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**INTRACTABLE EPILEPSY IN SOUTH AFRICAN CHILDREN:
BASED ON CRITERIA DEFINED BY THE INTERNATIONAL LEAGUE
AGAINST EPILEPSY (ILAE)**

By

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree
Masters in Philosophy (MPhil) in the subspecialty of Paediatric Neurology

**Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN**

Date of submission 28 July 2011

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DECLARATION

I, **HANI M. ALKHALDI**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABBREVIATIONS

| | |
|----------|---|
| ACTH | Adreno-cortico-tropic hormone |
| AED | Anti-epileptic Drug |
| CT | Computed Tomography |
| EEG | Electroencephalography |
| ES | Epilepsy Surgery |
| FDG | Fluoro-deoxy-glucose |
| HIE | Hypoxic Ischemic Encephalopathy |
| IBE | International Bureau of Epilepsy |
| IE | Intractable Epilepsy |
| ILAE | International League Against Epilepsy |
| IVIG | Intra-venous Immunoglobulin |
| MRI | Magnetic Resonance Imaging |
| MSI | Magnetic Source Imaging |
| PET | Positron Emission Tomography |
| RCWMCH | Red Cross War Memorial Children's Hospital |
| s.d. | Standard Deviation |
| SISCOM | Subtraction Ictal SPECT Co-registered to MRI |
| SPECT | Single Photon Emission Computed Tomography |
| SPM | Statistical Parametric Mapping |
| SUDEP | Sudden Unexplained Death in Epilepsy Patients |
| U/S | Ultrasound |
| VNS | Vagal Nerve Stimulator |
| WHO | World Health Organization |
| χ^2 | Chi-squared |

AKNOWLEDGEMENTS

I would like to thank my supervisor Professor Jo Wilmshurst for her guidance and providing me with the opportunity to carry out this important study and furthermore for providing me with an enabling environment within which I could train in Paediatric Neurology within evidence based medicine context and to this conduct research.

I would also like to thank Dr. Alvin Ndondo who also assisted me in gaining a deep clinical insight in the field of Paediatric Neurology within the context of Paediatric medicine having more of holistic medicine approach and principals of communication and involvement of families and care givers.

I would like to thank the other members in the Neurology team who participated in the study specially Dr. Gill Riordan who was able to enlighten me from her long term experience in the department in addition to Dr. Sally Ackermann, Dr. Kathy Walker, Dr. Wendy Mathiassen.

I also wish to thank Mr. Henri Carrara, analytical epidemiologist, Faculty of Health Sciences, UCT for his assistance in the statistical analysis and Mrs. Dianne Pryce Postgraduate Administrative Officer for giving a full orientation and guidance to thesis; with special thank to Ms. Geanine Hopley for coordinating the necessary meeting to achieve this goal.

I would also like to extend my thanks to the nursing staff, Clerks and interpreter who helped me in getting the consent and assign when necessary in different languages.

I wish to extend my special thanks to the Medical records at Red Cross War Memorial Hospital for their hard work and commitment in assisting me to retrieve all Medical record required for the study.

My achievement in completing this work would not have been possible without the moral support and continuous encouragement of my wife Dr. Ahlam Farzan and Children back at home.

Finally I would like to thank all children and their families for their cooperation and support throughout the study.

Synopsis

Introduction

The latest definition of intractable epilepsy by the International League Against Epilepsy (ILAE) provides clear inclusion criteria for this condition. It is estimated that about 20% of patients with epilepsy managed in a tertiary referral centre have intractable epilepsy. This study addresses the demographics, key markers, aetiologies, co-morbidities and therapeutic options associated with a group of patients who have epilepsy resistant to medication. Through greater understanding of our patient group, recommendations can be made to improve our approach to epilepsy through the clinical management, inclusive of the cost efficacy. This study aims to compare the differences of the centre's previously established concept of intractable epilepsy compared to the ILAE criteria. The study assesses how separating out this medication resistant group impacts on the long term care and enables earlier consideration of other interventions (e.g. Epilepsy surgery, vagal nerve stimulator and ketogenic diet). Early intervention with these alternative interventions may be more cost effective even for children managed in resource limited countries.

Methodology

Prospective identification was undertaken of intractability in children attending neurology and epilepsy clinics at Red Cross War Memorial Children's Hospital. A retrospective medical record review of the patients who met the ILAE definition of intractability was performed to obtain necessary demographic and clinical data.

Results

A total of 513 children were reviewed, 96 of whom met the inclusion criteria of intractable epilepsy (IE). This was 18.7% of the total group of children with epilepsy. Male to female ratio was 1.3:1 with a predominant mixed ancestry, followed by children of African descent. Ninety percent of the children with IE were from local urban regions. The median age was 7.9 years among children with IE. 57% of them had an epilepsy syndrome mainly Lennox-Gastaut syndrome (27.1%) followed by epilepsy with myoclonic atonic seizures (13.5%), West syndrome (12.5%), Dravet syndrome (2.1%) and Ohtahara syndrome (2.1%). Children with IE had a seizure age of onset median of 17 months (mean 29 month, s.d. 30) and mean frequency of 58 seizures per month (s.d. 180). The confirmation of the label IE took an average of 4.75 years. A median of 3 events per week with a median duration of 2 minutes

(excluding status epilepticus) was found despite poly-pharmacy. Status epilepticus occurred in 82% of children with IE. Hypoxic ischemic encephalopathy (HIE) constituted 33% of all aetiologies followed by infections (20%) and structural brain malformations (16%). The median number of medications used in the intractable group was 4 and the median duration before considering failure of trial was 11 months (mean 15, s.d. 19). Other interventions were seldom used including ACTH, which was used in only 6% of IE patients, prednisone 10.4%, pyridoxine 6%, and IVIG 1%. Only 2% of our cohort had vagal nerve stimulators and a similar percentage had epilepsy surgery. 54% of children with IE had neuroregression, 68% developmental delay, 16% had intellectual disabilities, 38% behavioural problems and another 8% had pervasive developmental disorders including autism.

Conclusions and recommendations

The latest definition of intractable epilepsy by the ILAE provided clear criteria to study the prevalence of IE among children with epilepsy. In comparison with local expert definitions IE was defined 4.1% more using ILAE definition. It took around 4.7 years to recognize intractability in our centre. Several key markers were flagged in our study which could assist earlier identification of patients at risk of IE including seizure onset frequency, aetiology, epilepsy syndromes. Only a small percentage of our children had access to epilepsy surgery, ketogenic diet, and vagal nerve stimulator (VNS). Several disabilities especially developmental, intellectual, behavioural and social in addition to financial and eventually death are expected outcomes of children with intractable epilepsy. Early recognition can be achieved if awareness of the definition of intractability and its predictors is raised. Early referral to enable access to essential resources such as epilepsy surgery, would improve the potential outcomes for these children.

INTRODUCTION

Epilepsy is one of the most important childhood diseases. It is one of the most common chronic neurological disorders, affecting more than 50 million people worldwide (1).

Epilepsy affects 3–5% of the population worldwide (2). It occurs in 1–2% of children, with the first 12 months of life carrying the highest incidence after which epilepsy plateaus until it decreases after 10 years of age (7, 8). More than 80 per 100 000 people develop new-onset epilepsy every year, most commonly during childhood and in old age (3). Studies suggest that the lifetime and active prevalence of epilepsy were 7.3/1 000 and 6.7/1 000 respectively for children in South Africa (4). Worldwide estimates are recorded at 4 -10/1000 (1). Fortunately, most of the patients are treatable, with good outcome (5, 6).

Because of un-standardized definitions as well as misdiagnoses, the incidence and prevalence of intractable epilepsy are somewhat uncertain (9). It is agreed on among the majority of references that up to 80% of people with epilepsy gain adequate seizure control with the use of a single appropriately selected antiepileptic drug used at the correct dosage and that despite the introduction of many second-generation antiepileptic drugs (AEDs) in the past 15 years, about 20% of patients with epilepsy remain refractory to all available pharmacological treatments (10) even if they have experienced long periods with no seizures at all (11). However the percentage reviewed historically varied widely between 10 – 40% (11-25).

Intractability was specifically estimated higher in very long follow-ups beyond the paediatric age. Difference between the reported frequencies of uncontrolled seizures was not only due to different geographical and socio-economical factors, but also for lack of a standard definition of intractable epilepsy (IE) as well (26-29). Failure to achieve remission pharmacologically is not always due to resistance and may be attributed to improper selection of an agent, poor compliance in its use, relapse after tapering of drugs, unavailability of the medication (27,30,31), or even lack of trace elements and electrolytes homeostasis (32). Identifying those children who are prone to develop uncontrolled seizures is critical for parental counselling and selecting patients for more intensive investigations and treatment, such as early consideration of epilepsy surgery (33). Resistance can extend even into alternative interventions such as steroids and the ketogenic diet.

Studies suggest that the newer agents are no more effective but may be somewhat better tolerated than the older agents (34); the pharmaco-sensitive children will respond well to monotherapy provided accurate recognition of the epilepsy semiology is made. These children can be managed in a cost effective manner with targeted investigations and treatment schedules. Categorizing this group allows the remainder of patients with epilepsy who have more complex seizure disorders to have access to the more costly resources.

Early detection and intervention of children with intractable epilepsy will result in better outcomes for co-morbidities, seizure control and cost (both emotional and financial for the child and their carers).

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CHAPTER 1

LITERATURE REVIEW

Historical aspects of the definition of Intractable Epilepsy

Concern relating to intractable epilepsy dates back to ancient Indian medicine and extended further when concepts about epilepsy became more developed during the Vedic period of 4500-1500BC and in the Ayurvedic literature of CharakaSamhita (dated to 400BC)(35).

In the Babylonian description of epilepsy 2000BC there are attempts to identify early intractability of epilepsy:

6. *[If an epilepsy demon falls many times upon him, and on] a given day he seven times pursues and possesses him, his life will be spared. If he should fall upon him eight times his life may not be spared.*

7. *[If an epilepsy demon falls many times] upon him, and for one year when he falls (The patient) has the fit at the (same) precise time, the situation is critical. Miqtu draws closest to a man at midday and it is then most serious for him.*

8. *[If an epilepsy] demon falls (many times) upon him and on a given day he seven times pursues him and he has a fit with loss of consciousness, and if when (the demon) has let him go he had the hand of the departed spirit of a murderer. He will die (36).*

In the past, epilepsy was associated with religious experiences and even demonic possession. In ancient times, epilepsy was known as the "Sacred Disease" (as described in a 5th century BC treatise by Hippocrates (37).

Because people thought that epileptic seizures were a form of attack by demons, or that the visions experienced by persons with epilepsy were sent by the gods. Among animist Hmong families, for example, epilepsy was understood as an attack by an evil spirit, but the affected person could become revered as a shaman through these otherworldly experiences (38).

In most cultures, persons with epilepsy have been stigmatized, shunned, or even imprisoned; in the Salpêtrière, the birthplace of modern neurology, Jean-Martin Charcot found people with epilepsy side-by-side with the mentally retarded, those with chronic syphilis, and the criminally insane. Even in current times in Tanzania, as with other parts of Africa, epilepsy is associated with possession by evil spirits, witchcraft, or poisoning and is believed by many to be contagious (39).

In 1857 Sir Charles Locock reported the efficacy of bromides in the treatment of Epilepsy (40), thus announcing the beginning of epilepsy's pharmacological treatment. In 1912 phenobarbital was shown to be effective. There was a haphazard release of a few drugs (for example, phenytoin, carbamazepine, and valproic acid) until the past 12 years when 10 new antiepileptic drugs (AEDs) drugs were approved for use. These newer drugs differ from the older ones in terms of pharmacokinetics and side-effect profiles, but there is no evidence that any are more efficacious in the treatment of epilepsy than the older AEDs (41).

Over the past few decades efforts to try defining intractable epilepsy was diverse and not very conclusive but as approaches become more organized and experiences accumulate, the definition is becoming more defined supporting earlier referral for epilepsy surgical assessment and other alternative interventions.

Although the concept of drug resistant epilepsy (often used interchangeably with "medically refractory/intractable" or "pharmaco-resistant") may appear self-explanatory and obvious, a precise definition has remained uncertain. This has resulted in diverse criteria used by different clinicians and researchers, or even a lack of explicit criteria in some cases, rendering it difficult to compare findings across studies and to make practice recommendations (42-45).

Since there is no agreed definition of intractable epilepsy (IE), it is not surprising that several diverse criteria for drug resistance are found in the literature (46, 47).

In response to this, the international league against epilepsy (ILAE) appointed a task force under the commission on therapeutic strategies to formulate a proposal for a consensus definition of drug resistant epilepsy.

Traditionally, therapeutic failure of three AEDs defined intractability (18, 19, 21, 44, 48, 49, 50, 51). With many new AEDs available in recent years, it might have been expected that more rather than fewer drug trials would be recommended before determining intractability. However, several prospective case series have shown that a high likelihood of medical intractability can be identified after two unsuccessful trials, as with each AED failure, the likelihood of successful treatment with other drugs (12, 19, 48, 52-54).

The ILAE definition of Intractable Epilepsy

There are several factors to be considered in a definition of medical intractability (Table 3), including the number of AED failures, minimum frequency at which seizures must occur to be considered intractable (daily, monthly, and so forth), duration of unresponsiveness to medication, epilepsy syndrome involved, causes of seizures in the absence of a clear-cut epilepsy syndrome, and patient age at the onset of seizures. (44) WHO, the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) are undertaking a global campaign to provide better information and raise awareness about epilepsy. They aim to strengthen public and private efforts to improve care and reduce the disorder's impact. A new revised classification of epilepsy exists for general practitioners and primary health care providers, listing simple therapies and straight-forward approaches for pharmacologically sensitive children with access to commonly used effective drugs. There has not been consistency as to the definition of the term "intractable epilepsy" (Table 1) (55).

TABLE 1 Published criteria used for determining intractable epilepsy

| Criteria | | | |
|----------------|---------------------|---|---|
| Study/Citation | Minimum AEDs failed | Seizures | Comments/qualifications |
| Connecticut | 2 | 1 seizure per mo for ≥ 18 mo and ≤ 3 mo seizure free during that time | The outcome had to be met within 3 years of diagnosis |
| Holland | Not specified | At 6 mo after diagnosis, failure to be ≥ 3 mo seizure free | Published criteria were not modified. This is an indicator of risk and not a criterion for intractability per se. |
| Philadelphia | 2 | At 2 yr after diagnosis, failure to be ≥ 6 mo seizure free | Criteria were used as published without modification |
| Canada | 3 | ≥ 1 seizure every 2 mo in last year of follow-up | Criteria were used as published without modification |
| Scotland | 2 | < 1 yr seizure free at last follow-up | Modified to be assessed at 5 yr after initial diagnosis |
| Surgery | 2 | Not explicitly stated | Outcome had to be met within 3 yr of diagnosis |

The ILAE appointed a task force which formulated a consensus document for a definition of drug resistant epilepsy. The task force comprised members with diverse expertise, including epidemiology, adult and paediatric epileptology, neurosurgery, clinical pharmacology and clinical trial design. Pertinent literature and discussion at relevant workshops were considered (218).

The proposed definition stated that drug resistant epilepsy is **the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules** (whether as monotherapies or in combination) **to achieve sustained seizure freedom**. Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer (56).

For treatment response the overall framework of the definition has two “hierarchical” levels: Level 1 provides a general scheme to categorize response to each therapeutic intervention, including a minimum dataset of knowledge about the intervention that would be needed; Level 2 provides a core definition of drug resistant epilepsy using a set of essential criteria based on the categorization of response from Level 1 to trials of antiepileptic drugs (tables 2 and 3).

Table 2 Scheme for categorizing outcome of an intervention for epilepsy

| Outcome dimension | | |
|----------------------|-------------------------------|------------------|
| Seizure control | Occurrence of adverse effects | Outcome category |
| 1. Seizure-free | A. No | 1A |
| | B. Yes | 1B |
| | C. Undetermined | 1C |
| 2. Treatment failure | A. No | 2A |
| | B. Yes | 2B |
| | C. Undetermined | 2C |
| 3. Undetermined | A. No | 3A |
| | B. Yes | 3B |
| | C. Undetermined | 3C |

(Copied from Kwan et al. Definition of drug resistant epilepsy, *Epilepsia*. 2009 Nov 3)

Table 3 Minimum dataset required to determine whether the trial of a therapeutic intervention is informative

| |
|---|
| Nature of the intervention (e.g., type of drug, in the case of antiepileptic drug treatment) |
| Mode of application (e.g., formulation, dose, dosing interval, and patient's compliance in case of an antiepileptic drug) |
| Duration of exposure |
| Occurrence of seizures and adverse effects during the trial period |
| Whether there was any effort to optimize dose |
| Reason(s) for discontinuation (if applicable) |
| Unsatisfactory seizure control |
| Adverse effects |
| Long-term seizure freedom |
| Psychosocial reasons, for example, planning for pregnancy |
| Administrative reasons, for example, lost to follow up |
| Financial issues, for example, cannot afford treatment |
| Patient/caretaker preference |
| Other reasons |

(Copied from Kwan et al. Definition of drug resistant epilepsy, *Epilepsia*. 2009 Nov 3)

Recognizing Intractability

Even though some studies suggest that epilepsy fails to come quickly under control with medicines in about one-third of cases, it is the definition of “uncontrolled” that is needed so that estimations of true prevalence can be made (57).

It is important to predict as soon as possible after diagnosis and starting treatment, which children are destined to develop medically intractable seizures and be at risk of increased morbidity and mortality (58, 59) and which child's epilepsy will remit and which will be a lifelong disorder (59).

In addition to providing parents with answers, this could allow for more aggressive treatment with modern antiepileptic drugs (AEDs) to obtain the maximal drug response to overcome drug-resistance without delay, if possible(60),if needed, early neurosurgical intervention in suitable cases(61).

Early recognition and interventions would improve the lives of children with intractable epilepsy (62).

Latency in recognizing intractability

Up to 20years delay are described to recognise intractable epilepsy, especially for focal epilepsy (63).

In a study of 333 patients latency time was 9.1 years and younger age at onset was strongly associated with longer latency time (51).

Even in the most specialized epilepsy surgical centres it was estimated that it took at least 5 years from the onset to recognize IE when referred from non specialized services outside the centre; however when referred from a paediatric neurologist it took 6.4 years and 6.6 years by the epileptologist. Much related to the duration of AED trials and the uncertainty of the definition (64).

Epilepsy may not be clearly intractable for many years after onset. This is especially true of epilepsy of childhood and early adolescent onset (51).

Predictors of Intractability

A number of prospective studies have attempted to identify factors that predict the risk of intractable epilepsy (IE). These studies have varied somewhat in their sampling (population-based versus hospital-based) and whether they included children, adults, or both (48). No single factor has been found to be uniquely useful in making accurate predictions. A combination of one or several of these factors may help to recognise IE.

Frequency of seizures

An average, four seizures every month, was often used as an entry criterion for adjunctive drug trials in drug-resistant partial epilepsy (65).

The definition of not being seizure-free for 1 year despite treatment (11, 12) is reasonable to consider as IE. In the UK National General Practice Study of Epilepsy with a follow-up of 9 years that included childhood-onset cases, the only independent predictor of one year and two-year remission was the number of seizures experienced by the patient in the 6 months after the first seizure (66, 67). In support other studies found that high seizures frequency even prior to diagnosis and treatment was definitive risk factors for IE (11, 13, 19, 21, 22, 24, 48, 49, 60, 67). Frequency of seizures (the lack of a three-month seizure-free period after six months of treatment) is a major prognostic factor for intractability (68).

Onset of seizures

Some studies suggest that age at presentation may be a factor in the development of IE (19, 21, 69). Some paediatric studies have found that seizure onset in later childhood or adolescence appears to be more likely to be associated with IE than seizures with onset between the ages of 5 and 10 years.(13, 26) Onset in the neonatal time period is associated with IE in at least one series (13). The varying risk of IE by age group likely relates to the underlying pathogenesis of epilepsy that also varies by age and brain maturation and vulnerability (71).

Datta *et al.* found that 38% of the 40 patients with an onset of seizures in the first year of life had uncontrolled seizures at follow-up. Early seizures onset with high frequency can predict long-term seizure control during antiepileptic drug treatment, but not mortality (12, 29).

Frequent seizures from the onset may be the first manifestation of various epileptic syndromes with a wide range of severity, particularly in childhood which can be used to predict intractability (70).

Aetiology

The underlying aetiology and seizure classification are also important.

Idiopathic syndromes, for both generalized and localization-related epilepsy, have a better prognosis than symptomatic/presumed symptomatic epilepsy in both paediatric and adult populations (11, 21, 22, 49, 72, 73).

Certain paediatric epilepsy syndromes are almost invariably intractable.

Aetiology is predictive of both seizure outcome and mortality in childhood-onset epilepsy (58).

Data that symptomatic aetiology adversely affects seizure outcome are consistent with a MRI-based study (73).

Several studies indicated that high initial seizure frequency and remote symptomatic aetiology were more common in IE (11, 12, 26, 29, 74-76).

Epilepsies with vascular lesions may be more treatment responsive than those with mesial temporal sclerosis (MTS), cortical dysgenesis, or dual pathology (19). MTS have some of the highest rates of medical intractability (18, 19).

Seizure type

Some studies did not find seizure type as a predictor of IE (13, 77).

It was found that the seizure types with the poorest control were infantile spasms, atypical absence, and myoclonic seizures (78).

Other studies found that myoclonic seizures or infantile spasms as initial seizure type are an independent predictor of IE (79, 80).

Febrile seizures were generally not found to be associated with intractability (11, 79) although this was contended (24).

Initial response to treatment

Response in the first 6–12 months was shown to be predictive of outcome in a study of new-onset epilepsy in children (81). One concept is that intractability can be predicted according to the initial response to medication trials (48). The response to the first AED trial is the most important and consistently cited predictive factor (11, 19, 27, 48).

While more than half of patients respond to the first AED prescribed, less than 20 percent are likely to respond to subsequent drug trials. With each number of failed AED trials, the risk of IE increases (21, 27, 47, 82).

In contrast with those presented above, It was found that nearly one in five children whose epilepsy is initially well controlled later develop drug resistance (83) and medical intractability may develop many years after the initial onset (51).

A few mechanisms are proposed as secondary pathogenesis (219).

Other predictors of intractability

Occurrence of status epilepticus either at the onset or subsequently was shown to be an independent predictor of intractability (11, 21, 22, 48, 49, 72).

An abnormal neurologic examination and/or developmental delay are also identified as risk factors for IE in some studies (13, 22, 84, 85).

The first abnormal EEG is another predictive factor for IE (21, 28, 49). Other studies do not support this (48, 86).

Other factors which may be considered as predictors include longer duration of epilepsy (60), family history of epilepsy (21, 22, 24), abnormal brain CT scan (28), history of neonatal seizure, and microcephaly (87).

Predictors of delayed intractability

Several studies show that epileptic patients may enter remission early in their course and develop IE later, after a period of remission that in some cases is as long as several years (63, 83, 88, 89). Factors that predict a later development of IE are not well defined.

Measuring intractability

Various rating systems are available to measure intractability. These definitions take into account the duration of epilepsy and response to antiepileptic drugs and do not take into account the epileptic syndromes. These definitions are useful in identifying older children with intractable epilepsy but not in infants and younger children with severe epileptic encephalopathies who should be considered IE from the beginning (79).

The Nova Scotia scoring system was very accurate when was used to predict outcome in children with epilepsy in Finland in a 30 years follow-up (59).

Apparent intractability

Non epileptic seizure constitutes 25-50% of cases of IE referred to a Neurologist or epilepsy centre (92). It is important to differentiate true versus apparent medical intractability. Reasons for apparent intractability include:

- 1) Wrong epilepsy diagnosis. One study showed that as many as 26 percent of individuals thought to have IE were incorrectly diagnosed most often as a result of incomplete history-taking and/or EEG misinterpretation (90).
- 2) An incorrect seizure type/ syndrome diagnosis leading to incorrect drug choice (18). In some instances, a narrow-spectrum AED can worsen seizure frequency (42, 90). With an inappropriate dosage (90) in contrast, seizures can also occur with AED toxicity (42).
- 3) Noncompliance in one case series, 71 percent of patients reported at least occasional dose omissions, and 45 percent reported a seizure after a missed dose (91). Providing a non-judgmental setting in which to elicit this history is important. Support from family members and physicians increases medical compliance (18).

Pathogenesis

- 1) Alteration in neural structure & circuitry: Pathologic and neuroimaging studies demonstrate an evolving process involving glial proliferation and dendritic sprouting with synaptic reorganization (21, 93). Alterations in neural circuitry conceivably may lead to an epileptic network that becomes drug resistant over time.
- 2) Alteration in drugs receptors, transporters and pharmacokinetics: Studies in animal models found drug-resistant temporal lobe epilepsy associated with altered expression of multidrug transporters, altered expression of AED targets, as well as morphologic alterations in the hippocampus (47). Distinguishing which of these findings is the cause versus the effect of IE, and if it has relevance in human IE, is part of ongoing investigations. While one study found an association with a polymorphism in the drug transporter gene (ABCB1 or MDR1) and drug-resistant epilepsy (94, 220) others did not (95, 96). Another hypothesis proposes that over expression of these multidrug transporters is induced by recurrent seizures, emphasizing the importance for early aggressive seizure treatment (47).

- 3) Other alterations, acquired or inherited, of AED absorption, metabolism, receptor-binding, and blood brain barrier permeability are also potential causes of pharmacoresistance (97, 98, 221).

Underlying aetiologies

Aetiology of the epilepsy was found to be a strong predictor of intractability.

The more recent report of the ILAE Commission on Classification and Terminology reclassified epilepsy based on three aspects including aetiology (genetic, structural/metabolic or unknown) (99). The aetiology of intractable epilepsy varies with age and is different among various geographic regions, and, importantly, with the thoroughness of investigative technology used to unravel the aetiology of epilepsy (11, 78, 100). Birth asphyxia was the leading cause of intractable epilepsy. In resource poor countries, common causes of epilepsy include perinatal asphyxia, infections of the central nervous system (meningitis, central nervous system tuberculosis) and parasite infestations, for example neurocysticercosis. These findings could be explained by the poor socioeconomics in these countries (101). Neurocysticercosis was defined as the leading cause of intractable epilepsy in other studies (101-103). These findings are in contrast with the reports in developed countries in which perinatal insult (104) and cortical developmental abnormality (105) are the major causes. Seizures are common complication of HIV but occur from multiple causes (106-109).

Response to Pharmacology

It was suggested that failure of seizures to respond to a single AED is a strong predictor of medically refractory epilepsy (27). Another definition of intractability is the occurrence of one or more seizures per month on follow up of one year or more with an adequate trial of two first line AEDs (for example carbamazepine and valproate) and one or more of the newer second line antiepileptic drugs (27).

When 2 AEDs for the correct seizure type and in adequate doses fail, there is only a 5–10% probability of achieving seizure control with a third drug (45, 48, 49, 110).

Another approach scores intractability by the number of drugs tried in mono and polytherapy regimens (13).

In two important studies, one by Mattson and colleagues (111) and the other by Kwan and Brodie (48) seizures are not controlled with a single AED, then adding a second will make them seizure-free only about 10% of the time. The second drug may help, but not usually to the point of complete control. Furthermore,

polypharmacy can lead to drug interactions (112) that limit effectiveness or increase side effects of another drug. Therefore, simplifying medications is sometimes the preferred option even this may seem to contradict the target of aim seizure control. It is important to always ensure optimization of pharmacology has occurred before judging its failure.

HIV-positive patients present special problems, especially with respect to drug-disease and drug-drug interactions. The older AEDs are protein-bound and largely depend on the cytochrome p450 system for their metabolism. The newer AEDs may be safer in patients on antiretroviral drugs. However, they are expensive, an important consideration in resource poor countries (113).

Investigating IE

Patients with IE should have further testing to confirm the diagnosis of epilepsy and also to better define the epilepsy syndrome and underlying classification in order to best direct treatment (114). The evaluation of IE should include video electroencephalography (EEG) monitoring, magnetic resonance imaging (MRI) and often a metabolic workup (115).

In some series, more than 25 percent of individuals referred for monitoring for refractory epilepsy are found to have no epileptic events, usually psychogenic events (90). EEG monitoring can also aid in seizure classification and is used for pre-surgical evaluation of IE patients. By the time a patient is considered to have IE, an MRI study will usually have been performed. In many cases, this should be repeated, particularly if the original study was unrevealing. Not all MRI findings are relevant and they should be correlated with the patient's seizure semiology and EEG results; some potentially epileptogenic lesions may be incidental. Children with medically intractable epilepsy should be considered for epilepsy surgery if the epileptogenic zone is reasonably localized with non-invasive pre-surgical evaluation (116, 117). Presence of visible MRI lesion not only warrants surgical candidacy, but also predicts a favourable surgical outcome(118-121). In the absence of a causative lesion on MRI, an epileptogenic focus can sometimes be defined in patients with localization-related epilepsy using advanced neuroimaging techniques including positron emission tomography (PET), single photon emission computed tomography (SPECT), magneto-encephalography (MEG) and magnetic source imaging (MSI). Data suggest that MEG and Subtraction Ictal SPECT Co-registered to MRI (SISCOM) are better tools for lobar localization than statistical parametric mapping (SPM) analysis of fluoro-deoxy-glucose (FDG) PET in children with nonlesional

epilepsy. A multimodality approach may improve surgical outcome as well as selection of surgical candidates in patients without MRI abnormalities (122). The overall seizure-free outcome was 50% when all 3 non-invasive modalities were used. This seizure-free outcome compares well with other published series of nonlesional epilepsy (120, 123). The consistency in identifying the same surgically remedial focus of all tests including MSI, FDG-PET, and ictal SPECT, predicts increased odds for seizure free outcome after surgery (124).

Management of Intractable Epilepsy

Resective epilepsy surgery is the treatment of choice for medically resistant lesional partial epilepsy as this has the most likely chance of producing remission. Further AED trials, vagal nerve stimulation, and the ketogenic diet can reduce seizure frequency and improve quality of life but are more likely to be palliative, rather than curative treatment options (114, 125, 126).

Epilepsy surgery

Epilepsy surgery should be considered in appropriate patients with IE when seizures are sufficiently frequent or severe enough to impact on the patient's quality of life (127). Early recognition and interventions would improve the lives of patients with IE (62). Resective epilepsy surgery has the best-established efficacy for individuals with lesional temporal lobe epilepsy (128). Patients with concordant abnormalities in one temporal lobe on MRI and EEG have a rate of seizure remission as high as 90 percent (129, 130). Patients with non-lesional temporal lobe epilepsy also have a high remission rate with surgical therapy. The efficacy is highest in patients in whom EEG and another imaging modality (e.g. SPECT, MEG) reveal a consistent location of the epileptic focus.

Other surgical treatments (lobar and multi-lobar resections, hemispherectomy, corpus callosotomy, multiple subpial transections) are sometimes employed for palliative treatment in children with catastrophic epilepsy syndromes.

Young children with this intractable disorder may be better candidates for aggressive surgical treatment because of the increased neuroplasticity of the developing brain (117, 131-133).

Successful epilepsy surgery improves life expectancy and health-related quality of life, whilst reducing health care costs as a result of reduced hospital admissions, emergency department visits, and the use of antiepileptic drugs (134, 135).

Surgical intervention for intractable epilepsy may provide a good opportunity to prevent irreversible decline of intelligence and cognitive function (136, 137). Some IE cases are highly responsive to surgery, and early surgical intervention is highly cost-effective for patients with surgically remediable syndromes and there would be no need to pursue exhaustive drug trials with these patients (138). Epilepsy surgery (ES) is addressed in relation to economic classifications of thousands of patients who could benefit from epilepsy surgery, but inequalities in healthcare provision mean that ready access to surgical facilities is largely restricted. It was found that ES is nonexistent in 98% of African countries, 86% of countries of the Western Hemisphere, 82% of Middle East countries, 76% of Asian countries and in 58% of European countries. The surgical outcomes achieved in developing countries are similar to those in the developed world, but at a fractional cost. To internationalize ES, outcome, cost and savings from care, evolution of assessment methodology is needed. Also needed is general support from the developed world (139).

Non Surgical management of IE

Steroids are effective in West syndrome (WS), Lennox Gastaut syndrome (LGS) and other IE of childhood (140). Adrenocorticotrophic hormone (ACTH) was initially introduced in the treatment of WS (141, 142). Ganaxolone is another synthetic neurosteroid analogue which is of use in WS. It has potent and selective positive allosteric modulator of gamma-Aminobutyric acid-A (GABAA) receptors (143). Immunoglobulins in IE are of unknown efficacy and unknown mechanism of action, a randomized multicentre double blind trial was started in 1993 including patients with WS and LGS. These showed a trend in favour of Intra-venous Immunoglobulin (IVIg) but lacked statistical significance (144). Use of pyridoxine in pyridoxine deficiency and dependency IE is self explanatory and well established and further it was found that the use of pyridoxine and pyridoxal phosphate in idiopathic IE to be effective in some studies (145-150).

Since 1921 Ketogenic diet (high fat, low protein and carbohydrate diet) is used in the treatment of children with IE. There has been renewed interest for this over the last decade. The cost for initiation is high and it was found to be effective in all types of IE in children (Generalised, partial & infantile spasms) (125, 151-153).

It may be continued for 1-2 years, prospective study of 150 children with intractable epilepsy who initiated the diet at Johns Hopkins found that 83 remained on the diet for >1 year, and most had a substantial decrease in the frequency of their seizures.

These children were reassessed 3–6 years after their diet initiation and 78% continued to have a >50% reduction in seizure frequency as well as a decrease in medications(152, 155).Class IV literature evidence on the effectiveness of ketogenic diet in the treatment of IE continue to emerge each day (222-230). Atkins diet restricts carbohydrates but does not restrictive consumption of calories or proteins. This was originally used for weight reduction. There is a preliminary report of its effectiveness in reducing seizures in IE(156).In case series a modified Atkins diet reduced seizure frequency by 50 percent or more in half of patients with IE (157).

Vagal nerve stimulation (VNS) is approved for adjunctive treatment of medically intractable partial onset seizures in adults and children. Approximately 30 to 40 percent of patients achieve a greater than 50 percent reduction in seizure frequency, a benefit that is sustained over time. Serious adverse events are rare. VNS is a valid treatment option for patients with well-documented IE, who are either opposed to epilepsy surgery, or who are not candidates, or whose seizures were not substantially improved by prior epilepsy surgery and in children who failed ketogenic diet (158-160).

Deep brain stimulation is sub-cortical stimulation paradigms which target the anterior and centromedian thalamic nuclei, the subthalamic nucleus, the caudate, and the cerebellum (161, 162). Controlled studies found that stimulation in these sites reduces seizure frequency by 50 percent or more in some patients (162). In a randomized clinical trial of stimulation in the anterior nucleus of the thalamus in 110 patients with drug-resistant epilepsy, stimulation therapy was associated with a 29 percent reduction in seizure and in 54 percent there was reduction of at least 50 percent.(163).Two small controlled trials found that stimulation of the hippocampus reduced seizure frequency in patients with mesial temporal lobe epilepsy (164-166). Another approach under investigation employs a closed-loop cortical stimulation unit coupled to a seizure-detection system. Studies found that this treatment may be associated with a substantial reduction in seizure number, intensity, and duration. A clinical trial is underway and results expected in 2011(167-172). Transcranial magnetic stimulation are low frequency transcranial magnetic stimulation also reduces cortical excitability (173).

Associated co-morbidities and Outcome of IE

It is important to understand the impact of IE in the context of the individual's life, schooling, and other psychosocial circumstances (114).

Epidemiological information from Olmstead County found predictors of outcome of childhood epilepsy to include neurological or intellectual deficit (14, 174).

Quantitative MRI evidence shows an adverse effect of early-onset epilepsy on brain structure (reduced volume of the corpus callosum or reduced whole brain white-matter or grey-matter volumes) in patients with childhood-onset partial epilepsy compared with adult-onset partial epilepsy(175, 176).

Catastrophic epilepsies beginning during the childhood developmental stage halt cognitive and social development with permanent long term effects (177).

Syndromes that are refractory to antiepileptic drugs are invariably associated with psychomotor co-morbidities (177-181).IE is also associated with disability and diminished quality of life (21, 50). Nonfatal injuries are also common in those patients with IE. These include head injury, burns, and fractures, among others; most are seizure-related (182).

Several studies explored the economical burdens of IE and some even have demonstrated the annual cost for patients with epilepsy to be very high and that IE contributes a substantive proportion of this cost (191-194).

Individuals with IE have an increased mortality rate (183-185). Sudden unexplained death in epilepsy patients (SUDEP) was found to be 24 to 40 times more likely among children with IE(185-187). Very few studies of death in epilepsy have included a substantial number of children with a long follow-up since the onset of their epilepsy (59, 177, 188, 189).In these studies, mortality increased with time and most of the deaths were related to the presence of a severe neurological deficit, remote symptomatic aetiology or both and not directly to the seizures themselves. Mortality increases with time (190).

CHAPTER 2:

Local experience of IE

Concerns about Epilepsy within South Africa reflected in the literature as early as 1964 under the title of "Epilepsy in South Africa an urgent problem" (195). In a publication relating to Epilepsy and the law in South Africa in 1970(196), to concerns of ILAE commission on the availability of AEDs and their non homogeneous distribution and availability in contrast to older and less effective drugs like Phenobarbital (197).

A local study revealed in over half of children onset of epilepsy was before the age of 2 years with the majority being symptomatic, 55% were intellectually handicapped. Acceptable seizure control was achieved in 71% of them and that 68% were treated with a single AED. It and other studies in the Western Cape concluded that a reduction in the incidence of epilepsy in the community could be achieved by improvements in obstetric/neonatal and reducing meningitis, tuberculosis, neurocysticercosis, and cerebral trauma services and by the raising of living standards (198, 199).

Christianson et al worked on determining the prevalence of epilepsy and its associated disabilities in rural South African children aged 2-9 years found the lifetime and active prevalence of epilepsy in these children were 7.3/1,000 and 6.7/1,000 respectively and associated developmental disability to be 71.4% (16.3% Moderate to severe) in affected children and that more than a half of the children with epilepsy did not receive AEDs (4).

Several *Searsia* species (Anacardiaceae) are used in South Africa traditional medicine to treat epilepsy. These plants may combine one or more γ -aminobutyric acid (GABA) (A) agonists with one or more NMDA antagonists, thus representing an efficient treatment for epilepsy (200).

Over the past 5 years, more than 250 patients have had successful epilepsy surgery in Cape Town (two university-affiliated neurology departments and a private epilepsy centre) with patients becoming seizure-free and with improvement in their quality of life (201). The authors current database now including some 600 patients less than 50 were managed in the government sector and 25-30 were children (personal communication J Butler).

There were no studies conducted on children with intractable epilepsy in South Africa. In a survey of the understanding of the definition of intractable epilepsy among paediatric neurologists from across the country at the *Complex Epilepsy day meeting*, Johannesburg August 2010, diversity in defining intractability was found. IE was defined very closely to the recent ILAE definition as the failure of adequate trials of two to three (4 specialists used the two drug definition and 3 used the three drug definition and 3 did not specify the number of drugs) appropriate AEDs whether as mono-therapies or in combination to achieve seizure freedom. One definition included a time frame of 6 months and another considered encephalopathy as an association (Table 4).

Table 4 Definitions of Intractability by paediatric neurologist working in different regions in South Africa

| Definition | No. of drugs | Region |
|---|--------------|--------------|
| Still fitting by the time the third drug is tried alone or in combination. | 3 | Johannesburg |
| Seizures, Non responsive to 3 drugs at optimal doses. | 3 | Johannesburg |
| Failure to control seizures adequately after use of 3 AED's. | 3 | Johannesburg |
| Fitting uncontrollably and the need to add a 3 rd drug. | 2 | Johannesburg |
| Failure of 2 drugs adequate doses and have to add a third drug. Also a time frame of 6 months. | 2 | Johannesburg |
| Uncontrolled seizures, not controlled by poly pharmacology 2 or more drugs and you have reached a point of frustration may /may not be part of an epileptic encephalopathy. | 2 | Johannesburg |
| No decrement in seizures with use of adequate doses of appropriate anticonvulsant. | NS | Johannesburg |
| Not responsive to 2-3 drugs, frequent seizures despite optimal treatment and frequent status despite treatment. | 2-3 | Cape Town |
| Failure of 2 appropriate, adequate drugs in doses and duration. | 2 | Cape Town |
| Failure to control seizures with standard antiepileptic therapy at appropriate dosage. | NS | Cape town |
| Pharmacoresistant to 2 drugs in optimal dose after adequate time of trial. | 2 | Durban |

CHAPTER 3:

Intractable Epilepsy in South African children (The study)

Aim

To identify the prevalence and characteristics of children with intractable epilepsy managed in a tertiary referral service.

Objectives

1. To identify the prevalence of intractable seizures in a tertiary setting.
2. To define the patient demographics and seizure types, underlying aetiologies and associated co-morbidities.
3. To assess the effectiveness and relevance of the current International League against Epilepsy (ILAE) guidelines for intractable seizures compared to previous perceptions in our context.
4. To identify key markers to allow early recognition of intractable epilepsy
5. To identify key needs of patients with intractable epilepsy in our context
6. To identify which patients may be remedial to interventions other than anti-epileptic drugs (AEDs) like surgery, ketogenic diet and vagal nerve stimulator (VNS).

Method

Study Design

A retrospective case note review, following prospective identification of the group.

Subjects

Patients attending the Epilepsy service at Red Cross War Memorial Children's Hospital (RCWMCH) in a 6 month period (August 2010 to February 2011) were prospectively screened for those who complied with the ILAE definition of intractability and the previous standard definitions of intractable epilepsy. This group was then enrolled in the study if they once met the inclusion and exclusion criteria, and parental / carer consent was obtained.

From the literature at least 20% of the patients with epilepsy were expected to respect these criteria (10- 25), Based on clinic's statistics about 100 children with diagnosis of epilepsy attend the neurology out-patients clinics each month. The

study aimed to recruit 400-600 patients with epilepsy with a minimum of 50 patients meeting the definition of intractable epilepsy. This figure is similar to that described in other single centre studies (202).

Data Collection procedure

All out-patients were screened using the standard neurology statistics template (Appendix 1) with the additional definition of intractable seizures included and a tick box for the attending clinician to use.

The study was explained and written consent (and assent when possible) taken by the attending clinician (Appendix 2, 3).

Medical folders of the patients were identified and reviewed for the additional necessary data (Appendix 4).

Inclusion criteria:

- Age: 0-18
- Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom ((Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer)).

Exclusion criteria

- Still initiating medication
- Non-compliance
- Neurodegenerative disorder
- Acute illness (e.g. Tuberculosis, Meningitis)

Data were captured using standardized form created for this study (Appendix 4) and eventually entered onto an Excel Microsoft Office© data sheet.

Measures

Demographic data

This included age, gender and ancestry. Ancestry as a demographic variable was recorded according to the RCWMCH standard coding system which classifies

patient into broad categories of African, European, Asian, and Mixed. The address was entered for all patients with intractable epilepsy to identify whether they are local or referred from outside the metropolis.

Epilepsy Semiology

The semiology of the epilepsy type was identified among both groups (Intractable and non intractable) and compared using the latest ILAE classification in 2009 (99).

Definition of Intractability

Having met the inclusion and exclusion criteria patients ticked as intractable epilepsy were further verified using the ILAE definition of intractability and all patients not ticked were also reviewed to identify possible missed cases and to correct their status.

Onset of epilepsy and frequency among the intractable group.

The onset of epilepsy, frequency and duration of seizures, provoking factors and family history of seizures was obtained as part of the background information.

Duration of time to recognize intractability.

Whether the confirmation of intractability was made prior to or after the commencement of this study was entered, i.e. whether the study itself resulted in the recognition that the child had intractable epilepsy. The total duration of time taken from the onset of epilepsy to label the patient as intractable was recorded.

Co-morbidities and aetiology

The occurrence of status epilepticus, neuroregression, intellectual disability, behavioural problems, developmental problems, learning difficulties and social problems were entered.

A variety of possible underlying and co-morbid conditions was entered including perinatal events, cerebral palsy, metabolic derangement, meningitis, structural brain malformations, vascular events, head trauma, HIV, Tuberculosis meningitis, Neurocutaneous disease (except TS), and clinical findings such as microcephaly, Macrocephaly, dysmorphism, bulbar dysfunction, speech, hearing and visual problems. In addition to other medical event that might be related to patients events or not gastro-oesophageal reflux, Gastrosotmy, fractures, allergies, infections, non-CNS tumours and so on.

Investigations

Whether patients had an EEG, video EEG telemetry, ultrasound of the head, CT scan, MRI, SPECT or Metabolic workup (ammonia, blood gas, lactate, glucose, , pyruvate, glycine, amino and organic Acids screens on urine, blood and cerebral spinal fluid as appropriate) data was entered.

Management and pharmacological treatment

The number of AEDs and compliance with medication in general that was used was recorded, as well as the name, dose, frequency, compliance with the specific medicine, duration of use and reason for discontinuation if a drug was discontinued. The occurrence of seizures or side effects during each AED use if not discontinued and whether the agent was optimized or not.

Other interventions.

Use of ACTH, prednisone, pyridoxine or other vitamins or elements was entered.

Other interventions if any was included such as the ketogenic diet with its duration, VNS, epilepsy surgery or others (We did not count patients who were either offered ketogenic diet or surgery and refused or were not compatible after the workup).

Ethics/consent

The protocol was submitted to the Red Cross War Memorial Children's Hospital Research Committee and to the University of Cape Town Committee for Human Health Sciences Ethics Committee for review. Approval to conduct the study was granted (Appendix 5).

Written consent was taken from the caregiver, and assent from the child when possible, giving approval to enrol the patient, access patient medical folder data and possibly verbally communicate with the caregiver in the future if specific data is needed. The caregiver was informed that the study is planned to be published in the peer reviewed literature. The individual information will remain confidential i.e. the nature of the study with grouped data will not allow the patient to be recognized. If the study identifies new interventions which could be in the patient's interest, this will be communicated to the caring clinician.

Costing

Dr Hani Alkhalidi is the principal investigator. There was **no additional cost to the patients or the hospital**. The investigator analyzed and wrote up the data.

STUDY SITE

Red Cross War Memorial Children's Hospital is a governmental funded health facility located in the Western Cape Province of South Africa. It is a tertiary referral centre for the region. This province is inhabited by approximately 5.2 million people, 2 million of whom are children aged 0 to 19 years of which 49.8% are males and 50.2% are females (203). Approximately 29% of the population of the Western Cape Province is composed of people of African ancestry. Those of mixed descent comprise approximately 51% of this population, while the proportion of those of European descent is estimated to be 19% (204).

At Red Cross War Memorial Children's Hospital the department of Paediatric Neurology and Neurophysiology run a weekly Epilepsy clinic reviewing 30 to 35 children (Department statistics). Children attending these clinics must be considered to have epilepsy. Multiple services are involved in their management including neurophysiology, neuroimaging, nursing, laboratory, developmental clinic, cerebral palsy clinic, physiotherapy, occupational therapy, speech therapy, pharmacy, dietician services and more according, to the specific need of every child with epilepsy.

STATISTICAL ANALYSIS

Normally distributed data were summarised using mean (standard deviation, s.d.); otherwise the median (interquartile range, IQR) was used. These results were presented in the form of charts and tables as applicable. We used the Shapiro-Wilk W test to check for normal distribution of any data. Data were analyzed as follows, proportions using Chi-squared (χ^2), means using T-test, medians using Wilcoxon test (Mann-Whitney) whenever appropriate.

All tests were two sided. A p-value < 0.05 was considered significant. Data were analyzed using Stata/IC 11.1 (StataCorp LP, 4905 Lakeway Drive, College Station TX 77845, USA) for Windows software.

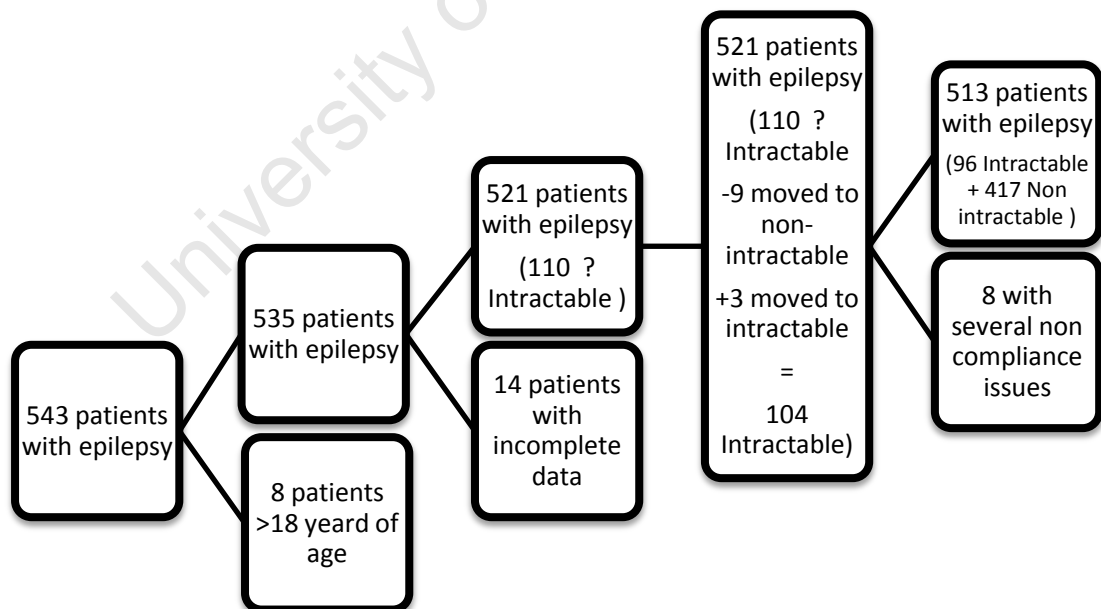
The Statistical analyses performed including exploring the relationship between intractability and variables such as gender, age, ancestry, number of medications, aetiologies, and co-morbidities.

RESULTS

Enrolment of patients in the study

Out of 5173 patients with neurological diseases in Neurology data base of Red Cross War Memorial Children's Hospital at the time when study was concluded, 2741(53%) had Epilepsy (Red Cross Neurology data base, March 2011). The Epilepsy clinic is visited by an average of 103 patients per month and during the 6 month period of the study 543 patients with epilepsy visited the clinic (Red Cross Neurology Epilepsy clinic stats, August 2010-February 2011). After reviewing the group 8 patients were excluded as they were older than 18 years of age and from the remaining 535 patients a further 14 patients were excluded because of incomplete data. From the recruited final 521 patients, 110 were identified by the clinician tick sheet as "intractable" but based on the study inclusion criteria 9 patients were found not to comply nor met the ILAE definition and removed, in addition 3 from the "non-intractable" group were in fact considered to have IE and was added (n=104). A further 8 patients were excluded from the IE group and the whole study because of non-compliance. As a result our final total number of patient enrolled in the study was 513 and among which we when left with 96 children with intractable epilepsy.

Figure 1 The enrolment of Children with Epilepsy in the study



Definition of Intractability

A total of 96 patient met the ILAE definition of intractable epilepsy constitute 18.7% of the total children with epilepsy in this study.

Demographic data

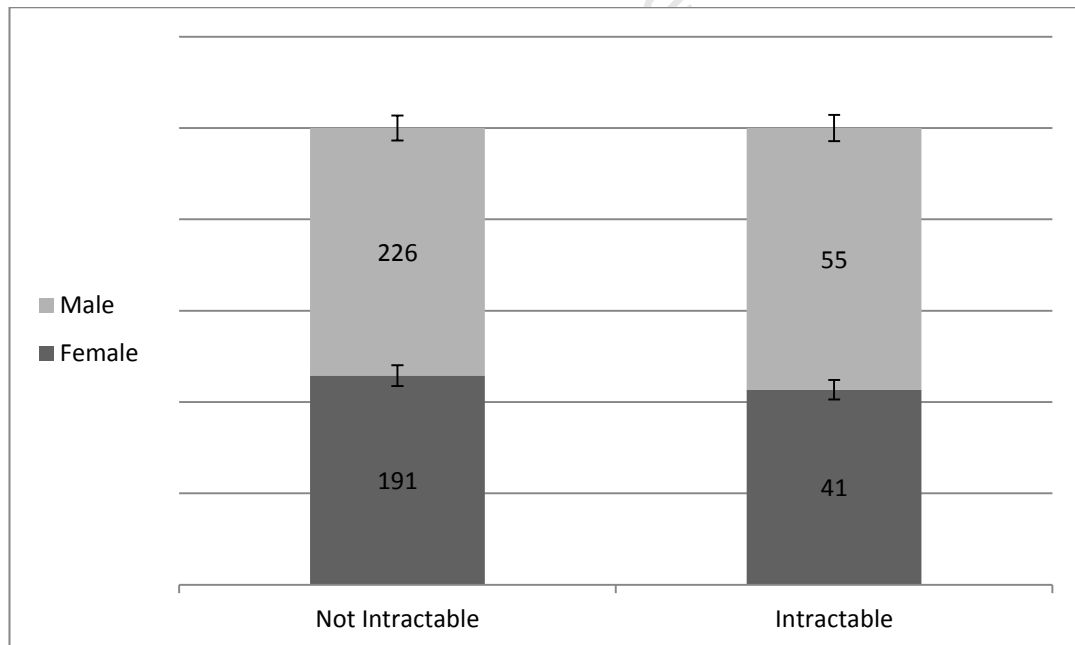
Out of the 513 Children with epilepsy, 281(55%) were males and 232 (45%) were females. When analyzed according to intractability there was no statistical difference between children with intractable epilepsy and those who are not intractable, considering sex distribution (p value 0.6).

Table 5 Relationship between gender and intractability

| Gender | Intractable (%) | Not Intractable (%) | Total (%) |
|--------|-----------------|---------------------|------------|
| Female | 41 (43%) | 191 (46%) | 232 (45%) |
| Male | 55 (57%) | 226 (54%) | 281 (55%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Pearson $\chi^2 = 0.3018$, 1 degree of freedom, p = 0.6

Figure 2 Relationship between gender and intractability



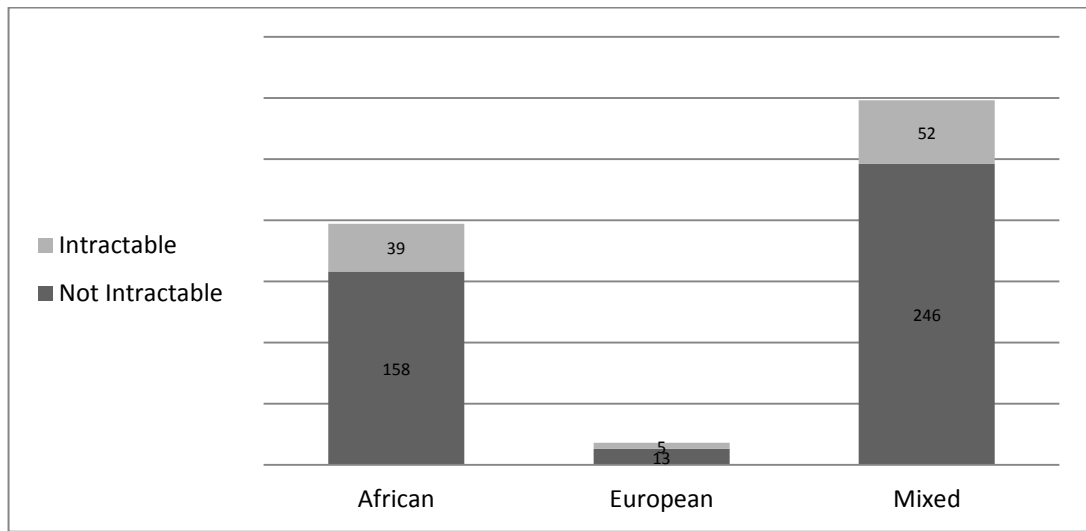
Mixed ancestry predominance 58%, African 38%, European 4% is observed when looked at the total number and there was no significant statistical difference between children with intractable epilepsy and those who are not intractable

Table 6 Relationship between ancestry and intractability

| Ancestry | Intractable (%) | Not Intractable (%) | Total (%) |
|----------|-----------------|---------------------|-------------|
| African | 39 (40.6) | 158 (37.9) | 197 (38.4%) |
| European | 5 (5.2) | 13 (3.1) | 18 (3.5%) |
| Mixed | 52 (54.7) | 246 (58.0%) | 298 (58.1%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Pearson $\chi^2 = 1.4372$, 2 degrees of freedom, $p = 0.5$

Figure 3 Relationship between ancestry and intractability



Age

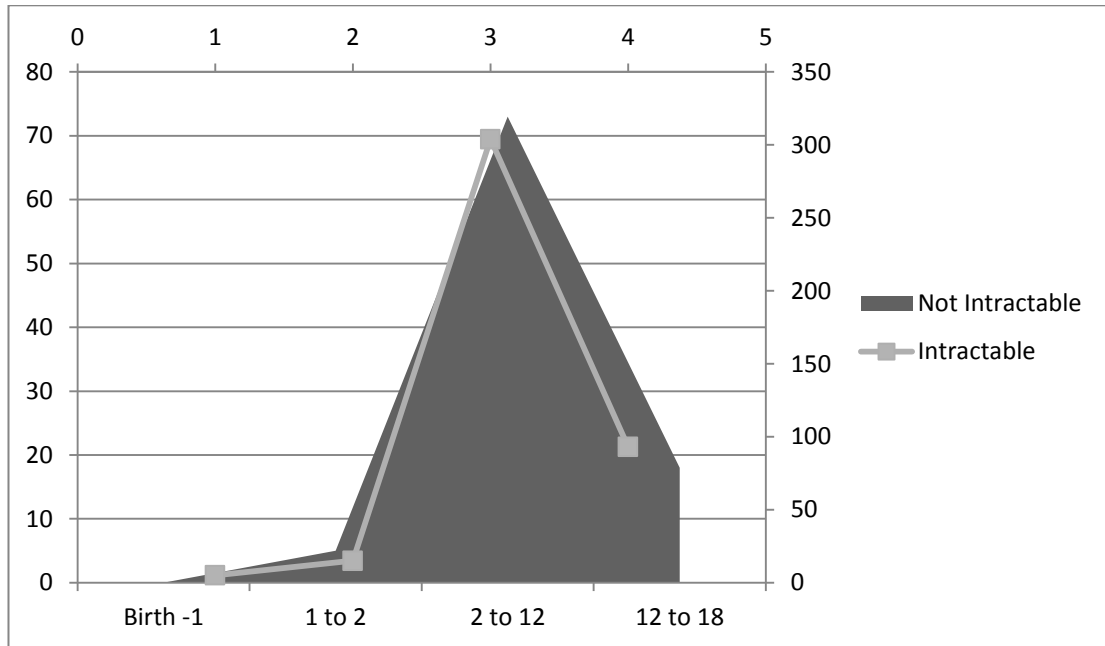
The patients were grouped according to age at the time of the study into 4 categories 0-1 years, 1 to 2 years, 2-12 and 12-18 years (Table 7)

Table 7 Intractability by age categories

| Age in years | Intractable (%) | Not Intractable (%) | Total (%) |
|--------------|-----------------|---------------------|-------------|
| 0 -1 | 0 (0.0%) | 5 (1.2%) | 5 (1.0) |
| 1-2 | 5 (5.2%) | 15 (3.6%) | 20 (3.9%) |
| 2-12 | 73 (76.0%) | 304 (72.9%) | 377 (73.5%) |
| 12-18 | 18 (18.8%) | 93 (22.3%) | 111 (21.6%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Pearson $\chi^2 = 2.2304$, $p = 0.5$

Figure 4 Comparing age categories



Median age of the non-intractable group was 8.5 years (minimum 7 months, maximum 17.8 years, mean 8.5 years, standard deviation (s.d.) 4.1), for the intractable group it was 7.9 years (minimum 1 year, maximum 16.7 years, mean 7.9, s.d. 4.23). Comparing median ages using the Wilcoxon (Mann-Whitney Test showed no significant difference by intractability ($z=1.329$, $p=0.2$).

89.6% of the children with intractable epilepsy lived in the local metropolis. However 10.4% travelled from outside Cape Town.

Epilepsy Semiology

The most recent ILAE classification was used to review the semiology of our cohort (99). Among the IE group the most predominant syndrome was Lennox-Gastaut syndrome (27.1%) followed by Epilepsy with myoclonic atonic seizures (Doose syndrome) (13.5%), West syndrome (Infantile spasms) (12.5%), Dravet syndrome (SMEI) (2.1%) and Ohtahara syndrome (EIEE) (2.1%).

Focal seizures with impairment of consciousness/responsiveness affected 31.2% of IE group compared to 33.1% in the non-intractable group.

Table 8 Semiology according to the recent ILAE classification

| Semiology | Intractable (%) | Not Intractable (%) | Total (%) |
|--|-----------------|---------------------|-------------|
| Absence Epilepsy, Atypical | 0 (0.0%) | 6 (1.4%) | 6 (1.1%) |
| Early onset benign childhood occipital epilepsy (Panayiotopoulos type) | 0 (0.0%) | 2 (0.5%) | 2 (0.4%) |
| Benign epilepsy with centrotemporal spikes (BECTS) | 0 (0.0%) | 3 (0.7%) | 3 (0.6%) |
| Benign familial infantile seizures | 0 (0.0%) | 1 (0.2%) | 1 (0.2%) |
| Benign infantile seizures | 0 (0.0%) | 1 (0.2%) | 1 (0.2%) |
| Benign familial neonatal seizures (BFNS) | 0 (0.0%) | 1 (0.2%) | 1 (0.2%) |
| Childhood absence epilepsy (CAE) | 0 (0.0%) | 18 (4.3%) | 18 (3.5%) |
| Focal Seizures Without impairment of consciousness/responsiveness | 0 (0.0%) | 19 (4.6%) | 19 (3.7%) |
| Focal Seizures With impairment of consciousness/responsiveness | 30 (31.2%) | 138 (33.1%) | 168 (32.8%) |
| Focal Seizures Evolving to a bilateral, convulsive seizure | 5 (5.2%) | 3 (0.7%) | 8 (1.6%) |
| Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) | 0 (0.0%) | 4 (1.0%) | 4 (0.8%) |
| Febrile seizures (FS) | 0 (0.0%) | 3 (0.7%) | 3 (0.6%) |
| Generalized Tonic Clonic Seizures | 5 (5.2%) | 111 (26.6%) | 116 (22.6%) |
| Febrile seizures plus (FS+) | 0 (0.0%) | 28 (6.7%) | 28 (5.5%) |
| Gelastic seizures | 0 (0.0%) | 1 (0.2%) | 1 (0.2%) |
| West syndrome | 12 (12.5%) | 33 (7.9%) | 45 (8.8%) |
| Lennox-Gastaut syndrome | 26 (27.1%) | 10 (2.4%) | 36 (7.0%) |
| Epilepsy with myoclonic atonic seizures (MAE) | 13 (13.5%) | 12 (2.9%) | 25 (4.9%) |
| Landau-Kleffner syndrome (LKS) | 0 (0.0%) | 2 (0.5%) | 2 (0.4%) |
| Juvenile myoclonic epilepsy (JME) | 1 (1.0%) | 2 (0.5%) | 3 (0.6%) |
| Familial focal epilepsy, variable foci | 0 (0.0%) | 2 (0.5%) | 2 (0.4%) |
| Ohtahara syndrome | 2 (2.1%) | 1 (0.2%) | 3 (0.6%) |
| Dravet syndrome | 2 (2.0%) | 2 (0.5%) | 4 (0.8%) |
| Myoclonic epilepsy in infancy | 0 (0.0%) | 2 (0.5%) | 2 (0.4%) |
| Mesial temporal lobe epilepsy | 0 (0.0%) | 12 (2.9%) | 12 (2.3%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Localization of epilepsy

In relation to localization of seizures, 43.8 % were localized in the non intractable group compared to 36.5 % in the IE group (p 0.2).

Table 9 Semiology by localization of seizures

| Semiology | Intractable | Not Intractable | Total |
|-------------|-------------|-----------------|-------------|
| Localized | 35 (36.5%) | 183 (43.9%) | 232 (45.2%) |
| Generalized | 61 (63.5%) | 234 (56.1%) | 281 (54.8%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Pearson $\chi^2(1) = 1.7613$, 1 degree of freedom = 0.2

Epilepsy Syndromes

We looked at the Epilepsy syndromes that were not labelled as benign in the new ILAE classification (West syndrome, Lennox-Gastaut syndrome, Epilepsy with myoclonic atonic seizures, Landau-Kleffner syndrome (LKS), Juvenile myoclonic, Ohtahara syndrome, Dravet syndrome) and we found that 57.3% of Children with IE had a Non benign epilepsy syndrome compared to only 14.4% in the non-intractable group (P <0.05).

Table 10 Semiology by Epilepsy Syndromes

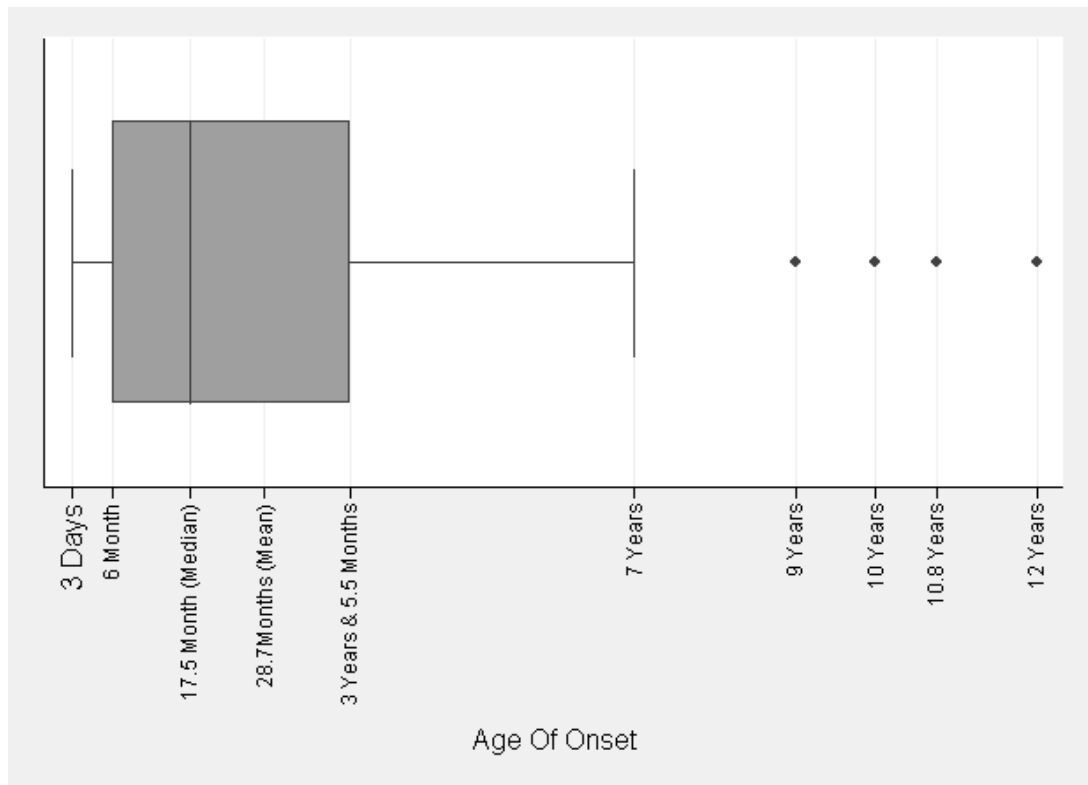
| Semiology | Intractable | Not Intractable | Total |
|------------------------------|-------------|-----------------|-------------|
| Non Benign Epilepsy syndrome | 55 (57.3%) | 60 (14.4%) | 115 (22.4%) |
| Not Syndromic | 40 (41.7%) | 285 (68.4%) | 325 (63.4%) |
| Benign Epilepsy syndrome | 1 (1.0%) | 72 (17.2%) | 73 (14.2%) |
| Total | 96 (100%) | 417 (100%) | 513 (100%) |

Onset of Epilepsy

Onset of Epilepsy and frequency of epilepsy among the intractable group

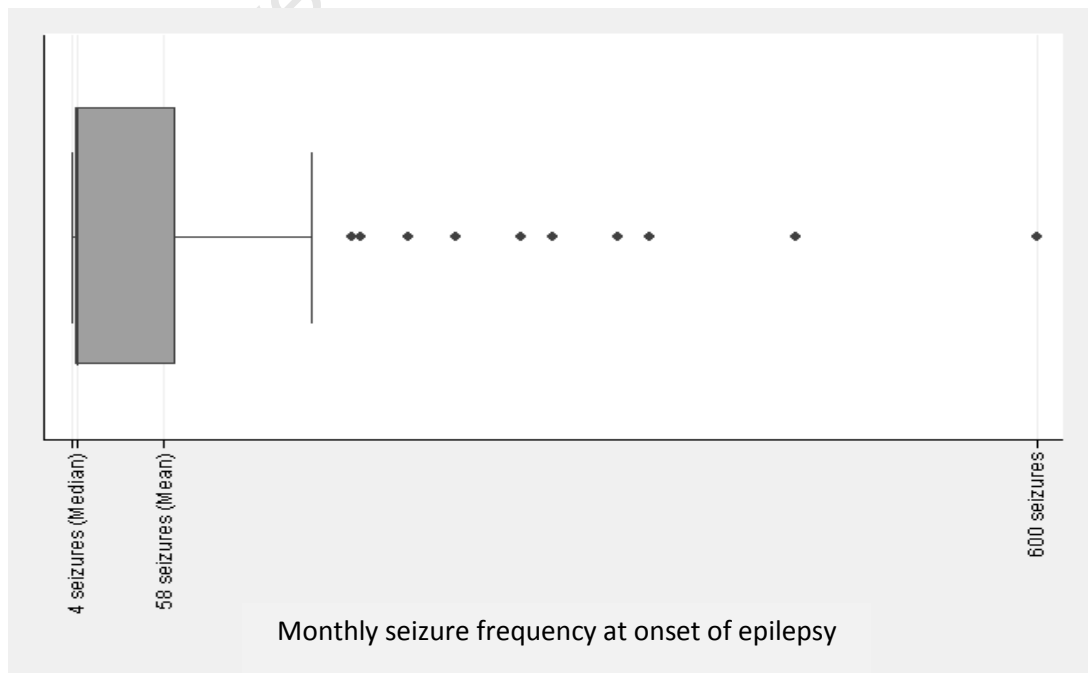
The onset of epilepsy minimum was 3 days of age, maximum 12 years, mean of 28.7months (s.d. 30.55months, p25 6months, median 17.5, p75 41.5 months)

Figure 5 Age of onset in patients with IE



Seizure frequency at onset was analyzed per month and showed a minimum of 1 event every months, Maximum 600 events per month, Mean of 58 events monthly (s.d. 108 /month, p25 3 / months, Median 4 / month, p75 66 / months).

Figure 6 Seizure frequency at onset in patients with IE

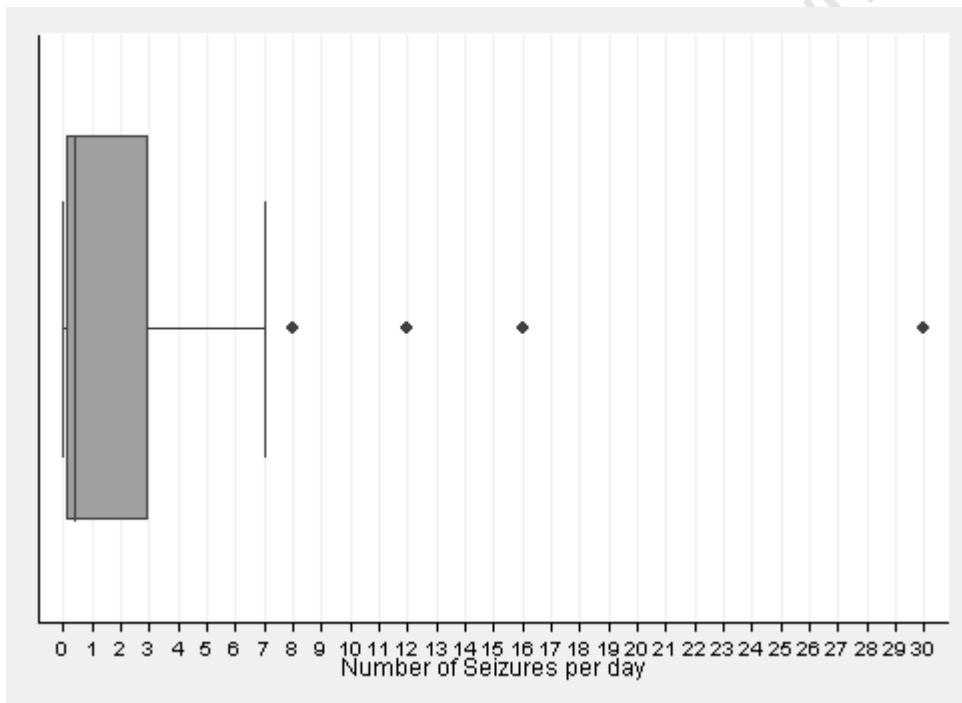


Seizure type at onset was also reviewed, 26% were generalized tonic clonic, 23% focal seizures with impairment of consciousness/responsiveness, 21% febrile seizures, 15% infantile spasms, 8% focal seizures with impairment of consciousness/responsiveness, 5% myoclonic seizures, 2% atonic seizures, and 1% focal seizures evolving to a bilateral, convulsive seizures.

Frequency of seizures amongst children with IE

Analysis frequency of seizures among IE group at the time of the study showed a minimum of 1 event every 3 months, with a maximum of 900 events per month(30 events daily), mean of 60 events monthly (2 events daily) (s.d.120 /month, median 12 per month)

Figure 7 Frequency of seizures in patients with IE despite the use of AED's



The minimum duration of an event was 2-3 seconds and the maximum was 5 minutes excluding status epilepticus with a mean of 2.2 minutes (s.d. 1.5 Minutes) and a median of 2 minutes.

46% of patients with intractable epilepsy had provoking factors (21.0% provoked by fever, 10.4% Upper respiratory tract infections, 10.4% infection not specified, 2.0% pneumonia, 1.0% Urinary tract infections and 1.0% emotional stress).

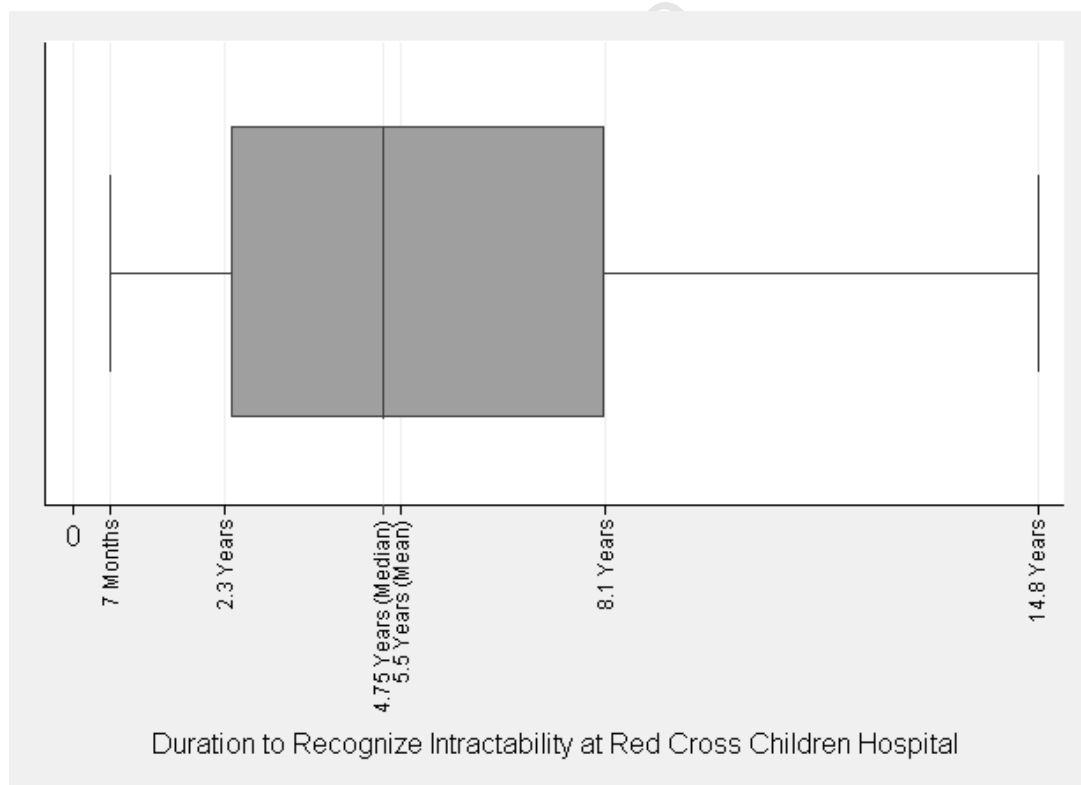
16% of the patients with IE had a family history of epilepsy.

Duration taken to recognizing intractability

Of the IE group only 33.3% (21.9% prior to commencement of the study and 11.4% after) were recognised to have intractability, or alternative diagnoses (drug resistant epilepsy, refractory epilepsy, severe uncontrolled epilepsy and so on) within the medical folders. The remaining 66.7% were did not have statements in the medical records that the children had IE despite most of them being ticked as intractable in the stats sheets by their treating doctors!!.

The duration needed to recognize intractability was found to be a median time of 4.8 years (mean 5.5 years, s.d. 3.6 years). The shortest duration was 7 months and the longest was 14.8 years from the onset of seizures.

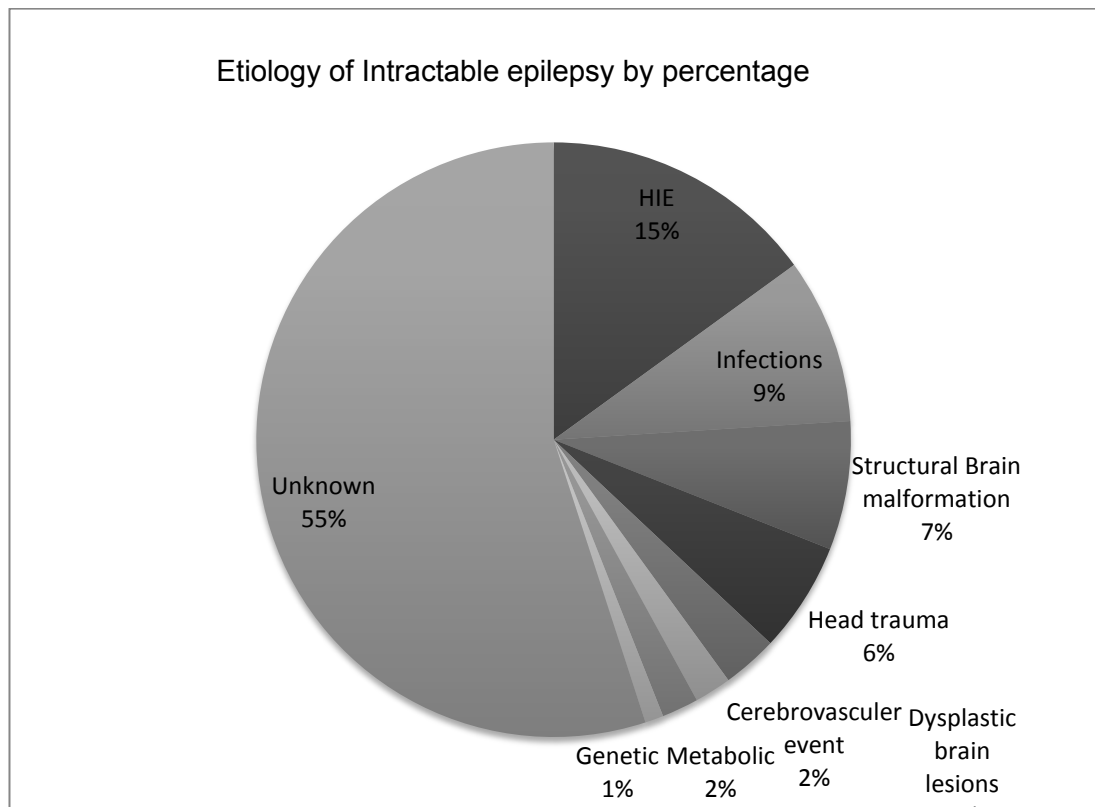
Figure 8 Duration required recognizing intractability from onset in patients with IE



Aetiology

In 55% of the patients with IE there was no clear underlying aetiology, about 15% had HIE, 9% Infections (3 % hypovolaemic shock secondary to gastroenteritis, 2% encephalitis, 2% meningitis, 1% HIV, 1% sepsis), 7% structural brain malformation, 6% head trauma, Dysplastic brain lesions 3% (1% granuloma, 1% Mesial temporal and 1% CNS tumours), 2% cerebrovascular event, 2% metabolic derangement, 1% genetic.

Figure 9 Aetiology in patients with IE



It is to be noted that we have not included patients with Tuberous Sclerosis (TS) in the study as they are all seen in a separate TS clinic that runs weekly.

In a study conducted in the same centre with the title of "Characteristics of tuberous sclerosis complex in a South African cohort" in 2009 it was found that the percentage of TS patients using more than two drugs was 18.5% which is very close to our percentage of children with IE, However they reported that 40.7% were not well controlled.

Associated conditions in patients with intractable epilepsy either an aetiology or not are summarized in table 11.

Table 11 Associated conditions and markers

| Condition | Number of patients (%) |
|--|--------------------------|
| Motor disability ((Cerebral palsy)) | 39 (41.0%) ((29 (30.0%)) |
| Perinatal asphyxia markers | |
| Delivery problems | 17 (18.0%) |
| Fetal distress | 16 (17.0%) |
| Postnatal event | 12 (12.5%) |
| Low apgar score | 11 (11.5%) |
| Pregnancy problems | 8 (8.0%) |
| Central nervous system postnatal insults | |
| Meningitis | 5 (5.0%) |
| head trauma | 6 (6.0%) |
| Structural brain lesions or abnormalities | |
| structural brain malformation | 6 (6.0%) |
| Birth Microcephaly | 5 (5.0%) |
| Macrocephaly | 4 (4.0%) |
| CNS tumour | 4 (4.0%) |
| Syndromes & complex diseases | |
| Neurocutaneous disease except TS | 9 (9.0%) |
| Dysmorphism | 9 (9.0%) |
| Chromosomal Syndromes | 2(2.0%) |
| Metabolic disease | 2(2.0%) |
| Infections (Except CNS infections) | |
| HIV | 4 (4.0%) |
| Tuberculosis | 9 (9.0%) |
| Other Infections | 11 (11.0%) |
| Other conditions | |
| Allergies | 9 (9.0%) |
| Non CNS tumours | 3(3.0%) |
| Fractures | 3(3.0%) |
| Others | 33 (34.0%) |

Investigations

As shown in Table 9. Electroencephalogram (EEG), Computed Tomography (CT) and Magnetic Resonance Imaging scans were the most frequent investigations performed in our patients with intractable epilepsy and even though MRI (50% were abnormal, performed in 67%) was more yielding than CT (40.5% abnormal, performed in 87%) it was done less frequently.

The frequencies of abnormal results detected by the investigations are summarized in Table 12.

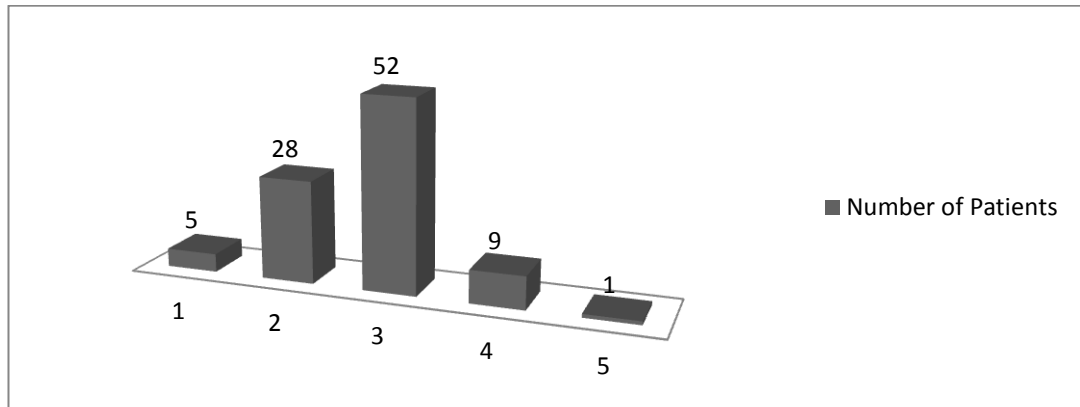
Table 12 Frequency and Results of investigations performed

| Investigation | Frequency (%) | Abnormal (%) |
|---------------|---------------|--------------|
| EEG | 96 (100.0%) | 96 (100.0%) |
| Telemetry | 9 (9.0%) | 6 (6.0%) |
| Ultrasound | 1 (1.0%) | 1 (1.0%) |
| CT | 84 (87.0%) | 34 (34.0%) |
| MRI | 64 (67.0%) | 34 (34.0%) |
| SPECT | 2 (2.0%) | 2 (2.0%) |

EEG was performed in all patients with IE and more than once in the majority of them. We looked at all available EEG results done near the onset of epilepsy and found that Thirty-five (41%) of the abnormal EEG's showed focal discharges, 50 (59%) of the abnormal EEG's showed generalized discharges, 27(32%) of the abnormal EEG's showed non post-ictal and drug related slowing or suppression and 13 (15%) typical Hypsarythmias.

As shown below, 52 (54%) of the patients had at least three types of investigations performed while 28 (29%) patients had at least two different types of investigations.

Figure 10 Number of different investigations per patient in patients with IE



Management and pharmacological treatment

Table 13 summarises the number of medications used in both groups. The mean for the intractable epilepsy group was 4 drugs, median 4 AEDs, minimum 2 AEDs, maximum 7 AEDs (s.d. 1).

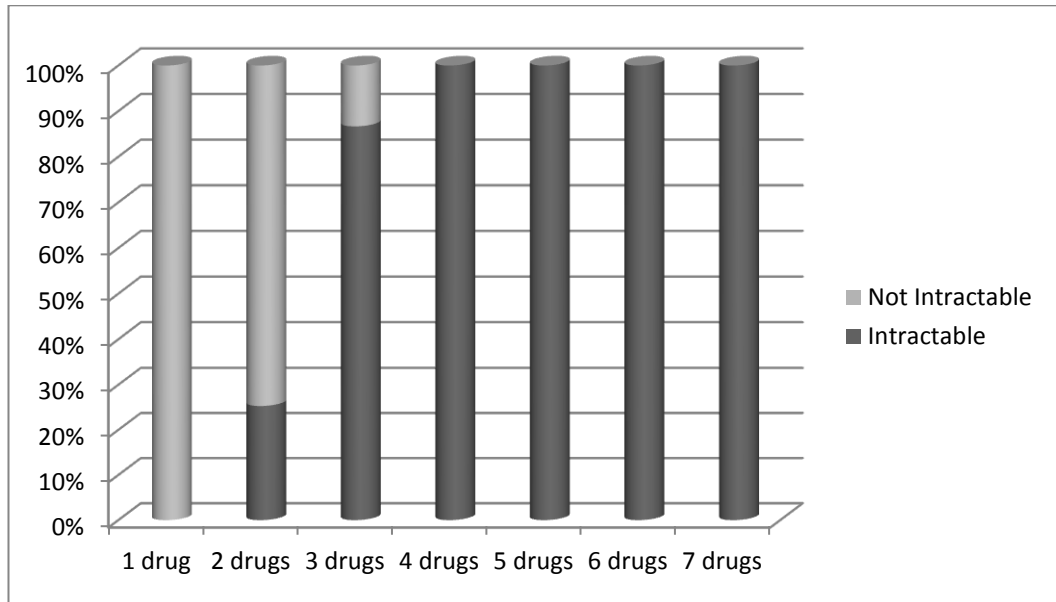
The median for the non-intractable epilepsy group was 1AED, minimum 1 AED, maximum 3 AEDs.

Comparing both groups and running a Chi2 test revealed a p value of <0.05 indicating a significant difference between both groups as the number of medications used is in average about 3-4 times more than that used in the non-intractable group.

Table.13 Number of drugs administered sorted by intractability

| Number of drugs | Intractable | | Not Intractable | | Total | |
|-----------------|-------------|---------|-----------------|---------|-------|---------|
| | No. | (%) | No. | (%) | No. | (%) |
| 1 | 0 | (0.0%) | 351 | (84.6%) | 351 | (68.7%) |
| 2 | 21 | (21.9%) | 62 | (14.9%) | 83 | (16.2%) |
| 3 | 26 | (27.1%) | 4 | (1.0%) | 30 | (5.9%) |
| 4 | 22 | (22.9%) | 0 | (0.0%) | 22 | (4.3%) |
| 5 | 14 | (14.6%) | 0 | (0.0%) | 14 | (2.7%) |
| 6 | 11 | (11.5%) | 0 | (0.0%) | 11 | (2.2%) |
| 7 | 2 | (2.1%) | 0 | (0.0%) | 2 | (0.4%) |

Figure 11 Number of drugs administered sorted by intractability



Some of the non-intractable group medications exceeded 2 drugs but the 3rd medication was considered an adjunctive therapeutic medicine. This was typically Clobazam and patient's seizures were controlled.

Compliance with medication

Non-compliance was one of the exclusion criteria and was defined as total non-compliance with prescribed medication rather than missing occasional doses.

As a result 8 patients were excluded from the study.

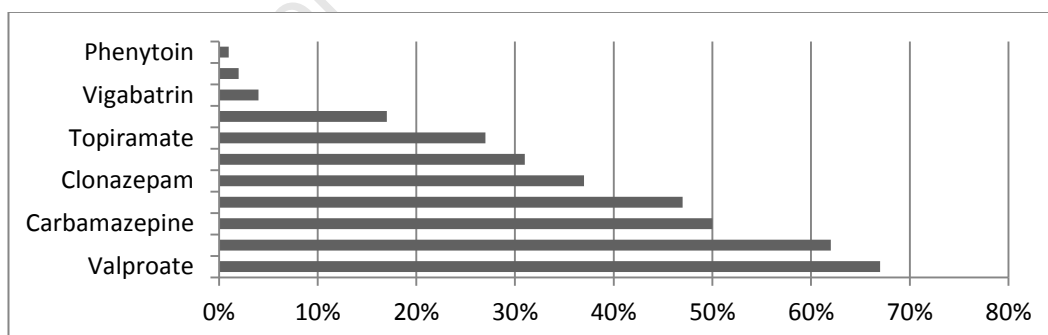
AEDs used in the patients with IE

The most frequently used medications when Valproate (67%) and Lamotrigine (62%), followed by Carbamazepine (50%) and Clobazam (47%). Medications such as phenytoin were rarely used. Other agents were used for specific syndrome indications such as Stiripentol in patients with MAE and SMEI and Vigabatrin for a few patients with West syndrome.

Table 14 Name of medications used by patients with intractable epilepsy

| Name of drug | No. of patients | Percentage (%) |
|----------------|-----------------|----------------|
| Valproate | 64 | 67% |
| Lamotrigine | 60 | 62% |
| Carbamazepine | 48 | 50% |
| Clobazam | 45 | 47% |
| Clonazepam | 35 | 37% |
| Phenobarbitone | 30 | 31% |
| Topiramate | 26 | 27% |
| Levetiracetam | 16 | 17% |
| Vigabatrin | 4 | 4% |
| Stiripentol | 2 | 2% |
| Phenytoin | 1 | 1% |

Figure 12 Percentage of patient's usage of each drug



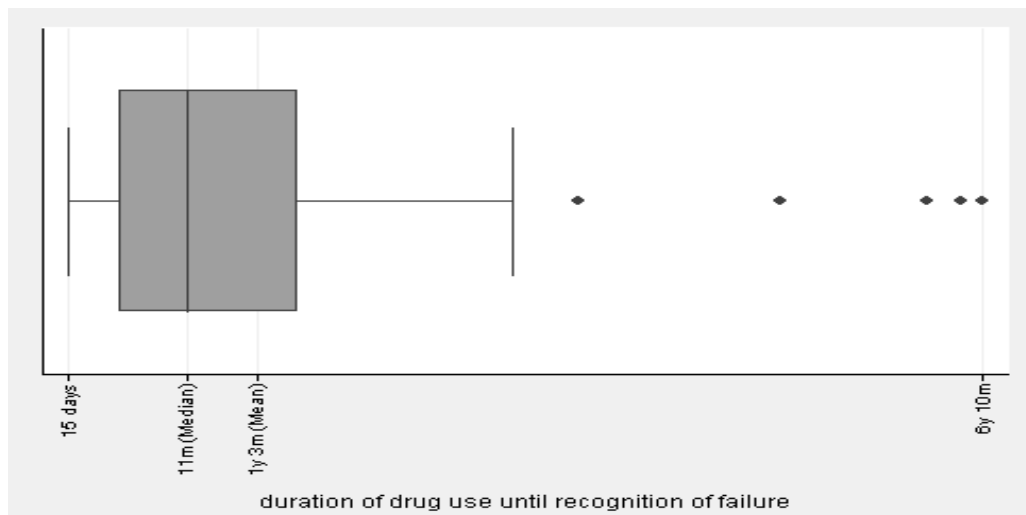
Appropriateness of trials

Each medication was reviewed for appropriateness of indication, dosing, optimization, frequency and compliance with specific medicine. Confirmation was important as they were prerequisite to be enrolled in the study.

Duration of trials of AEDs

The duration of each medication before consideration of adding another AED or discontinuation because of failure was reviewed. The date of the initiation and of termination of each drug to calculate the duration was noted. The mean duration was 15 months (s.d. 19 month), the minimum was 15 days and that was due to occurrence of adverse event, maximum was 6 years and 10 months with a median of 11 months.

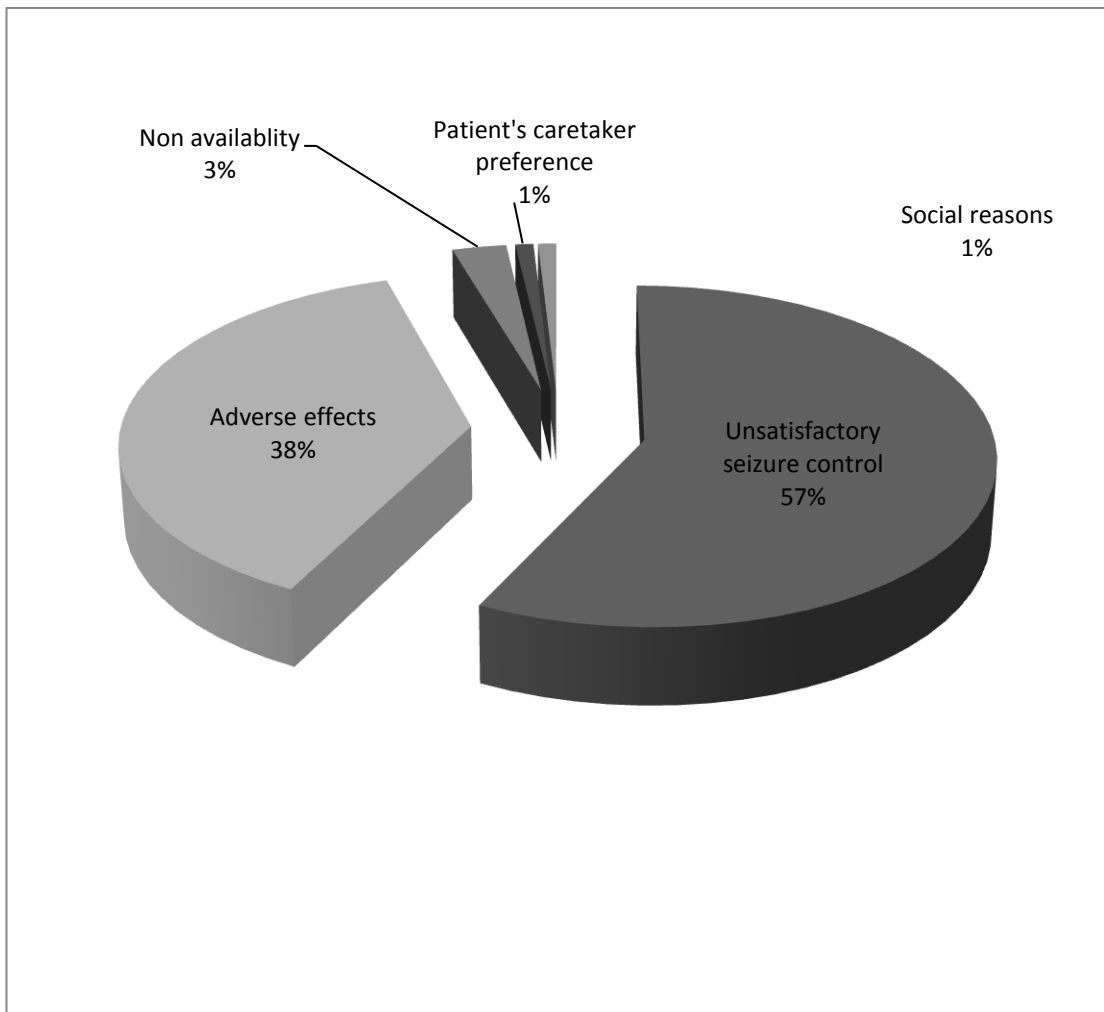
Figure 13 Trial durations in patients with IE



Reasons for discontinuation of AEDs

A total of 331 drug regimes given to our patients with intractable epilepsy were reviewed and found that 108 (33%) trials were discontinued. The most common reason for discontinuation was unsatisfactory seizure control (57%) followed by adverse events (38%) and rarely due to non-availability of the medication (3%), patient's care taker preference (1%) and social reasons (1%).

Figure 14 Reasons for discontinuation of AED's among patients with IE



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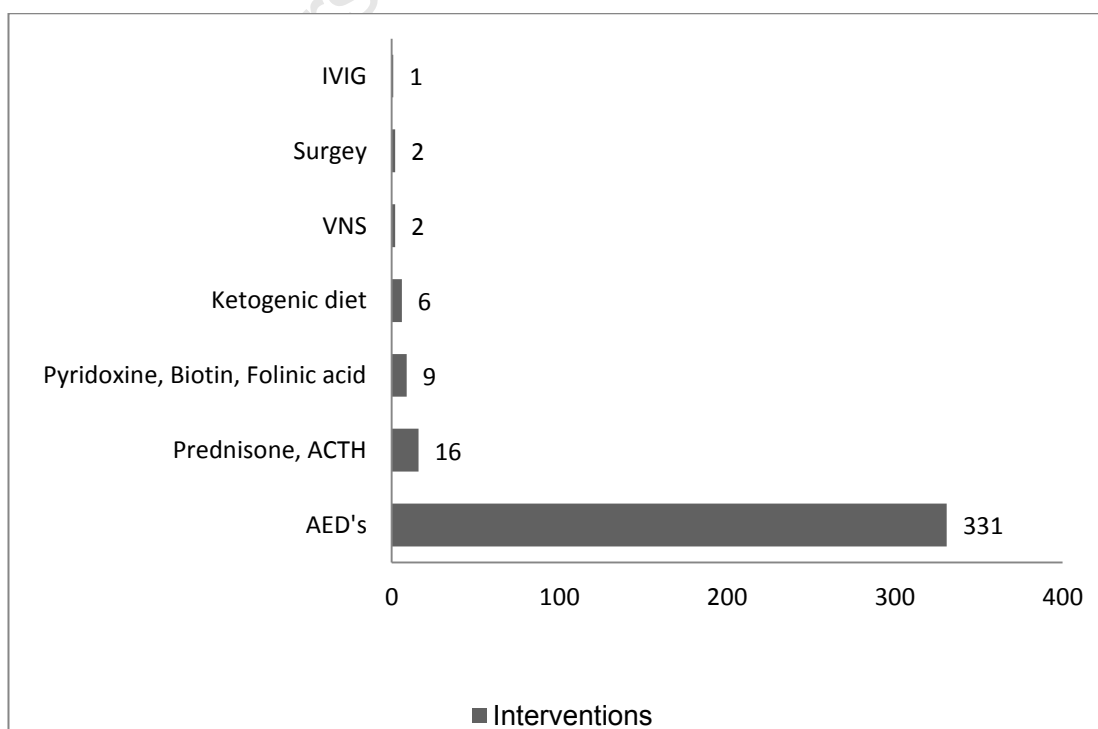
Other interventions

Other interventions included the use of ACTH, prednisone, pyridoxine or other vitamins or elements, ketogenic diet, VNS, epilepsy surgery and others are summarized in table 15. Ketogenic diet was trialled in 6 patients but only succeeded in one (83% of KD trials were unsuccessful to control seizures),

Table 15 Other interventions used among patients with intractable epilepsy

| Intervention | No. of patients | Percentage |
|-----------------------------|-----------------|------------|
| Prednisone | 10 | 10.4% |
| ACTH | 6 | 6.3% |
| Pyridoxine | 6 | 6.3% |
| Ketogenic diet | 6 | 6.3% |
| Biotin | 2 | 2.1% |
| Vagal Nerve Stimulation | 2 | 2.1% |
| Epilepsy surgery | 2 | 2.1% |
| Folinic acid | 1 | 1% |
| Intravenous Immunoglobulins | 1 | 1% |

Figure 15 Percentage of all interventions used including medications



Complications, co-morbidities and outcome

Table 16 Aetiology in patients with IE

| Co-morbidity | No. of patients | Percentage |
|---------------------------------------|-----------------|------------|
| Occurrence of Status epilepticus | 79 | 82% |
| Developmental problems | 65 | 68% |
| Apparent Neuroregression | 52 | 54% |
| Behavioural problems | 37 | 38% |
| Intellectual disability | 35 | 36% |
| Speech delay | 16 | 17% |
| Visual problems | 16 | 17% |
| Learning difficulties | 15 | 16% |
| Microcephaly after onset of Epilepsy | 14 | 15% |
| Social problems | 13 | 13.5% |
| Motor disability after epilepsy onset | 8 | 8% |
| Bulbar dysfunction | 7 | 7% |
| Pervasive developmental disorder | 8 | 8% |
| Hearing impairment | 6 | 6% |
| Gastro-oesophageal reflux disease | 5 | 5% |
| Gastrosotmy | 4 | 4% |

DISCUSSION

Out of a total of 513 children with epilepsy who attended the outpatient Epilepsy services at Red Cross War Memorial Children's Hospital in Cape Town, South Africa from August 2010 to the end of February 2011, 96 children were identified to meet the recent ILAE definition of intractable epilepsy (56).

The percentage of children with intractable epilepsy using this definition was found to be 18.7% which parallels the prevalence described in the literature of about 20% (10-25).

In the Western Cape Province there is an almost equal proportion of male to female gender (203). Our cohort reflected this population with a slight but non-significant male predominance especially in the intractable epilepsy group (male to female ratio 1.3:1). Other studies had male predominance (79, 87).

A higher percentage of patients with IE were of African ancestry and lower European when compared to the provincial ancestral distribution (203, 204).

This discrepancy is likely related to the study being sited in a governmental facility at which the proportion of the population services is more directed towards children of African and mixed ancestry.

Most children with IE were between 2 and 12 years of age (mean 7.9 years) at the time of the study, only 3.5 % were more than 12 years of age. In the government service children over 13 years of age are expected to be referred to the adult services. Complex patients undergoing changes in medication are allowed to remain in the paediatric service but new referrals over 13 years will be directly referred to the adult unit. About 10% of children were not local, this followed the usual referral patterns as that the centre is a tertiary referral centre.

It is well known that epilepsy syndromes are associated with a higher risk of medical intractability in children.(178, 205-208)We have found that Epilepsy syndromes that were not labelled as benign in the new ILAE classification constituted 57% of our patients with IE compared to only 14% in the non-intractable epilepsy group, this is a statistically significant finding. Among the IE group the most predominant syndrome was Lennox-Gastaut syndrome (27%) followed by epilepsy with myoclonic atonic seizures (13.5%), and West syndrome (12.5%). This supports that early recognition of non-benign Epilepsy syndromes could be predictors of intractability in children.

Berg *et al* supported this (49), when other studies were more conflicted, some not concurring (77, 87), and others agreeing (58, 79, 80).

some studies suggested that The age of onset may be a factor in the development of IE (19, 21, 69) however studies suggest different stages from the neonatal period, (13), the first year of life (209), through into later childhood and adolescence (13, 26).. In our group the median age of epilepsy onset was 17.5 month this reflected the prevalent epilepsy syndrome types which formed our IE group.

Rather than the age of onset, a stronger predictor is the frequency of early seizures (11, 13, 19, 21, 22, 24, 48, 49, 60, 66, 67). In our study the onset of seizures frequency was consistent with this with a median of 4 per month (mean 58 / month (s.d. 108). However this figure was skewed by the children with infantile spasms who had as many as 600 seizures per month.

At the onset only 21% of the group had typical febrile seizures, which were considered positive predictors in some studies (24), but not others (11, 79). Other seizure types, such as infantile spasms, (15% of our group with IE) are logically considered to be predictors of IE (80).

From the IE group of children a median of 12 events per month (mean 60, s.d. 4), despite poly-pharmacology, occurred which compares to children with intractable epilepsies in several studies worldwide and illustrates the need to revisit the management of these children promptly (89).

Only 16% of our patients with intractable epilepsy had family history of epilepsy. This was considered in some studies as an independent risk factor of IE (21, 22, and 24).

Only 33.3% of our IE group were documented in the medical folders to have intractable epilepsy or an alternative equivalent diagnosis (drug resistant epilepsy, refractory epilepsy, severe uncontrolled epilepsy and so on). This study has raised the awareness of specifically questioning whether the patients managed in the Epilepsy service could be intractable. Recognition of this group far earlier in their course should increase the chance of identifying these children for aggressive management in a targeted manner.

Analyzing the duration taken to recognize intractability found that the median time was 4.75 years (Mean 5.5 years, s.d. 3.6 years), these figures were similar to other centres worldwide.(63, 64) With more awareness and better application of the definition and determination of time needed for each drug trial this figure should reduce further.

In 45% of our patients with intractable epilepsy there was an identified underlying aetiology. Various aetiologies are important predicting factors of intractability (11, 21, 22, 49, 72).HIE contributed to 33% of underlying causes, 20% infections, and 16% structural brain malformation. As such HIE was the leading apparent cause of intractability, this is well described in previous studies.(100, 104, 105) In resource poor countries more infectious causes were demonstrated when compared to developed settings, in our study infectious causes were the second leading cause. (101) only 2% of these children had HIV and seizures and a direct link to intractability could not be demonstrated in this group, contrary to previous studies.(210, 211)

As regards risk factors for developing IE, of those patients with HIE, 18% had delivery problems, 17% had fetal distress, 11.5% had low Apgar scores and 11% postnatal problems. Antenatal pregnancy problems were observed in 8% and microcephaly noted at birth in 5%.These findings illustrate the compounding challenges of avoidable complications prevalent in resource poor settings leading to potential development of IE. .

Although MRI was abnormal in 50% of our children with IE compared to 40% who underwent CT, MRI was performed less frequently. Further according to the medical records the most frequent explanation was that the patients defaulted their MRI bookings. In our setting MRI investigations require special preparations compared to CT which is often performed during acute admissions. This is especially the case for patients from outside Cape Town. The yield of neuroimaging positive findings concur other studies and support that MRI, if available, is a preferred imaging tool to CT when investigating epilepsy patients, especially when surgical intervention is considered.(212-215)

In thirty –two percent of EEG studies performed early, at the onset of epilepsy, among our children with IE there was generalized slowing or suppression recorded, not considered to be post-ictal or related to drug toxicity, indicating a possible

correlation between EEG findings and intractability as suggested in other studies. (21, 28, 49)

Based on the definition which requires the use of at least 3 AEDs, as used by other centres, only 14.6% of the total group would be defined as IE compared to the larger number identified using the ILAE definition. A reasonable definition accepted universally is important for practical as well as research reasons.

The mean duration of the use of the AEDs before considering agent failure was 1 year and 3 months (s.d. 1 year and 7 months, median of 11 months) indicating that a minimum of 1 year occurred before considering failure of a regimen. This follows the ILAE definitions in relation to seizure freedom where it was defined that freedom from seizures for a minimum of three times the longest preintervention interseizure interval, or 12 months, whichever is longer. Alternatively, treatment failure is defined as recurrent seizure(s) after the intervention has been adequately applied (56).

Other non-surgical interventions were used in a very limited number of our patients with IE. Some of these interventions did not demonstrate the level of efficacy reported elsewhere. The ketogenic diet was used in 6 trials and only 1 succeeded (16%) compared to an expected higher success rate in the literature (125, 151-153). VNS and surgery resulted in variable levels of improvement in IE children's seizure but this area would need to be studied separately and in more detail to be able to comment on the outcome and use. Overall there was a gross under-utilization of alternative therapy. This stresses the need to motivate for access to these interventions, based on the service capacity which is typically challenged in resource limited settings. The need to improve resources have already been identified and flagged by the developing countries report on epilepsy surgery (DCRES) (139).

Although there was a high level of co-morbidities in our children, as described in other studies, the overall the proportion was lower than that found reported (14, 174). 15% developed microcephaly after onset of epilepsy. In infants with epilepsy this is observed and thought related to negative impact on the maturing brain when onset is early, (175) our affected group complied with this having onset at a young age. Significant impact with learning difficulties, behavioural problems, visual impairment, and bulbar dysfunction in the group with IE indicated how severely the children were affected. Early intervention and optimization of seizure control may reduce such co-morbidities.

Status epilepticus occurred in 82% of our children with intractable epilepsy and several times in each patient which increases the impact of their disease. Admission to hospital is inevitable and need for high levels of Phenobarbitone to control the status.

This phenomenon is unavoidable in the IE group and considered a known predictor when occurring near the onset of intractability in several studies (11, 21, 22, 48, 49, 72)

Even though some of the above co-morbidities or complications may be due to underlying aetiologies, further studies are needed to verify how much of these problems are related directly to intractability rather than an indirect result of underlying aetiology.

University of Cape Town

CONCLUSIONS

The latest definition of intractable epilepsy by the ILAE provided clear criteria to study the prevalence of IE among children with epilepsy at Red Cross Children's Hospital in Cape Town, South Africa. The prevalence was found to be 18.7% among children with epilepsy.

When compared to the definitions used by some local experts the prevalence dropped by 4.1%, a significant proportion who would have been missed otherwise.

This study identified syndromic epilepsy, onset of epilepsy under 2 years of age, high frequency of seizures at the onset of the epilepsy and identification of underlying aetiologies were key markers to allow early recognition of intractable epilepsy.

It took a mean of 4.7 years to recognize intractability. This period could become even shorter as more awareness of the definition is incorporated in routine epilepsy management. Directing available resources in a more targeted approach would utilise limited resources with most efficacy.

Only a small percentage of our children had access to epilepsy surgery, ketogenic diet and vagal nerve stimulator (VNS). This study confirmed an under-utilisation of this reflecting the limited resources even in a tertiary setting.

Several disabilities, specially developmental, intellectual, behavioural and social in addition to financial and eventually death, are expected outcomes of intractable epilepsy.

RECOMMENDATIONS

Early recognition of IE can be achieved universally if awareness among all physicians in the country of the definition of intractability and its predictors are raised.

Encouragement and creating channels for early referral of children with intractable epilepsy to specialized centres for further intervention and management should be possible

Looking at the long lasting and sometimes permanently disabling and distressing physical, mental, social and financial outcome and co-morbidities associated in children with intractable epilepsy it should be mandatory to establish all the basic needs to develop dedicated epilepsy intervention programs in South Africa which could provide epilepsy surgery.

More studies are needed in the field of intractable epilepsy in childhood in South Africa to further evaluate predictors and outcomes of intractable epilepsy in children.

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Appendix 1 Standard Neurology statistics template



| Neurology Patients | | | |
|--------------------|--|-------|----|
| Dr: | Clinic: | Day: | |
| | | Date: | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |
| Patient Sticky | Diagnosis: | | NP |
| | Code: | | OC |
| | Comment: Tick if intractable Epilepsy: <input type="checkbox"/> | | |

Intractable epilepsy is failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan and others, 2009)

Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre intervention inter seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer.

Appendix 2 Consent form

CONSENT

Dear Carer

We would like to ask for your permission to include your child in a research study currently on-going in the department of neurology at Red Cross Children's Hospital.

The aim of this study is to improve the overall management of all children suffering from severe epilepsy.

I ----- the parent/legal guardian of ----- give my consent for the records of this child to be used for research regarding the Intractable Epilepsy study in children.

The doctor has explained to me the study and how it affects my child. I have had the opportunity to ask questions relating to the study.

I also consent for the information to be stored on a confidential database and to be used as part of a published article.

I understand that my child's confidentiality will be respected and that this study will not allow another individual to recognize my child.

I understand that I am free to withdraw my child if I wish.

Geagte Ouers/ Wettige Voog

Ons wil graag u toestemming hê vir ŉ deelname aan n navorsing / studie in Neurlogie Department by die Rooikruis Kinder Hospitaal, dat u kind deel van die navorsing kan wees.

Die studie sluit in om die behandeling te verbeter van kinders wat aan fits/ aanvalle/ epilepsie ly.

Ek ----- naam van ouers / wettige voog ----- gee toestemming dat my kind deel van die navorsing studie kan wees.

Die Dokter het my ten volle ingelig oor die aard van die studie, en was ook toegelate om enige vrae te vra – oor die navorsing.

Ek as ouer/ voog vertrou dat alle informasie van my kind, hoogstens vertroulik en gerespekteer sal word.

Ek verstaan ook dat indien ek sou besluit om nie my kind tot die studie toe te laat nie, of hom / haar te onttrek sonder geen probleme.

Mgcini Womntwana Obekekileyo

Sicela imvume yakho edibanisa umntwana kwizifundo / ucwaninga ebhekisa kwicandelo lezengqondo kwisibhedlele sase Red Cross Children's Hospital.

Injongo zezizifundo kukuphuhlisa ulawulo lwabantwana abaphatheke kakhulu sisifo sokuwa.

Mna ----- mzali okanye umgcini womntwana ngokusemthethweni -----

---- Ndinika imvume yokuba uphando olumalinga nezifundo zabantwana abanesisifo sokuwa.

Ugqirha undichazele ngezifundo nendlela ezichaphazela ngayo umntwana wam.

a. Ndibenalo ithuba lokubuza imibuzo malunga nezifundo.

b. Ndivumelene ukuba ulwazi lugcinwe lubeyimfihlelo, lusetyenziswe njenge nxalenye lenqaku elesasazwayo.

c. Ndiyayiqonda imfihlelo yomntwana wam ukuba izakuhlonipheka nokuba ayizuvumelana, nokuba umqaphela umntwana wakho.

d. Ndiyayiqonda ukuba ndivumelekile ndimhroxise umntwana wam ukuba ndiyafuna.

Signature \ Hantekening \ Utyikityo:

**Date \ Datum \ Umhla: \ **

Witness \ Getuie \ Inggqina:

Signature \ Hantekening \ Utyikityo:

Appendix 3 Assent form

Assent form

You are being invited to take part in a study about people with epilepsy. We would like your permission to record information about your fits in a database which only the doctors looking after you will be able to access.

If you agree to be part of this study you will not need to do anything in addition to your hospital appointments and taking your medicine as usual.

You do not have to take part in this study and you can change my mind later about being part of the study.

If you decide not to take part in the study it will not affect how you are treated at the hospital in anyway.

Only my doctors and people who are involved in the study will know you are part of it.

When the study is finished, the doctors will write a report about what was learned.

This report will not say your name or provide an information by which you can be recognized.

Participant name:

Signature:

Date: \ \

Witness:

Signature:

University of Cape Town

Appendix 4 Proforma

Demographics

| Count | Number | Surname | Name | DOB | Sex | Ancestry | Local | Address |
|-------|---------|---------|--------|------------|-----|----------|-------|---------|
| 6 | xxxxxxx | xxxxxxx | xxxxxx | 25/07/2004 | F | B | 1 | Khy |

Clinical findings

| Semiology | Syndromic | Local | Ticked Intractable | Intractability | Intractable label | Date of labeling intractability | | |
|----------------|--------------------------|---------------------|--------------------|-----------------------|-------------------------|---------------------------------|-------------------|-----------------------------|
| LGS | 1 | 2 | 1 | 1 | 1 | 16/03/2008 | | |
| Etiology | Admin.Frequency Duration | Episode length | Seizures numbers | Age Of Onset | Onset Semiology | Frequency at onset per month | | |
| Unknown | 90 | 1 | 1 | 17 | FS | 1 | | |
| Family History | Status Epilepticus | Neuro-regression | Provoking factors | factors | Pregnancy risk | Delivery | fetal distress | |
| 2 | 1 | 1 | 1 | Fever | 1 | 1 | 2 | |
| low appar | birth microcephaly | Postnatal insult | Meningitis | SBM | Tumor | PM Event | | |
| 2 | 2 | 2 | 2 | 2 | 2 | None | | |
| RVD | TB | Head Trauma | CVA | Metabolic | Metabolic conditions | | | |
| 2 | 1 | 2 | 2 | 1 | Normal | | | |
| # Invest. | Telemetry | tResult | EEG | eegResult | US | usResult | | |
| 3 | 0 | None | 2 | xxxxxxx | 0 | None | | |
| CT | ctResult | MRI | mriResult | SPECT | spectResult | | | |
| 1 | Normal | 2 | xxxxxxx | 0 | None | | | |
| Neurocutaneous | ncType | Developmental delay | Motor disability | mdType | PDD | pddType | | |
| 2 | None | 1 | 2 | None | 2 | None | | |
| Behavioral | behavType | Microcephaly | Dysmorphism | dysmoType | Cerebral palsy | cpType | | |
| 1 | NS | 2 | 2 | None | 2 | None | | |
| Speech delay | VMI | Visual impairment | Hearing impairment | Learning difficulties | Intellectual disability | Blindness dysfunction | | |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| GORD | Gastrosotmy | Social problems | | | | | | |
| 2 | 2 | 2 | | | | | | |
| Ketogenic diet | Effective | VNS | Surgery | Others | Type1 | Type2 | Type3 | Type4 |
| 2 | 0 | 2 | 2 | 2 | None | | | |
| # of Drugs | Compliance concerns | | | | | | | |
| 3 | 2 | | | | | | | |
| Drug1 | Dosing interval hours1 | Dose mg/Kg/Day1 | Compliance1 | Duration1 | Occurrence of seizures1 | Occurrence of adverse effects1 | Optimized dose1 | Reason for discontinuation1 |
| Clob | 24 | 0.4 | 1 | 40 | 1 | 2 | 1 | 2 |
| Drug2 | Dosing interval hours2 | Dose mg/Kg/Day2 | Compliance2 | Duration2 | Occurrence of seizures2 | Occurrence of adverse effects2 | Optimized dose2 | Reason for discontinuation2 |
| Clob | 24 | 0.4 | 1 | 40 | 1 | 2 | 1 | 2 |
| Allergies | Type of Allergy | Syndromes | Type of Synd. | Fractures | Type of Fracture | Infections | Type of infection | |
| 2 | | 2 | | 2 | | 1 | TB Spine | |
| NSR Tumor | Tumor Type | Macrocephaly | Other1 | Other2 | Other3 | | | |
| 2 | | 2 | Hirschprung | | | | | |

Appendix 5 Ethics Approval



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Grootte Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
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21 October 2010

HREC REF: 483/2010

Dr H Alkhalidi
Paediatric Neurology & Neurophysiology
Red Cross

Dear Dr Alkhalidi

PROJECT TITLE: INTRACTABLE EPILEPSY IN SOUTH AFRICAN CHILDREN AS DEFINED BY THE INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE) PROPOSED CRITERIA

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee to the queries raised by the Committee.

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

Approval is granted for one year until 28 October 2011.

Please send us an annual progress report (website form FHS 016) if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR IM BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWAD0001637.
Institutional Review Board (IRB) number: IRB00001938

Imjcdl