, generalised non motor, focal epilepsy, early age of onset of epilepsy, use of carbamazepine and sodium valproate were associated with cognitive dysfunction.

Table 9: Multivariate analysis on factors associated with cognitive dysfunction

Seizure variable	n (%)	Cognitive dysfunction n (%)	P	Adjusted OR (95% CI)
Convulsions				
Frequent>2 convulsions/year	59 (35.8)	36 (53.7)	<0.001	3.78 (1.91 - 7.47)
Less frequent	106 (64.2)	31 (46.2)		REF
Epilepsy				
Generalised motor	112 (63.3)	33 (45.8)		REF
Generalised non-motor	22 (12.4)	10 (13.9)	<0.001	4.71 (0.93 - 7.96)
Focal motor	43 (24.3)	29 (40.3)	0.028	4.72 (1.18- 18.85)
Age of symptom onset (Years)				
≤5	118 (66.7)	58 (80.6)	0.002	2.77 (1.35 - 5.69)
>5	59 (33.3)	14 (19.4)		REF

Treatment	n	Cognitive dysfunction	P	Adjusted OR (95% CI)
Carbamazepine				
Yes	62 (35.0)	39 (54.2)	<0.0001	4.89 (2.44 - 9.66)
No	115 (65.0)	33 (45.8)		REF
Sodium Valproate				
Yes	73 (41.2)	37 (51.4)	0.036	1.95 (1.04 - 3.63)
No	104 (58.8)	35 (48.6)		REF

6. DISCUSSION

In this crossectional study, the primary outcome was cognitive dysfunction, which was assessed using a validated standardised tool called the modified mini mental state exam. The prevalence of cognitive dysfunction was 40.6%.This is higher than a large multicentre study done in the United States of America to assess cognitive function of epileptic children which reported a prevalence of 26.4% (12).This could be due to differences in population characteristics like socioeconomic status. Low socioeconomic status in sub-Saharan Africa increases the likelihood of untreated epilepsy since use of anticonvulsants is dependent on the buying power of the patient. Poor control of the epilepsy increases the risk of cognitive disturbances. This higher prevalence could also be due to differences in the study tool. This prevalence is however comparable to studies done here in Africa on Nigerian children estimating the prevalence of cognitive dysfunction at 41% and 47.5% (24).The results of cognitive dysfunction in this study mirror a study done by in KNH to asses for emotional and behavioural problems in children with epilepsy, which is part of a large spectrum of cognitive disturbances and reported the prevalence of behavioural problems at 46% (5).

Cognition involves the ability to solve problems, memorise information or to focus attention (51). A considerable body of research highlight that memory; sustained attention and motor fluency appear to be particularly vulnerable areas of functioning in epilepsy (9)(52). In this study, the composite mean scores in the domains of attention, language and recall were lower in those children with cognitive dysfunction compared to children who had normal cognitive function on the MMSE.This finding is consistent with several other studies which highlight this (14)(13)(5).

Approximately three in every four children had generalised motor epilepsy. This is comparable to two Kenyan studies that estimated 76.8%of children had generalised motor epilepsy (5). More than half (67.4%) of those with cognitive dysfunction had focal motor epilepsy. Generalised non motor epilepsy and focal motor epilepsy were associated with cognitive dysfunction. A diagnosis of either focal motor epilepsy or generalised non motor epilepsy increased the likelihood of cognitive dysfunction by four five folds. This finding is consistent with literature which highlight the cognitive effects in focal and absent seizures are due to the underlying pathophysiology (31)(7)(8).

Majority of the children (62.7%) were on single drug regimen. Phenobarbital and sodium valproate were the most prescribed anticonvulsants. This may be attributed to easy availability and more affordable compared to phenytoin and carbamazepine. The two drugs that were associated with cognitive dysfunction were carbamazepine and sodium valproate. Phenobarbital and phenytoin were not associated with cognitive dysfunction. Many studies reveal that old generation anticonvulsants have worse cognitive side effects than new generation anticonvulsants (37)(15). This study however does not reflect this. This could be because most of those on sodium valproate and carbamazepine were on combination therapy. Use of more than one anticonvulsant has an additive effect on cognitive disturbance (40). This is reflected in this study as the likelihood of having cognitive dysfunction was higher in those on combination drug regimen compared to single drug regimen. The drug effect is usually dose dependent measured by serum levels, however this was not evaluated.

Most children (64.2%) had inactive epilepsy which is defined as less than two convulsions in a year. Those with frequent convulsions had a higher likelihood of having cognitive dysfunction. This is consistent with several studies which indicate that seizure control is crucial in optimising cognitive function in epilepsy (13)(53). More than 60% of the participants had an early onset of epilepsy. The men age of onset of epilepsy was years1.33 (±0.47).Early onset of seizures increased the likelihood of cognitive dysfunction by three folds compared to later childhood or adolescent onset. This finding correlates with several authors(28)(54). Earlier onset of epilepsy predisposes the brain to longer exposure to seizure effects. This is crucial since early childhood marks the onset of learning.

Strengths

This study had several strengths that include use of a validated tool for cognitive assessment. The research assistants were trained clinicians in the field of psychology hence conversant with the tool. The study was conducted in a well-established neurology clinic where more than 90%of the participants had EEG scans.

Study limitations

The major limitation of this study was that it was a cross-sectional study, meaning that exposure and outcome were measured at the same time hence causal relationship could not be ascertained. The study relied to caretaker narration on some of the aspects of the seizure variables and drug

us is subject to misinformation and re-call bias. Accurate classification of the type of seizure and epilepsy syndrome was difficult as it requires genetic testing to formulate a precise diagnosis. The modified mini mental state exam tool has a limitation in that it cannot detect mild cognitive dysfunction.

7. CONCLUSION

There is a high prevalence of cognitive dysfunction in children living with epilepsy on follow up in the paediatric neurology clinic of KNH.The domains of cognition that revealed poor performance include: Attention, recall, language and orientation.

Factors that are significantly associated with cognitive dysfunction included: Type of epilepsy (focal motor and generalised non motor epilepsy), type of anticonvulsant drug (carbamazepine and sodium valproate), higher frequency of convulsions and early onset of epilepsy.

8. RECOMMENDATION

i. Cognitive assessment is recommended as part of evaluation of patients with epilepsy.

ii. Clinicians in the paediatric neurology clinic should be sensitised to risk stratify children with epilepsy based on the significant factors associated with cognitive dysfunction: sodium valproate, carbamazepine, focal motor epilepsy, and early age of onset and high frequency of seizures.

iii. A larger study where serum drug levels are measured and correlated with cognitive dysfunction is recommended.

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APPENDIX I: CONSENT FORM

PARTICIPANT INFORMATION AND CONSENT FORM

PARENTAL CONSENT

Title of Study: PREVALENCE OF COGNITIVE DYSFUNCTION IN EPILEPSY

Principal Investigator: Dr. Esther opuba.

Supervisors: Dr.Nyambura Kariuki, Dr. Diana Marangu, Dr.Josephine Omondi

Institutional affiliation: Department of paediatrics, university of Nairobi.

Introduction:

I would like to tell you about a study being conducted by Dr. Esther Opuba. The purpose of this consent form is to give you the information you will need to help you decide whether or not your child should participate in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits, the rights of your child as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide if you want your child to be in the study or not. This process is called 'informed consent'. Once you understand and agree for your child to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: Your child decision to participate is entirely voluntary .You child may withdraw from the study at any time without necessarily giving a reason for his/her withdrawal. Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities.

May I continue? YES / NO

For children below 18 years of age we give information about the study to parents or guardians. We will go over this information with you and you need to give permission in order for your child to participate in this study. We will give you a copy of this form for

your records.

If the child is at an age that he/she can appreciate what is being done the he/she will also be required to agree to participate in the study after being fully informed.

WHAT IS THE PURPOSE OF THE STUDY?

The researchers listed above are interviewing children with a diagnosis of epilepsy. The purpose of the interview is to assess the mental status in children living with epilepsy. Participants in this research study will be asked questions **that evaluate their thought process, mental speed and language.**

There will be approximately 200 participants in this study randomly chosen. We are asking for your consent to consider your child to participate in this study.

WHAT WILL HAPPEN IF YOU DECIDE YOU WANT YOUR CHILD TO BE IN THIS RESEARCH STUDY?

If you agree for your child to participate in this study, the following things will happen:

You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 15minutes.First you will be asked questions pertaining to your child's diagnosis .These will include questions that will be administered from a questionnaire to characterise your child's convulsions, and the drugs that they take. After completing the questionnaire, the interviewer will guide your child through a short exercise that includes asking questions that asses if the child knows his or her identity, the date and time, list some simple objects and draw a simple shape. At the end of the mental status examination we will tell you the total score and interpret it for you. We will give you a copy of the results and if your child needs further assessment and interventions you will be counselled and guided on how to go about it.

ARE THERE ANY RISKS, HARMS, DISCOMFORTS ASSOCIATED WITH

THIS STUDY

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting confidentiality can be absolutely secure so it is still possible that someone could find out your child was in this study and could find out information about your child.

If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

All study staff and interviewers are professionals with special training in this examination.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Your child may benefit by receiving free mental assessment. You may be counselled on how to detect subtle impairment of cognitive function. We will refer your child to a hospital for care and support if necessary. This information is a major contribution to science and medicine.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

You are not expected to pay anything to be in this study.

IS THERE REIMBURSEMENT FOR PARTICIPATING IN THIS STUDY?

There is no monetary benefit of being in the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about your child participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your child's rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits.

Just inform the study staff and the participation of your child in the study will be stopped. You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counsellor. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw it any time.

I understand that all efforts will be made to keep information regarding me and my child's personal identity confidential.

By signing this consent form, I have not given up my child's legal rights as a participant in this research study.

I voluntarily agree to my child's participation in this research study:

	Yes	**No**
I agree to have my child undergo cognitive testing.	Yes	No
I agree to provide contact information for follow-up.	Yes	No

Parent/Guardian signature /Thumb stamp:_____ Date _____

Parent/Guardian printed name: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____

Signature: _____

Role in the study:_____

Witness Name _____

Signature:_____**Date**; _____

APPENDIX II: CONSENT INFORMATION DOCUMENT (SWAHILI)

HATI YA RIDHAA

Andiko:
Idadi ya shida za hisia na tabia miongoni mwa watoto wanaotibiwa ugonjwa wa kifafa katika kliniki ya neurology ya watoto ya hospitali kuu ya Kenyatta.
Mpelelezi:
Dr. Esther Opuba
Wasimamizi:
Dr.Nyambura Kariuki
Dr. Diana Marangu
Dr.Josephine Omondi

Utangulizi
Mimi Dr.Esther Opuba ni mwanafunzi wa uzamili katika chuo kikuu cha Nairobi.

Ningependa kufanya utafiti huu kuhusu idadi ya shida za hisia na tabia miongoni mwa watoto wanaotibiwa ugonjwa wa kifafa katika kliniki ya neurology ya watoto ya hospitali kuu ya Kenyatta.
Ningependa kukukaribisha katika utafiti huu.

Maelezo kuhusu utafiti na lengo la utafiti
Huu ni utafiti wa maelezo miongoni mwa watoto wanaopokea matibabu ya ugonjwa wa kifafa ambao wanafuatiliwa katika kliniki ya neurology ya watoto katika hospitali kuu ya Kenyatta. Wagonjwa watakaohusishwa wako na umri katikati ya miaka saba na miaka kumi na ta na wazai wao wako tayari kushiriki katika utafiti
Huu utafiti unalenga kupata kiwango cha shida za hisia na tabia miongoni mwa watoto walio na ugonjwa wa kifafa.
Washiriki wapatao mia moja, sabini na saba (177) watahusishwa katika muda wa yapata miezi miwili katika ukusanyaji wa takwimu.

Mahitaji ya kushiriki
Ili kushiriki katika utafiti huu mtoto wako anahitajika;

1. Kuwa na umri katikati ya miaka sita na miaka kumi na minane
2. Kuwa anatibiwa ugonjwa wa kifafa

Utaratibu
Ukikubali kushiriki katika utafiti huu;

1. Utaulizwa kutia sahihi fomu ya kuridhia kushiriki kwa hiari yako.

2. Utaulizwa maswali kuhusu jamii yako na maisha yako na ya mtoto wako ya kila siku, na maswali kuhusu tabia za mtoto wako. Hii itakuwa katika dodoso litalochukua muda wa dakika ishirini (20).

Faida

Hakuna faida ya moja kwa moja kwa kushiriki katika utafiti huu.

Hata hivyo, matokeo ya utafiti huu yatasaidia wagonjwa, walezi na madaktari kuelewa vyema ushirikiano baina ya magonjwa ya akili na ugonjwa wa kifafa katika watoto. Hii itasaidia kuboresha matibabu ya wagonjwa na pia katika utekelezaji wa mikakati ya matibabu ya ugonjwa wa kifafa katika watoto.

Mtoto wako akipatikana na ugonjwa wa akili, atatumwa kutibiwa katika kliniki ya magwonjwa ya akili ya watoto katika hii hospitali.

Hatari Ya Usumbufu

Kuna uwezekano unaweza kuhisi wasiwasi ukipeana habari kuhusu tabia za mtoto wako.

Nugependa kukuarifu ya kwamba maelezo yoyote utakayopeana itawekwa kwa faragha na itatumika kwa huu utafiti pekee.

Kushiriki Kwa Hiari

Kushiriki kwako katika utafiti huu ni kwa hiari yako na ukiamua kushiriki una uhuru wa kuondoka kwa wakati wowote. Unaweza pia kuamua kutojibu baadhi ya maswali.

Uamuzi wako kutoshiriki ama kuondoka kutoka kwa utafiti hautaadhiri matibabu ya mtoto wako katika hospitali kuu ya Kenyatta kwa sasa au katika siku za usoni.

Faragha

Utambulisho wa mtoto wako utawekwa kwa faragha. Jina la mtoto wako wala namna yoyote ya kumtambulisha hazitatumika kwa ripoti yoyote ya utafiti huu. Badala yake atapewa nambari ya kulinda utambulisho.

Dodoso (Fomu ya maswali ya utafiti) utakayojaza itahifadhiwa kwa usalama, hakuna mtu ataweza kuifikia isipokuwa mimi au wasimamizi wangu. Takwimu zitakazokusanywa katika utafiti huu zitahifadhiwa kwa komputa an kuzuiliwa kwa watu wengine. Komputa zitakazohifadhi takwimu zitalindwa na nywila au namba za kisiri ili kulinda takwimu kutokana na matumizi yasioidhinishwa, kupotea ama marekebisho.

Fidia

Hakuna fidia yoyote kwa kushiriki katika utafiti huu.

Maelezo Zaidi

Iwapo unahitaji ufafanuzi zaidi au una maswali yoyote kuhusu utafiti huu unaweza kuwasiliana na:

1. Mpelelezi:
Dr. Esther Opuba
Mobile No. 0711392444

2. Wasimamizi wa upelelezi:
a.Dr.Nyambura Kariuki nkariuki@gmail.com
b.Dr.Diana Marangu dmarangu@uonbi.ac.ke
c.Dr.Josephine Omondi josephineomondi@yahoo.com

FOMU YA RIDHAA

Mimi,..... (jina la mshiriki)
Nimesoma/nimeskiza na kuelewa yaliyotolewa kuhusu utafiti huu " **Idadi Ya shida za hisia na tabia miongoni mwa watoto wanaotibiwa ugonjwa wa kifafa katika kliniki ya neurology ya watoto ya hospitali kuu ya Kenyatta.**

Nilikuwa na nafasi ya kuuliza..... (jina la anyechukua ridhaa); maswali katika lugha ninayoelewa na sasa ni wazi na nimeridhika.
Naelewa kwamba kushiriki kwangu katika utafiti huu ni kwa hiari yangu kabisa na naweza kujiondoa wakati wowote natakapo bila ya kutoa maelezo kwa kufanya hivyo. Mimi naelewa kwamba kuondoa ushiriki wangu, hukutaadhiri huduma yangu kwa njia yoyote.
Naelewa kwamba taarifa zote nitakazotoa, pamoja na taarifa binafsi itakuwa siri. Mimi ninakubali kushiriki katika utafiti huu.

Jina la mshiriki: .....

Sahihi ya mshiriki:.....Tarehe:.....

Sahihi ya shahidi: .....Tarehe:.....

Jina la anayechukua ridhaa:.....

Sahihi: ..... Tarehe: .....

Utapokea nakala ya fomu hii
Iwapo unahitaji ufafanuzi zaidi au una maswali yoyote kuhusu utafiti huu unaweza kuwasiliana na;
Dr.Esther Opuba 0711392644 eopuba@gmail.com

APPENDIX III: ASSENT FORM

Project Title: PREVALENCE OF COGNITIVE DYSFUNCTION IN CHILDREN WITH EPILEPSY

Investigator(s): DR.ESTHER. OPUBA

We are doing a research study about how the brain works in children with epilepsy.

Permission has been given to do this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee.

This research study is a way to learn more about people. At least 200 children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be asked to simple questions about date time, simple mathematic calculations and naming of simple objects .The activity will take about 15minutes.Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. We think these benefits might to know how good your brain functions.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study. You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

I, , want to be in this research study.

(Signature/Thumb stamp) (Date)

APPENDIX IV: ASSENT FORM (SWAHILI VERSION)

Andiko

Idadi ya shida za hisia na tabia miongoni mwa watoto wanaotibiwa ugonjwa wa kifafa katika kliniki ya neurology ya watoto ya hospitali kuu ya Kenyatta.

Mpelelezi:

Dr. Esther Opuba
Uko hapa kwa nini?

Madaktari wangetaka kukuambia kuhusu andiko wanalofanya kuhusu watoto walio na ugonjwa wa kifafa. Wangetaka kujua kama ungependa kuhusika katika hili andiko. Hii fomu itakuelezea kuhusu hili andiko. Kama kuna kitu ambacho huelewi, tafadhali uliza wazazi wako, walezi wako ama daktari.
Wanafanya hili **andiko kwa nini?**

Wangetaka kuelewa zaidi shida ambazo watoto walio na ugonjwa wa kifafa hupitia, tabia na jinsia zao.

Nini kitafanyika kwako?

Daktari atauliza mzazi ama mlezi wako ajaze fomu iliyo na maswali kuhusu ugonjwa wako, na pia tabia na jinsia zako. Hii itatumia muda wa dakika kumi.kisha tutakuuliza maswali machache.
Andiko litakuwa na athari yoyote kwako?

Itabidi ungoje kidogo wakati mzazi ama mlezi wako atakuwa akijibu maswali.

Utapona ukihusika katika hili andiko?

Hili andiko halitafanya upone. Lakini kuna uwezekano wa madaktari kutambua jambo litakalosaidia watoto wengine kama wewe baadaye.Unaweza kuuliza maswali wakati wowote, saa hii ama baadaye.Unaweza kuongea na madaktari, wazazi ama walezi wako.
Nani atajua nililofanya katika andiko?

Maelezo yote utakayopea madaktari itawekwa siri. Jina lako halitakuwa katika karatasi la andiko na hakuna atakayejua kuwa ulihusika katika hili andiko ila madaktari.
Ni lazima uwe katika hili andiko?

Si lazima uwe katika hili andiko. Hakuna atakayekukasirikia kama hutaki kufanya hivi.

Kama hutaki kuwa katika hili andiko, sema tu. Pia tutauliza wazazi ama walezi wako kama wangetaka uwe katika hili andiko. Hata kama wazazi ama walezi wako wangetaka uhusike katika hili andiko umeruhusiwa kukataa. Madaktari bado wataendelea kutibu ugonjwa wako..
Hata ukikubali saa hii umeruhusiwa kukataa baadaye. Uamuzi ni wako.

Kibali

Ningetaka kuhusika katika hili andiko. Najua ninaweza kubadilisha nia wakati wowote Kibali kimepeanwa kwa mdomo.

Ndio

Jina la mtoto

Kibali cha kuandikwa, mtoto akiamua kupiga sahihi kibali.

Sahihi ya motto…….. Miaka……..

APPENDIX V: QUESTIONNAIRE

PREVALENCE OF COGNITIVE DYSFUNCTION IN CHILDREN WITH EPILEPSY ON FOLLOWUP IN THE NEUROLOGY CLINIC, KNH

1. DEMOGRAPHICS

DATE (dd/mm/yyyy).....

PATIENT INITIALS.....

DATE OF BIRTH (dd/mm/yyyy).....

AGE (years).....

LEVEL OF EDUCATION .....

GENDER.....

WEIGHT (KG to one decimal point) .....

RESIDENCE .....

2. DIAGNOSIS.....

TYPE OF EPILEPSY

GENERALISED ☐

FOCAL ☐

MOTOR ☐

NON MOTOR ☐

3. THE DIAGNOSIS WAS FORMULATED BY?

CLINICAL ASSESMENT ☐

ELECTROENCEPHALOGRAM ☐ FINDINGS

CT SCAN AVAILABLE ☐ FINDINGS

4. SEIZURE VARIABLES

WHAT WAS THE AGE AT FIRST ONSET OF SYMPTOMS?).....

HOW FREQUENT ARE THE CONVULSIONS? (number of seizures in the highlighted duration) _____

1. DAILY
2. WEEKLY
3. MONTHLY
4. YEARLY
5. 5 YEARLY

When was the last convulsion?

YEAR.....

MONTH.....

4. TREATMENT+DOSE IN (MG/KG)

PHENOBARBITAL.....

PHENYTOIN .....

CARBAMAZEPINE.....

SODIUM VALPROATE.....

CLONAZEPAM .....

OTHER .....

5. ADEQUANCY OF THE DOSING OVERDOSE☐ ADEQUATE☐ UNDERDOSE☐

DO YOU USE ALL THE DRUGS EVERYDAY?

YES ☐

NO ☐

IF NO WHAT ARE THE REASONS?

a. AVAILABILITY OF THE DRUG ☐

b. FINANCES ☐

c. ADVERSE DRUG EFFECTS ☐

SPECIFICY.....

d. PILL BURDERN ☐

e. OTHER (SPECIFY) ……..

DURATION OF TREATMENT……

6. ARE YOU ON ANY OTHER CHRONIC MEDICATIONS?

.....

7. Is there any family history of epilepsy?

NO☐ Yes☐?

APPENDIX VI - MODIFIED MINI MENTAL STATUS EXAMINATION

A.ORIENTATION–1point for each correct answer

	CORRECT ANSWER – 1	WRONG/NOANSWER-0
GENDER		
FIRST NAME		
LAST NAME		
RECOGNIZES RELATIVE		
TOTAL		
CURRENT PLACE		
CITY		
COUNTY		
COUNTRY		
TOTAL		
DAY		
DATE		
MONTH		
YEAR		
TOTAL		

B. REGISTRATION AND SENSORY PERCEPTION (3 points)

Score 1 point for each correct answer.

Name the following three objects.

Pen, watch, glasses

C. **ATTENTION AND CONCENTRATION**

Recite a minimum of 2 and a maximum of 5 digits forward

DIGITS RECITED	**SCORE**
NONE	**0**
1	**0**
5-3	
4-7-2	
5-9-3-1	
2-7-5-9	

Score1 point for each number greater than 2, total score 4

Recite a minimum of two and a maximum of four digits backward

Score1point for each point greater than two

DIGITS RECITED BACKWARDS	**SCORE**
3-6	
2-9-5	
4-1-9-7	

D**. RECALL**

Recall 3objects previously presented.

Score one point each, total score 3.

E. LANGUAGE

I. Name 5 body parts. (Score 1 point each total score 5)

part	score
foot	
knee	
nose	
hand	
ear	

Follow a 3tep command.
(1 point for each correct step)

Take a paper in your right hand,
Fold it in half and
Put it on the floor.

Repeat sentence (Total score1)

I would like to go home.

Reading his or her name. Total score1

Writes his or her name. Total score1

II. Copy a design-Total score 1 mark

SCORES:

AGE GROUP	**CUT-OFF**
3-5 YEARS.....	24
6-8 YRS.....	28
9-11 YRS…….....	30
12-14 YRS ……	35

APPENDIX VII: MORDIFIED MINI MENTAL STATE EXAMINATION (SWAHILI VERSION)

ALAMA MOJA KWA KILA JIBU SAHIHI

A.ORIENTATION

Jina lako la kwanza ni nani?
Jina lako la pili ni nani?
Huyu mko naye ni nani kwako?
Wewe ni mvulana au msichana?

MAZINGIRA

Nchi yetu inaitwaje?
Hii ni kaunti gani?
Hili ni jiji gani?
Hapa tulipo ni wapi?

WAKATI

Leo ni siku gani ya wiki?
Leo ni tarehe gani?
Huu ni mwezi gani?
Huu ni mwaka gani?

B.Taja majina ya vitu hivi.
Kalamu Saa Miwani

C.Rudia nambari hizi kama zilivyosemwa.
Rudia nambari hizi ukianza na nambari iliyosemwa mwisho.

D.Unakumbuka majina ya vitu tatu nilizokuonyesha hapo awali?

E.**Taja sehemu za mwili utakazoonyeshwa**
Mguu Goti Pua Mkono Sikio

Fuata maagizo haya.
Chukua karatasi kwa mkono wako wa kulia, kunja mara mbili kasha liweke chini sakafuni.

Rudia sentensi hii.
Ningependa kwenda nyumbani.
Soma jina ambalo limeandikwa.
Andika jina lako hapa.

Chora picha inayofanana na iliyochorwa hapa