PREVALENCE OF GENERALISED CONVULSIVE STATUS EPILEPTICUS IN PATIENTS ADMITTED TO KENYATTA NATIONAL HOSPITAL AND THE SHORT TERM OUTCOMES

A DESSERTATION SUBMITTED IN PART FULLILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE BY:

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NOVEMBER 2006

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I certify that this dissertation is my own original work and has not been presented for a degree at any other university

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DEDICATION

To my lovely wife Jackie and son Ian for bearing with my absences during the study and their constant understanding and encouragement!

ACKNOWLEDGEMENTS

To my supervisors for their fatherly advice and guidance through this whole project right from writing the proposal to this finished dissertation.

To my assistants for the dedication they showed in assisting me follow up and arrange the data. Really I would not have done it without you!

To my statistician, 'kudos' for the swift and precise analysis. It was a joy working with you!

To Sanofi Aventis and Astra Zeneca for the financial and material support which enabled me to carry out this study in good time and to such a completion.

Thank you very much!

Table of contents

LIST OF TABLES **PAGE**

LIST OF FIGURES **PAGE**

LIST OF ABBREVIATIONS

GCSE	Generalized Convulsive Status epilepticus
NCSE	Non- Convulsive Status Epilepticus
KNH	Kenyatta National Hospital
CNS	Central Nervous System
EEG	Electroencephalogram
SE	Status Epilepticus
ILAE	International League against Epilepsy
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
PET	Positron Emission Tomography
MRI	Magnetic Resonance Imaging
BC	Before Christ
AEDs	Anti Epileptic Drugs
HAART	Highly Active Anti-Retroviral Therapy
SOL	Space occupying lesion
WBCs	White blood cells
HB	Hemoglobin level
Mm 3	Cubic millimeter
TDM	Therapeutic dose monitoring
NMDA	N-Methyl-D-Aspartate receptors
ELISA	Enzyme linked immunosorbant assay

ABSTRACT

Background: Generalized Convulsive Status Epilepticus (GCSE) is a sub-group of status epilepticus that is accompanied by visible body movements and loss of consciousness. It has a high complication rate including disability or death. Generalized convulsive status epilepticus is known to occur in both known epileptics and non epileptics, where it may be a manifestation of another underlying primary cause. Other factors that have been shown to influence outcomes in patients with GCSE are age and the underlying primary etiology.

No studies have been done in Africa hence its magnitude and its influence on patient's outcomes is unknown.

Objectives: This prospective study was primarily aimed at determining the prevalence of GCSE in patients admitted to KNH and the length of admission. Secondary objectives were to document the primary etiological causes and treatment given to these patients.

Study design: This is a longitudinal prospective study. The subjects were screened and those fitting the criteria for GCSE recruited and followed up to either death or discharge.

Study period: The study was carried out over a three calendar month period between 1/1/2006 and 1/4/06 both days inclusive.

Sampling method: Patients were recruited consecutively.

Study location: The study was carried out at Kenyatta National Hospital. The wards involved included; all medical wards, all surgical wards, the obstetric and gynecology wards, the maternity unit, the renal unit, the burns unit, the intensive care unit and the high dependency unit.

Methodology: All patients admitted to KNH between January and April 2006 with suspected convulsions, coma or confusional states were screened and those with GCSE recruited. They

were followed up on a daily basis with documentation of the primary etiology, investigations and treatment given till death or discharge.

Approval to carry out the study was obtained from the KNH ethics and research committee. Participation was on a voluntary basis following an informed written consent.

Results: The prevalence of GCSE was 0.48% of all patients admitted to KNH. Males were 62% while females accounted for 38% of the study population. The mean age was 28.9 years with a median of 27 years. 62% we referral cases having been seen and attended to at a peripheral health facility. The mean in-hospital stay was16.83 days. Persons living with epilepsy accounted for 40% of the GCSE while infectious causes accounted for 38% of the primary causes of GCSE. The crude case fatality rate for GCSE is 16% with infections being most important cause of death.

Conclusions: The local prevalence of GCSE is high occurring at a lower age group compared to data from western studies. It leads to a prolonged in-hospital stay which may lead to an increase in both direct and indirect medical costs. Non adherence to AEDs and infections are the most common causes of GCSE. Infections especially HIV\AIDS related opportunistic infections were the primary diagnosis associated with 80% of mortalities in GCSE patients.

INTRODUCTION

Status epilepticus is a relatively common neuromedical emergency whose worldwide epidemiology is still being written but data from developing countries is minimal. A few differences in the etiology and incidence between developed and developing countries have been noted. While Studies done in developed countries show a low burden of CNS infections, the developing countries including Kenya have infections high up in their lists. Some examples include the 'hot water epilepsy' which is a kind of reflex epilepsy induced by immersion in hot water baths a common practice in south India and the higher burden of chronic CNS infections, especially cysticercosis, seen in developing countries (1). It is a fact that one of the complications of cerebral malaria includes seizure episodes; more recent data suggest the existence of a higher prevalence of epilepsy in malaria endemic regions in the Kenyan coast amongst children (2). Another factor that is thought to increase occurrence of seizure illness is the increased incidence of irritative focal brain lesions in HIV / AIDS patients. Meningitis and encephalitis are proven etiological causes of status epilepticus in adults (3).

Both community and hospital-based studies have mainly been recruiting elderly subjects, with most of them being above 60 yrs (4, 5, 6, 7, 8). This can be explained by the fact that the population in these countries is aging. It follows that with aging the prevalence co-morbid conditions, especially cerebrovascular, increase and these are known to cause GCSE. The incidence of status epilepticus has been shown to be higher among the elderly above 60 yrs (54.5 / 100,000) than in young adults (4.2 / 100,000) (4). This is explained by the higher rates of cerebrovascular diseases in those above 60years. Locally the presumed causes include CNS infections that are in high incidence in younger age groups as a result of the HIV/AIDS pandemic.

Mortality was significantly high in the elderly persons due to mortality from cerebrovascular diseases. Childhood febrile seizures, which are generally less harmful, contributed to the higher incidence rates. The mortality difference can be explained by the etiological differences, so with a change in the profile of causes one can expect a change in mortality!

In a review article on 'Emergency department drug therapy for status epilepticus', Lockey et al notes that the most common and dangerous type is the GCSE with an incidence of between 180 to 280 cases per million in the U.K and a mortality of about 10 to 15% (9).

In Africa, a study done in Mbam valley, Cameroon showed that epileptics had a 6.2 higher risk of death when compared to the general population, with the major contributor being status epilepticus (56.6% of deaths in the epileptic cohort) (10).

A 30- year cohort study of epileptics in rural Tanzania by Jilek – Aall et al, found that epileptics had a death rate that was twice that of the general population. Further analysis showed that 50% of the deaths were epilepsy- related such as status epilepticus, drowning, burns and dying in or after a seizure (11).

In Kenya the prevalence and mortality of this condition is scanty. A community-based investigation in Kilifi district by Snow R.W et al showed that 77% of deaths in epileptics had occurred while patient was in status epilepticus (12).

The prevalence of generalized convulsive status epilepticus has been evaluated in five studies three done in the U.S.A and two in Europe. Groups that demonstrated a high incidence of GCSE in these studies were the children below five years, the elderly over 60 yrs and blacks. The major

predictors of mortality were etiology and age. Seizure duration was only significant in those that lasted over 24 hours (13, 14, 15, 16, 17, 18).

Literature review

Modes of Classification

The worldwide co-ordination of all antiepileptic activities falls under the auspices of ILAE. In 1981 a sitting of ILAE defined status epilepticus as; 'a seizure that persists for a prolonged period of time or is repeated frequently such that recovery between attacks does not occur'. Obviously this definition was very ambiguous and difficult to use since it omitted a very important detail in the specific time duration of the seizure. This void was filled by various physicians to be between 20 – 30 minutes of seizure activity, being basically the estimated period of time necessary to cause injury to the central nervous system. It is for obvious reasons that the emergency physicians have picked the shorter duration of 20 minutes (19). Pro-active thinkers argue that status epilepticus is an emergency whose treatment is initiated well before the period of 20 - 30 minutes is over if we are to lower its morbidity and mortality. This means the time guideline given is impractical for initiating treatment. It is on this basis that many scholars including Daniel H. Lowenstein are advocating for the newer operational definition of status epilepticus as either: continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness (20).

According to the guidelines for epidemiological studies on epilepsy seizure types, status epilepticus is classified as follows:

a) Generalized status epilepticus: where there is no indication of an anatomic localization or clinical evidence of a focal onset.

   Subgroups:

- Convulsive: Tonic, clonic, or tonic-clonic

- Non convulsive: absence
- Myoclonic

b) Partial status epilepticus: where there is evidence of focal onset.

Subgroups:

- Simple: no impairment of consciousness
- Complex: consciousness impaired
- Secondarily generalizing

c) Unclassified status epilepticus

Neurophysiologists classify status epilepticus based on the EEG pattern. Classes include:

a) Spike wave form – this will basically be the EEG tracing of absence status epilepticus and is associated will low risk of brain injury.

b) Non-spike waveform – these have a higher risk of brain injury especially the generalized convulsive status epilepticus variety.

The obvious down side with this kind of classification is the difficulty in getting intra- ictal EEG's (21).

Prevalence studies on status epilepticus

There are only a handful of studies examining the incidence of status epilepticus, all of which are from the developed world. The oldest is a retrospective population based study in Rochester, Minnesota by Hersdorffer et al (9). This study covered the period 1st January 1965 to 31st December 1984. They used the Rochester Epidemiology project records-linkage system to ascertain all first episodes of status epilepticus receiving medical attention in Rochester, which is

the primary service area of the Mayo clinic. In total they sampled 199 patients with first episode of S.E, making the incidence of S.E in this population to be 18.3 / 100,000. GCSE accounted for 45% of all S.E and had an annual incidence of 8.3/100,000. It is worth noting that the population is 96% white and non-whites constituted a merge 4% of the study population. Secondly, over 50% of the study subjects were older than 60 years. This is a reflection of the population pyramid of developed countries with a narrow base. As expected the annual incidence was higher in those above 65 yrs i.e. 62.5 / 100,000, which can be explained by the higher rates of cerebrovascular diseases in this age group. Males were shown to have a higher incidence of S.E when compared to females though there was no explanation for the gender difference. This was a community based study since it captured information from out-patient clinics, home visits and in-patient hospitalizations. It was also established that this population was not optimally treated with anti-epileptic drugs.

Another study is a prospective study in Richmond, Virginia by Delorenzo et al (6). Here a systematic review of all cases above one month of age admitted to the medical college of Virginia was done. In total they sampled 253 adults with S.E and hence put the annual incidence of S.E in this population at 41/100,000 with a bi-modal distribution which has an early peak in those aged less than five years and another in those over 60 years. This was more than twice the incidence found at Rochester especially bearing in mind that both studies used the same case definitions. There was also no credible explanation on any new factors that could have come into play to explain a difference of this magnitude between the Rochester data covering a period starting 1965 – 1984 and this Richmond data covering 1994. One possible explanation to this leap in incidence has to do with the study design. The Rochester study was a retrospective study

based on data entered into a linkage-record system while this study was a systematic prospective review. All retrospective studies have the limitation of the amount of data collected, the collector's error and the lack of real-time validation systems. This simply means that there could have been a lot of omitted data. This is further supported by another retrospective study done in California which also reported lower incidence rates of S.E (10). The annual incidence of GCSE was three times higher at 29/100,000 and accounted for 74 % of all S.E patients. More interestingly, a sub-analysis showed that blacks had a significantly higher incidence of GCSE at 39.9/100,000. Blacks made up over 50% of the study population compared to the Rochester study where whites accounted for over 96% of the study population (9). This racial difference could explain the difference in incidence of GCSE in the two populations. This epidemiological finding has not been supported by any concrete reason/s which makes blacks more susceptible to GCSE than their white counterparts in the same environments. Further more race did not influence mortality but age and etiology did clearly predict mortality.

In comparison to the Rochester and Richmond studies, the retrospective study looking at the incidence and mortality of GCSE in California by Wu et al found a lower incidence of GCSE at 6.18/100,000(5). This is due to the fact that they sampled a different age group which did not include pediatric patients despite other studies showing that they have a high incidence of S.E. Since their methodology involved reviewing discharge codes of S.E they missed out on outpatient and home visit data. Thirdly in their study population blacks accounted for only 15.3% while whites were 58.7% and as a result the incidence rates of GCSE had dipped down to resemble those of white dominated Rochester population. In tandem with the Richmond study blacks were shown to have a higher incidence of GCSE at 13.35/100,000. This is about twice for

the general population in California. Again when data was controlled for age and etiology, race had no influence on mortality. As expected incidence rates were higher in the older age groups (22.32/100,000 in the group over 75 years and a 15-fold increase in case fatality), which is a reflection of cardiovascular diseases in this population and its importance in causation of GCSE.

The results of a prospective study by the status epilepticus study group Hessen (SESGH), looking at the incidence and case fatality rate of status epilepticus in Hessen were similar to those found in Rochester despite the difference in methodology(5). The study populations were quite similar in that both consisted mainly of whites and most of the study subjects were above 65 years. In their methodology the investigators used a prospective design where a systematic review of all patients admitted in the 16 hospitals within zip code area 35 was done. Despite the difference in study design they got a low crude annual incidence of 17.1/100,000 for S.E in this population, which was similar to the 18.3 /100,000 reported in Rochester but lower than another prospective study done in Richmond(6). This could be explained in part by the different times when the studies were done which will basically translate to an improvement in the primary control of diseases that lead to seizure disorders. The primary underlying etiologies did not differ much but it is interesting that 50% of the patients with S.E had a previous diagnosis of epilepsy. So by extrapolation one can assume that better control of epilepsy could account for the reduction in the incidence of S.E in this population. They also found a higher incidence in older men, which was reflective of the prevalence of cerebrovascular disease in this age group. There was no sub-analysis according to race.

Another prospective study carried out in tertiary care academic hospitals in Geneva estimating the annual incidence of status epilepticus in French speaking Switzerland by Coeytaux et al sampled yet another elderly white dominated population(8). By doing a systematic review of all patients admitted with status epilepticus in all hospitals in that region, they found an age adjusted annual incidence of 10.3/100,000 for S.E. This is even lower than that found in other white dominated populations though this could be attributed to the high rate of under ascertainment. For example Geneva which is the most developed of the six cantons enlisted in the study had the highest incidence of S.E at 16.3 / 100,000. This is because it had a better ascertainment due availability of 24 hour EEG facilities and adequate man power than other cantons. They also left out post anoxic encephalopathies which in Rochester study had accounted for about 10% of the study population. Just like in Rochester males had a tendency of a higher risk for S.E but this was found not to be significant after correction for etiology. Also a bimodal distribution with two peaks was shown, one being in the under fives and the other in the elderly of over 60 years. One interesting finding was the higher risk for S.E in urban as compared to rural populations for which there were no proper explanation.

In Africa, studies on status epilepticus are lacking and the incidence /prevalence rates of this condition are unknown. However some studies on epilepsy did capture some scanty data on status epilepticus. Examples of such studies include a study done in Mbam Valley, Cameroon by Kamgno et al that found a majority of epileptic patients described a seizure pattern fitting a generalized convulsive seizure (101 out of 125) (13).

A 30-year follow up of an epileptic cohort in Mahenge, rural Tanzania found only 21.9% were still alive. Causes of death were epilepsy-related (status epilepticus, drowning, burns and dying

in or after a seizure) in over 50%. These epilepsy-related deaths were higher in the sub-groups that had poor seizure control, those receiving drugs irregularly and those who had stopped taking the drugs (20).

A two year community- based investigation of mortality in Kilifi, Kenya targeting deaths in individuals above 5 years as reported by bereaved relatives revealed that 3.5% of all deaths had occurred in epileptics. Out of which 77% had occurred while the patient was in status epilepticus (14).

Etiology

The initiators of status epilepticus can be viewed as acute or chronic processes (20).

- Acute causes include: CNS infections, stroke, head injury, drug toxicity, metabolic derangements and brain hypoxia from any source.
- The chronic causes include: status in known epileptics which is usually due to lack of compliance or breakthrough seizures, chronic alcoholism, or other slow or remote CNS afflictions such as tumors etc.

Generally the slow or chronic processes have a better response to anticonvulsant therapy.

The importance assumed by each etiological agent will also depend on its magnitude in a given geographical area. This explains why studies done in the west where obesity, diabetes, hypertension and other cardiovascular risk factors are prevalent show a predominance of cerebrovascular diseases (7, 13, 14). Other reasons that might account for the low prevalence of infective causes include:

- Many were done in the pre HIV era where aids related opportunistic infections were not a major problem.

- Their study population mainly consists of elderly individuals who have more cardiovascular co-morbidities.

It is known that CNS infections lead to seizure disorders, status epilepticus included, but new data seems to show that it may also lead to increased prevalence of epilepsy. Annegers et al looked at the risk of unprovoked seizures after encephalitis and meningitis and concluded that the prevalence of epilepsy increases for up to 20 years after infection (3). Recent literature in Kenya suggests that the incidence of encephalitis and meningitis has risen due to the HIV/AIDS pandemic. Carter et al working at the centre for geographical medicine at Kilifi, Kenya showed that about one third of the children with cerebral malaria have status epilepticus of the generalized tonic- clonic variety.

The other big group consists of poorly controlled epileptics. Those who omit doses or are given sub-optimal drug doses can relapse back to convulsive disease. Even more interesting is the fact that an overdose of some antiepileptic drugs e.g. phenytoin can result in repeated convulsions (19). Aminoff et al in their review of 98 patients with generalized major motor status epilepticus found that the single most common cause to be non compliance with anticonvulsant drug which accounted for 53% of patients with previous seizure disorder.

Local data estimate that over 50% of epileptics are poorly controlled. In his thesis Peter Mativo, showed that only 60% of epileptics attending KNH adult neurology clinic were well controlled (22). With such a high incidence of poor control of epileptics attending a specialized clinic in a tertiary institution, one can only imagine its contribution to status epilepticus in our set-up.

Neurological diseases at KNH constitute about 7.5% of all cases admitted to the medical wards or seen at the medical clinics. Out of these, over 50% is accounted for by meningitis (23.1%), epilepsy (16.6%) and cerebrovascular disease at 15.0% (23).

For easy of analysis, the commission of epidemiology and prognosis of ILAE, has introduced a classification of etiological into:

i. Acute symptomatic / provoked: these are basically recent onset conditions resulting in status epilepticus within 7 days of onset.
ii. Remote symptomatic / unprovoked: encompasses all past or slowly progressing conditions which can eventually lead to status epilepticus e.g. a past head injury
iii. Undetermined causes / unprovoked of unknown origin

EFFECTS OF STATUS EPILEPTICUS

Mortality and morbidity

Status epilepticus is a medical emergency with a high mortality and morbidity. In a review article of current concepts in status epilepticus Lowestein et al put the mortality at about 20 % in the USA. Long term follow up of those who survived the initial 30 days, showed an increased mortality of up to three times that of the general population at ten years (20). The major contributors to mortality in S.E are the etiological cause as acute symptomatic status epilepticus, myoclonic type of S.E, and S.E lasting over 24 hours (24).

Status epilepticus may be complicated by hyperthermia, brisk peripheral leucocytosis, cerebral spinal fluid pleocytosis, and a systemic acidosis. These complications have not been shown to influence the mortality (13).

Kamgno et al while looking at the demographic impact of epilepsy in Mbam Valley, Cameroon, found that the risk of dying was 6.2 times higher in epileptics than the control cohort of non epileptics. The major causes of death were epilepsy related such as; status epilepticus (56.6%), sudden unexpected death during an epileptic seizure (18.9%) and drowning during a seizure (10.8%) (10). This was corroborated by a study in Kenya and one in Tanzania which showed that over 50% of deaths in known epileptics were epilepsy related and occurred mostly when patient was in status epilepticus(11,12). We did not find any hospital-based study that has estimated the mortality from status epilepticus in Kenya.

Other Factors influencing outcomes

Questions have always arisen on the magnitude of injury caused by the seizure activity and more so does it vary in immature and adult brains? Haut et al looked at the susceptibility of immature brains to seizure effects and concluded that features of seizure induced injury in the immature brain were different from those in adults. Other factors that influence the outcome include; the duration of seizures, the number of seizures, cause of seizures, presence of pre-existing abnormalities and genetics (25).

Claassen et al reviewed the predictors of functional disability and mortality after an episode of status epilepticus, and found that age and acute symptomatic seizures were the main predictors of mortality. Functional deterioration was at about 23% upon discharge with the main predictors being increased length of hospitalization and acute symptomatic seizures (15).

The higher prevalence of status epilepticus seen in males has not been seen in all studies but possible explanations to a lower female risk include:

i. *Males have higher rates of cerebrovascular disease*

ii. *Some of the etiological causes e.g. head trauma are mostly seen in men due to their behaviour patterns*

iii. *Gender difference in seizure threshold : Hormonal influence on the GABA- sensitive region of the substansia nigra(it is associated with the regulation of seizure threshold)*

The higher incidence of status epilepticus in the black population has been consistently seen in most studies but no good explanation has been found and most studies are not geared to assess this racial bias (6, 8).

Contribution of Non convulsive status epilepticus (NCSE)

It is estimated that about 8% of all comatose patients develop status epilepticus, out of which NCSE accounts for between 20 – 23%. In about 14% of patients, GCSE patients convert to NCSE following therapy (26).

A study that looked at critically ill patients, in an intensive care setting by Young et al, reported a mortality of 50% (22). This was similar to what Litt et al found in critically ill elderly patients with NCSE i.e. 52 %. The major predictors of mortality were; a primary acute medical cause and presence of severe mental status impairment (27).

In most of these population-based studies the contribution of NCSE was pretty low. De Lorenzo R.J et al working in Richmond, Virginia found NCSE to represent about 5% of all status epilepticus cases. In a hospital-based study in French speaking Switzerland it accounted for up to 33% of all S.E episodes.

This is a relatively difficult diagnosis to make since an intra-ictal EEG is mandatory for diagnosis thus studies in hospital setting report higher prevalence's than community-based studies. We found no studies on this form of status epilepticus in Africa.

Economic and social costs

Perberthy et al looked at the economic burden of status epilepticus to the health care system. They concluded that the median reimbursement from insurance for a patient with status epilepticus was $8417 with the average length of admission being 12.9 days. This was a 30 – 60% higher refund as compared with other acute health problems including acute myocardial infarction or congestive heart failure. Major factors that influenced cost were mainly age and etiology (29).

An economic evaluation of epilepsy in Kiremba, Burundi showed that the costs of treating an epileptic averaged US$ 48.4 which is more than a seven fold increase compared to the US$ 7.3 needed for treatment of other medical conditions. This presented a 600% increase in direct costs and 10.2 disrupted days to patient and family as indirect costs annually (30).

Refractory status epilepticus

Some cases of status epilepticus fail to remit with treatment i.e. refractory status epilepticus (RSE). RSE has been estimated to occur in about 30% of all S.E cases where it leads to an increased length of hospital stay and functional disability, though curiously does not lead to an increased mortality. Other studies show that status epilepticus lasting more than 24 hours was an important predictor of long term mortality (24).

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Where do these patients get admitted?

Ward admission distribution shows that most of status epilepticus patients needing admission are admitted to internal medicine group wards (50%), followed by the intensive care unit (30%), then specialized neurological ward (10%) and the rest of the other wards the remaining 10% (9).

Usefulness of the EEG

In 1971 the EEG was first introduced in Kenya but its use has remained confined to the large urban centers where the facility and expertise exists. A review of the importance of this diagnostic tool at KNH showed that it was mainly ordered in suspected cases of epilepsy (58.5% of the requests) and convulsions of uncertain cause (11.8% of requests). Of note was that epilepsy did not seem to benefit maximally from inter-ictal EEG's in diagnosis with a positive rate of only 36.0% (31).

Falope et al working on Nigerian epileptics found that only 30 to 50 % of probable epileptics had epileptiform patterns on the first EEG. They noted that to increase this yield multiple EEG's were needed, a fact that was not practicable in developing countries where resources are lacking. It should be noted a normal EEG does not exclude the diagnosis of epilepsy and that non-epileptics are know to have abnormal EEG's. They also found no relationship between the frequency of seizures and epileptiform patterns on EEG. Hence they concluded that the diagnosis of epilepsy, and for that matter other convulsive disorders status epilepticus included, was a clinical matter. This underscores the importance of history, physical examination and eyewitness accounts in the diagnosis of such conditions (32).

PATHOPHYSIOLOGY

Kindling mechanisms

In a normal brain there occurs a synchronous discharge in restricted groups that accounts for the normal EEG. The spread of these electrical activities usually occurs in a restricted pattern, these are the normal conduction pathways.

During seizures large groups of neurons are activated repetitively and hyper synchronously leading to the high voltage spike and wave pattern on EEG's. At the same time the spread occurs in a haphazard manner.

The origin of this increased neuronal discharge can be localized or affect the whole brain. Such areas that are origins of this seizure phenomenon are termed epileptogenic focci. It is postulated that such areas may arise:

i. Congenital: where one is born with neurons predisposed to hyper-excitability. This may be as a result of things like; abnormal migration of cells in utero, intra-uterine infections etc

ii. Acquired: where an event modifies the function of pre-existing neurons making them more prone to hyper-excitability e.g. trauma, tumours, infections etc

At a cellular and molecular level status epilepticus is a dynamic process that evolves over time in a predictable manner with an established sequence of EEG, motor, physiologic and cellular changes (33).

Kindling, which refers to the initial event that starts the seizure process, has been a subject of many scientific researches. Currently numerous mechanisms are thought to be involved depending on the primary etiology of the seizure.

The results of Akcali et al, in looking at the role of apoptosis in a temporal lobe epilepsy-kindling model, showed an increased expression of apoptotic proteins Bax and Bax-x_L but no DNA fragmentation was noted. Thus they concluded that perhaps neuronal death might be both a cause and a result of epileptic changes (34).

Genetic predispositions are seen in up to 30% of epileptics, who usually have a history of seizures in first-degree relatives. The exact modes of inheritance are uncertain, but well over 200 genetic disorders have been documented to have seizures as part of their manifestations.

Chemical neuronal transmission has fuelled the thinking that the basic underlying mechanism may be associated with abnormal neuronal connections, poor synaptic connections, neurotransmitter abnormalities or perhaps a receptor defect. Mathew E. Barton et al looked at the role of the NR2B subunit of NMDA receptors on acquisition and expression of kindled seizures, and concluded that they contribute to the expression of fully kindled secondarily generalized seizures though other mechanisms seem to play a larger role (35).

This kindling riddle continues to stir many neuroscientists especially as the world of neuro-imaging continues to evolve.

Synchronization mechanisms

What ever the seizure kindling mechanism, these single neuronal bursts have to be added up together in a process termed synchronization to make up the giant epileptic discharges seen on EEG's. Neuroscientists have always been tussling as to whether chemical or electrical transmission forms the main communication channel between neurons (36). Theoretically four mechanisms are thought to add to this phenomenon as shown below:

i. Recurrent excitatory chemical synapses: this is believed to be the most important mechanism of neuronal communication under normal conditions and the basis of most neurological diseases. Its existence is supported by:

- ❖ Direct dual intracellular recordings from the hippocampus (37).
- ❖ The discovery of numerous neurotransmitters, chemical receptors and their strong association to most neurological diseases (37).
- ❖ Computer simulation models. Traub et al found that the field potentials and intracellular recordings observed during inter-ictal spikes of penicillin treated hippocampus slices were reproducible by a mathematical model of a network of 100 hippocampus neurons (38).
- ❖ A further review of the penicillin mechanisms in seizure causation, by Phillip et al at Stanford University, showed that penicillin caused a block in cellular inhibitory postsynaptic potentials hence allowing remote intrinsic excitatory events to enter the cell soma and trigger action potentials (39).

ii. Electronic coupling via gap junctions: Bennet in 1997 described the ultra-structural specialized nature of gap junctions capable of conducting electrical signals between neurons. This is further supported with the find that blocking chemical synaptic transmission using low calcium solutions did not completely stop the fast synchronization of action potentials by pyramidal cells (21, 40). Though the participation of these structures is not in doubt there importance is thought to be minimal due to:

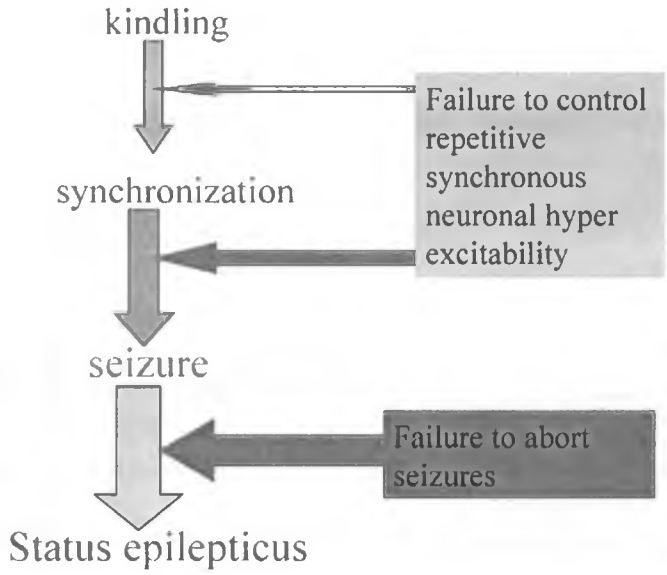
- ❖ These structures are rare in adult mammalian brains.

- ❖ Dye coupling and electrophysiological evidence suggest that electronic coupling occurs to one or a few neighboring neurons hence can't explain the fast wide spread synchronization.

iii. Ephatic interactions i.e. electrical field effects: basically this refers to neuronal interactions mediated by electrical current flow through the extra cellular space (36). Taylor et al in 1982 used differential recording (i.e. intracellular recording minus extra cellular recording) to show that electrical fields associated with synchronized action potentials create a field effect depolarization in inactive pyramidal cells hence synchronizing activity of neurons into an epileptic discharge.

iv. Changes in the concentration of extra cellular ions e.g. potassium that causes cell swelling or shrinkage that alters cell function: anatomical studies have for long shown that hippocampus pyramidal cells and dentate granule cells have extraordinary tight packing. This phenomenon led Green and Maxwell, in 1964, to hypothesize that this close association could lead to electrical interactions that could potentially contribute to synchronization of electrical activity. Dudek et al proved this in 1990 when they discovered that the hyperkalemia induced synchronous bursts can be blocked by hyperosmolar solutions that cause cell shrinkage. Roper et al in 1992 went further to show that, dilute media that caused cell swelling and reduction in the extra cellular space induced seizure activity.

Figure 1:Pathophysiology of status epilepticus



Status epilepticus

Status epilepticus principally results when there occurs a failure in the body's' mechanisms that normally abort a single seizure (see figure 1). This altered balance may result from either excessive/ persistent excitation or a failure of effective recruitment of inhibition mechanisms. The exact nature, sequence and relative contribution of these processes are poorly understood. Experimental studies suggest the existence of reverberating seizure circuits between different brain regions, which produce distinct electrographic changes (20).

Physiological mechanisms that abort a seizure include:

- Neuronal fatigue
- Active inhibition from inhibitory neurons stimulated by the seizure.

Most notable insights in the pathophysiology of status were gathered in 1987 following the ingestion of mussels contaminated with domoic acid in the USA. Domoic acid is an analogue of glutamate, which is the principal brain excitatory neurotransmitter. This led to some patients

getting prolonged seizures hence suggesting excessive excitatory amino acids have a causative role. Other compounds e.g. penicillin that diminish gamma- amionobutyric acid, which is the main inhibitory neurotransmitter result in prolonged seizures. So it is likely that numerous mechanisms are involved and the relative contribution of each will depend on the underlying cause.

STUDY JUSTIFICATION

Status epilepticus is a medical and neurological emergency whose epidemiology is in course of definition. Most studies have been from the developed countries with data from developing countries being scarce and far between. These realizations lead to the Indo-U.K workshop held in Chennai India under the auspices of the international league against epilepsy (ILAE). It was noted that developing countries showed higher incidences of epileptic syndromes, different population distribution and differences in etiology. The epidemiology of status epilepticus in Kenya is no exception. Factors that may influence the local occurrence of GCSE include: the population distribution, high burden of tropical infections such as malaria and the HIV/AIDS pandemic e.t.c. It was against this background that the workshop set research priorities for developing nations that included:

i. Urged for more and better quality research output from the developing world. This study will not only add to the number of studies from developing countries but will adopt internationally recommended guidelines to ensure quality.

ii. The need to develop uniform research protocols. This purely hospital-based study design adds a novel and cheap way for clinicians to gather data at their sites of work. Data which is reliable and can be replicated in other areas easily.

iii. Twinning of developed and developing nations for research. As part of our recommendations, we hope other countries in Africa and Europe can in future have similar studies running concurrently for better comparison of results.

iv. Training of more personnel in developing countries with a view of increasing research output in future. This is a good eye opener for the principal investigator to gather research skills.

The prevalence, morbidity and mortality of GCSE in Kenya is unknown though it may contribute to causing loss of life and increased medical costs. It is estimated that status epilepticus increases medical costs by between 30 – 60 % compared to other acute health conditions such as acute myocardial infarction and congestive heart failure (25). This study will quantify the magnitude of the problem forming a basis for proper medical planning and budgeting.

On the international arena the definition of status epilepticus has been changing with more pressing for the decrease in the operative duration from thirty to five minutes. This has been fuelled by the need to treat aggressively before the thirty minutes are over so as to minimize occurrence of complications. Though being a very plausible idea data to support such a move is lacking. This study has been designed to look at the magnitude of the problem in our setting and the in-hospital mortality of this condition using the current standard definition of status epilepticus (seizures of half an hour or longer) and will follow them up to death or discharge.

Study objectives

MAIN OBJECTIVES

1. To determine the prevalence of generalized convulsive status epilepticus (GCSE) in patients admitted in KNH.

2. To determine the in-hospital mortality rate of patients admitted with GCSE at KNH

SECONDARY OBJECTIVES

3. To document the etiological causes of GCSE in patients admitted to KNH

4. To document the treatment given to patients admitted to KNH with GCSE.

STUDY DEFINITIONS

Generalized convulsive status epilepticus: Refers to a type of status epilepticus that is associated with visible external whole body movements which may or may not occur in persons previously diagnosed to suffer from epilepsy.

Status epilepticus: Refers to a single epileptic seizure of more than 30 minute duration or a series of seizures during which consciousness is not regained between ictal events in a period exceeding 30 minutes. (I.e. according to the guidelines for epidemiological studies on epilepsy as proposed by the commission on epidemiology and prognosis of the International league Against Epilepsy)

***** Operative diagnosis of epileptic seizure will be ascertained in the following cases:***

i. *An epileptic motor phenomenon that is observed by a consultant neurologist (9).*
ii. *An epileptic motor phenomenon is observed by the principal investigator or medically trained assistant and one other eye witness (32)*
iii. *An epileptic motor phenomenon is clearly described by at least two eyewitnesses orally or well reported in casualty doctors' patient notes (5, 32).*
iv. *Impairment of consciousness will be a pre-requisite and its description clearly documented*

***** Operative definition of the duration will be demonstrated and measured by:***

i. *By direct witness present from the beginning of the seizure to the end of a period exceeding 30 minutes (9).*

ii. *By direct witness present after onset of the seizure or before the real end of a group of seizures lasting more than 30 minutes (9)*

Epilepsy: refers to two or more seizure episodes in ones life time (9)

Non-adherence of AEDs: this was from history, only where one is reported to have missed any single drug for a period exceeding two days.

In-hospital fatality ratio: refers to death occurring with in hospital in any patient known to have had GCSE. The primary cause of such a death need not be directly attributed to the convulsive episodes. As a conservative principle all patients still alive by the thirtieth day shall be deemed to be survivors (6, 13, 16).

** As a rule one will be deemed to have died when the primary doctor certifies the body as dead and documents the same in the patients file.

Prevalence rate: Refers to the number of GCSE patients found during the 3 month study period compared to the total number of patients above 13 years of age admitted to KNH.

** Prevalence rate shall be expressed as a percentage.

The length of hospital stay: refers to the number of days spent in hospital by each patient. This will be calculated as the difference in days between the date of death or discharge and the date of admission.

** Date of admission shall be defined as the first day the patients lands in the A&E department and not the day the patient enters a ward.

** Date of death shall be taken to be the date that the primary doctor certifies the patient dead by writing the same in the patients file.

** Date of discharge shall be taken to mean the day that the primary doctor allows the patient home and not the day that the patient clears the hospital bill and leaves the ward.

METHODOLOGY

This was a prospective study carried out over a three calendar month period between 1/1/2006 and 30/3/06. The study was carried out at Kenyatta National Hospital general medical wards, oncology ward, dermatology ward, chest medicine ward, infectious diseases ward, all surgical wards, ENT wards, neurosurgery ward, cardiothoracic surgery ward, the obstetric and gynecology wards, the maternity unit, the renal unit, the burns unit, the intensive care unit and the high dependency unit. The subjects were screened and those fitting the criteria for GCSE recruited consecutively then followed up to either death or discharge. We included all Patients aged 13 years and above, who fitted the operational definition of generalized convulsive status epilepticus and gave an informed written consent. We excluded all Patients who did not meet the criteria for generalized convulsive status epilepticus and those who were seen at KNH and admitted to the private wing or other hospitals.

Methods and tools

Screening and recruitment

Prior to starting the study, the primary doctors working in A&E departments and wards were informed of the study, its starting date and requested to report to the principal investigator any suspected cases with coma, confusion or convulsions.

Posters soliciting for patients pinned in all the wards, the A&E departments and the intensive care unit. Regular interviews with the primary physicians in these wards were conducted to

encourage them to report all cases with a presumptive diagnosis of seizures, confusional state or loss of consciousness

Methods at A&E departments

At the A&E departments the medical officers held on to relatives or care givers of the suspected convulsing patients for further interview by the principal investigator.

The principal investigator then screened all patients with suspected seizure disorder. This was achieved by taking a medical history and performing a comprehensive physical examination. To ensure a full history was obtained, a pre-coded questionnaire was used as a guide (see appendix I for details). Eye witness accounts were carefully documented and corroborated whenever possible.

All findings noted on the physical examination were entered in a prepared proforma and discussed with the primary doctor.

All investigations and the results as requested by the primary doctor were logged into the patients' follow-up sheets. The ward into which the patient was admitted was noted for purposes of continuing follow up. A log was kept detailing the total number of admissions and those that were admitted to the private wing or other hospitals.

Methods in the wards

All ward doctors were asked to report any old ward patients who developed a seizure, coma or confusional state to the principal investigator, who then screened them by:

i. A full medical history taken from eye witnesses or the care givers as guided by a pre-coded questionnaire.

ii. A comprehensive physical examination

iii. Careful documentation of eyewitness accounts

All findings were discussed with the primary doctor with a view of improving the patient care.

Patients' follow up

All patients who fulfilled the criteria of GCSE were recruited and followed up on a daily basis with the help of four medically trained assistants. At each follow up visit the following were documented:

i. All investigations requested

ii. The investigations done and their results

iii. Treatments prescribed

iv. Treatments given

v. The day that the ward doctor discharges the patient or the date of death.

All this information was recorded in daily tables in each patient follow-up sheet.

Case ascertainment

To avoid missing any cases and to confirm cases, the principal investigator carried out all the screening. Where difficulties arose, the cases were referred to one of the supervisors who were also consultant neurologists.

To ensure uniformity the study adopted ILAE case definitions and requirements.

Ethical considerations

Prior to commencing the study approval from the Kenyatta National Hospital ethics and research committee was obtained.

Participation was on a voluntary basis. An explanation of the study was given to each patient or the next of kin where the patient was not in a position to do so. Informed consent was obtained in a written format (see appendix I for sample of consent forms) both in English and Swahili. For minors and the unconscious, consent was obtained from parents, guardians or the next of kin. A further verbal explanation and consent was sought prior to carrying out any investigations.

All data and materials obtained from the study were treated with utmost respect and confidentiality. The sole purpose was in writing this thesis and for scientific publications only.

The study findings were shared with the primary care physician for purposes of improving patient care.

STATISTICAL METHODS

DATA MANAGEMENT

All data collected was entered into a computer, cleaned, verified and analyzed using the SPSS 10.0 software.

Study outcomes:

1. Prevalence of GCSE in patients admitted to KNH expressed as a percentage: this will be computed by taking the total number of GCSE cases found during the study period divided by the total number of patients admitted to all the wards listed in the study area during the study period. This will then be multiplied by 100

2. Length of in-hospital stay: is expressed as the average number of days a GCSE patient stays in hospital during the study period. This was arrived at by totaling all in-hospital days of each patient starting on the day of admission to the date of death or discharge. This will then be added up to get the cumulative total stay before dividing it with the number of GCSE patients to arrive at the mean in-hospital stay.

3. Crude case fatality rate of GCSE expressed as a percentage: this was computed by dividing the number of patients that died during the study period by the number of GCSE patients then multiplied by 100. All causes of death will be included and it may not be necessarily related to GCSE.

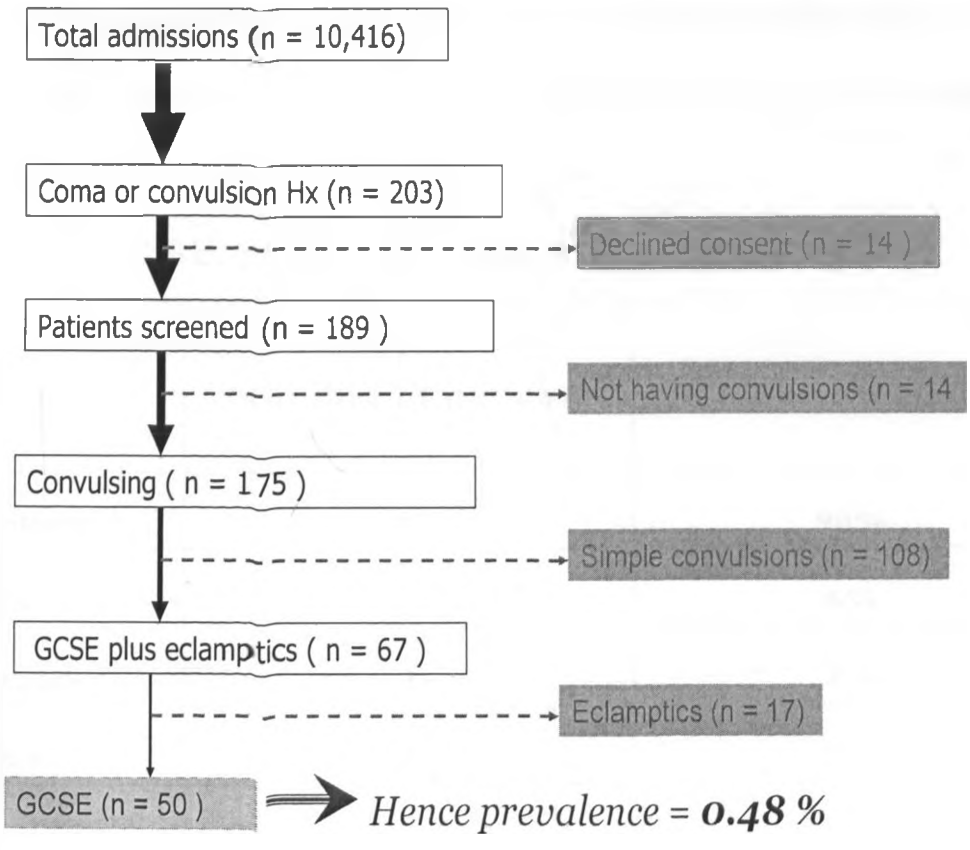
4. Documentation of treatment was done on a daily basis where the drugs prescribed by the primary doctor were noted. A summary of the number of drugs needed to control the seizures per a patient was noted. Seizures that needed more than three agents were termed as refractory seizures.

5. Documentation of the primary etiology was lifted from the impressions of the primary doctor. Though the investigations and results were noted, the diagnosis was only changed after the primary doctor had revised it in the patient's notes. Any diagnosis entered by the primary physician was accepted as the patient's diagnosis whether it was proved or not so as to cater for diagnostic dilemmas in the third world. All referral notes were reviewed for the primary diagnosis and reason for referral.

RESULTS

During the three month study period there were 10,416 patients admitted to KNH general wards. This is per the hospital records kept at the casualty and accident & emergency departments. The recruitment process is as displayed in figure 2 below.

Figure 2: screening and recruitment flow diagram



Those who had a history of co nvulsion or coma or unexplained changes in mental condition were 203. Fourteen patients declined to give consent hence were excluded. These were thirteen females and one male patient. Seven were in ICU and HDU, two in burns unit, one in maternity

and four in the medical wards. Majority of the declines were by the next of kin, reason being they found it inappropriate to consent to a study as a proxy. Other reasons included the next of kin felt the patients were too sick for any study and some not wanting to participate in any study. This number was very small compared to the total number of screened patients.

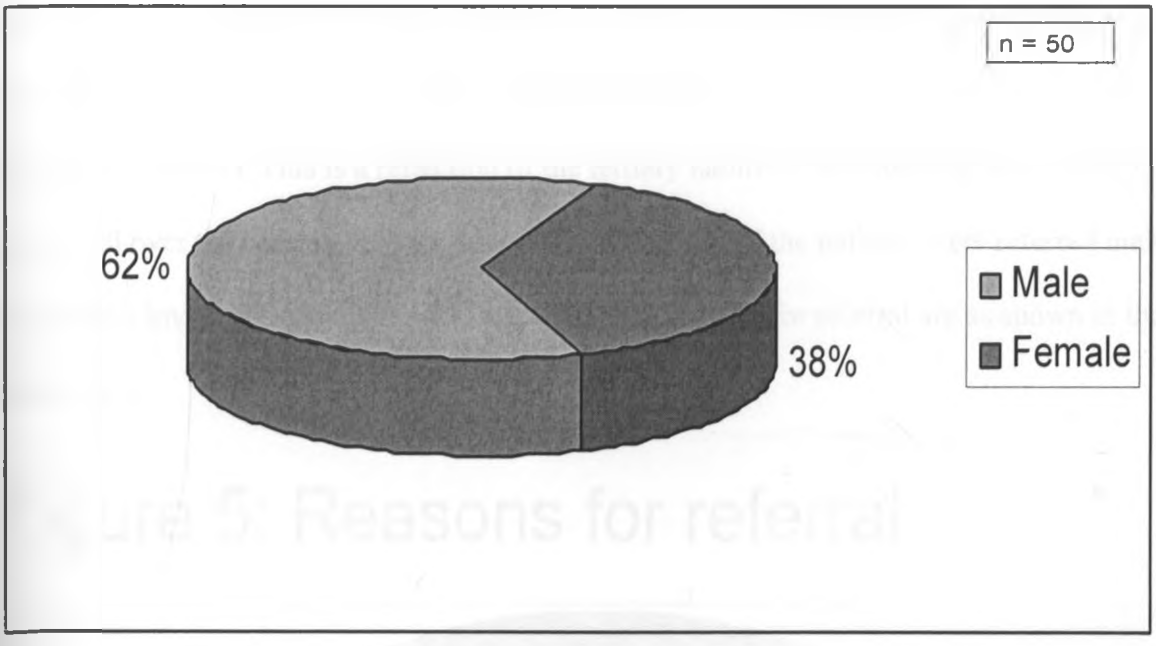
There were 189 patients who were screened after consenting. Fourteen were excluded because they did not have convulsions. Of these 11 had tremors and tremulousness, 2 had twitches and one had tetanus. This left 175 patients who had seizures disorders. Seventeen patients were excluded for having eclampsia leaving 50 patients with GCSE. This gave a GCSE period prevalence of 0.48%.

Table 1: GCSE patients: ward distribution

Ward	Number of patients	Percentage
Medical	45	90%
HDU	3	6%
Surgery	1	2%
ICU	1	2%

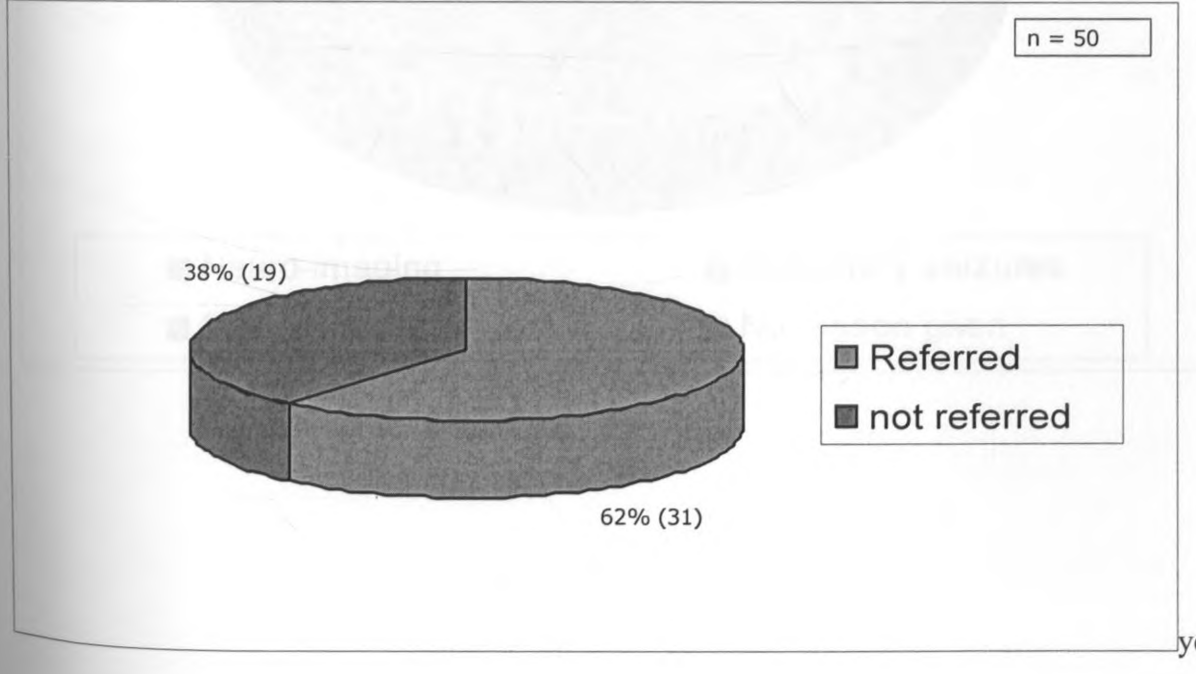
Ninety percent of the patients who fulfilled the criteria of GCSE were in the medical wards with the other departments contributing only 10 % as shown in table 1 above.

Figure 3 : Gender distribution of GCSE patients



Males accounted for 62 % of all patients with GCSE and females were 38%. The overall mean age was 28.9 ± 1 years with a range of 14 to 68 years. The males had a mean age of 26.6 years while the females had a mean age of 32.2

Figure 4: GCSE patients referral status



years

Sixty two percent of the GCSE patients who presented to the A & E departments had presented elsewhere during the acute presentation and ended up at K.N.H as referrals from such out centers (see figure 4 above). This is a reflection of the tertiary nature of this hospital which people come to from all over the country for specialized care. Majority of the patients were referred mainly for imaging investigations mainly CT scanning. The reasons for referral are as shown in the pie-chart below.

Figure 5: Reasons for referral

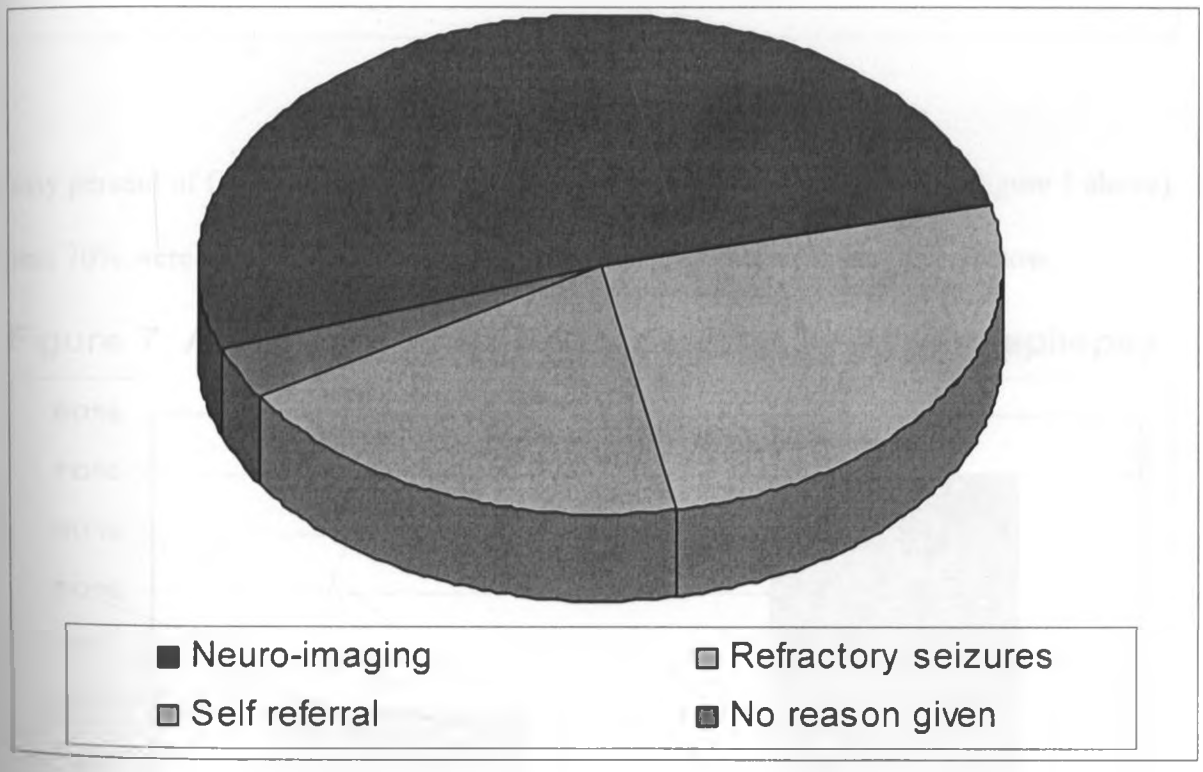
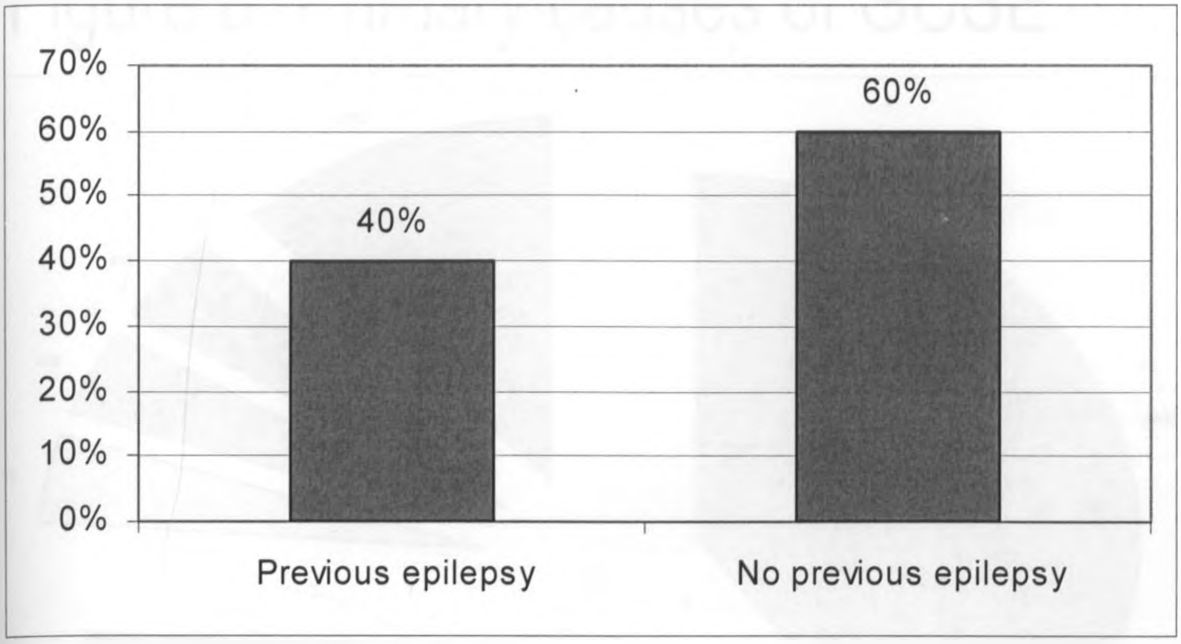


Figure 6: Previous convulsive state of GCSE patients



Forty percent of GCSE patients are known persons living with epilepsy (see figure 5 above). Of these 70% were reported not to adhere to their AEDs as shown in the figure below.

Figure 7: Adherence to AEDs by persons living with epilepsy

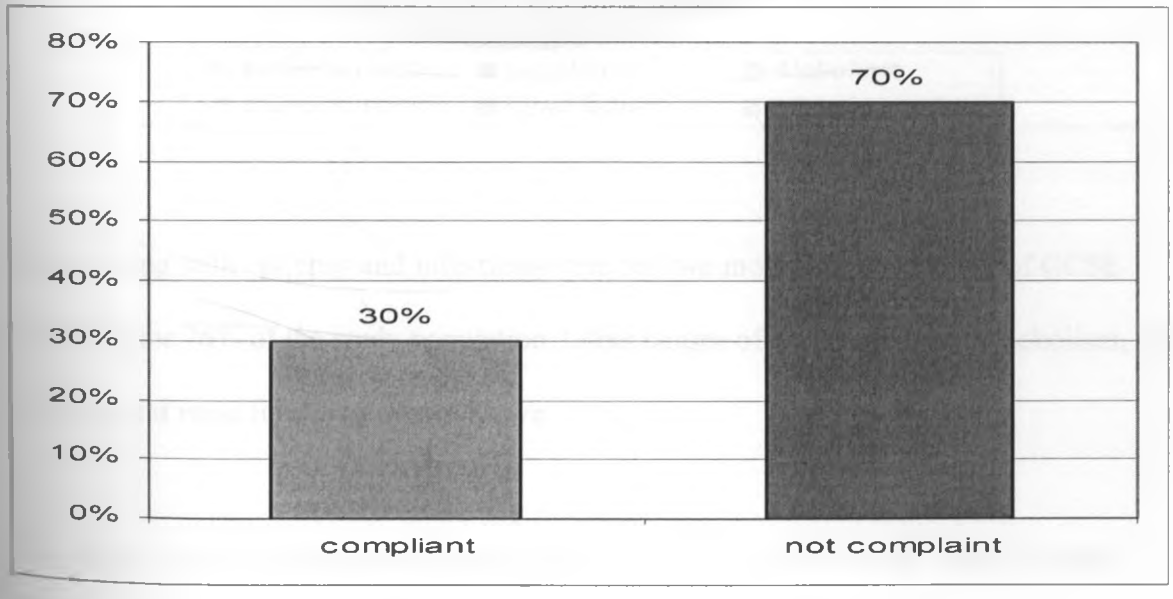
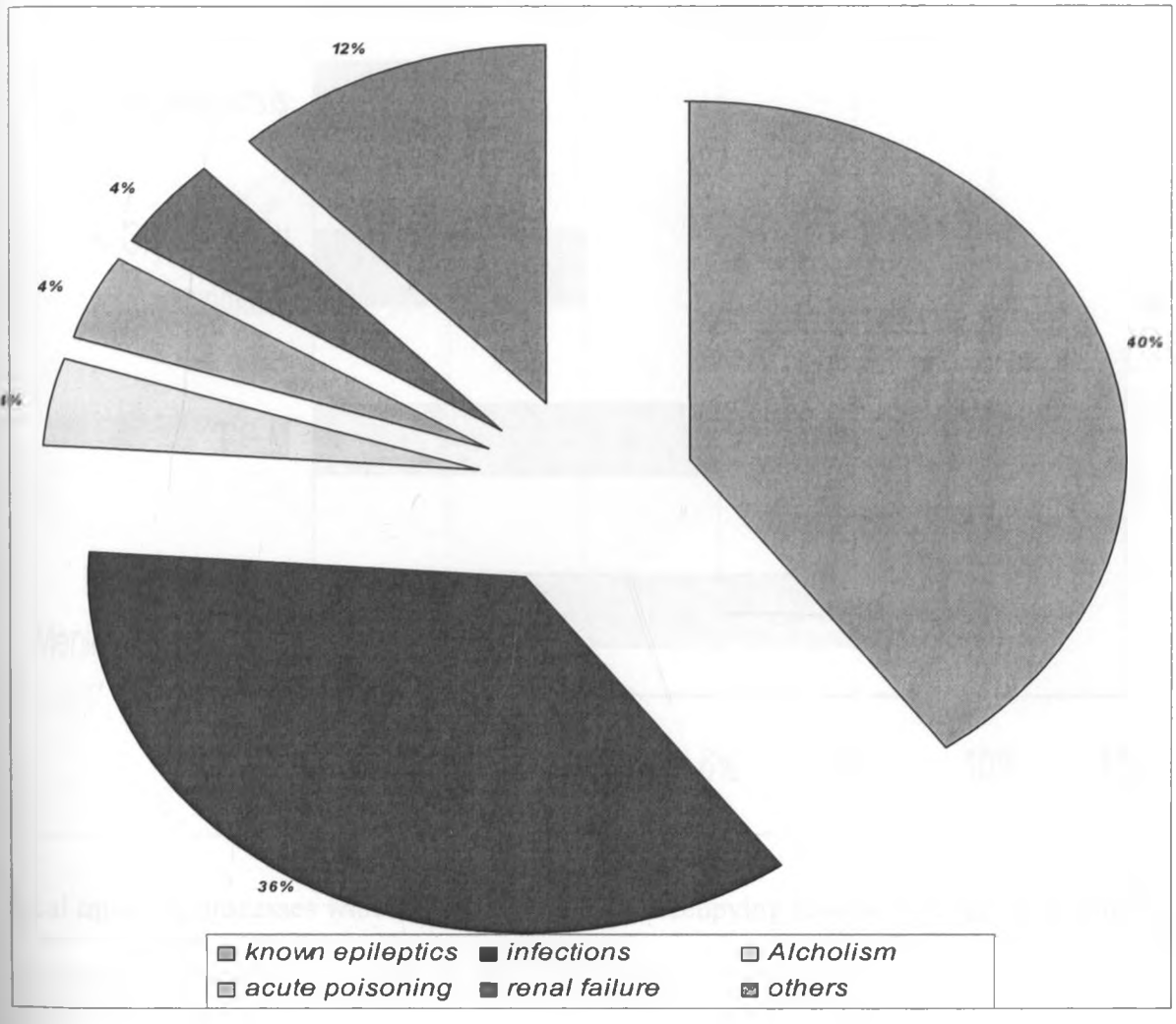


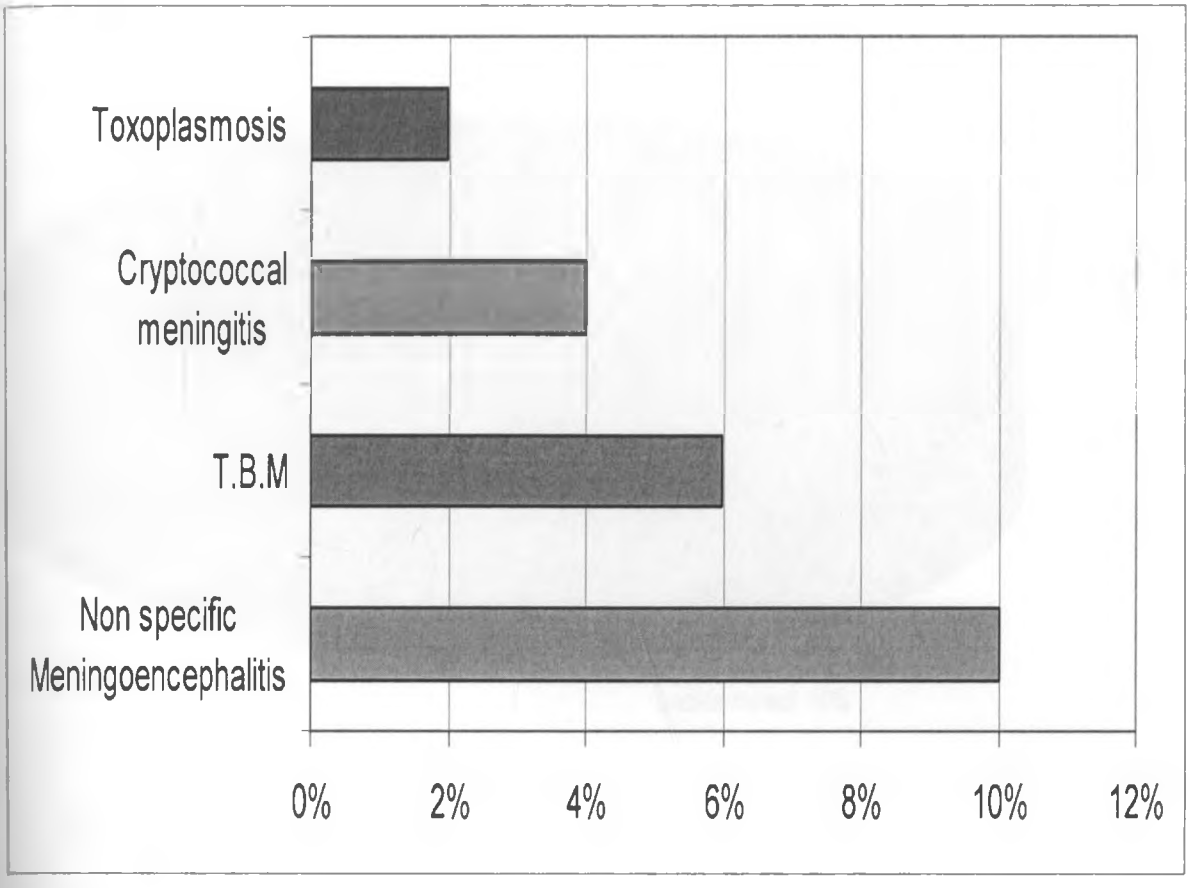
Figure 8: Primary causes of GCSE



Persons living with epilepsy and infections were the two most common causes of GCSE accounting for 76% of the study population. Other causes of GCSE included alcoholism, acute poisoning and renal failure as shown above.

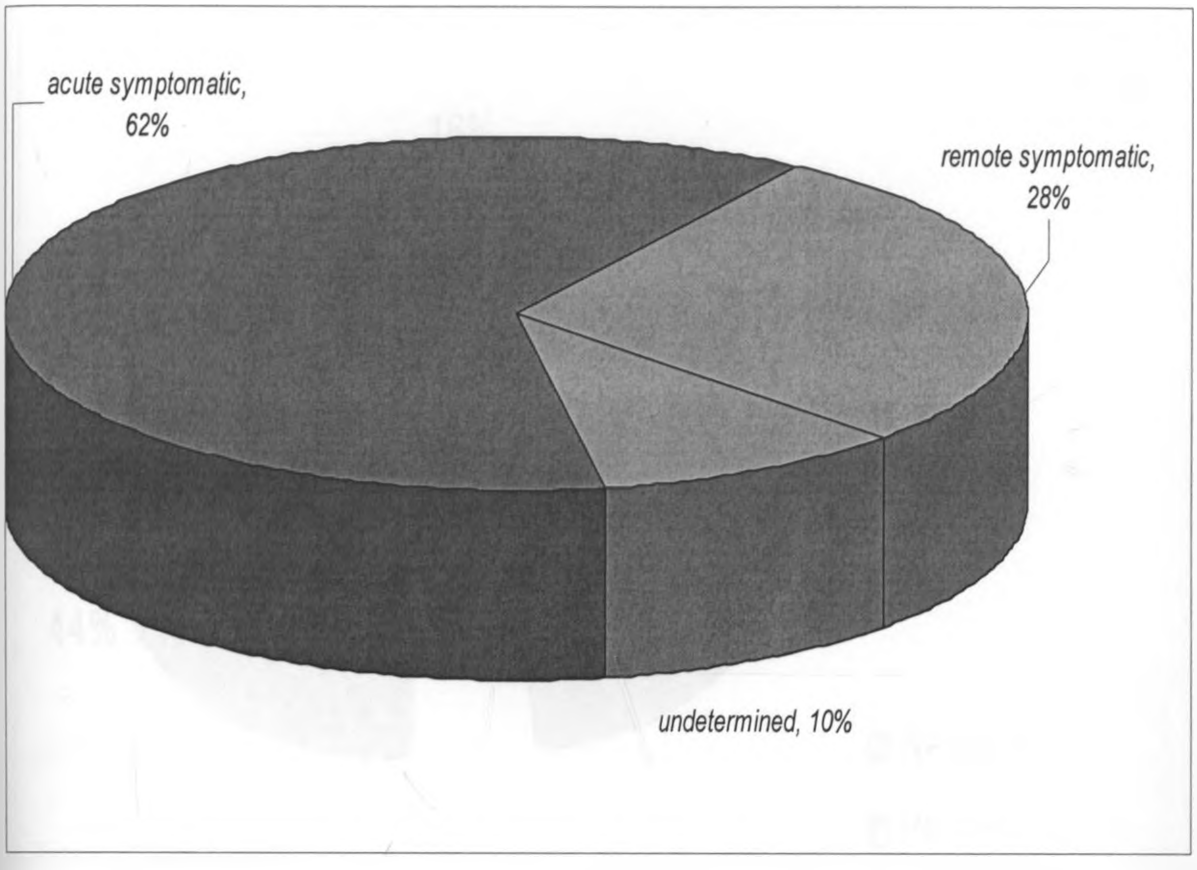
Infections as a group contributed to 36% of the primary causes of GCSE. The individual infections are as shown in figure 8 below.

Figure 9: Infections causing GCSE



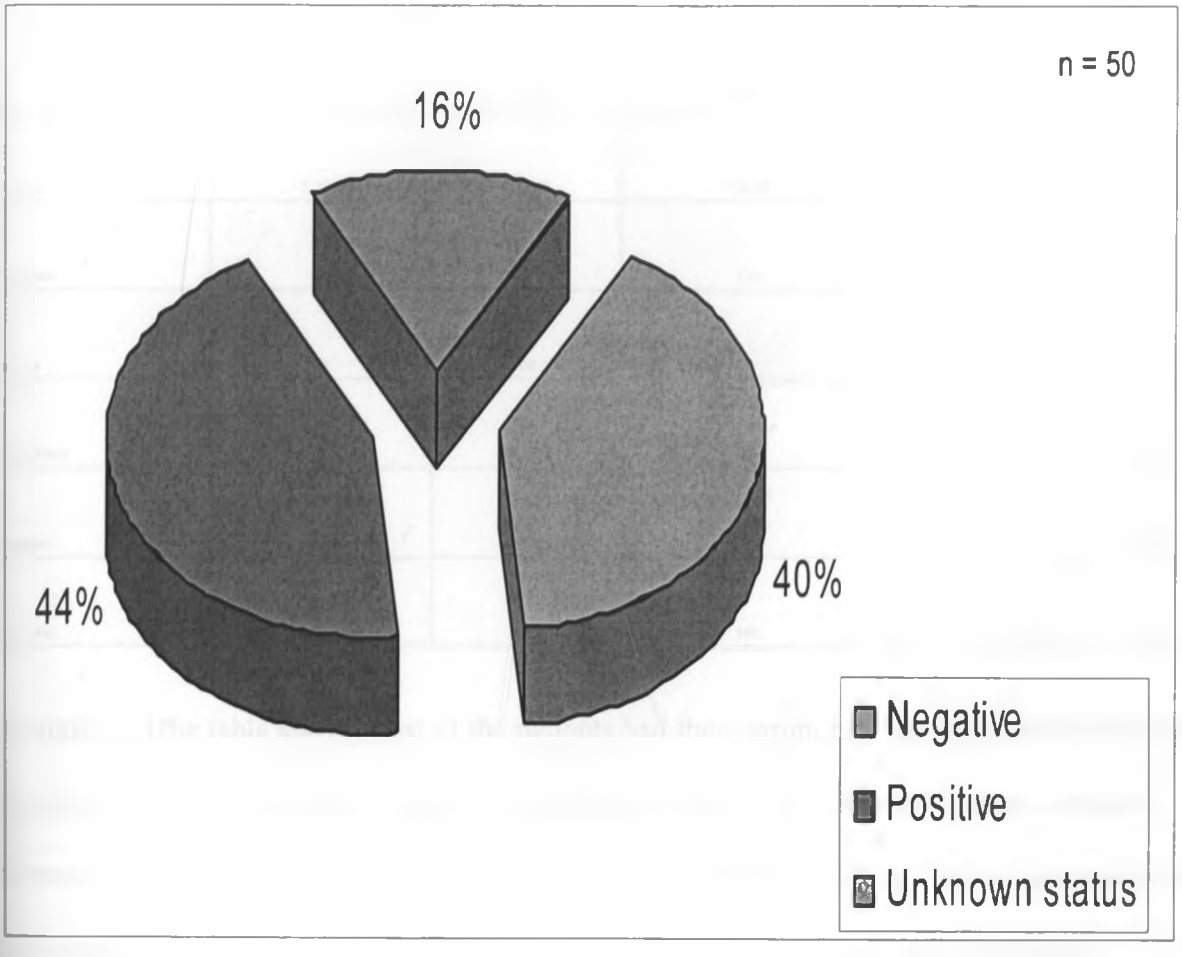
Focal infective processes which presented as space occupying lesions were the most common accounting for 14 % of all GCSE patients, followed by meningoencephalitis at 10%. Tuberculous meningitis, cryptococcal meningitis and toxoplasmosis which are AIDS defining illnesses accounted for 12%. There were 14% of the patients who presented with space occupying lesions that a conclusive diagnosis was not reach due to investigative difficulties such as carrying out brain biopsies.

Figure 10: ILAE proposed Classification of causes of GCSE



The international league against Epilepsy (ILAE) has proposed classification of causes of GCSE based on the perceived time duration the cause has been operational in the patient. It basically has three classes with the acute symptomatic having been present for seven days or less while those present for over one week are considered to be remote symptomatic causes and those in whom causes are unknown or time is difficult to estimate are classified as undetermined causes. In this study acute symptomatic causes accounted for about 62% with remote symptomatic contributing 28% as shown in figure 9 above.

Figure 11: HIV sero-status of GCSE patients



HIV serology testing was carried out in 84% of the GCSE patients. The Kenyatta laboratory uses an ELISA based test for the presence of antibodies to both HIV 1 and 2. In our study population serology for HIV was positive in 44% of the patients as shown in figure 10 above.

Other investigations carried out on patients presenting with GCSE included serum urea, creatinine and electrolytes whose results are as summarized in table 2 below.

Table 2: Serum urea, creatinine and electrolytes of GCSE patients

	urea	Creatinine	sodium	potassium	chloride	Calcium
mean	8.705	126.67	132.88	4.135	96.82	1.86
median	7.3	113.5	134	3.8	98	2.01
done	44	48	48	48	48	19
not done	6	2	2	2	2	31
lowest	2.6	68	133	3.28	94	1.65
highest	52.4	1236	148	6.4	108	2.64

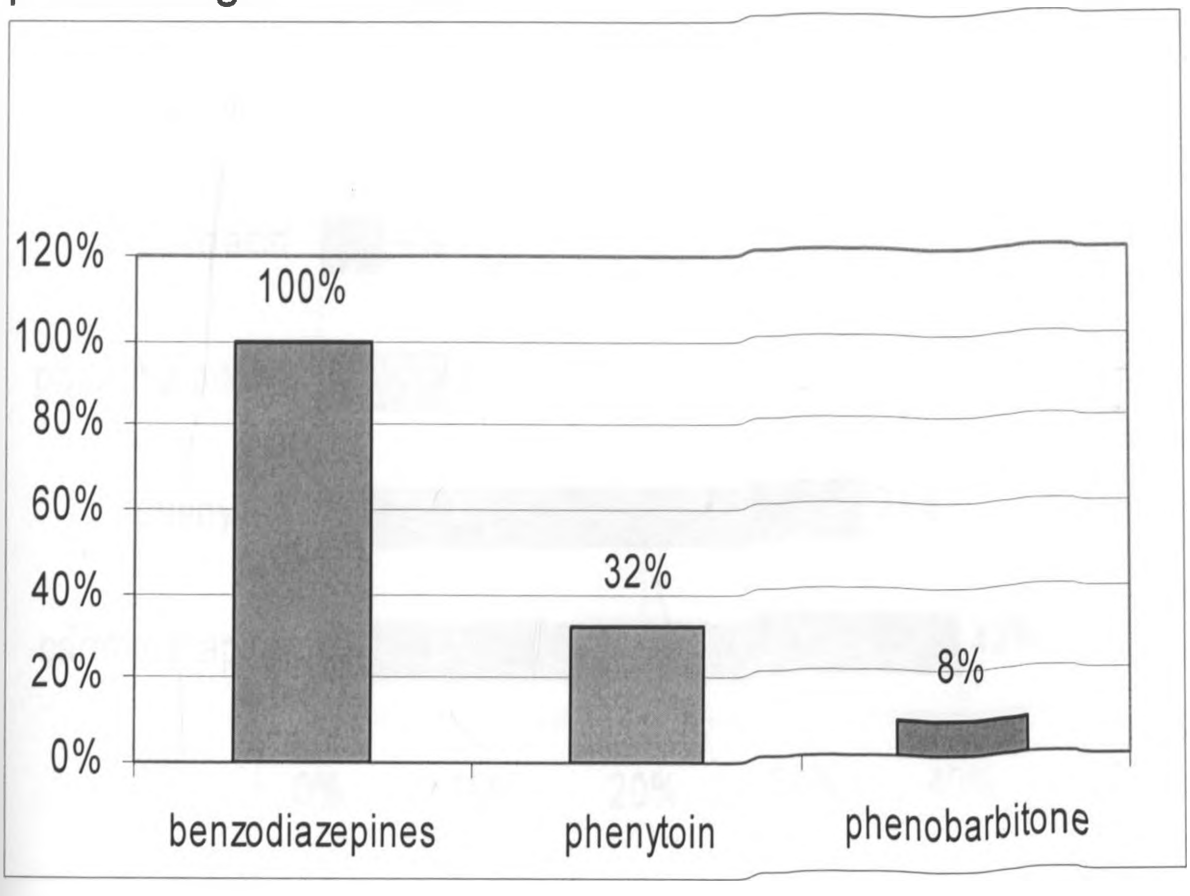
As shown in the table above most of the patients had their serum biochemical profiles done with exception of two in whom no requests were placed. Four patients had their serum urea not determined due to technical errors due some reagents that were missing. The serum calcium level was determined in 38% of the GCSE patients. The failure to carry out serum calcium determination in 62% was first due to lack of reagents in 40% patients and no requests were placed for the remaining 22% of the patients. The mean and median serum sodium level was lower than the normal reference range of 135 to 145 mmol\lt. The other means or medians were with in the normal reference ranges, as shown in table two above but a few outliers skewed some of the means. For example the mean creatinine level was slightly elevated at 126.67 mmol\lt while the median was normal 113.5 mmol\lt reflecting the effects of skewed data due to a few outliers.

Table 3: Hematological investigations done on GCSE patients

	Hb (mg\dl)	WBC \mm 3	Platelets\ mm 3
mean	12.22	9212.5	245,000
median	10.3	7050	234,000
n	50	50	50
lowest	6.8	2,800	125,000
highest	15.6	28,000	437,000

A summary of the hematology investigations done on the patients presenting with GCSE is as shown in table 3 above. All the 50 GCSE patients had their complete blood counts determined. The means and the median levels of the hematological investigations were all in the normal ranges as shown in table 3 above. Hemoglobin level was 12.22 gms\dl with a median of 10.3 gm\dl, the normal ranges being 10 – 16 gms\dl. The white blood count mean was 9212.50 cells/ mm^3 with a median of 7050 cells/ mm^3 the normal range is 3500 – 10,500 cells/ mm^3. The mean platelet count was 245,000 particles/ mm^3 and a median of 234,000 particles/ mm^3 both of which are with in the normal range of 150,000 – 450,000 particles/ mm^3.

Figure 12: Emergency drugs prescribed for patients presenting in GCSE



The emergency treatment given to patients with GCSE is as shown above. All the 50 patients received a bolus injection of a benzodiazepine. The benzodiazepine used in all these situations was diazepam. Further to this, 86% of the patients got two or more repeat doses of diazepam. Thirty two percent got a second drug which was a loading dose of phenytoin while a third drug, a loading dose of phenobarbitone, was prescribed in 8% of the patients.

Figure 12: Emergency drugs prescribed for patients presenting in GCSE

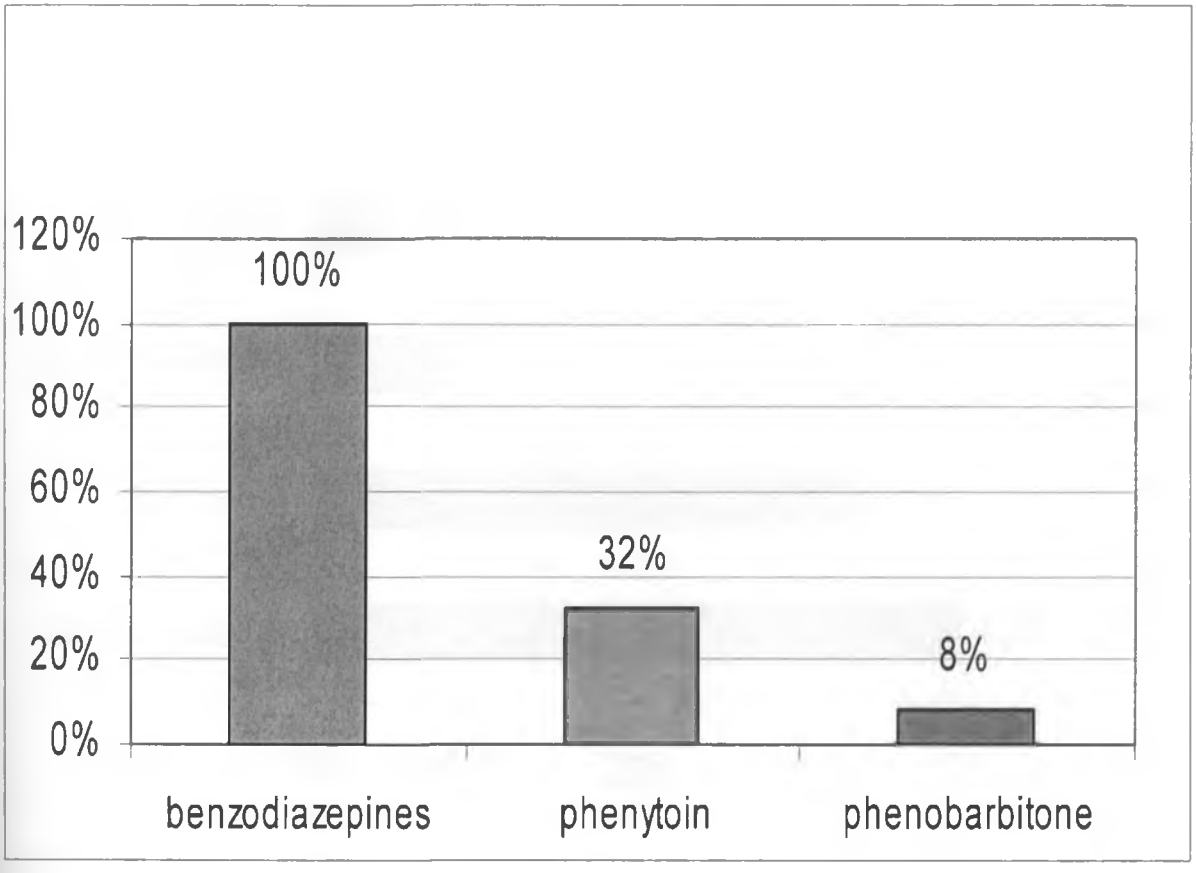


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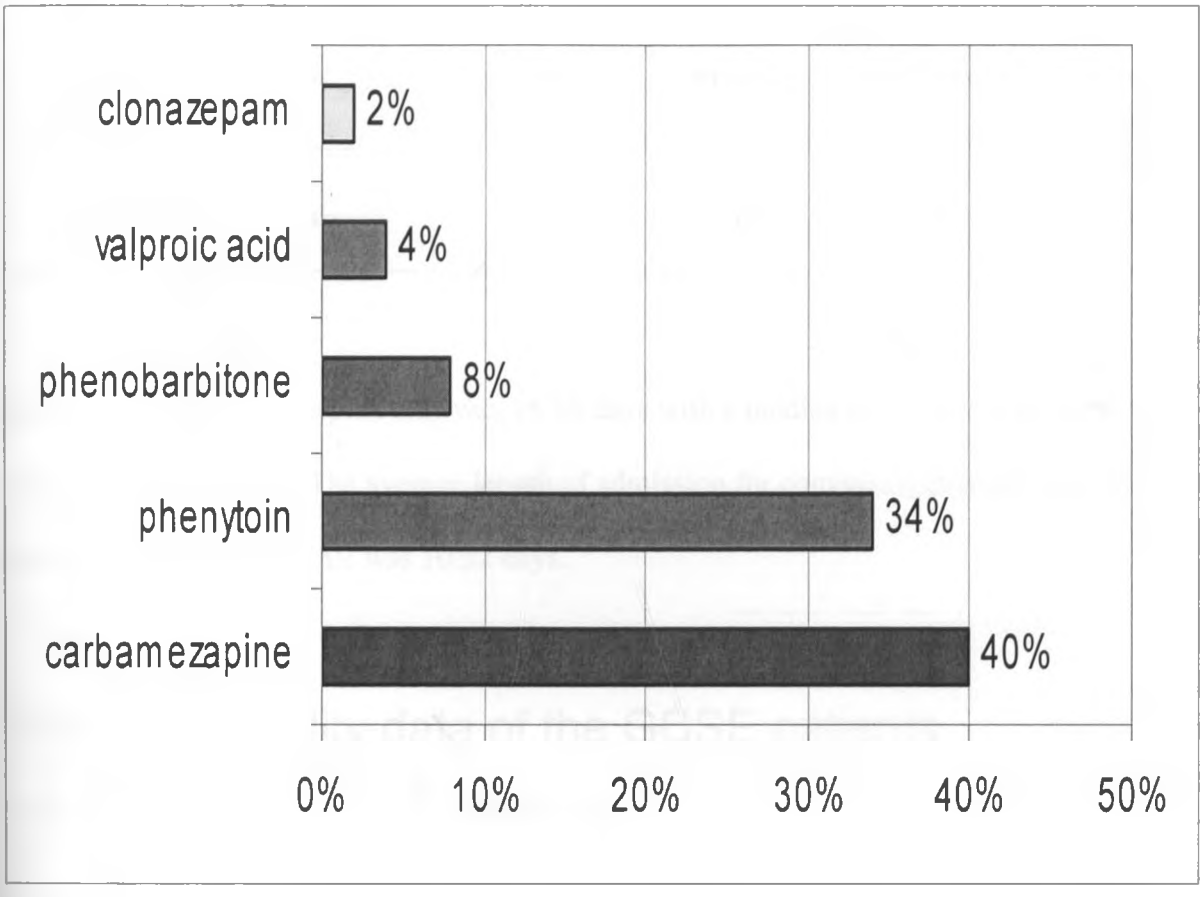
Figure 13: Discharge medications for patients with GCSE



Eighty percent of patients received oral maintenance medication, of these 8% received two or more drugs. Carbamezapine was the most prescribed oral maintenance drug having been prescribed to 40% of the patients followed by phenytoin prescribed in 34%. Clonazepam was the least prescribed at 2% as shown in figure 12 above.

Table 4: Length of hospital stay for patients with GCSE

Mean	n	SD	Median	Minimum	Maximum
16.83	50	14.52	13	2	65

The mean length of in-hospital stay was 16.83 days with a median of 13 days with the range being 2 days to 65 days. The average length of admission for convulsing patients who did not satisfy the criteria for GCSE was 10.52 days.

Table 5: Mortality data of the GCSE patients

- 8 deaths (5 males , 3 females)
- Crude case fatality rate: *16% of all GCSE patients*
- Median duration of hospital stay = *5 days*
- Most common diagnosis :
  - *Meningo-encephalitis : 6*
  - *Stroke : 1*
  - *Acute intoxication: 1*

During the follow up period there were 8 deaths, five males and three females. This made the crude death rate to be 16 % of all GCSE patients. The mean duration of hospital stay for the

patients who died was 5 days. The primary pathology that was associated with death was infection to the brain and meninges which was responsible for six out of the eight deaths.

DISCUSSION

Generalized Convulsive Status Epilepticus (GCSE) is a medical emergency with a high mortality and morbidity. Very few studies have been done in Africa on this disease. The knowledge of the prevalence, causes, morbidity and mortality factors will fill the current knowledge gap and lead to better management of this condition. We recruited 50 patients from those admitted to KNH general wards, intensive care and high dependency units during the three month study period and followed them to either discharge or death.

Demographic profile

The mean age of the patients was 28.96 years with a median of 27 years. This is younger than the mean ages in the studies done in western countries where the mean and median ages range between 50 – 60 years (4, 5, 6, 7, 8). The reason for this apparent age difference could be due to the differences in the population distribution where the western countries have a larger aging population leading to a narrow-based population pyramid.

Furthermore cerebrovascular diseases, an etiology associated with the elderly population, contributed only to 2% of the primary causes. Western studies have also shown that the risk for GCSE increases with advancing age (4, 5, 6, 7). Wu et al found a prevalence rate of 22.32 \ 100,000 in the age group over 75 years compared with 6.18 \ 100,000 in the general population. The explanation for the above was the high rate of cerebrovascular diseases in the elderly.

The male to female ratio was found to be 1.6 to 1. This male predominance has been observed in other studies (4, 6, 8). Various theories have been advanced including lower rates of head injury

in women, less drug abuse cases in women, but the most credible has been the low rate of cardiovascular diseases in women especially pre-menopausal women.

Majority (62%) of the patients had been referred from other health care facilities. This is an expected finding for KNH which is a tertiary referral hospital. The major reasons for these referrals were inadequate investigative facilities in the primary centers, especially imaging studies such as the CT scanner. The other reason was the failure to respond to the initial treatment given at the primary facility. This means that the difficult cases refractory to treatment are likely to be admitted to KNH.

Prevalence of GCSE

Some of the community studies have shown a high prevalence of GCSE in the black population. De Lorenzo et al working in Richmond, Virginia reported a GCSE rate of 29/ 100,000 in the black population compared to a prevalence rate of 8.3 / 100,000 among whites living in the same area. He observed that blacks had a two to three fold risk of GCSE compared to their white counterparts in the same environment(5). This find was also shown by Wu et al working in California who reported a prevalence rate of 13.35 \ 100,000 among blacks compared with a prevalence rate of 6.18 \ 100,000 in the general population(7). The reason for this difference could not be ascertained.

This study looks at a black African population and found a high prevalence of 0.48%. This is higher than that found in the studies discussed in the above paragraph. Explanations for this finding include that this was a purely hospital-based study in which uses a patient population as a

denominator for comparison as opposed to community studies which use the general population as the reference point.

The study was prospective in design unlike the earlier community studies that have been retrospective. Retrospective studies have the problems of missing out many cases due to lost records and low case finding attributable to lack of an active screening process.

Coeytaux et al did a study in six cantons in the French speaking Switzerland and concluded that urban areas had higher prevalence's of GCSE than rural populations(8). Our study was set in an urban area.

Duration of stay

A Study done in French speaking Geneva by Coeytaux et al showed mean admission duration of 13 in patient days while Wu et al found with 6.8 days by in California(7,8). Coeytaux explained that the difference in in-hospital duration was mainly attributable to the better and faster investigation rate in California. He gave the example of imaging studies such as computerized tomography scanning (CT scan) and magnetic resonance imaging (MRI) which we available in California 24 hours a day compared to the rural cantons that lacked such facilities and patients had to be referred to Geneva for investigations.

This study found a mean admission duration of 16.83 in patient days which is longer than any of the two earlier studies. One of the reasons contributing to a prolonged in-hospital stay was lack of adequate neuro-imaging facilities especially CT scanning. The major reason for referral in this study was for neuroimaging studies which accounted for about half of the reasons for

referral. It was also noted that neuro-imaging studies delayed the time taken to reach a conclusive final diagnosis of the primary cause of the GCSE. Up to 14% of the GCSE patients had space occupying lesions that had not been completely characterized due to the inadequacy of imaging facilities by the time they were discharged.

About 20% of the referral was due to refractory GCSE. These represent a group of patients with a severe disease that has failed to respond adequately to treatment. These will most likely require higher or combinations of medications, further investigations all of which will lengthen their in-hospital stay.

By definition loss of consciousness was a must for one to be included as a case of GCSE. This translated to low level of consciousness at admission. Coma states are associated with various complications such as aspiration pneumonia and physical injuries that contribute to a prolonged in-hospital stay.

Our primary etiologies were different from those found in western studies that reported shorter in-hospital duration. It is a fact that certain diagnoses are associated with longer hospital stay than others. For example a diagnosis of cryptococcal meningitis in a HIV sero-positive patient is likely to be longer than that of an alcoholic presenting in hypoglycemia.

The emergency management was done by registrars not consultant neurologists. It was observed that about 86% of the GCSE patients got repeat doses of diazepam. This reflected poor adherence to standard protocols of treating GCSE in the emergency setting which results in a

slower rate of seizure activity control. Eventually 40% of the GCSE patients needed a second or third anticonvulsant drug for adequate control. This could represent a group of patients with refractory seizures taking a longer duration to control or a group that was treated less aggressively.

It may have been possible that GCSE is a marker of severe illness which needs a longer duration of hospital stay.

Etiology of GCSE

Up to 40% of those who presented in GCSE were known to be persons living with epilepsy. This finding is similar to that of Knake et al in Hessen Germany who observed that up to 50% of the patients with GCSE were known persons living with epilepsy(4). The major reason for the GCSE in persons known to suffer from epilepsy was that up to 70% of them were not compliant to prescribed antiepileptic drugs. This is a known factor that contributes to poor seizure control and may predispose such individuals to GCSE.

Mativo in a master's dissertation titled 'factors causing poor compliance among epileptic patients presenting at the KNH neurology clinic' observed a 62% non compliance rate in patients on long term anti epileptic medication. The individual factors responsible for the poor compliance were poverty, low level of education and low social economic status (22). The current study did not look at factors contributing to poor compliance but the results suggest an increased GCSE risk in persons living with epilepsy who do not adhere to their AEDs. This is an area where a major reduction can be undertaken to reduce this high prevalence. Interventions such as patient

education and availing drugs will lead to better seizure control which eventually leads to a lowering of the prevalence.

Furthermore most of the patients had poor control as judged by frequent seizures. Whether this was due to the poor drug adherence or the primary condition was outside the scope of this study.

Infections were the second commonest cause of GCSE accounting for 36% of all patients. Infection with a focal presentation accounted for 26% compared to 10% causing diffuse brain and meningeal infections. This is in contrast to the etiologies from western studies where the leading cause is cerebrovascular diseases with infections playing an insignificant role. This difference can be explained in several ways. Firstly our study population was younger with a lower burden of cerebrovascular diseases. Secondly it could be due to a low incidence of infectious causes in the western countries such that non infectious causes like cerebrovascular diseases predominate. Also the huge burden can represent a failure of health preventative measures which is common in developing countries.

Known AIDS defining illnesses including tuberculous meningitis, cryptococcal meningitis and toxoplasmosis accounted for 12% of the primary etiologies associated with GCSE. This coupled with the finding of a 44% sero positivity rate for HIV in patients presenting in GCSE underscores the importance of neurological manifestations of HIV\AIDS.

Nature of investigations

As expected investigations usually focus on the perceived likely cause of the ailment and were skewed towards causes prevalent locally. This explains the active search for infective causes on

all GCSE patients by carrying out complete blood counts. Despite infections ranking second as a common cause of GCSE the mean and median white blood cell counts were in the normal ranges. Kenya is at the epicenter of the HIV\AIDS pandemic, this can explain the 84% screening rates in the GCSE patients which led to the finding of a 44% HIV sero-positivity in the GCSE patients. HIV/AIDS manifestations in the central nervous system are protean ranging from mild confusion, acute psychotic episodes to myelopathies and unconscious states. All these can either be attributed to the HIV itself, opportunistic infections or treatment. From this preliminary data it would seem that HIV\AIDS contributes significantly to the cause of GCSE. This would be an area where a prospective study on the relationship between the two would be necessary.

The biochemical parameters were generally normal. However the screening rate for serum calcium levels was low at 38%. Hypocalcaemia is known to cause convulsions and failure to determine serum calcium levels in 62% of the patients may have missed many patients. The ILAE guidelines recommend calcium screening in all convulsing patients. Out of the 19 patients who had their serum calcium level determined two were found to have hypo-calcemia after correction for the serum albumin level. The diagnosis of hypocalcaemia associated GCSE was entered in one patient who had symptomatic hypocalcaemia with a corrected serum calcium level of less than 1.65 mMol\lt. This makes the prevalence of hypocalcaemia to be 5.26%. This is higher than what has been reported in other studies and could have contributed by the small number of patients (4, 8, 10).

Nature of treatment

The emergency treatment decisions of GCSE patients were done by registrars and some did not conform to the universally laid down guidelines. This can explain the less aggressive use of second and third drug loading doses and the repeated loading doses of diazepam given to GCSE patients. Two patients got a diazepam drip for their continued convulsions. Diazepam is oil based hence immiscible in fluids thus putting it in a drip is not recommended (28, 44, 46). This is not the best clinical practice for standard protocols have emphasized the use of the above drugs. The main reason for non use was the unavailability of the drugs. Furthermore clinicians rarely prescribed it in the treatment sheet. Adherence to the treatment protocol, availability of phenytoin sodium will go a long way to reduce the mortality and duration of hospital stay

The majority (90%) of the GCSE patients were managed in the general medical wards with 8% admission into the intensive care unit or the high dependency unit. This is in contrast to the western studies where over 50% of the patients were in ICU or specialised neurological wards (4, 5, 7). GCSE is a medical emergency which should be closely monitored and intervention done on a real time basis to improve outcomes. The major reason that the patients never got to such units was mainly due to a restricted bed space. This would definitely contribute to the high mortality we observed.

Mortality

The crude fatality rate was 16% which is higher than the 10.7% found by Wu et al in California (7). This has to be taken in the context of the small sample. The high mortality rate can be

largely explained by the differences in the primary causes of GCSE. In the California study a primary diagnosis of cerebral anoxia was associated with a high risk of death followed by infective causes. However the total burden of infections was low due to the low prevalence of infective causes in their locality ranking as the tenth cause of GCSE. This is in contrast the current study where infections were 38% of the primary causes.

Mean duration of hospital stay before death was five days. This is similar to that found by Wu et al in California who found a mean hospital stay of 6.7 days before death in patients presenting with GCSE (7).

Six out of the eight fatalities were due to meningoencephalitis. They had also tested positive for HIV on ELISA examination done at the KNH laboratories. Two out of the six patients who died during the study were on antiretroviral therapy for HIV. This goes further to emphasize the role of HIV/AIDS not just in causing GCSE but in increasing to its mortality.

Conclusion

This study has shown that:

i. The prevalence of GCSE is relatively higher in our setting and that it occurs in relative younger age groups.

ii. Epilepsy is the single most common etiological factor in GCSE. Most of those result from poor drug compliance.

iii. Infections are the second most important primary cause of GCSE.

iv. GCSE contributes to a longer in hospital stay in our set up than in other parts of the world.

v. Providing adequate neuro-imaging facilities in other hospitals can significantly reduce t referral rate of GCSE patients and improve their management.

vi. HIV/AIDS contributes significantly to both causation and mortality of GCSE. An area that needs urgent further studies in view of the scaling up program of antiretroviral therapy.

RECOMMENDATIONS

1. Counseling on living with epilepsy, drug adherence, destigmitisation and availing antiepileptic drugs will ago along way in reducing non compliance rates in persons living with epilepsy and consequently reduce the prevalence of GCSE.

2. Improving and expanding intensive care facilities will improve management of medical emergencies GCSE included.

3. Adhering to standard treatment protocols will standardize and improve care for patients of GCSE.

4. More studies are needed to look at the role of specific diseases in causation of GCSE especially HIV/AIDS in our set up.

STUDY LIMITATIONS

1. The study was carried in a short duration of time (three months) which is may not be a good indicator on the true prevalence.

2. The study did not carry out postmortem to ascertain the causes of death in the patients who presented with GCSE.

3. The study did not follow the patients discharged on a long time which could uncover minor disabilities such as learning difficulties that could be attributed to GCSE that might not be picked up by a short term mortality study.

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Appendix I

Part one

Patient questionnaire client number_____

Prevalence of generalized convulsive status epilepticus in patients admitted to Kenyatta National Hospital and their short-term outcomes

PATIENT INFORMATION SHEET (English version)

Dear Sir / madam / master / ms

I'm conducting a study on the prevalence of generalized convulsive status epilepticus and the short-term outcomes in patients admitted to K.N.H. This small note is to seek to inform you about the study and seek your support.

Your patient has been admitted to this hospital following the harrowing experience of losing consciousness accompanied by uncoordinated movements of the limbs. This is called a seizure in medical terms. Such activity results from uncontrolled excessive discharges from neurons in his brain.

The exact cause of this phenomenon is not known but it is a documented fact that an insult to the brain can predispose to this condition. Such brain insults can take the form of a head injury, infection, disturbance in body electrolytes etc. we don't know what is contributing to such disease in your patient and our community at large. By participating in this study you can help uncover what tour patient and others who get similar seizures have so that it will be easier to plan their treatment in future.

Further more if this seizure activity continues for a long time it can cause brain damage. Specifically any such seizure lasting over half an hour is thought to be dangerous to life, and constitute a medical emergency called status epilepticus. Many medical people insist that one should treat such condition before the lapse of thirty minutes but evidence is

scanty for such a decision. So your participation will help resolve this quagmire and may just be one of the voices of evidence to support early intervention in your patient and all future patients.

To gather all this data we will need to do various tests on you or your patient which will include both radiological where the patient will be exposed to x-rays and laboratory methods which will involve taking blood or other body fluids for analysis. Any risks for such procedures such as pain at injection will be explained to you or your patient prior to taking the said samples.

Lastly you / your patient should know the following:

1. **Your participation in the study is very important to all patients who suffer seizure illnesses.**
2. **Standard medical treatment will be used as prescribed by your doctor. There no drugs which will be administered in this study.**
3. **All information acquired during this study shall be treated confidentially and only used for scientific purposes.**
4. **Participation in the study is voluntary**
5. **You are free to withdraw from the study at any point and there are no consequences for such action**
6. **All the results will be made available to you and your doctor for purposes of managing your disease**
7. **For any extra questions you may have my contacts are:**

Dr George M. Nyale
University of Nairobi
Department of medicine
P.O BOX
Nairobi
Tel:
My supervisors are:

Prof. Adam - Consultant Neurologist, Department of Medicine, University of Nairobi

Prof Amayo - Consultant Neurologist, Department of Medicine, University of Nairobi

Dr Jowi - Consultant Neurologist, Department of Medicine, Kenyatta National Hospital

CONSENT FORM FOR NEXT OF KIN

I _____ being the parent / legal guardian of _____ do affirm that I have read the patient information sheet and that I have fully understood the study as explained to me by _____. I have appended my signature below on a voluntary basis and as evidence of my consent to participate in the study. I also have the right to withdraw from the study at any stage without any dire consequences to my patient or myself. I have done so on:

Date:

Signature:

Witness: date

Signature:

ASSENT FORM FOR MINORS

I _____ do allow my parents / guardian to consent on my behalf and that I have also been explained to the purpose for this study. I also know my rights that I can withdraw from the study even if my parents / guardians have consented to it and that I shall not be required to give an explanation.

Signature:

Date:

CONSENT FORM FOR SUBJECT

I _____ consent to participate in this study on generalized convulsive status epilepticus as has been explained by _____. I fully understand the purpose, benefits and risks of this study. Further to this I know I can withdraw from this study at any stage without any dire consequences.

Subjects: signature:

Date:

Witness: signature:

Date

Part two

PROFORMA FORM

Age: ☐ **gender: male** ☐ **female** ☐

DoA: ☐ **ward:** ☐

1. Is it the first episode? Yes ☐ no ☐
2. Is the patient a known epileptic? Yes ☐ no ☐

   a. If yes has he / she been taking his medication as prescribed?

   Yes ☐ NO ☐

CONSENT FORM FOR SUBJECT

I _____ consent to participate in this study on generalized convulsive status epilepticus as has been explained by _____. I fully understand the purpose, benefits and risks of this study. Further to this I know I can withdraw from this study at any stage without any dire consequences.

Subjects: signature:

Date:

Witness: signature:

Date

Part two

PROFORMA FORM

Age: ☐ **gender: male** ☐ **female** ☐

DoA: ☐ **ward:** ☐

1. Is it the first episode? Yes ☐ no ☐
2. Is the patient a known epileptic? Yes ☐ no ☐

   a. If yes has he / she been taking his medication as prescribed?

   Yes ☐ NO ☐

b. Do you know the drugs he is taking?

Yes ☐ No ☐

3. How many people witness today's seizure? ☐

4. Did he / she:

(a) Loose consciousness? Yes ☐ no ☐

(b) Throw hands and legs? Yes ☐ no ☐

(c) Pass urine / stool on themselves? Yes ☐ no ☐

(d) Bite their tongue? Yes ☐ no ☐

(e) Froth at the mouth? Yes ☐ no ☐

5. How long did this convulsive movements last?

a. Below thirty minutes ☐

b. Between thirty minutes to one hour ☐

c. Over one hour ☐

6. After the convulsions were over what happened to the patient?

a. Ran off ☐

b. Went to sleep ☐

c. Was confused ☐

d. Another convulsion started ☐

7. Was this episode preceded by any fever or illness in the past one week?

   Yes ☐ No ☐

8. Do you attribute this condition to any incidents / illnesses in the past?

   Yes ☐ No ☐

   If yes please state which:

   _____

   _____

   _____

   _____

9. What other illnesses / disabilities does this patient have?

Examination findings

General condition of patient: coma ☐ confused ☐ alert ☐

Pallor ☐ jaundice ☐ cyanosis ☐ edema ☐

Dehydration ☐ oral thrush ☐

Any neurological deficit :(5 part neurological examination)

1) **Look at the patient**

a. General demeanour

b. Speech

c. Gait

d. Arm swinging

2) **Examine the head**

a) Facial movements

b) Tongue

c) Eye movements

d) Pupils

e) Fundi

3) **Examine the upper limbs**

a) Posture of outstretched arms

b) Wasting, fasciculation

c) Power, tone

d) Co-ordination

e) Reflexes

Part three

Day of discharge:

Functional level at discharge (circle on the karnofsky score chart)

THE KARNOFSKY PERFORMANCE INDEX

Performance status	**Functional capability of patient**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death is not imminent
20	Very sick; hospitalization necessary, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Part three

Day of discharge:

Functional level at discharge (circle on the karnofsky score chart)

THE KARNOFSKY PERFORMANCE INDEX

Performance status	**Functional capability of patient**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
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50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death is not imminent
20	Very sick; hospitalization necessary, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead