# CLINICAL PROFILE OF CHILDREN PRESENTING WITH FEBRILE SEIZURES AND FEBRILE STATUS EPILEPTICUS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

**BY**


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## DECLARATION

I declare that this dissertation is my own work. It is being submitted for the Master's degree in Paediatrics and Child Health at the University of Zambia, Lusaka. It has not been submitted before for any degree or examination at this or any other University.

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## ABSTRACT

Febrile seizures (FS) are the most common seizure disorder in childhood. FS and febrile status epilepticus (FSE) are a common presentation at the University Teaching Hospital (UTH) in Lusaka, Zambia. Despite this, the clinical characteristics of children with FS and the associated causes of fever have not been documented. Simple FS have no serious adverse outcome on the neurological development of the child while complex febrile seizures (CFS) have been shown to increase the risk of developing epilepsy. This study sought to document the clinical characteristics of children with FS and FSE as well as document the association of FS/FSE with malaria, HIV and Human herpesvirus-6 (HHV-6) at the UTH, Lusaka, Zambia. This was a case control study carried out in the Department of Paediatrics and Child Health, UTH. Recruitment of participants began in January, 2015 and ended in May, 2016. Participants ages ranged from 6 - 60 months and had a febrile illness with or without FS. Febrile seizures were defined as seizures occurring in febrile children between the ages of 6-60 months who did not have an intracranial infection or history of afebrile seizures. A medical history and physical examination was carried out on eligible participants and blood was drawn for the detection of malaria, HIV and HHV-6.The peak age for the FS was 18-36 months. There was significantly more children with FS than those without seizures in the 18-36 months age group. There was no significant differences in sex distribution as well as temperature level between the two groups. A family history of FS was noted in 14% of the participants with FS compared to 2% in those without seizures.Acute febrile illness without focus was the number one diagnosis associated with FS. Tonsillitis, coryza and malaria were other diagnoses made with malaria accounting for 15 % of the cases with FS and 11% of children with febrile illness. Among the children with FS, 54% had CFS with 13% having FSE. Of the participants with FSE, 52% had acute febrile illness without focus and 24% had malaria. CFS were noted in 56% of the seizures associated with malaria of which 36 % met the criteria for FSE. The HIV prevalence was 2.2% with no significant differences between children with FS and those without seizures. In this study, the clinical characteristics of children with FS and FSE were found to be similar to that described in worldwide studies and in malaria endemic regions. There was a higher incidence of CFS/FSE compared to western reports but similar to what has been documented in other SSA studies. It is recommended to follow up children presenting with CFS/FSE, particularly those associated with malaria, due to the higher risk of developing neurological deficit and epilepsy. The result for HHV-6 differed significantly with world literature and the local studies, therefore a repeat testing is advisable.



**Key words-** Febrile seizure, Febrile status epilepticus, HHV, HIV

## DEDICATION

To my beautiful wife Wongani and our daughter Kutowa for the support and encouragement given to me during my studies.

To to my parents (Rodrick and Brenda Chandwe) for the support and for having invested greatly in my education.

Love you all.

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## ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| FBC | Full Blood Count |
| CFS | Complex febrile seizure |
| ciHHV-6 | Chromosomally integrated Human Herpesvirus-6 |
| CNS | Central Nervous System |
| DNA | Deoxyribonucleic Acid |
| FS | Febrile Seizure |
| FSE | Febrile Status Epilepticus |
| HHV | Human Herpesvirus |
| HIV | Human Immunodeficiency Virus |
| HS | Hippocampal Sclerosis |
| MRI | Magnetic Resonance Imaging |
| PCR | Polymerase Chain Reaction |
| PI | Principal Investigator |
| RI | Roseola Infantum |
| SSA | Sub-Saharan Africa |
| TLE | Temporal Lobe Epilepsy |
| UCLMS | University College London Medical School |
| UNZA | University of Zambia |
| UTH | University Teaching Hospital |

# CHAPTER ONE

## INTRODUCTION

### 1.1 Background

Seizures are common in the paediatric population worldwide. Most children never experience a recurrence but a seizure may be an initial presentation of a serious medical condition. Determining whether a seizure was provoked or unprovoked helps determine treatment options and prognosis.

Common causes of provoked seizures are central nervous system (CNS) infections, metabolic derangements, high fever and head trauma (Hauser *et al*.,1991). Febrile seizures (FS) are the most common type of seizures seen in childhood. In Western countries, up to 5% of children under 5 years of age will experience a FS, with a peak age of onset being in the second year of life (Shinnar *et al*.,2003. AAP.,2008.). Other regions have reported FS prevalence rates of 8-11 % (Iloeje,1991). FS are seizures that occur in febrile children commonly between the ages of 6-60 months without an acute CNS infection or insult, or history of afebrile seizures (AAP.,2008). They can be classified into two types, namely simple and complex FS (CFS). A simple FS is characterized by a generalized tonic-clonic seizure which lasts less than 15 minutes and does not reoccur within 24 hours of the same febrile illness. A CFS on the other hand is characterized by one or more of the following features; (a) focal seizures, (b) duration more than 15 minutes and (c) recurrence within 24 hours of the febrile illness (Nelson *et al*.,1978). Most children will present with generalized tonic-clonic seizures but up to 5% may present with non-convulsive seizure presenting as unconsciousness, eye deviation or cyanosis (Wakae *et al*., 1990). FS affects more males than females with a male:female ratio being up to 2:1. Some studies have however shown no significant gender difference in incidence (Stafstrom *et al*.,2002).

A subset of patients with CFS will have febrile status epilepticus (FSE) which is a FS lasting more than 30 minutes or recurrent seizures lasting a total of more than 30 minutes without fully regaining consciousness (Epstein *et al*.,2012. Mitchell *et al*.,2002). The children with complex FS have up to 2.4% risk of developing subsequent unprovoked seizures or epilepsy. The risk is even more (up to 49%) in those who experience FSE (Annergers *et al*.,

1987). A link between childhood FS and adulthood epilepsy has been suggested by the finding that hippocampal injury may occur after a FSE which may eventually develop into hippocampal sclerosis, a feature observed in adults with difficult to treat TLE in adults. (Lewis *et al*.,2014. Cersósimo *et a*l.,2011, Scott *et al*.,2003).

Common causes of fever in children with FS/FSE are acute otitis media and viral infections. The viral infections include influenza, parainfluenza, adenovirus and Human herpesvirus-6 (HHV-6) (Chung *et al*.,2007). In sub-Saharan Africa (SSA), there is a higher prevalence of epilepsy as compared to European countries (Ngugi *et al*.,2013. Forsgren *et al*., 2005. Birbeck *et al*.,2004). Most of these SSA regions are malaria endemic areas which have been noted to have higher rates of CFS compared to Western countries where the rates of malaria infections are extremely low (Kariuki *et al*.,2011). Malaria is the number one cause of FS in rural Zambia (Chomba *et al.,*2008). SSA is also plagued with high rates of Human Immunodeficiency Virus (HIV) with seizures being one of the many manifestations of advanced HIV infection (WHO.,2015).

In In Western countries HHV-6 is well established as a serious cause of hospitalization due to FS in healthy children (Hall *et al.*,1994). The prevalence of HHV-6 in children presenting with FS being between 18-42%. (Laina *et al*.,2010. Hukin *et al*.,1998). In Zambia, the prevalence of HHV-6 was found to be 30% in infants presenting with their first febrile episode (Kasolo *et al*.,1997) . A second study by Bates *et al* in 2009 noted that the prevalence of HHV-6 in asymptomatic infants aged 6 months was 15%.

## 1.2 Statement of The Problem

Recent studies have suggested a link between childhood febrile seizures and temporal lobe epilepsy (TLE) in adulthood. There is evidence of acute hippocampal injury after childhood FSE which may lead to hippocampal sclerosis, a feature found in adult patients with TLE. There is also a higher rate of FSE and other FS meeting the criteria of CFS in SSA (especially in malaria endemic areas) and these types of seizures have been shown to increase the risk of developing future epilepsy.

Zambia and other SSA countries have a high prevalence of active convulsive epilepsy coupled with high malaria and HIV infection rates. Malaria and HIV are known to cause seizures in both children and adults. However, the link between childhood FS, malaria/ HIV and adulthood epilepsy in Zambia has not yet been established even though malaria has been shown to be the number one cause of FS in rural Zambia. FS are also a common presentation at UTH with an average of 8 children/month being diagnosed as having FS (unpublished emergency room records), but the clinical characteristics of children presenting with these conditions and the association between FS/FSE and malaria, HIV and HHV-6 has not been described in this population. The percentage of how many of such children develop epilepsy in adulthood in Zambia is currently unknown as there is no long term follow up of children with FS/FSE. Children with FSE are known to have a higher risk of developing future epilepsy. Knowing the clinical characteristics and associations would help in identifying which children would benefit from long term follow up. This would result in early identification of epilepsy and the institution of appropriate management.

## 1.3 Research Question

1. What are the clinical characteristics of children presenting with FS/FSE at UTH?

2. Are children with febrile seizures more likely to have HIV or malaria?

3. Is HHV-6 significantly associated with FS/FSE at UTH?

## 1.4 Objectives

### 1.4.1 General Objective

To describe the clinical characteristics of children with FS and FSE presenting at the University Teaching Hospital, Department of Paediatrics and Child Health.

### 1.4.2 Specific objectives

1. To document the clinical diagnoses made in association with FS/FSE.

2. To determine the association between FS/FSE and malaria.

3. To explore the association between FS/FSE and HIV.

4. To determine the prevalence of HHV-6 in children 6-60 months old with FS and FSE

# CHAPTER TWO

## LITERATURE REVIEW

Febrile seizures (FS) are seizures that occur in febrile children commonly between the ages of 6-60 months without an acute CNS infection or insult, or history of afebrile seizures (AAP.,2008). The peak age of onset of FS is in the second and third year of life with most studies showing a slightly higher prevalence in males (Winkler *et al*.,2013.,Esmaili *et al*.,2012. AAP.,2008. Shinnar *et al*.,2003). They are classified as either simple or complex febrile seizure (CFS). Most FS are simple FS, that is, generalized tonic-clonic lasting less than 15 minutes without recurrence within 24 hours (AAP,2008. Wakae *et al*., 1990 ). A CFS on the other hand is characterized by one or more of the following; (a) focal seizures, (b) duration more than 15 minutes and (c) recurrence within 24 hours of the febrile illness (Nelson *et al*.,1978). The average degree of fever noted in children with FS is 38$^{o}$C (Offringa *et a*l.,1994). FS are usually benign in nature with no serious adverse outcomes on the motor and cognitive development of the child (AAP., 2011) .

A family history of FS seizures may be found in 18-50% of children with FS (Esmaili *et al*., 2012. Esch *et al*.,1994. Offringa *et a*l.,1994). The risk of seizure recurrence is higher in those with a positive family history and CFS. In the Western world, features of complex seizures are seen in about 32% of the children with FS while in SSA this figure has been observed to be as high as 71% (Berg *et al*.,1996. Winkler e*t al*.,2013). CFS increase the risk of epilepsy by 3.6 times compared to the general population with multiple FS increasing the risk by 10 times, making it a powerful prognostic factor for the development of subsequent epilepsy (Pavlidou *et al*.,2013. Annergers e*t al*.,1987). In addition, FSE accounts for up to 80% of the status epilepticus observed in children below the age of 2 years and it is associated with an increased risk of temporal lobe epilepsy (TLE) (Shinnar *et al*.,1997, 2003). Acute hippocampal injury has been noted after FSE and this may lead to hippocampal sclerosis, a feature that is seen in adult patients with TLE (Lewis *et al*.,2014. Cersósimo *et a*l., 2011, Scott *et al.*,2003). SSA has been noted to have a higher prevalence of active convulsive epilepsy (7.0-14.8/1000) compared to high income countries in Europe (4.5-7/1000)

(Ngugi *et al*.,2013. Forsgren *et al*.,2005. Birbeck *et al*.,2004). Zambia has an adjusted prevalence of 12.5/1000 with the age specific rates being highest for children aged 5-15 years at 26.2/1000 (Birbeck *et al*.,2004). The higher frequency of CFS in SSA may thus be related to the reported higher prevalence of epilepsy in sub-Saharan Africa.

Viral infections and malaria have been identified as common causes of fever in children with FS/FSE. These include influenza, parainfluenza, adenovirus and HHV-6 (Chung *et al*., 2007). Malaria is an important cause of acute seizures in children worldwide with up to 88% of the malaria cases occurring in Africa (WHO,2015). In malaria endemic areas of SSA, falciparum malaria is the most common cause of acute symptomatic seizures in children (Idro *et al*.,2008. Kariuki *et al*.,2011). Most of the seizures associated with malaria are likely to be acute symptomatic seizures rather than pure FS as the infected erythrocytes adhere to the blood vessels in the brain (Idro *et al*.,2005.Kariuki *et al*.,2011). In a Kenyan retrospective study, more than 40% of the seizures observed in children with malaria were attributed to cerebral malaria and the rest to acute symptomatic seizures or FS (Ikumi *et al*.,2008). Seizures associated with malaria are often characterized by complex features including status epilepticus, making malaria the number one diagnosis associated with status epilepticus in malaria endemic regions (Waruiru *et al*.,1996. Idro *et al*.,2008). Such complex seizures are associated with a higher risk of neurological sequelae and epilepsy (Birbeck *et al*.,2010. Idro *et al*.,2007).

Malaria endemic areas have been noted to have a higher incidence of CFS compared to other regions. A Tanzanian study found that up to 71.4% of children with FS had complex seizures compared to 35% found in high-income, low malaria areas (Winkler *et al*.,2013.Berg *et al*.,1996). The study noted that the children with CFS either had more than one seizure within 24 hours, focal seizures or seizures lasting more than 15 minutes. In this study, the diseases frequently associated with FS were respiratory infections, gastroenteritis, fever of unknown origin and malaria in that order. The importance of malaria as a disease associated with acute symptomatic seizures was also noted in a Kenyan study which showed that a reduction in the incidence of malaria was associated with a corresponding decrease in acute symptomatic seizures. The reduced incidence of seizures was similar to

the predicted decline estimated using modeled malaria-attributable fractions for seizures and this suggested that the decrease was an approximate measure of childhood seizures attributable to malaria (Kariuki *et al*.,2011).

In rural Zambia, up to 65 % of children presenting with FS were observed to have malaria (Birbeck., 2000), making malaria the number one cause of FS in rural Zambia (Chomba *et al.*,2008). Most countries in SSA have implemented elaborate malaria prevention programs and as such there has been a substantial decline in malaria mortality. Malaria was the leading cause of death in children under the age of five in SSA in 2000 compared to 2015 where it was fourth (WHO, 2015). By 2015, malaria accounted for 10% of the under five mortality compared to 17% in 2000. Zambian data also shows that there was a substantial decline of in-patient cases and deaths attributable to malaria between 2000-2008 with a slight resurgence in 2010 (Masaninga *et al*.,2013). This decline was attributed to the expansion of the indoor residual spraying program, use of insecticide treated nets and artemisin-based combination therapy. Despite this, malaria complications still remain major contributors of morbidity and mortality in children under the age of 5 years. Such complications include anemia, acute symptomatic seizures and cerebral malaria. Children previously hospitalized with cerebral malaria and those with acute symptomatic seizures have an increased risk of developing epilepsy compared to children without such a history. The prevalence of epilepsy in children with cerebral malaria is similar to that observed after encephalitis and bacterial meningitis 6 months or more after the insult (Carter *et al*.,2004).

SSA is also an area hard hit by the HIV pandemic. It accounts for two-thirds of the global new HIV infections (WHO.,2015) with Zambia having a prevalence of 13% among adults aged 15-49 (ZDHS.,2013). The interaction between HIV and malaria is of important note. HIV infection is correlated with increased malaria infection, burden and treatment failure (French *et al*., 2001. Whitworth *et al*.,2000). The association becomes more pronounced with advancing immunosuppression. The CNS is affected in a number of ways in patients with HIV infection. Seizures associated with HIV are commonly caused by opportunistic CNS

infections but subclinical HIV-1 infection may be responsible for seizure activity (Dore *et al*.,1996).

The clinical outcomes of children with FS is generally good. It is therefore recommended that procedures such as lumbar puncture, or brain neuroimaging need not be carried out routinely. An elaborate panel of investigations is usually not needed in a neurologically normal child who presents with a simple FS. Focus should be directed identifying the cause of the fever rather than the seizure itself (AAP., 2011). Consideration for further evaluation may be made in a child who presents with a CFS. These would include lumbar puncture and neuroimaging if the neurological examination is abnormal. Ruling out meningitis and encephalitis becomes important especially for children below the age of 18 months who present with complex FS (AAP., 2011).

HHV-6 is the causative agent of Roseola Infantum (RI), which is also known as exanthem subitum (Yamanishi *et al*.,1988). In immunocompetent patients, primary HHV-6 infection mainly has a self limited course and passes without sequelae (Asano *et al*.,1994). Currently, there is no drug approved for the treatment of HHV-6 infections but anti-cytomegalovirus agents foscarnet and ganciclovir have shown some in-vitro activity against HHV-6 (Manichanh *et al.*,2000. Pohlmann *et al*.,2007). Artesunate, used for treatment of malaria, has recently shown excellent *in vitro* efficacy against HHV-6 and was successfully used to treat a child with HHV-6B myocarditis (Hakacova *et al.*,2013. Efferth *et al*.,2008). In the United States of America (USA), Europe and Japan, HHV-6B infection is commonly associated with FS and FSE and together with Human Herpesvirus-7 accounts for up to one third of FSE in children 1 month to 5 years (Epstein *et al*.,2012). FSE accounts for 70% of status epilepticus in the second year of life (Shinnar *et al*.,1997). Zambia was the first country to document a prevalence of HHV-6A that was higher than that of HHV-6B in primary childhood HHV-6 infections (Kasolo *et al*.,1997, Bates *et al*.,2009). These results are very significant in Zambia, an HIV endemic country. This is because co-infection with HIV-1 and HHV-6A has been demonstrated to accelerate progression to AIDS both in animal models and humans (Kositanont *et al*.,1999. Lusso *et al*.,2007).

## 2.1 Summary of Literature Review

FS are the commonest type of seizures in childhood with the peak age of onset being in the second year of life. Simple FS have no serious adverse outcome on the neurological development of the child while CFS on the other hand have been shown to increase the risk of developing epilepsy by 10 times. The incidence of CFS is higher in SSA compared to the Western world. Literature also shows that SSA has a higher prevalence of active convulsive epilepsy. In SSA, malaria is an important cause of fever associated with CFS and it is the number one cause of FS in rural Zambia. HIV is another infection that plagues the SSA region with seizures being one of its manifestations. Worldwide, HHV-6 has been noted to be a significantly associated with CFS with some studies showing a possible link between childhood HHV6 infection and adult TLE.

# CHAPTER THREE

## METHODOLOGY

### 3.1 Study design

This was a case control study carried out from January 2015 to May, 2016.

### 3.2 Target Population

Children between the ages of 6-60 months presenting with a first episode of febrile seizure and those presenting with febrile illness without seizures.

### 3.3 Study site

The study was conducted from the pediatric emergency room and admission ward at the University Teaching Hospital in Lusaka. The pediatric department has an approximate bed capacity of 374 catering for patients coming from various parts of Lusaka as well as receiving referrals from all parts of Zambia.

### 3.4 Eligibility

Any child with a febrile illness of a temperature equal to or above 37.5$^{o}$C with or without FS/FSE was eligible to participate in the study. Patients who did not fit into the study definitions of a febrile illness or FS/FSE were not be enrolled.

#### 3.4.1 Inclusion Criteria

1. Children aged 6-60 months with first episode of FS and FSE presenting within 48 hours of a febrile seizure.
2. Children aged 6-60 months with a febrile illness without seizures presenting within 48 hours of a febrile illness.

### 3.4.2 Exclusion Criteria

1. Children with signs and symptoms of central nervous system (CNS) infection (eg, neck stiffness, positive Brudzinski sign, positive Kernig sign and persistent altered level of consciousness) were excluded.

2. Children with clinical evidence of CNS anomalies such as hydrocephalus, cerebral palsy and microcephaly were excluded.

3. Children younger than 6 months or older than 60 months were excluded.

4. Children with known seizure disorders were excluded.

**5.** Children already enrolled in other studies were excluded.

### 3.5 Sample Size

Based on an estimated expected 74% prevalence of malaria in children with FS and 59% in children without seizures (Chomba *et al.,*2008), we needed to enroll 150 participants in each group.

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

r = ratio of control:cases =1

P = Mean proportion exposed in cases and controls = (0.74.2+0.59)/2= 0.665,

$P_1$ = Proportion of cases exposed = 0.742, $P_2$ = Proportion of controls exposed = 0.59

$Z_{\beta}$ = Desired power = 0.84, $Z_{\alpha/2}$ = significance level for 0.05 = 1.96

= 2(0.665)(0.335)(7.84)/0.023)

*n*= 150 cases and 150 controls**, Total = 300**

### 3.6 Sampling method

Every infant or child who presented to the Pediatric emergency room or admission ward at UTH with a febrile illness with or without a first episode of FS/FSE and was aged between 6-60 months was invited to participate in the study.

A standardized data entry form was used to collect demographic and clinical details of each participant (Appendix iii). A participant code was used to identify the patient. The highest temperature recorded for the participant was entered. A physical examination was then carried out taking note of any localizing sign of infection. Level of consciousness and any abnormalities that would make the participant ineligible for the study were also determined.

About 3ml of blood was collected from a peripheral vein and placed in labelled EDTA tubes and spun. The plasma was drawn from the tubes and stored at -81$^{o}$C. Plasma samples had DNA extracted using the QIAGEN QIAamp® DNA Mini Kit as per the manufacturer's instructions. HHV-6 DNA analysis by Subtype-specific, probe-based, real-time PCR (SSPBRT-PCR) was done in the University of Zambia-University College London Medical School (UNZA-UCLMS) laboratory. This was done using a quantitative PCR assay as described in Lou *et al*, 2011. We used a cut off of 200 copies/ml to be indicative of an active infection.

HIV testing was offered to all those with unknown status as per hospital practice. A malaria test was also carried out using rapid diagnostic kits (RDT) or a malaria parasite slide.

### 3.7. Study Definitions

For the purpose of the study, fever was defined as an axillary temperature of 37.5$^{0}$ C and above.

1. **Febrile seizure (FS)** - Seizures that occurred in a febrile infant or child between the ages of 6-60 months who clinically did not have an intracranial infection, metabolic disturbance, or history of afebrile seizures.

2. **Complex febrile seizure (CFS) -** A FS characterized by one or more of the following; (a) focal seizures, (b) duration more than 15 minutes and (c) recurrence within 24 hours of the febrile illness

3. **Febrile status epilepticus (FSE) -** FSE was defined as any febrile seizure lasting more than 30 minutes or recurrent seizures lasting a total of more than 30 minutes without fully regaining consciousness. It is a subset of CFS (Mitchell *et al*, 2002).

### 3.8 Data Management

Data collected from the standardized data entry form was double entered into Apple Numbers spreadsheet and a hard copy made with the data bases being matched. It was later entered into the SPSS Statistical package for analysis. This included demographic and clinical details. A participant code was used to identify the patient. Apart from the parent/guardian phone number, no other personal details that may identify participants appeared on the form.

#### 3.8.1 Data Analysis

The main outcome of the study was a description of the clinical characteristics of children presenting with FS/FSE at the University Teaching Hospital, Department of Paediatrics and Child Health. The independent variables considered in the study were age, sex, malaria, HIV and HHV-6 infection.

The data was analyzed using the SPSS Statistical package version 21. Means and Medians were compared and a t-test was used for statistical significance .P-values of $\leq 0.05$ was considered to be statistically significant. Proportions were compared and a chi-

square test used for statistical significance. Subgroups analysis were based on seizure type (simple, complex and febrile status epilepticus) as well as the focus of infection.

### 3.9 Ethical Considerations

Ethical approval was sought from the Research Ethics Committee (Ref No. 2014-Sept-003). Permission was obtained from the University Teaching Hospital Pediatrics department. Written consent was obtained from the parents/ guardians of the participants as they were aged between 6-60 months of age.

Blood for the identification of HHV-6 using DNA PCR was collected at the same time of other blood samples collected as clinical practice, so as to avoid multiple pricks.

#### 3.9.1 Confidentiality

Participants were identified by a study number. Only the principal investigator (PI) and supervisors were privileged to contact information so as to communicate laboratory results to the parents/guardians and in some cases, the attending clinician.

#### 3.9.2 Benefit

Participants and their guardians/parents were clearly informed that management would not differ from the usual management of FS and FSE. Parents were informed that even in case of positive results for HHV6, management would be the same of any other viral infection as there is currently no protocol or approved medication for the treatment of HHV-6. Patients in which HHV6 was isolated, especially if presenting with FSE, were to be scheduled for closer follow up owing to the higher risk of developing TLE in these patients.

The information collected from the study is meant to serve as baseline data that could be used in further studies that may look at etiologies and management of patients with FS and FSE. Effective treatment/prevention of these conditions may reduce the number of children who eventually develop epilepsy, especially TLE.

# CHAPTER FOUR

## RESULTS

A total of 315 participants were enrolled. Nine participants where not included in the final analysis because of missing information such as temperature on the data entry form. This brought the total number to 306. A total of 164 participants had a diagnosis of FS and 142 where children who had an acute febrile illness without seizures. Out of those with FS, 14% (23/164) had a family history of FS in a first degree relative (parents and siblings) compared to only 2% (3/174) among those without seizures. The participants were all residents of Lusaka.

Of the 164 with seizures, 56% (92/164) were male and 44% (72/164) were female. The sex distribution was similar for those without seizures, 52% (74/) for males and 48% (68/142) for females (Figure 1).

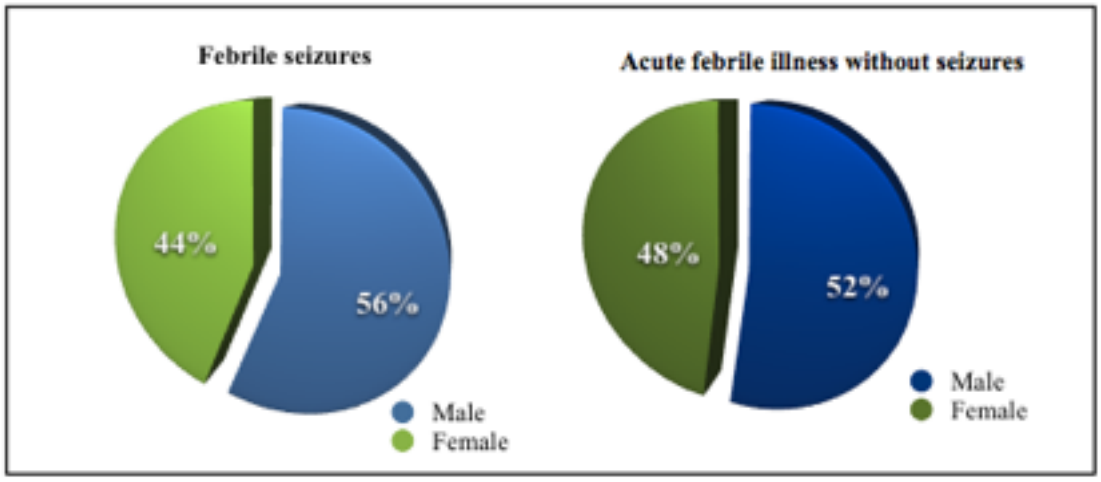


**Figure 1. Sex Distribution of Participants**

Most of the participants were aged between 18-36 months [37% (113/306)] with the ratio of those with seizure to those without seizures being 2:1 in this age group (Figure 2). The majority of participants with FS fell in the 18-36 months age group, 48% (78/164) **(p=0.03**) while the majority of those without seizures fell in the 6-18 months age group, 43% (61/142). The average age for the 306 participants in the study was 30 months. The

age range for children with FS was from 6-60 months with a mean of 29 months while the mean age for those without seizures was 28 months (**two sample t(304)= 0.31, p=0.54**)

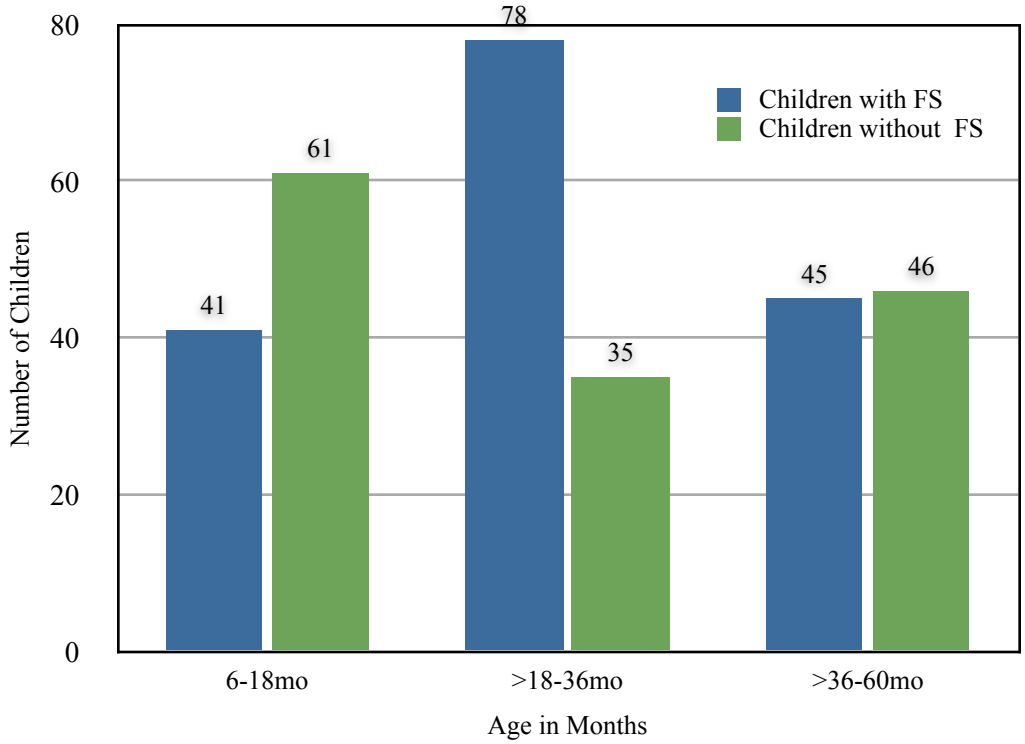


**Figure 2. Age distribution of Participants**

The study definition for fever was axillary temperature equal to or above 37.5$^{o}$C. The highest temperature recorded during the acute illness was entered onto the data entry form. This was either the temperature on the referral form or recordings made on admission. Temperatures for the 306 participants ranged from 37.5 to 41$^{o}$C (Table 1). The average temperature for the participants with FS/FSE was 38.5$^{o}$C with the highest temperature being 40.1$^{o}$C amongst this group. For the participants without seizures, the average temperature was 38.7$^{o}$C and the highest temperature recorded was 41$^{o}$C (Table 1).

**Table 1. Fever patterns of participants**

| | Children with FS/ FSE | Children without seizures | t-test |
|---|---|---|---|
| Minimum temperature (°C) | 37.5 | 37.7 | |
| Maximum temperature (°C) | 40.1 | 41 | |
| **Average temperature (°C)** | **38.5** | **38.7** | **Two sample t(304)=1.76, p=0.07** |

ll the participants were brought to the pediatric emergency room with complaints of an acute onset of a febrile illness. The duration of illness prior to admission was less than 3 days. The admission diagnosis ranged from coryzal illnesses to mumps (Table 2). Acute febrile illness without a focus of infection was the commonest diagnosis made in patients with a FS, 28% (46/164). This was followed by tonsillitis, coryza and the fourth commonest was malaria which accounted for 15% (25/164) of the children with FS (Figure 3).

The commonest diagnosis made with respect to children who presented with an acute febrile illness not associated with seizures was coryza, 27% ( 38/142). The second and third commonest was tonsillitis and pneumonia respectively. All the top three diagnoses were respiratory system related conditions (Figure 4). Forty children out of the 306 participants had a diagnosis of malaria made by RDT (38/40) and malaria parasite slide (2/40). The average age and temperature for those with malaria are shown in Table 3. Seizures were noted in 63% (25/40) of those with malaria while remaining 37% (15/40) did not have seizures. The sex distribution of the 15 children with malaria not associated with seizures was 67% (10/15) male and 27% (4/15) female (2.5:1). Those with seizures comprised of 56% (14/25) male and 44% (11/25) females.

**Table 2. Admission diagnosis of all participants**

| | FS | No FS | *Two tailed p*-Value |
|---|---|---|---|
| Coryza | 34 | 38 | **0.22** |
| Tonsillitis | 37 | 23 | **0.11** |
| Acute Febrile Illness without focus | 46 | 11 | **0.00001** |
| Malaria | 25 | 15 | **0.23** |
| Acute diarrhea Disease | 14 | 26 | **0.011** |
| Pneumonia | 3 | 19 | **0.001** |
| Enteric Fever | 1 | 5 | **0.07** |
| Bronchiolitis | 0 | 4 | **0.03** |
| Urinary Tract Infection | 3 | 0 | **0.11** |
| Febrile illness with Conjunctivitis | 0 | 1 | **0.282** |
| Mumps | 1 | 0 | **0.35** |
| **Total** | 164 | 142 | |

Of the 164 participants with a diagnosis of febrile seizure, 95% (155/164) were reported or observed to have had generalized tonic-clonic seizures while 5% (9/164) had focal seizures. This was from the description given by the guardian or observation made by the attending clinician. The classification of FS was either simple or complex (Figure 5 and Figure 6).

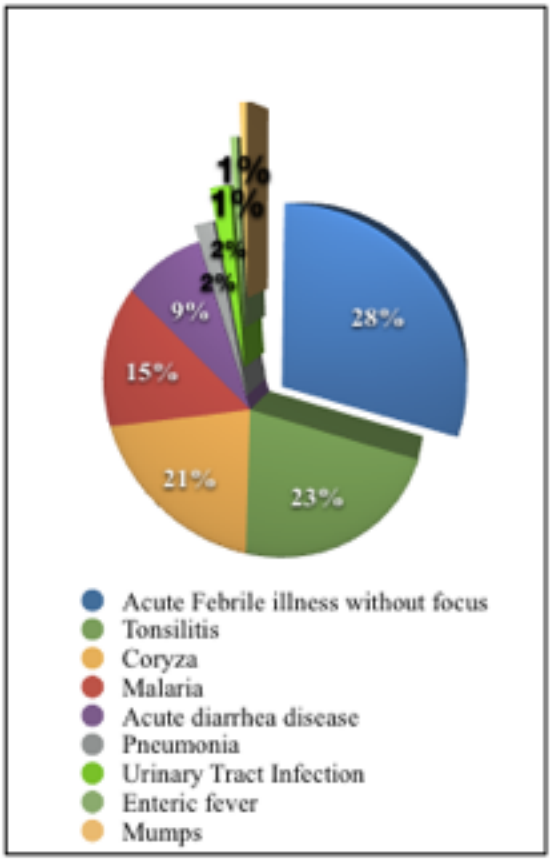


**Figure 3. Diagnosis associated with FS**

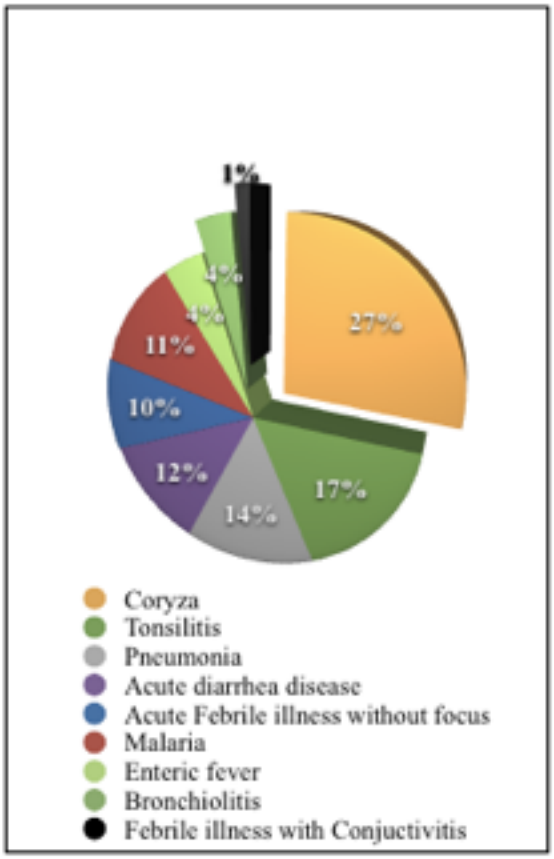


**Figure 4. Diagnosis associated with febrile illness without seizures.**

**Table 3. Participants with Malaria**

| Participants with Malaria | FS | No FS | t-Test *p*-value |
|---|---|---|---|
| Average Age (Months) | 38 | 41 | 0.74 |
| Average Temp (C°) | 38.7 | 39 | 0.37 |
| Seizures | 25 | 15 | - |

The simple FS made up 46% (76/164) while those with CFS comprised 54% (88/164) of the participants with FS. The CFS by definition, included seizures lasting more than 15 minutes (including FSE), multiple seizures within 24 hours, and/or focal seizures. Amongst those with CFS, 24% (21/88) met the criteria for FSE.

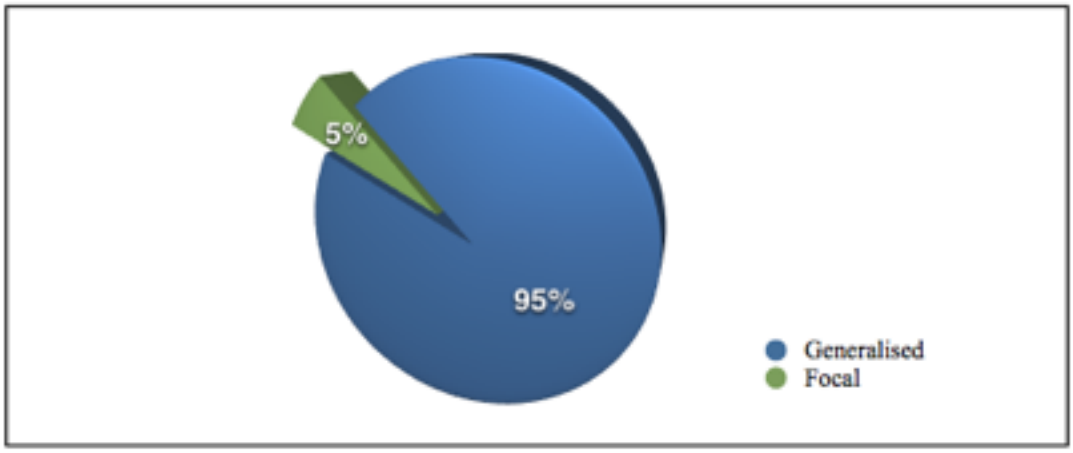


**Figure 5. Seizure Classification**

For patients with malaria/FS, simple FS were noted in 44% (11/25) while 56% (14/25) had CFS. Out of a total of 88 participants with CFS, malaria was found in 16% (14/88) of these patients. Further more, 36% (5/14) of the participants with malaria/CFS met our criteria for FSE.

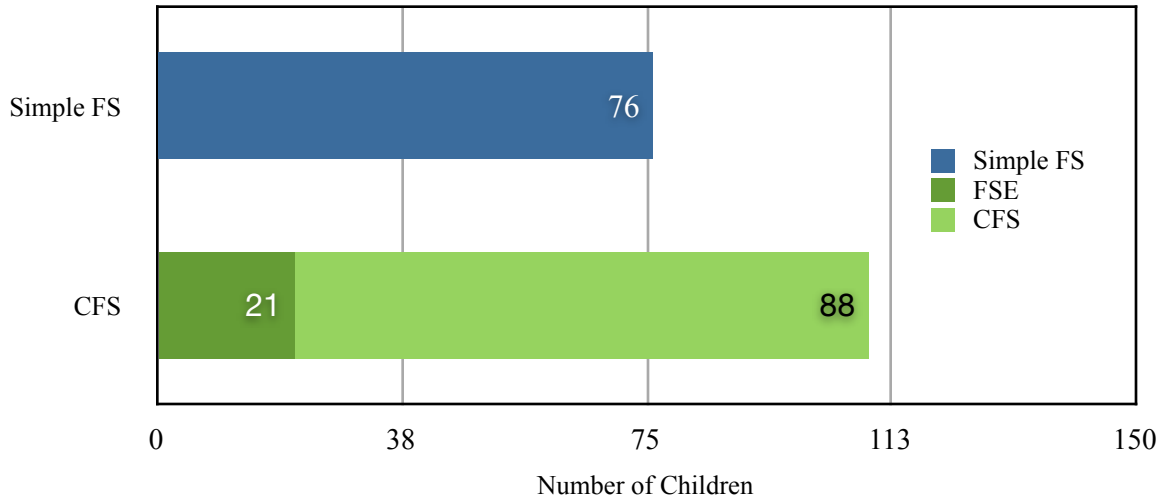


**Figure 6. Seizure type of participants with febrile seizures**

The duration for most of the seizures was less than 5 minutes [70% (115/164)] as reported by the caregiver or observed by the admitting clinician and the PI. Those with seizures lasting more than 30 minutes made up 13% (21/164) of the participants. This included those with a single seizure reported to have lasted more than 30 minutes and those with multiple seizures lasting a total of more than 30 minutes without fully regaining consciousness (Figure 7).

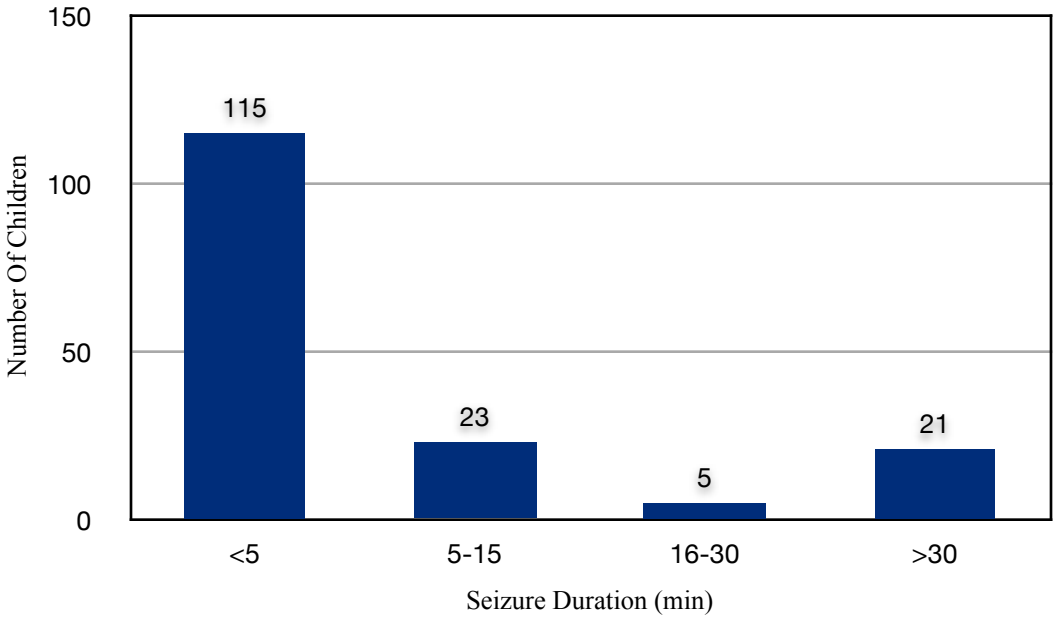


**Figure 7. Duration of Seizure**

FSE was defined as any febrile seizure lasting more than 30 minutes or recurrent seizures lasting a total of more than 30 minutes without fully regaining consciousness. This group of participants made up 13% (21/164) of the children with seizures and comprised of 11 males and 10 females. FSE accounted for 24% (21/88) of the children with CFS. The diagnoses made in patients with FSE were acute febrile illness without focus 52% (11/21), malaria 24% (5/21), tonsillitis 10% (2/21), while pneumonia, coryza and ADD accounted for 5% (1/21) each (Figure 8). For the rest of the participants with CFS, a diagnosis of malaria was made in 16% (14/88) of the children.

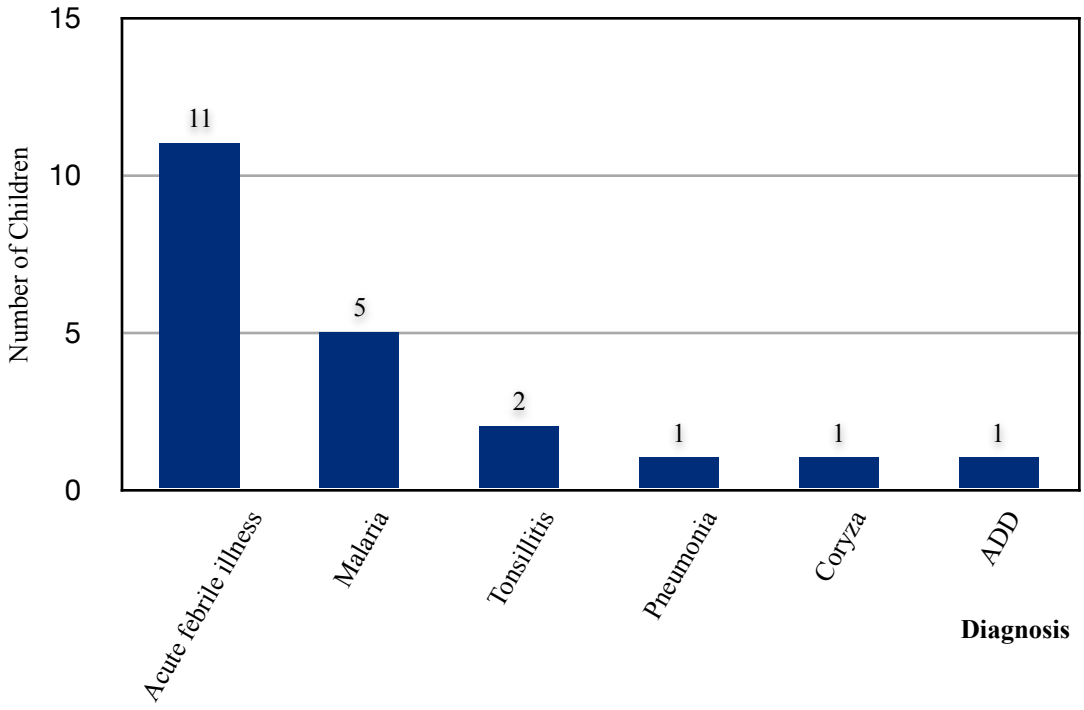


**Figure 8. Diagnosis associated with FSE**

Multiple seizures during the acute febrile illness was noted in 34% (56/164) of the participants. The average number of multiple seizures was 1.7 times (Table 4).

**Table 4. Multiple Seizures**

| Number of Seizures | Male | Female |
|---|---|---|
| 1-5 | 57% (32/56) | 36% (20/56) |
| 6-10 | 4% (2/56) | 4% (2/56) |
| >10 | 0 | 0 |

The multiple seizures were mainly noted in children who had a diagnosis of an acute febrile illness with no identifiable cause of the fever 34% (19/56). Those with malaria and multiple seizures made up 14% (8/56) (Figure 9).

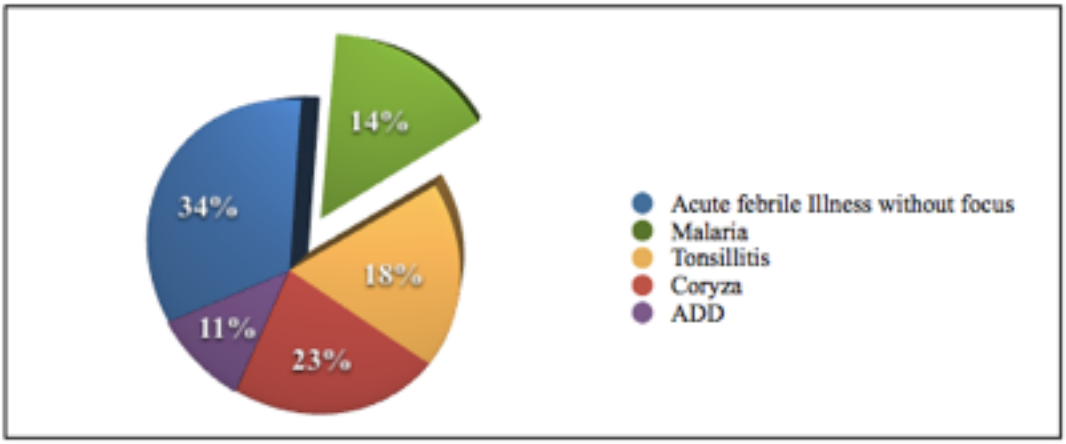


**Figure 9. Diagnosis with recurrent seizures**

In terms of the HIV status, 18 of the participants were either exposed or infected. The HIV status was determined by the information on the under-five card and rapid testing in admission ward. All the participants admitted during weekdays were tested on the admission ward. Those attended to on the weekends were missed due to absence of HIV counsellors on weekends. About 80% (245/306) of the participants were HIV negative, 2.3% (7/306) positive, 3.6% (11/306) exposed and 14% (43/306) were missed (Figure 10). Only 1.2% (2/164) of the patients with FS were HIV positive while 3.5% (5/142) of those without seizures were positive ($p$=0.13).

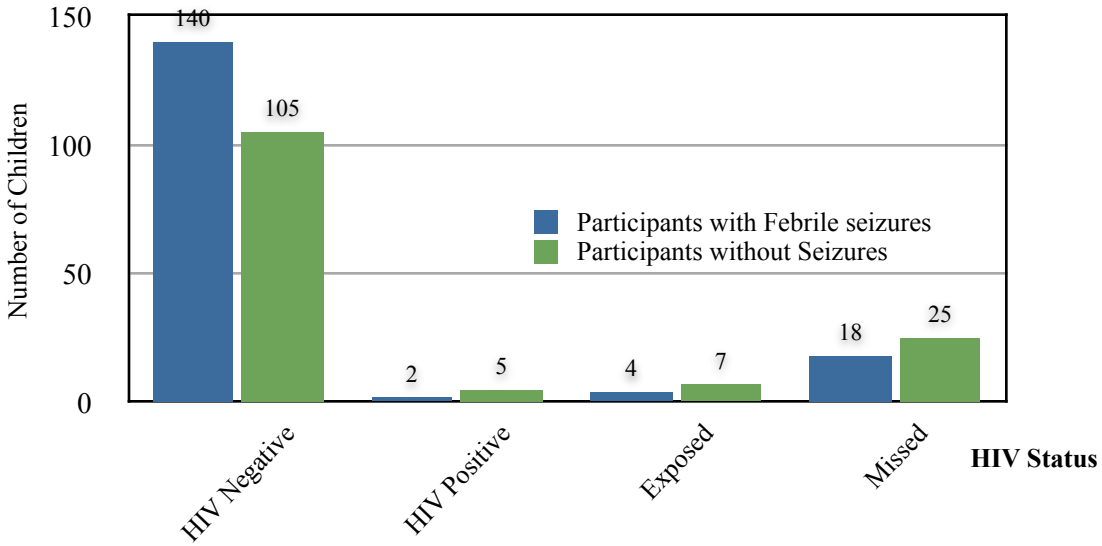


**Figure 10. HIV Status of Participants**

For the detection of HHV-6 DNA we used Subtype-specific, probe-based, real-time PCR (SSPBRT-PCR) at the UNZA-UCLMS laboratory. Plasma samples had DNA extracted using the QIAGEN QIAamp® DNA Mini Kit as per the manufacturer's instructions. Table 5 shows primer and probe pairs from Lou *et.al*, 2011 and cycling conditions used.

**Table 5 . Primers and probes for the detection of HHV-6**

| Primer or Probe | Sequence (5'-3') | Position |
|---|---|---|
| Forward primer | GGAGTGCCGTGGGTATTC | 2566-2584 |
| Reverse primer | CTAAGGTGAGCCAGATTCG | 2720-2702 |
| HHV6A probe | HEX-TGCAGCCATTTCTTTGGAAAGC-TMARA | 2691-2670 |
| HHV6B probe | FAM-TGCAGCCACCTCCTTGGAAAG-TMARA | 2691-2671 |

| Cycle | Cycle Point |
|---|---|
| Hold @ 94°c, 5 min 0 secs | |
| Cycling (55 repeats) | Step 1 @ 94°c, hold 15 secs |
| | Step 2 @ 60°c, hold 60 secs, acquiring to Cycling A([Green][1][1], [Yellow][2][2]) |

We did not detect any HHV-6 in serum collected from the 164 participants with febrile seizures. This includes the 25 participants with malaria and the two HIV positive participants with febrile seizures. Only 1 serum was positive for HHV-6B out of the 142 participants with an acute febrile illness without seizures.

# CHAPTER FIVE

## DISCUSSION

### 5.1. Clinical Characteristics of Children with FS

In this study, we analyzed a total of 306 children seen at the Department of Pediatrics and Child Health, UTH. Of these, 164 children had FS and 142 had acute febrile illnesses without seizures. All the study participants presented to the hospital within 3 days of a febrile illness. There were slightly more males with FS compared to females with a male:female ratio of 1.3:1 (Figure 1). Some studies have shown a male:female ratio of up to 2:1 but others have shown no significant difference in the incidence (Stafstrom *et al*., 2002). The male:female ratio for those without seizures was similar at 1.1:1. History of FS in a first degree relative was noted in 14% of the participants with FS compared to only 2% (3/174) among those without seizures. This was mainly history from one parent/ guardian who was nursing the patient at the time. In Western Europe, 24% of children with a first FS have a family history of FS while in non-West European children, only 10% have a family (Berg *et al*.,1992).

The age groups were similar in both the FS and febrile children without seizures (Figure 2) with most participants falling in the >18-36 months age bracket (48% [78/164] and 25% [35/142] respectively). The second highest age group was the 6-18 months with 25% (41/164) of children with seizures and 43% (61/142) without seizures falling in this age group. The age group >36-60 months comprised of 27% (45/164) of the participants with seizures and 32% (46/142) of those without seizures. This is in comparison with worldwide studies which have shown that the peak age of onset for FS is in the second year of life (Shinnar *et al*.,2003. AAP.,2008.). In our study, this was the age group with a statistically significant highest number of children for FS. Our study results therefore agreed with worldwide studies that have found the age of onset for FS to be in the second year of life.

Temperatures was recorded for the 306 children and ranged from 37.5-41$^{o}$C (Table 1). The average temperature of children with FS was 38.5$^{o}$C and that for children without

seizures was 38.7°C. There was no statistically significant difference in the average temperatures between the two groups. The average temperature for the participants with multiple seizures was very similar to those with only one seizure (38.6°C vs 38.5°C). The highest temperature recorded was 41°C, seen in a 36 month old male with malaria not associated with seizures. The average temperature for the patients with malaria was 38.7°C, which did not significantly differ from those without malaria. These findings were similar to that documented in literature. FS usually occurs at temperatures at or above 38°C (Johnston-*Nelson Textbook of Pediatrics*.18th edition). Seizures are known to occur even with a fever of 37.5°C. The children who have seizures at temperatures below 38°C have a higher risk of having recurrence of FS in future. The higher the peak temperature, the lower the risk of recurrence of FS in future febrile illnesses (Berg *et al*.,1997).

The main admission diagnoses associated with FS was acute febrile illness without focus, tonsillitis, coryza and malaria [Figure 3]. This finding agrees with what has been observed from studies in USA and India which had fever with undetermined origin and upper respiratory infection as the top two diagnoses (Kimia *et al*.,2010. Batra *et al*.,2011). Participants with the diagnosis of acute febrile illness without focus were suspected to have a viral infection based on the history and clinical evaluation. HHV-6 and other viruses have been known to be common causes of FS worldwide (Chung *et al*.,2007. Laina *et al*.,2010). Apart from the baseline FBC, malaria test, HIV test, HHV-6 DNA-PCR and sometimes urinalysis, no further investigation was carried out to find the exact etiology in these patients. This group remains an area of interest so as to know the etiological agents and if these predispose to multiple FS.

In terms of seizures, 95% were described as generalized tonic-clonic seizures while 5% as focal seizures (Figure 7). This is consistent with what is reported in literature (Wakae *et al*., 1990. Johnston-*Nelson Textbook of Pediatrics,* 18th edition ). Of these participants with seizures, 46% had simple FS while 54% had complex FS (Figure 6). Western studies noted that 32% of the cases of FS had at least one feature of complex FS (Berg *et al*,1996) compared to 42-71% found in studies done in SSA (Winkler *et al*.,2013. Storz *et al*.,2015). The higher number of participants with CFS in our study could possibly be attributed to inaccurate

duration of the seizure as reported by the caregivers. We tried to get the best estimation of the duration as witnessed by the caregivers but some may have recalled wrong durations in the panic that ensured as the child was convulsing. Recollection of multiple seizures was more reliable as the caregivers could easily recount any seizure repetitions and the postictal state. The other reason for the high incidence of CFS in our study could be due to the different etiological agents (mainly malaria) seen in this region as compared to the Western countries. This group (malaria) was one of the main contributors to the number of patients with multiple seizures and FSE. Malaria was however not significantly associated with FS. Malaria is known to be a common cause of seizures in SSA and these seizures are often associated with complex features (focal, prolonged and multiple seizures) (Idro *et al*.,2008. Sadarangani *et al*.,2008), hence it is expected that more children would present with CFS as compared to children with simple FS in the Western world. Children with exposure to malaria associated with complicated seizures have an increased propensity for epilepsy compared to children without these exposures (Carter *et al*.,2004).

Out of a total of 164 participants with FS, 13% had FSE (Figure 8 and 9). This represented 24% of the children with CFS. This is higher than with studies done from other countries which put the proportion of FSE among those with FS at 5-8% (Hesdorffer *et al*., 2011). One explanation for this could be the difference in etiological agents (specifically malaria) between the western world and SSA. Children with CFS (of which FSE is at the far end of this spectrum) have been noted to have an increased risk of eventually developing unprovoked seizures later on in life, with multiple episodes of FS being a good prognostic indicator for the development of subsequent epilepsy (Pavlidou *et al*.,2013. Berg *et al*., 1996. Annergers *et al*.,1987). The participants with CFS in our study may in future contribute to the observed high prevalence of epilepsy in SSA (Ngugi *et al*.,2013. Birbeck *et al*.,2004).

From our study, 52% of the participants with FSE had an acute febrile illness with no identifiable focus and the second diagnosis was malaria with 24%. It was not known what

the etiological agents could have been in patients with acute febrile illness but a viral origin was suspected.

### 5.2. Malaria and Febrile seizures

In our study, 13% of the children had malaria with 63% having seizures and 37% without seizures. There was however no statistically significant association between malaria and FS. There was also no significant difference between the number of males and females with seizures associated with malaria. Most of the participants with seizures observed in patients with malaria had CFS 56% compared to 44% with simple FS. These seizures in malaria were most likely due to acute symptomatic seizures rather than FS but it is difficult to clinically make a clear distinction between the two (Idro *et al*.,2005. Kariuki *et al*., 2011). Considering all other diagnoses associated with CFS, malaria contributed 16% (14/88) and 25% (3/12) of those with FSE had malaria.

Acute febrile illness without focus was significantly associated with FS. In addition to acute febrile illness without focus, coryza, tonsillitis, malaria and ADD were other diagnoses made in participants with multiple seizures with the frequency in that order (Figure 10). This is in line with published literature from rural Zambia that identified malaria as a major cause of febrile seizures and that it is associated with CFS (Birbeck., 2000. Chomba *et al*.,2008). Children with a febrile illness not associated with seizures were diagnosed to have coryza 27%, tonsillitis 17%, pneumonia 12% and ADD 10% as the top four diagnoses. Malaria in this group was sixth commonest diagnosis made.

### 5.3. HIV and Febrile seizures

The overall prevalence of HIV for all the study participants was 2.2% (Figure 5). Only 1.2% of the children with FS were HIV positive with one already on anti-retroviral therapy. There was thus no significant association between HIV and FS. The percentage of HIV positive children was also low for the children without seizures (3.5%). None of these participants were positive for HHV-6 by serum DNA.

Of the 164 children with FS, 85% were HIV negative. Most of these had mothers who were also HIV negative (97%) but a few were initially exposed but confirmed to be negative by DNA PCR or rapid test after 18 months. This could be attributed to the one or more prevention of mother to child transmission strategies that these exposed children had received. The rest of the HIV exposed infants were either awaiting results for the DNA PCR done at the local clinic or were discovered to be HIV exposed at the time of admission for the febrile seizure. The children who were missed for HIV testing were those admitted over the weekend when the HIV counsellors and test kits were unavailable. None of the participants positive for HIV were positive for HHV-6 by serum DNA.

### 5.4. Prevalence of HHV-6

In this study, the prevalence of HHV-6 in children with FS and FSE was found to be 0%. This was based on DNA PCR analysis of serum taken from the 164 participants with FS and FSE. Only 1 participant's serum was found to be HHV-6B positive among the 142 children with febrile illness and no associated seizure. This was an 11 month old male infant who had a coryzal illness associated with a fever of 38.5$^{o}$C.

This finding is very different from world literature and from the data obtained in Zambia by Kasolo *et al* in 1997 when they analyzed whole blood taken from 53 infants who had acute febrile illnesses. Kasolo *et al* were able to demonstrate that 44% of the HHV-6 isolates were HHV-6A. This study used whole blood to detect HHV-6 DNA whereas we used serum in our study. One of the main reasons we used serum was to avoid detection of latent HHV-6 infection in peripheral blood mononuclear cells (PBMC) (Carseta *et al.*, 1994). After primary infection, the HHV-6 virus may remain latent in PBMC and the central nervous system. Some patients may also have detectable HHV-6 DNA secondary to chromosomally integrated HHV-6 (ciHHV-6) which may be passed on from an infected pregnant woman to her fetus (Gravel *et al.*,2013). The best way to detect an active or primary infection is therefore through detection of serum viral DNA.

The second study by Bates *et al* found an HHV-6 sera DNA prevalence of 15% in infants aged 6 months and 19% at 18 months, with 125 of the children being seen at both time points. This was a prospective study that examined sera from healthy children at two time points, namely 6 and 18 months. One explanation as to the difference in the results with our findings could be that our age group went far beyond 18 months with only 31% being 18 months old or less (Figure 2). From literature, most of the children would have already been exposed to HHV-6 by 24 months and nearly 100% at 36 months (Zerr *et al.*,2005). The chances of having an active infection after the age of 24 months is therefore drastically reduced. This does not however explain the very low result of this study and an undetectable error in the laboratory is highly suspected. Another plausible explanation could be that the above study could have been carried out during an HHV-6 outbreak.

Of the patients with malaria, none were detected to have an active HHV-6 infection by serum DNA PCR. All the patients with seizures associated with malaria were treated with artesunate, a drug that has shown some efficacy against HHV-6 (Hakacova *et al.*,2013. Efferth *et al*.,2008). Some of the participants with malaria were recruited in the admission ward where at least one dose of artesunate was given. We did not separately record those who did not receive the drug from those who had at the time of blood collection. Those who received artesunate may possibly have had a reduction in HHV-6 viremia if it was present before treatment, hence reducing the possibility of detection.

It is likely that a good number of children could have been exposed to HHV-6 as shown be the 30% prevalence in whole blood analysis (Kasolo *et al*.,1997). The possibility of ciHHV-6 cannot also be ruled out (Gravel *et al*.,2013). Our results on the prevalence of HHV-6 differ significantly with world literature and the local studies. The possibility of laboratory error cannot be completely ruled out. Repeat testing of the samples is advisable and is currently underway.

# CHAPTER SIX

## CONCLUSION

### 6.1.Summary of Results

In this study, the clinical characteristics of children with FS and FSE was found to be similar to those described in worldwide studies and in malaria endemic regions. The peak age for the FS was 18-36 months. There were more children with FS than those without seizures (2:1) in the 18-36 months age group, compared to the other age groups. There were no significant differences in sex distribution as well as temperature level between the two groups. A family history of FS was noted in 14% of the participants with FS compared to only 2% among those without seizures.

Acute febrile illness without focus was the number one diagnosis associated with FS. This was followed by tonsillitis, coryza and malaria in that order. The percentage of children with CFS was 54% and those with FSE were 13%. CFS were noted in 56% of the seizures associated with malaria of which 36% met the criteria for FSE. Malaria was found in 11% of children with febrile illness and 15% of all cases with FS but this was not statistically significant.

The HIV prevalence was 2.2% with no significant differences between children with FS and those without seizures.

The prevalence of HHV-6A/6B in children with FS and FSE was 0% (0/164) and 0.7%(1/142) in children with febrile illnesses without seizures. The result differ significantly with world literature and the local studies, therefore a repeat testing is advisable.

### 6.2. Recommendations

From this study, the most common diagnosis associated with febrile seizures was acute febrile illness with unknown focus of infection. We therefore recommend that more studies be done to identify associations and causes of fever in children presenting with febrile seizures at UTH. Other viruses like Adenovirus, Cytomegalovirus and Enteroviruses would make interesting candidates.

We also recommend follow up of the participants with CFS, and in particular FSE, as these have a higher risk of developing subsequent epilepsy.

Repeat studies for HHV-6 together with IgG and IgM is advisable. Cerebral spinal fluid studies may possibly shed more light on the actual picture of the prevalence of HHV-6 and other viruses in children with FS.

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## APPENDICES

**Appendix i : INFORMATION SHEET**

# UNIVERSITY OF ZAMBIA

UNIVERSITY TEACHING HOSPITAL, PEDIATRICS DEPARTMENT

**STUDY TITLE:**

**CLINICAL PROFILE OF CHILDREN PRESENTING WITH FEBRILE SEIZURES AND FEBRILE STATUS EPILEPTICUS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA**

Principal Researcher: **Dr Kanta Chandwe**

Supervisors: Dr. Ornella Ciccone and Dr. Evans Mpabalwani

**INTRODUCTION**

I am Dr. Kanta Chandwe, I work in the Pediatrics and Child Health Department at the University Teaching Hospital (UTH). I am pursing a masters degree in Pediatrics and Child Health. This study is being conducted as part of the degree program. My main source of funding for this study is coming from The University of Zambia-University College London Medical School (UNZA-UCLMS) Research and Training Program.

**PURPOSE OF STUDY**

The purpose of the study is to find out how many children who have fever with or without convulsions are infected with Human Herpesvirus-6 or 7. These viruses are known to cause fever which is complicated by convulsions in children worldwide. We however, do not know if this is the same case in our patients in Zambia. The study is looking at children between the ages of 6 month to 6 years. The information from the study will help in future research which may look into treatment of children with fever

and convulsions caused by or associated with Human Herpesvirus-6/7. This may also possibly help prevent development of epilepsy in children who have convulsion associated with Human herpesvirus-6/7.

**VOLUNTARY PARTICIPATION**

The decision to allow your child participate in the study is voluntary. Your decision not to participate will not negatively affect the level of medical care for your child.

**WITHDRAWAL FROM STUDY**

You can decide to participate now, but later withdraw your consent without losing the benefit of the medical care your child is entitled to.

If you decide to withdraw your child's participation in the study, kindly notify Dr. Kanta Chandwe at +260977-806-816, Email kantachandwe@yahoo.com

**PROCEDURE**

Once you agree to have your child take part in this study, you will sign this consent form to show your willingness to take part. Following this, you will be asked some questions from a questionnaire about your child's illness. The answers to the questions will be entered on the form. Your childs name will not be entered on the questionnaire.

Your child will be examined and his/her weight, height, temperature and head circumference measured.

Blood collection to determine whether your child is infected with the Human Herpesvirus-6 will be done at the same time as that for routine full blood count and MPS/ RDT. The total amount of blood to be collected will be approximately 3ml ( 1ml for detection of HHV-6/7, 2ml for routine full blood count analysis). This will be done to avoid causing further pain from multiple needle pricks. The blood will be sent to the laboratory to be analyzed and the results will be communicated to you in person if the child is still admitted or by phone if discharged.

**RISKS**

The main risk is that of pain from the needle prick. It will be done under aseptic (clean) conditions by a doctor so as to minimize the risk of infection.

**BENEFITS OF PARTICIPATION**

The results for Human Herpesvirus-6A/6B/7 will not alter the management of your child. This is because there is currently no laid down protocol for treating HHV-6. However, Patients found to have HHV-6 and convulsions will be followed up in our neurology clinic as these are at risk of developing subsequent epilepsy. This will allow your child to receive an early diagnosis and treatment in case of epilepsy, which can prevent further neurological complications

**PAYMENT FOR PARTICIPATION**

You will not be paid in any form for your participation in this study. You will not be required to pay anything in order to take part in this study.

**CONFIDENTIALITY**

The information you give will not be shared with anyone apart from the researcher, supervisors and University of Zambia examination board. Your name will not be indicated on the forms used to collect information. You will instead be identified by a code. You will not be personally identified in the write up of this research or in future publications.

**QUESTIONS ABOUT THE RESEARCH**

If you have any questions about the research, please contact the researcher, Dr. Kanta Chandwe on +260977-806-816 or email kantachandwe@yahoo.com . You may also contact the ERES Converge IRB chairperson for any concerns at 33 Joseph Mwilwa Road, Rhodes park, Lusaka. Telephone +260-955-155-633, +260-955-155-634, +260-966-765-503 or email eresconverge@yahoo.co.uk

**Appendix ii: CONSENT FORM**

**CLINICAL PROFILE OF CHILDREN PRESENTING WITH FEBRILE SEIZURES AND FEBRILE STATUS EPILEPTICUS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA**

**Principal Researcher: Dr Kanta Chandwe**

Supervisors: Dr. Ornella Ciccone and Dr. Evans Mpabalwani

I .....consent to have my child take part in this study conducted by Dr. Kanta Chandwe. The nature of the study and what is involved have been clearly explained to me and I understand them. I am not waiving any of my legal rights by signing this form. My signature/thumb print are indicated below as an indication of my consent.

Signature/Thumb: .....

Date (D/M/Y): ...../...../.....

**PERSON OBTAINING CONSENT**: I .....have explained this research study to the participant. I am available to answer any questions now or in the future regarding the study and the subject's rights.

Signature of Investigators

Signature:.....

Date (D/M/Y): ...../...../.....

For any questions about the research, please contact the researcher, Dr. Kanta Chandwe on +260977-806-816 or email kantachandwe@yahoo.com . You may also contact the ERES Converge IRB chairperson for any concerns at 33 Joseph Mwilwa Road, Rhodes park, Lusaka. Telephone +260-955-155-633, +260-955-155-634, +260-966-765-503 or email eresconverge@yahoo.co.uk

**Appendix iii : DATA COLLECTION FORM**

PARTICIPANT CODE { } .

Date : ...../...../.....

**1.0 SOCIO-DEMOGRAPHIC DATA**

1.1 Sex: Male { } Female { }

1.2 Age ( at last birthday): .....

1.3 Residential Address: .....

1.4 Parents/ Guardian Education Level: None { } Primary { } Junior Secondary { } Senior Secondary { }.

Occupation of Parents/Guardians:.....

Phone Number: .....

**2.0 CURRENT MEDICAL HISTORY**

2.1 Presenting complaints : .....

2.2 Duration of Current illness/Symptoms : .....

2.3 Seizures Type : Focal { } Generalized { }

Description of seizure.....

Duration Of Seizure : <5min { } 5-15min { } 16- 30 min { } >30min { }

Seizure recurrence within 24hr of first episode: Yes{ } No { }.

If yes, number and type of seizures.....

**3.0 PAST MEDICAL HISTORY**

3.1 Birth history: Term { } Pre-Term { } Birth weight: .....Kg

Congenital Anomalies noted: Yes { } No { }

If yes, specify .....

Birth Related complications: Yes { } No { }

If yes, Specify .....

3.3 Developmental milestones attained :

Social smile : ..... Sitting : .....

Crawling : ..... Standing : .....

Walking : ..... First words : .....

3.4 History of Convulsions/ Epilepsy in Family: Yes { } No { }

3.5.Drug History.....

3.6. Immunization History/date

OPV 0 ..... BCG .....

OPV 1 ..... DPT-HepB-Hib 1 .....

OPV 2 ..... DPT-HepB-Hib 2 .....

OPV 3 ..... DPT-HepB-Hib 3 .....

OPV 4 ..... MEASLES .....

PCV 1 ..... ROTA 1 .....

PCV 2 ..... ROTA 2 .....

**4.0 PHYSICAL EXAMINATION**

4.1 Weight: .....Kg Height/Length.....cm Head Circumference: .....cm

Temperature: on admission/examination.....$^{o}$C Home/Referral center .....$^{o}$C

Pallor{ } Jaundice{ } Cyanosis { }

Ear/Nose/throat:.....

4.2 Respiratory System: Respiratory rate ...../min Lung air entry.....

4.3 **Cardiovascular system:**

Radial/Femoral pulses.....

Heart sounds.....

Heart rate...../min

Capillary refill time: <2sec { } 2-3sec{ } >3sec { }

4.4 **Abdomen.**

Tender { } Non-tender{ }

Bowel sounds: Normal{ } Reduced{ } Increased{ } absent{ }

Organomegally: Yes{ } No{ }

If yes, specify: .....

4.5 **Central nervous system**

Level of consciousness (AVPU) .....

Meningeal signs : Yes { } No{ } .If yes, specify.....

Focal Neurological Deficit: Yes{ } No{ } .If yes,

specify.....

.....