UNIVERSITY OF NAIROBI

PROFILE OF CEREBROSPINAL FLUID FINDINGS IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH FEVER AND CONVULSIONS AT KENYATTA NATIONAL HOSPITAL

A Dissertation Submitted in Partial Fulfillment for the Degree of Master of Medicine in Paediatrics and Child Health at the University of Nairobi

DR. JEMIMAH K. MUGO

H58/74528/2014

2017

DECLARATION

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

Signed.....Date.....

Dr. Jemimah K. Mugo (M.B.Ch. B)

Department of Paediatrics and Child Health, University of Nairobi

This dissertation proposal has been presented with our full approval as supervisors:

Signed.....Date.....

Professor Francis Ephraim Onyango (M.B.Ch. B, M.Ed. M.P.H., FCP, F. Clin Epid, CTM, CLM)

Associate Professor,

Department of Paediatrics and Child Health, University of Nairobi

Signed.....

Date.....

Dr. Jacqueline Oliwa (M.B.Ch. B, M. Med, M.Sc. Epidem)

Lecturer,

Department of Paediatrics and Child Health, University of Nairobi

Signed.....

Date.....

Dr. Marianne Mureithi (BSc, Ph.D.)

Lecturer,

Department of Medical Microbiology, University of Nairobi

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to:

The almighty God for the strength to carry out this study.

The lecturers and my supervisors for their guidance and support.

My parents and siblings Muthoni and Andrew for their endless encouragement.

My special friends especially Lorraine, Chege and others for their prayers and practical support.

My statisticians Brian Khasimwa and Philip Ayieko.

The registrars of the Department of Paediatrics and Child Health

The staff at the Paediatrics Emergency Unit and the paediatrics wards at KNH.

The entire staff of the Lancet Laboratory.

All guardians and the children who participated in the study.

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LISTOFABBREVIATIONS

ABM	Acute Bacterial Meningitis
BM	Bacterial meningitis
CNS	Central Nervous System
CSF	Cerebrospinal fluid
g/dl	grams per deciliter
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
KNH	Kenyatta National Hospital
LP	Lumbar puncture
mm^3	millimeter cubed
mmol/L	millimole per litre
N.meningitidis	*Neisseria meningitidis*
S.pneumoniae	*Streptococcus pneumoniae*
PCV	Pneumococcal conjugate vaccine
UON	University of Nairobi
WBC	White blood cell
WHO	World Health Organization

OPERATIONAL TERMS

Fever: Recorded axillary temperature of 38.0ºC or higher.

Convulsion: Sudden onset of involuntary contractions of muscle groups of the upper or lower limbs or both. This may be accompanied with eye rolling, drooling, urine or stool incontinence or loss of consciousness.

Bacterial Meningitis: Acute onset of fever (recorded axillary temperature of 38.0 °C or higher), headache and one of the following signs: altered consciousness, convulsions, neck stiffness or bulging fontanelle.

Febrile seizure: A convulsion that occurs in a child between the age of 6 months and 5 years with a temperature of 38º Celsius or higher and there is absence of neck stiffness or altered consciousness after ruling out other causes of convulsion.

Normal cerebrospinal fluid: CSF white cell count of less than 5/mm^3, CSF glucose of >2.7mmol/L, CSF protein of 20-45mg/dl, absent organisms on gram stain.

Abnormal cerebrospinal fluid: CSF results that have values outside the normal CSF values.

Cerebrospinal fluid: A clear fluid that fills and surrounds the brain and spinal canal.

Lumbar puncture: A procedure that is performed whereby cerebrospinal fluid (CSF) is accessed from the spinal canal for laboratory analysis.

Epilepsy: History of two or more unprovoked seizures in the past

ABSTRACT

Background:

Fever and convulsions in children can be caused by bacterial meningitis, encephalitis, severe malaria, febrile convulsions and other central nervous system pathologies.

Performance of a lumbar puncture is important in order to differentiate the various clinical causes of fever, convulsions and altered consciousness.

There is need to find out if there has been any change in the pathogens causing meningitis which is a leading cause of fever and convulsions in children in Kenyatta National Hospital (KNH) since the introduction of the *Haemophilus influenzae* type b (Hib) and pneumococcal vaccine. Information on current etiology of meningitis and antibiotic sensitivity of bacteriological organisms will go a long way in informing the health care workers on judicious use of antibiotics and general management of the child presenting with fever and convulsions.

Methods

This was a cross sectional study carried out at the Paediatric Emergency Unit and general paediatric wards of Kenyatta National Hospital from September 2016 to April 2017. The study population was children between the ages of 3 months to 12 years who presented with fever and convulsions at KNH. Children whose parents consented to have a lumbar puncture were included in the study. The following served as exclusion criteria; those with signs of raised intracranial pressure, those who needed cardiopulmonary resuscitation, a known history of epilepsy, head injury, cerebrovascular accident, brain tumour, coagulopathy, hydrocephalus and those who had a lumbar puncture performed at the referral facility. The following study procedures were followed. Children with fever and convulsions were recruited into the study and informed consent was sought from the care givers. Clinical history and physical examination was done and the findings were included in a questionnaire. The child had a lumbar puncture performed aseptically and CSF was ferried to the laboratory. A copy of the CSF results was put in the patients' files. Data was entered and analyzed using SPSS.

Results:

Eighty-four children were enrolled into the study. An overall 69(82.1%) patients had normal CSF while 15(17.9%) patients had abnormal CSF findings. Five (5.9%) CSF

samples had organisms identified either on gram stain or culture. Three (3.6%) CSF samples had positive growth on culture. The organisms isolated on CSF culture were *Haemophilus influenzae, Enterococcus and Escherichia coli* and were all sensitive to meropenem. Fever for more than 24 hours, neck stiffness, irritability, lethargy and positive kerning sign were associated with abnormal CSF results. Multivariable logistic regression model showed that the odds of having abnormal CSF was eight fold higher (OR = 8, 95% CI 1.6-40.62) among children who had neck stiffness compared to those who did not have this sign.

Conclusions:

High index of suspicion for abnormal CSF is needed in children less than 2 years presenting with fever and convulsions especially if they have a stiff neck. Carrying out a lumbar puncture is important as CNS infections may present in a subtle manner

1. BACKGROUND

Fever and convulsions in children can be caused by a number of conditions. Bacterial meningitis, encephalitis and severe malaria are common causes of fever and convulsions in children especially in developing countries.(1) These three diseases are serious and cause considerable morbidity and mortality. Febrile convulsions also cause fever and convulsions in children and occur between the age of 6 months and 5 years when they have a temperature of 38º Celsius and higher. It is a diagnosis of exclusion occurring in the absence of intracranial infection, metabolic disturbance or history of non-febrile seizures. They are classified into simple and complex febrile seizures whereby a simple febrile seizure is one that is generalized, tonic clonic in nature, occurs once within 24 hours and lasts less than 15 minutes. A complex febrile seizure's duration is more than 15 minutes, is focal in nature and recurs within a 24-hour period. (1) Performance of a lumbar puncture (LP) is important in order to differentiate the various potentially fatal causes of fever, convulsions and altered consciousness from the more innocuous febrile convulsions. Correct diagnosis ensures prompt treatment.(2)

Kneen et al (3) in a study in the United Kingdom, it was reported that out of 52 children with suspected central nervous system (CNS) infection, only 25(53%) children had a lumbar puncture done. In three quarters of those patients, a lumbar puncture helped in the medical management by confirming or ruling out meningitis. Many children who should need lumbar punctures to be performed are not getting this test.

A Kenyan study by Njuguna et al in 2006 (4) reported that of 170 children with clinical presentation of altered consciousness, a lumbar puncture was done in only 56(32.9%). Further -more, only twenty-three of the 44 children (52.3%) with a final diagnosis of meningitis ever had a lumbar performed indicating that nearly half of children had a diagnosis of meningitis based solely on clinical suspicion. There is a possibility that some of these children did not have bacterial meningitis. Since fever and convulsions are a common presentation in sick children, the purpose of this study is to describe the profile of cerebrospinal fluid (CSF) findings in children aged 3 months to 12 years presenting with the fever and convulsions at Kenyatta National Hospital (KNH). It is also important

to find out if there has been any change in the organisms that cause bacterial meningitis in children since the introduction of *Haemophilus influenzae* (Hib) and pneumococcal vaccine in Kenya in 2001 and 2010 respectively. Previous studies on CSF findings in children at KNH were carried out more than seven years ago.(5)

2. LITERATURE REVIEW

2.1 Definitions

The World Health Organization (W.H.O) defines paediatric bacterial meningitis as characterized by acute onset of fever (usually 38.0 °C axillary or > 38.5 °C rectal), headache and one of the following signs: altered consciousness, neck stiffness, or other meningeal signs.(6)

The definition of febrile convulsions is a convulsion in a child aged 6 months to 5 years accompanied by fever of 38º C or higher and occurs in the absence of intracranial infection, metabolic disturbance or history of non-febrile seizures.(1)
The definition of meningoencephalitis is an acute inflammatory process involving the meninges and brain tissue to a variable degree,.(7)

In severe malaria, one presents with complications of malaria such as severe anaemia, hypoglycemia, acute renal failure, circulatory shock, acidosis, convulsions and others. The term cerebral malaria is restricted to the syndrome in which altered consciousness, associated with a malarial infection, could not be attributed to convulsions, hypoglycaemia, sedative drugs alone or to a non-malarial cause.(8)

2.2 Organisms that may cause fever and convulsions in children

The main bacterial organisms that cause bacterial meningitis in children beyond the neonatal age group are *Streptococcus pneumoniae (S. pneumoniae), Neisseria meningitidis (N. meningitidis)* and *Haemophilus influenzae* type b (Hib). The global incidence of pneumococcal meningitis in the year 2000 in children less than 5 years was 17 per 100000. (9)The global incidence of Hib meningitis in the year 2000 in children less than 5 years was 31 per 100000.(10)A systematic review in 2001 by Peltola on the

burden of meningitis in African children reported that pneumococcus was the most common agent in 20 of 50(40%) reports, *H.influenzae* in 13 (26%) reports and meningococcus in 10(20%).(11) *Salmonella* was mentioned as another causative agent of bacterial meningitis. However, the global incidence of bacterial meningitis in young children has significantly decreased since the introduction of vaccines against Hib and *(S.pneumoniae)*.(12) Hib and pneumococcal vaccines were introduced to the Kenyan population in 2001 and 2010 respectively.(13)

Enterovirus is the most common cause of viral meningoencephalitis in children. Other viruses that cause meningoencephalitis are herpes simplex virus, arboviruses, cytomegalovirus, varicella zoster virus, HIV, Epstein-Barr virus, mumps, influenza, parainfluenza, rubella virus, rabies amongst others. Viral meningoencephalitis may also result from live virus vaccinations against rubella, polio, measles or mumps.(7) The organisms causing viral meningoencephalitis in a study in 87 Indian children were enterovirus in 71(42%),measles (21%), herpes simplex virus(10.5%), varicella zoster virus (15.8%) and mumps(10.5%).(14)

2.3 Epidemiology of diseases that cause fever and convulsions in children

Bacterial meningitis is a serious condition that causes high morbidity and mortality in children. A 2013 systematic review by Luksic et al (15) on estimating global and regional morbidity from acute bacterial meningitis in children found that globally, the median incidence of bacterial meningitis was 34 per 100000 child-years. Regionally, the highest median incidence of bacterial meningitis was reported in Africa at 143.6 per 100000 child years. Globally, bacterial meningitis causes 2% of all childhood deaths. The median case fatality rate of 31.3% is highest in the African region.

Factors such as age, type of virus, geographical location, animal exposure, season and climate affect the epidemiology of encephalitis. In a Finland study, the annual incidence of presumed viral meningoencephalitis was 219 per 100 000 in infants under 1 year and 27.8 per 100 000 in children below fourteen years.(16)

Globally, as reported by the W.H.O, 214 million cases of malaria and 438000 deaths were noted. Sub Saharan African countries mainly account for 80% of malaria cases and about 78% of the deaths globally. Children less than 5 years of age are at high risk of infection and death. It was reported that more than 70% of all malaria deaths occur in children less than 5 years of age.(17)

The cumulative incidence of febrile seizures in China is 1%, 5-10% in India, 14% in Guam and 8.8% in Japan. The incidence of febrile convulsions is not specifically reported in developing countries.(18)

2.4 Clinical presentation in children with fever and convulsions

The symptoms of bacterial meningitis in children beyond the neonatal period include fever, vomiting, poor feeding, lethargy, irritability, headache and convulsions. Signs of bacterial meningitis in children include presence of a bulging fontanelle in infants, photophobia, neck stiffness and reduced consciousness. However, symptoms and signs of meningitis may be minimal or totally absent in children less than 18 months of age. (2)

The signs and symptoms of meningoencephalitis may be preceded by non-specific symptoms of febrile illness. Headache, convulsions, focal weakness, vomiting, retrobulbar pain, neck pain, back pain, photophobia, bizarre movements, hallucinations and stupor are some of the symptoms reported to occur in meningoencephalitis. The physical findings of viral meningoencephalitis include alteration of consciousness, dysphasia, ataxia, hemiparesis, cranial nerve deficits amongst others(7)

Children with severe malaria may present with fever, pallor, respiratory distress, multiple seizures, prostration, jaundice, confusion, reduced urine output amongst other signs. A study by Idro et al (19) in Kenya in 2004 reported that out of 900 children, malaria was the primary diagnosis in 50% of the patients admitted with acute seizures. Those children also had higher seizure frequency and some were reported to have status epilepticus.

A prospective study by Berkley et al (20) in Kenya in 1999 studied 905 children who underwent a lumbar puncture. Presence of neck stiffness and having multiple seizures was strongly associated with laboratory evidence of acute bacterial meningitis. Thirty of

76 children (40%) with neck stiffness on admission had proven or probable acute bacterial meningitis compared with 41 of 829 (5%) children without neck stiffness (odds ratio 12·5[95% CI 6·9–22·8]).

A prospective study was done in 2003 by Farag et al (21) in Egypt on the epidemiologic characteristics and clinical indices affecting the prognostic profile of children with meningitis. Of 310 children aged 3 months to 15 years, 202(65.2%) had bacterial meningitis from both clinical and laboratory findings. Children older than 1 year presented with high fever, vomiting and seizures. Infants mostly presented with refusal to feed and irritability. 108(34.8%) of the children had aseptic meningitis. This study mentioned some socio demographic factors common in those found to have meningitis (bacterial and aseptic) as those coming from a lower socioeconomic class, overcrowding and exposure to more than two smokers at home. There was no clear information about the vaccination status of these children.

Berkeley J et al (22) in another prospective study carried out in Kenya in 2004 reported that the greatest discriminatory value for bacterial meningitis was more than one feature of a bulging fontanelle, cyanosis, partial seizures, neck stiffness , impaired consciousness and seizures outside the febrile convulsions age range (specificity:80%,sensitivity: 79%).
In a retrospective study by Herbert et al in 2004 (23) on indications of lumbar punctures and CSF results in paediatric wards of 2 hospitals in Tanzania and Kenya, the main physical findings in the 607 children who had a lumbar puncture were convulsions, neck stiffness and prostration.

A prospective study by Gichina et al (5) in 2009 in Kenya reported that among 163 children aged between 2 months and 12 years presenting with suspected meningitis or encephalitis,17 (10.4%)had herpes simplex encephalitis. 10(58.8%) children with herpes simplex encephalitis were less than one year of age. The key symptoms in these children were vomiting, seizures and headaches. The key physical findings in these children were irritability, reduced consciousness, photophobia, neck stiffness and bulging fontanelle in those less than 18 months of age.

A systematic review published by Curtis et al (24) in 2010 on the clinical features of bacterial meningitis found that reported history of the following increased the likelihood of bacterial meningitis; bulging fontanelle (likelihood ratio of 8 [95%CI:2.4-26], neck stiffness (likelihood ratio of 7.70 [95% CI:3.2–19]), seizures outside febrile-convulsion age range (likelihood ratio of 4.40 [95% CI:3.0–6.4]), and reduced feeds (likelihood ratio of 2.00 [95% CI:1.2–3.4]). On physical examination; presence of neck stiffness (likelihood ratio of 4.00 [95% CI:2.6–6.3]), Kerning sign (likelihood ratio of 3.50 [95% CI:2.1–5.7]), bulging fontanelle (likelihood ratio of 3.50 [95% CI 2.0–6.0]), fever >40 and Brudzinski sign all raised the probability of meningitis.

A 3-year retrospective review done from 2011-2013 by Kuti et al (25) in Nigeria among 81 children aged 1 month to 15 years reported that children with bacterial meningitis over 5 years of age mostly presented with vomiting and neck stiffness. Irritability was a common presentation in those under 5 years of age. 61(75.3%) children presented with seizures.

2.5 Diagnosis

A lumbar puncture (LP) is an important procedure that should be done in children who present with fever, convulsions and/or altered consciousness. Analysis of cerebrospinal fluid (CSF) is done to confirm a diagnosis of acute bacterial meningitis.(26)

According to the W.H.O. laboratory criteria for diagnosis of bacterial meningitis should be confirmed by the three methods listed below.(6)

- Culture method: isolation of a bacterial pathogen from a normally sterile clinical specimen such as blood or CSF.
- Antigen detection methods: identification of a bacterial antigen in normally sterile fluids (i.e. blood or CSF) by such methods as counter immune electrophoresis or latex agglutination.
- Gram stain results

The normal CSF profile is shown on Table 1. According to the Kenyan basic paediatric protocols, an LP in children over the age of 60 days should be carried out in those with

fever and at least one of these features; stiff neck, bulging fontanelle, convulsions if age less than 6 months or more than 6 years, focal fits and reduced consciousness.(27) Those above the age of 60 days with fever and any convulsion need an LP if their mental state is not completely normal. Contraindications of an LP are anisocoria (unequal pupils), signs of raised intracranial pressure such as bradycardia and hypertension with irregular breathing or 6^{th} or 3rd cranial nerve palsy with reduced consciousness, cardiopulmonary compromise requiring resuscitation, skin infection at the lower back, focal neurological signs such as paralysis of any limb. Relative contraindications of an LP include thrombocytopenia and coagulopathy.

Clinicians use clinical signs and abnormal CSF findings as shown on Table 1 to make a diagnosis of acute bacterial meningitis. In a retrospective study, Nigrovic et al (28)found out that antibiotic pretreatment (72 hours within performance of an LP), did not affect CSF WBC count or CSF absolute neutrophil count but was associated with lower CSF protein levels, higher CSF glucose and a lower rate of culture positivity. Despite negative CSF cultures, a diagnosis of bacterial meningitis can still be made presumptively. (26)
Performance of a lumbar puncture may carry some risks. Rennick G et al(29) reported that 19(4.3%) of 445 children suspected to have bacterial meningitis developed complications of cerebral herniation after lumbar puncture. These children had focal neurological signs, decerebrate or decorticate posturing or were unresponsive to pain. Cellulitis, furunculosis or epidural abscesses are other rare occurrences after lumbar puncture. (30) Ebinger F et al(31) reported post lumbar puncture headache in 27% and back ache in 40% of children who had undergone lumbar punctures.

Normal CSF should be clear. CSF from a patient with acute bacterial meningitis will have increased white cells and other deranged biochemical parameters as shown in Table 1.

Table 1: Features of normal CSF and CSF in bacterial and viral meningitis

Test	**Normal CSF**	**CSF in acute bacterial meningitis**	**CSF in viral meningitis/meningoencephalits**
Colour	Colourless	Turbid	Colourless
Pressure	50-80mmH_2O	100-300mmH_2O	Normal or slight elevation(80-150mmHg)
White blood cell count	0-5WBC /mm^3	100-10000 or more/mm^3	Rarely more than 1000/mm^3
Absolute neutrophil count	<1/mm^3	Raised	Lymphocytosis or monocytosis
Protein(mg/dl)	20-45mg/dl	100-500 mg/dl	50-200mg/dl
Glucose(mmol/L)	>2.7mmol/L(60% of blood glucose level)	<2.2mmol/L(<50% of blood glucose)	Generally >2.7mmol/L(60% of blood glucose level)
Gram stain	Negative	Organisms seen	Negative
Culture	Negative	Organisms seen	Negative

From Kliegman, Stanton:*Nelson Textbook of Paediatrics,19th edition*,Philadelphia, 2011,Elsevier pg 2088 Table 595-1

Cerebrospinal fluid can be sent for Polymerase Chain Reaction (PCR) tests when viral meningoencephalitis is suspected. Specificity of above 95% is reported for enterovirus, Epstein Barr virus, herpes viruses, Varicella Zoster Virus, HIV, rabies virus and herpes simplex virus 1 and 2. Sensitivity of above 95% is reported for enterovirus, Epstein Barr virus, rabies virus, human herpes virus 6, herpes simplex virus 1 and 2.(32)

Peripheral blood films stained by Wright, Field or Giemsa methods are used in diagnosis of malaria. After a film is stained, it is visualized under a microscope. Thick films are used to check on parasitemia whereas thin films may be used to assess the staging of malaria parasite development. Malaria rapid diagnostic tests are immunochromatographic

tests that identify either malaria antigens (commonly the parasite enzyme Plasmodium lactate dehydrogenase or Plasmodium falciparum histidine-rich-protein 2) (8)

Neuroimaging is important in a child whose diagnosis may be complex. Head CT scan or MRI are the main modalities of neuroimaging used to assess brain pathologies. The main indication of head CT scan in meningitis is when the diagnosis is uncertain, if there are signs of raised intracranial pressure or if other causes of meningism are suspected for instance brain abscess. (2) Neuroimaging in encephalitis may show swelling of the brain parenchyma or focal findings especially involving the temporal lobes in Herpes simplex encephalitis (26)

A retrospective study by Kneen et al (3) in the United Kingdom reported that out of 415 case records of children, 52 (12.5%) had suspected CNS infection. These children had a fever and at least one of the following clinical signs; photophobia, bulging fontanelle, neck stiffness, irritability, headache, convulsions, reduced level of consciousness or focal neurological signs. LP was done in only 25 (53%) patients. CSF biochemistry was not reported in the study. CSF was abnormal in seven (25%) patients. *N. meningitidis* was cultured in the CSF of 2 patients. *Escherichia coli* was cultured in 1 patient's CSF. 4 patients had CSF pleocytosis but no growth on culture. It was reported that a CSF analysis gave additional clinical information (diagnosis or exclusion of bacterial meningitis) in 18(72%) of the 25 patients it was performed on. The study concluded that many children who need a lumbar puncture for proper diagnosis do not get one.

In a prospective study by Berkley et al (20) in Kenya, LPs were performed in children with any features of impaired consciousness, a history of seizures and any clinical suggestion of meningism. 45(5%) children were proven to have bacterial meningitis. 37(4%) cases had a pathological organism isolated from the CSF. 17(46%) cases with *S. pneumoniae*,14(37.8%) cases with *H. influenzae*, 3(8.1%) cases with non typhi salmonella,1(2.7%) case with *Pseudomonas aeroginosa*,1(2.7%) case with group A streptococcus and 1(2.7%) case with group B streptococcus. 12.6% of the CSF samples had CSF leucocytes of $>50\times10^6$/L, 47.4% of the samples had CSF blood/glucose ratio of

0.1 or less and CSF total protein of 1g/L or more. However, it was reported that 41% of children with neck stiffness or apparent CSF turbidity had normal CSF laboratory results. It was further suggested that in a sub Saharan district hospital without reliable laboratory facilities, acute bacterial meningitis may be missed in about a third of children with. They concluded that for the diagnosis of acute bacterial meningitis to be made, performance of CSF culture is ideal.

A prospective study in Ghana by Owusu et al (33) in the year 2000 investigated 608 children aged 3 months to 15 years who had presented with fever and convulsions. 186(30.5%) of the patients had lumbar punctures performed. 19 (10.2%) of all patients had acute bacterial meningitis from laboratory findings with CSF white cell count of $>0.005\times10^9$ /L, CSF protein of >4g/dl, CSF glucose of <1.0 mmol/L with or without bacteria seen on gram stain or culture. No information of organisms isolated was provided. 30(16.1%) of patients had cerebral malaria and 29(15.6%) had febrile convulsions. CSF microscopy and biochemistry were essentially normal in these patients. Therefore, routine LPs have a role in assisting the clinician to make a diagnosis of bacterial meningitis as both cerebral malaria and meningitis have similar clinical presentations.

A prospective study by Farag et al (21) in 2003 in Egypt reported that of 310 children aged 3 months to 15 years,202(65%) had bacterial meningitis as suggested by laboratory results. The organisms isolated were Hib in 42 (21%) CSF samples, *S. pneumoniae* in 28 (13.9%) samples, *N. meningitidis* in 29(14.2%) samples and other undetermined bacteria. Mean CSF white blood cell count was 121cells/mm^3, mean CSF protein was 169mg/dl and mean CSF glucose was 1.05mmol/L.

In a Kenyan study by Berkeley J et al (22) in 2004 on indicators of bacterial meningitis, out of 999 children above the age of 2 months who had LPs performed, 91(2%) of the admissions had meningitis from abnormal CSF findings of positive CSF latex agglutination test or positive CSF culture or bacteria present on Gram stain, or CSF blood/glucose ratio <0.1,or CSF leucocyte count>50 per µL. 58 (64%) of the meningitis

cases had bacterial pathogens cultured from the CSF specimens. *S. pneumoniae* was cultured in 31 (53.4%) cases, *H. influenzae* in 24 (41.4%) cases, non typhoidal *Salmonella* in 2 (3.4%) cases and *Pseudomonas aeroginosa* in 1(1.7%) case. It was reported that among children within the febrile convulsions age range (6 months-5 years), a history of generalized seizures and no other abnormalities was associated with 3(0.5%) of 570 cases of meningitis. They concluded that routine lumbar puncture or empirical treatment for meningitis after an apparently uncomplicated febrile convulsion alone without presence of other indicators is unjustified.

A Kenyan prospective study by Idro et al (19) was carried out in 2004 to 2006 on the incidence, etiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital. 900 children presenting with seizures between the ages of 0-13 years were recruited. An infectious illness caused 80% of the seizures. Malaria was the primary diagnosis in 479 (53.2%) children. The children with malaria had the highest seizure frequency and duration. A lumbar puncture was performed in 594(66%) children. Meningitis was diagnosed in 44 (7.4%) children. *S. pneumoniae* was cultured in 9 (20.5%) CSF samples, Hib in 2(4.5%), *Escherichia coli* in 1(2.3%) and non typhi *Salmonella* in 1(2.3%)CSF sample.

In a retrospective study by Herbert et al (23) in 2004 on indications and CSF results in paediatric wards of 2 hospitals in Tanzania and Kenya. Out of 8741 children admitted in those wards, a lumbar puncture was performed in 607(6.9%) children. Abnormal CSF findings were in 32(7.1%) CSF samples from the Kenyan hospital and 6(5%) samples from the Tanzanian hospital. Mean CSF glucose was 2.9mmol/L and mean CSF protein was 0.6g/l. Bacterial isolates were obtained in 13(2.3%) CSF samples. *S. pneumoniae* and *Salmonella* species were found in 6(1.06%) and 2(0.35%) CSF specimens respectively and were the commonest cause of pyogenic meningitis in both hospitals. Only one case of *H. influenzae* meningitis was detected in Tanzania. It was also noted that lack of proper guidelines and delays in getting CSF results may have contributed to the low rate of doing LPs.

A prospective study was carried out in Nepal by Batajoo J et al (34) in 2004-2005 and involved 175 children between the age of 6 months and 5 years presenting with first episode of febrile seizure. 30 (17%) children were diagnosed with bacterial meningitis.22 of these had CSF cytological or biochemical criteria of bacterial meningitis with CSF WBC >5/mm^3, CSF protein> 40 mg% and CSF glucose <2/3 of blood glucose.8 (4.5%) patients had culture positive bacterial meningitis. Hib was found in 3(1.7%) cases, *S. pneumoniae* in 2(1.1%)cases and *Staphylococcus aureus* in 3(1.7%)cases. All children with culture proven bacterial meningitis were aged 6 to 12 months. Conclusions made were that it was necessary to carry out lumbar punctures in children aged 6-12 months presenting with first episode of febrile seizure as these patients may have bacterial meningitis even in the absence of meningeal signs.

An audit by Njuguna et al (4) in 2006 in Kenya in 170 children aged 1 month to 12 years presenting with altered consciousness reported that a lumbar puncture was indicated in 128(75%) of all child records reviewed but only performed in 56(32.5%) children. Only 5(9%) LPs were performed on the day of admission. Four organisms were found on CSF examination. *H. influenzae* in 1 out of the 56(1.8%) CSF samples, *S. pneumoniae* in 2(3.6%) and Gram positive cocci in 1 CSF sample (1.8%). 4(7.1%) CSF samples had cell counts above 5 leucocytes. CSF glucose below 1.1mmol/L was found in 18(32.7%) samples. CSF protein of above 40 mg/dl was found in 12(21%) samples. 21 of 44 children (48%) diagnosed with meningitis had the diagnosis based solely on clinical signs. Therefore, they recommended that a standard guideline on assessment and investigations be made for children presenting with altered consciousness.

Gichina et al (5)in 2009 in a Kenyan study reported that among 163 children aged 2 months to 12 years with suspected meningitis or encephalitis,17 (10.4%)had herpes simplex encephalitis on CSF Polymerase Chain Reaction (PCR) .11(7%) of the CSF samples had positive bacterial cultures. Only 3 of the patients with bacterial growth had concurrent herpes simplex encephalitis. 7 of the 11 CSF samples grew *S. pneumoniae*, 2 had Enterococci, 1 had Group B streptococci and 1 had *Staphylococcus aureus.* Mean

CSF WBC was 0, median CSF glucose was 4 mmol/L and median CSF protein was 0.1g/dl.

A 3 year retrospective review was done from 2011-2013 by Kuti et al (25) in Nigeria among children aged 1 month to 15 years. 57(62.7%) of the children with meningitis had bacterial growth from their CSF culture while 24(37.3%) had the diagnosis of bacterial meningitis made by Gram stain and CSF biochemistry of elevated CSF protein >45mg/dl and CSF glucose of less than one half of blood glucose. The CSF was turbid in 70 (86.4%) of the samples. 51 (89.4%) of the CSF bacterial isolates were *H. influenzae* and *S. pneumoniae* especially in children under 5 years. The rest of the isolates were from the *Pseudomonas* and *Klebsiella* species. *N. meningitidis* was isolated in school age children.
A prospective study in India by Suresh et al (35) done in the year 2009-2011 involved 120 children who were aged between 6 and 18 months and who presented with the first episode of febrile seizure. Seventy-seven (64.2%) children presented with simple febrile seizures whereas 43 (35.8%) children had atypical febrile seizures.5 (4.2%) children were found to have acute bacterial meningitis. One case had gram positive cocci in the CSF. Three cases showed growth of CSF culture of *S. pneumoniae*, *Streptococcus agalactiae* and Salmonella. The fifth case did not show growth on CSF culture but there was growth on blood culture of *Staphylococcus haemolyticus*. It was noted that four of the cases of bacterial meningitis were found in children aged 6-12 months. It was also interesting to note that none of these children had clinical signs of bacterial meningitis, yet their CSF examination pointed towards the diagnosis. The conclusion of the study was that bacterial meningitis should be suspected in children aged 6-18 months' even if the child presents with simple febrile seizures.

Sangeeta V et al (36) in a retrospective study in India in the year 2011- 2014 involved 505 children aged between 6 and 24 months who presented with a first episode of febrile seizures. 322 (63.7%) patients had a lumbar puncture performed whereby 203(63%) patients had simple febrile seizures while 119(37%) patients had complex febrile seizures. They reported that 5(4.2 %) children presenting with complex febrile seizures had CSF findings suggestive of bacterial meningitis with mean CSF WBC of 35/mm^3,

CSF glucose of 36g/dl and CSF protein of 61g/dl. All CSF cultures were sterile which may have been attributed to prior antibiotic usage in 66% of the patients. It was noted that none of the children diagnosed to have meningitis had been vaccinated against Hib or *S. pneumoniae*. None of the children with simple febrile seizures had suggestive CSF findings. Recommendations made were that carrying out a lumbar puncture is important for children below the age of 18 months as clinical signs of meningitis may be subtle.

Sadek et al (37) in a prospective study in Egypt in 2012-2013 investigated 85 children aged between 1 month and 12 years who presented with fever and convulsions. The median age of the children was 19 months. 24% of patients had increased protein and 6% of patients had decreased glucose. 17 cases (20%) had CSF WBC of between 5-1000 per high power field and three cases (3.5%) had CSF WBC of 1000-10000 per high power field. *Streptococcus pneumoniae* was present in the three cases that had CSF WBC count of more than 1000. There was a statistical significance correlating the signs of increased intracranial pressure and presence of meningeal irritation signs to the presence of abnormal CSF white blood cell count (p=0.01).

Table 2: Summary of Literature Review

Reference	**Target population**	**Abnormal CSF results (CSF glucose,protein,culture)**	**Type of organisms grown**
Berkley (20)	n=905 Children with impaired consciousness, seizures, meningism	CSF leucocytes of $>50\times10^6$/L= 108(12.6%) CSF samples, CSF blood/glucose ratio of <0.1 &CSF total protein of >1g/L= 47.4% samples. Positive culture=37(4%)	*S. pneumonia*= 17 cases, *H.influenzae* type b=14 cases Salmonella typhi=3 cases, *Pseudomonas aeroginosa*=1 case Group A streptococci=1case, Group B streptococci=1 case
Berkley 2004	n=999 Children more than 2 months old	Positive culture=58(5.8%)	*S. pneumoniae*= 31cases, *H. influenzae*= 24 cases, non typhoidal *Salmonella*= 2 cases,*Pseudomonas aeroginosa* = 1case.

Idro	n=594 Children with seizures between the ages of 0-13 years	Elevated protein & reduced glucose=31(5.2%) cases Positive culture=13(2.2%)	*S. pneumoniae*= 9 cases, Hib in 2 cases *Escherichia coli*=1case and non typhi *Salmonella* =1 case
Batajoo	n=175 Children aged 6 months to 5 years with first episode of febrile seizure.	CSF WBC >5/mm^3, CSF protein> 40 mg% and CSF glucose <2/3 of blood glucose=22(12.5%) children Positive culture=8(4.5%)	*H. influenzae* type b=3 cases, *S. pneumonia*= 2 cases, *Staphylococcus aureus*=3 cases
Kuti	N=1470 Children aged 1 month to 15 years with fever and convulsions	Elevated CSF protein & reduced glucose= 24(1.6%) children; Positive culture=57(3.9%)children	*H. influenzae* type b=28 cases, *S. pneumonia*=23 cases. *Pseudomonas=2, Klebsiella*=2. *N. meningitides*=2 cases
Farag	N=310 Children aged 3 months to 15 years	Positive culture=99(32%)	*H.influenzae*=42 cases, *S.pneumoniae*= 28 cases, *Neisseria meningitis*= 29 cases
Njuguna	n=56 Children aged between 1 month and 12 years with altered consciousness	CSF glucose<1.1 =32.7%,CSF protein >40 mg/dl =21%,CSF WBC >5/mm^3 =7.3% Positive culture=4(7.1%)	*Hib*=1 case, *S.pneumoniae*=2 cases, gram positive cocci=1 case
Gichina	N=163 Children aged 1 month-12 years with suspected meningitis or encephalitis	CSF PCR positive herpes simplex=17(10.4%) Positive bacterial culture=11(7%)	*S.pneumoniae*=7 cases Enterococci=2 cases, *Staphylococcus aureus*=1 case, Group B *streptococci*=1 case
Suresh	N=120 Children aged 6-18 months with first episode of febrile seizures	Positive culture=5(4.2%)	Positive gram stain=1 case, *S.pneumoniae*=1 case, *Salmonella=1 ,Streptococcus agalactiae*=1

3. JUSTIFICATION AND UTILITY

A lumbar puncture is an important investigation in children who present with fever and convulsions. The clinical examination and CSF results of a sick child assist a medical doctor to arrive at a diagnosis and to decide the type, route and duration of treatment. A study reported that children with fever and convulsions are admitted to paediatric wards and treated for meningitis without lumbar punctures being performed.(4) A child admitted to hospital for a long period is at risk of being exposed to nosocomial infections. In the end, this is costly to the patient, the family and the hospital in general. Since fever and convulsions are common in children, this study seeks to find out the profile of CSF findings in children aged 3 months to 12 years who present with fever and convulsions at Kenyatta National Hospital. There is need to find out if there has been any change in the pathogens causing bacterial meningitis in children in KNH since the introduction of the Hib and pneumococcal vaccine. Information on current etiology of acute bacterial meningitis and antibiotic sensitivity of causative organisms will go a long way in informing the health care workers on judicious use of antibiotics and general management of the patient.

RESEARCH QUESTION

- What is the profile of CSF findings in children aged 3 months to 12 years presenting with fever and convulsions at Kenyatta National Hospital?

4. OBJECTIVES

1. Broad objective:
    - To describe the profile of CSF findings (biochemistry, microscopy, culture and sensitivity) in children aged 3 months to 12 years presenting with fever and convulsions at KNH.
2. Specific objective:
    - *i.* To describe the socio demographic characteristics of children presenting with fever and convulsions
    - *ii.* To describe the clinical presentation associated with normal and abnormal CSF findings.

iii. To describe the CSF findings in children who presented with fever and convulsions and who were suspected to have meningitis.

5. STUDY METHODS

5.1 Study Design

Hospital based cross sectional study.

5.2. Study Area

The study was carried out in the Kenyatta National Hospital (KNH) which is the largest teaching and tertiary referral hospital in Kenya. KNH is located in Nairobi. The hospital caters for patients from the Nairobi and its environs. The bed capacity of the hospital is about 1800 beds. There are four general paediatric wards which has a bed capacity of 80 each. The bed occupancy in these wards is over 100%. Sick children are admitted to the ward through the Paediatric Emergency Unit. The patients are triaged by nurses who have a desk at the entrance of the emergency unit. Those who are seriously ill are then escorted to the paediatric registrars' desk. These patients are seen, stabilized and admitted for inpatient care. The children who are unwell but stable are seen by Clinical Officers. Most of these children are treated and sent home with prescriptions for medication needed. About 30 patients are admitted daily. Clinical care in the wards is done by nurses, medical officer interns, paediatric registrars and consultant paediatricians.

5.3. Study Population

Children aged between 3 months and 12years presenting with fever and convulsions.

5.3.1 Inclusion Criteria:

- Children aged between 3 months to 12 years with presentation of fever and convulsions.
- Children whose parents consented for their child to take part in the study.

5.3.2 Exclusion Criteria

- Children with a known history of epilepsy, head injury, cerebrovascular accident, brain tumour, hydrocephalus
- Children in whom an LP was contraindicated (those who required cardiopulmonary resuscitation; very sick children in unstable clinical state(severe respiratory distress and cardiovascular compromise); those with signs of increased intracranial pressure-bradycardia, hypertension, irregular breathing; those with unequal size of pupils; papilloedema; those with skin infections at the site of LP; those with signs of focal paralysis on any of the limbs, those with coagulopathy and thrombocytopenia of less than 50 platelets).
- Children who had a lumbar puncture performed from a referral facility.
- Children whose parent/guardian did not consent to take part in the study.

5.4. Sample Size Calculation

$$n = \frac{z^2 p(1-p)}{d^2}$$

Z=1.96. Score for 95% confidence interval

P=0.07(7% children had bacterial isolates in CSF in the Gichina study done at KNH in 2009.(5)

d=0.05(degree of precision of 5%)

n=minimum calculated sample size

$$\frac{3.8416 \times 0.07 \times 0.93}{0.0025} = 100$$

n=100

Finite population correction

$$na = \frac{nr}{1 + \left(\frac{nr-1}{N}\right)}$$

Where n_a is the adjusted sample size

N_r is the original sample size. This was 100

N=is the population of children normally seen with fever and convulsions at KNH during a 4-month period (equivalent to the proposed study period). This was 480

$$83 = \frac{100}{1+(99\div480)}.$$

Adjusted sample size is 83.

5.5. Sampling Methods

Consecutive sampling of patients who fit into the inclusion criteria until the sample size was achieved.

5.6 Study Tools

The tools used were questionnaires and laboratory result pro formas. A questionnaire was used to record information on the demographics and clinical presentation of the child. The laboratory results of CSF biochemistry, microscopy, culture and antibiotic susceptibility was recorded on a laboratory results pro forma.

5.7 Study Procedures

A child who presented to the Paediatric Emergency Unit with fever and convulsions was handled as an emergency. The child was received by the nurse who sat at the triage desk and who then directed the caregiver and the child into the emergency area. All sick children received at the Paediatric Emergency Unit were managed according to the Kenyan basic paediatric protocols. (27) The convulsing child was laid down on a firm couch on the left lateral position and oxygen was started. The mode of oxygen delivery was either by nasal prongs or a mask with a non-rebreather bag. A sample for random blood glucose was taken (either heel prick or a prick on the fingertip). A random blood glucose level of 2.5mmol/L and below signified hypoglycemia and was treated by rapid intravenous administration of 10% dextrose at a dose of 5ml/kg. An intravenous line was accessed on the patient. Routine blood samples such as full haemogram, urea electrolytes and creatinine, calcium and magnesium levels and liver function tests were accessed from the patients' intravenous line. (These are usually done for all admitted patients.)

Time was continuously checked on a wall clock as this determined the point at which drugs might be given. If the child convulsed for 5 minutes, he or she received diazepam at a dose of 0.3mg/kg intravenously or 0.5mg/kg per rectally. Close monitoring of the vital signs and oxygen saturation was done. If the child convulsed again at the 10^{th} minute, a second dose of diazepam at the mentioned doses was given. If the child happened to convulse at the 15-minute mark despite two doses of diazepam, an intramuscular loading dose of phenobarbitone was given at 20mg/kg. Once the child was stable after the acute convulsive episode, the screening and recruitment into the study took place at the Paediatric Emergency Unit.

The principal investigator visited the Paediatric Emergency Unit from 8 a.m to 8 p.m all days of the week including weekends. The principal investigator and a research assistant screened and recruited children aged 3 months to 12 years who present with fever and convulsions from the Paediatric Emergency Unit and the general paediatric wards. The screening tool used is shown on Appendix 3. The study assistant was a clinical officer trained by the principal investigator. The study assistant screened patients and assisted the principal investigator to administer the questionnaire. Principal investigator was responsible for specimen handling.

For the screened children who fulfilled the inclusion criteria, the principal investigator recruited them into the study and informed consent was sought from the caregivers (Appendix 1). The consent form was counter signed by the principle investigator. Those who consented to participate in the study had a predesigned questionnaire administered to them (Appendix 2). The principal investigator then performed the lumbar puncture before the child was admitted to the ward. After the lumbar puncture was carried out at P.E.U, intravenous antibiotics were started at the Paediatric Emergency Unit. The antibiotic treatment was continued in the ward. In most cases, the antibiotic started was ceftriaxone at a dose of 100mg/kg/day as recommended by the Kenyan Paediatric Protocols for treatment for meningitis. (27)

Once an LP was done, a note was made on the colour, turbidity and pressure of the CSF before it was taken to the laboratory. The CSF specimen was labelled using study identification number, date and time of collection. These samples were ferried to The Lancet laboratory. The CSF results were relayed to the principal investigator in a predesigned form (Appendix 5). The principal investigator was the only one who had the names of the patient with their correlated serial numbers and thus communicated these results to the doctors in the ward. The treatment of patients was changed depending on the laboratory results.

There was a possibility of a child with fever and convulsions being admitted to the paediatric ward without having a lumbar puncture done. This sometimes was due to lack of sterile bottles for CSF culture and also due to the fact that the Paediatric Emergency Unit is very busy and the admitting doctor may not have been able to do the LP at night. In this case, the principle investigator visited the particular admitting ward, looked at the admission register at the ward, looked at the nursing cardex and identified the target patients by getting patient's file. If an LP had not yet been done, the caregiver of the child was spoken to and informed consent was sought. The questionnaire was administered to the child's care giver and a lumbar puncture was performed according to the clinical procedures outlined. However, if an LP had been done, the child was excluded from the study.

The routine tests of blood slide for malaria parasites and random blood sugar were done in the Paediatric Emergency Unit before a child was taken to the ward. Random blood sugar results were recorded immediately. The results of the blood slide for malaria parasites were checked from the patients' file on the second day of admission. A team from the Comprehensive Care Clinic at Kenyatta National Hospital performed a HIV test using the Provider Initiated Testing and Counseling model to all new admissions (children and the accompanying parent) on the second day of admission as standard of care in all paediatric wards. Pre-test and post-test counseling was provided by the HIV counselor. The HIV results were then recorded in the respective patient's file and thereafter the principle investigator recorded the HIV result in the questionnaire.

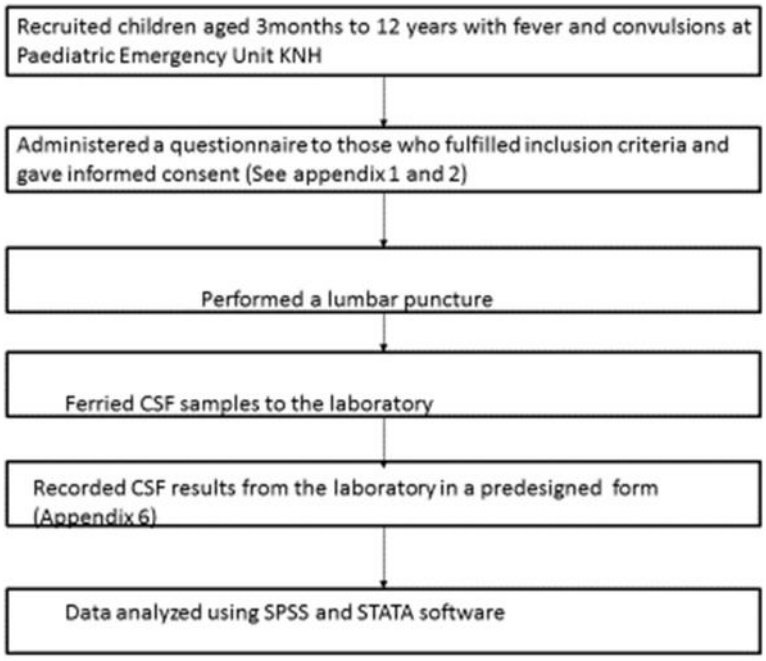

Figure 1: Flow Diagram of Study Procedure

5.8 Clinical Procedures

A random blood sugar was done by the following procedures:

1. Gloves were worn.
2. The child's finger was cleaned at the pulp with an alcohol swab. The finger was allowed to dry before it was pricked.
3. The glucometer was switched on and a glucose strip was prepared.
4. The finger was pricked using a gauge 23 needle. A drop of blood was allowed to fall from the side of the fingertip onto the glucose strip until it absorbed enough blood to begin the test.
5. The glucometer read the blood sugar level within seconds.

The principle investigator recorded the blood glucose level on the questionnaire to enable correlation with CSF glucose.

The principle investigator performed the lumbar punctures. An assistant was asked to hold the child and keep him/her still as the lumbar puncture was being done. An LP was performed with the child lying on their side or sitting up. For the younger child, the

lateral decubitus position was preferred and this was achieved by flexing the child at the waist and the neck to approximate the knees towards the chin. An older child sat on the examination bed with their legs dangling and their waist and neck flexed. The assistant held this child in position. The other procedures that were followed are shown below;

- When the child's back was flexed, an imaginary line was drawn between the top of the iliac crests. This intersected the spine at approximately the L3-L 4 interspace.
- The L3-4 or L4-5 interspace was aimed. This area was marked with a thumb nail or marker. Hands were washed and sterile gloves were worn.
- The skin was prepared with povidone-iodine and sterile drapes were set up.
- Adequate time was allowed for the skin preparation to dry.
- The covers of the specimen collection tubes were taken off, ensuring that they remained sterile.
- The gauge 21 or 23 needle was inserted on the intended interspace at a slightly cephalad angle, directing it toward the umbilicus. The needle was advanced slowly into the spinous ligament until there was a fall in resistance. The CSF flow, pressure and colour was noted.
- CSF was collected into the 2 labelled sterile tubes-1ml for biochemistry (glucose and protein) and 1ml for microbiology.
- The needle was then removed.
- Pressure was applied briefly to the puncture site and sterile dressing was done. The patient was then placed in the supine position for a few minutes.

5.9 Laboratory Procedures

i) Sample transport

The CSF specimens were properly sealed, placed on a rack in a cool box and taken to the Lancet laboratory. The CSF samples were taken to the laboratory within an hour of sample collection.

ii) Quality control of the laboratory

The laboratory that carried out the tests was accredited by the Kenya National Accreditation System (KENAS) and was also internationally certified (ISO 15189:2012 certified. Internal quality control was carried out daily at the laboratory. Internal quality control checks were run daily prior to sample analysis and external quality control of this laboratory was under the THISTLE system.

iii) Sample storage

If a delay in processing a CSF sample at the laboratory was unavoidable, then the specimen was maintained at ambient temperature. (It was not refrigerated).

iv) Sample processing

The CSF specimens were received by a laboratory technologist who logged the specimen in an appropriate specimen book and assigned a specimen lab number. The specimens were processed immediately and all pipetting was done in a Class 2 bio safety cabinet. Laboratory procedures of gram stain, WBC count, culture, protein and glucose determination are shown below.

iv. a.) Procedure of Gram Stain

1. The CSF was centrifuged at 3000g for 10 minutes.
2. The CSF sample to be examined was spread in a thin layer on a glass slide. It was allowed to dry completely. It was fixed by quickly passing the back of the slide through a flame from a Bunsen burner three times or covering the slide with a few drops of 70% methanol for 2 minutes or by. Once the sample was fixed, the gram stain procedure began.
3. The smear was covered with crystal violet stain for 60 seconds.
4. The stain was washed off with clean water and drained. The smear was covered with iodine for 60 seconds.
5. The iodine was washed off with clean water and decolorized rapidly with acetone–ethanol for 2 –3 seconds.
6. The smear was covered with carbol-fuchsin stain for 2 minutes.
7. The stain was washed off with clean water and the slide was placed upright in a slide rack to drain and air-dry.(38)

Microscopic examination: The slide was first examined using the X 40 objective to see how the smear was distributed and then the X 100 oil-immersion objective was used.

Gram-positive organisms appeared dark purple and gram –negative organisms appeared red.

iv. b.) Leucocyte Cell Count Procedure

1. The counting chamber was covered with the coverslip supplied.

2.The CSF specimen was mixed in a Class 2 biosafety cabinet

3. The CSF was pipetted into the counting chamber using a fine Pasteur pipette.

4. The counting chamber was left on the bench for 5 minutes to allow the cells to settle. The chamber was placed on the microscope stage.

5. The cells were counted in 1 mm3 of CSF, using the X 10 objective and was reported in standard international units as "number X 10^6 /L";

Example: 150 cells per mm3 were reported as "150 X 10^6 /L".

- If the improved Neubauer chamber was used, the cells were counted within the entire ruled area, which is 9mm^3. If undiluted CSF was used, the number of cells counted were multiplied by 10 and divided by nine to give the number of cells per mm3 of CSF.
- If the CSF appeared cloudy, a 1 in 20 dilutions was made a using 0.05 ml of the CSF and 0.95 ml of Türk solution. It was pipetted into a small bottle and mixed. If this dilution of CSF was done and a neubauer chamber was being used, the number of cells counted was multiplied by 20 and divided by nine to give the number of cells per mm^3 of CSF.

iv. c.) CSF Protein Determination

The machine used was the fully automated Cobas Integra 400/800 analyzer, Roche Diagnostics (Germany).

Method

The sample was pre-incubated in an alkaline solution containing EDTA which denatured the protein and eliminated interference from magnesium ions. Benzethonium chloride was added and this produced turbidity that was read at 512 nanometers.

iv.d) CSF Glucose

The machine used was the fully automated Cobas Integra 400/800 analyzer, Roche Diagnostics (Germany).

Method

- Enzymatics reference method with hexokinase which catalyzed the phosphorylation of glucose by ATP to form glucose 6 phosphate and ADP. Glucose 6 phosphate dehydrogenase was used to catalyze oxidation of glucose-6-phosphate by NADP to form NADPH. The concentration of NADPH formed was directly proportional to the glucose concentration and this was determined by measuring the increase in absorbance at 340nanometers.

iv. e) CSF culture

- The CSF was centrifuged at 3000 g for 10 minutes. The following media were inoculated with a drop of concentrated CSF and incubated as documented in the table below.
- The plates were read daily and all growth was followed up.

Table 3: Culture plates and conditions

Media	Incubation temperature (^oC)	Atmosphere	Length of incubation
Blood Agar	35-37	5-10% CO_2	48 hours
Chocolate agar	35-37	5-10% CO_2	48 hours
MacConkey	35-37	Aerobic	48 hours

- The modified Kirby-Bauer disc diffusion method was used to perform the antimicrobial susceptibility testing. The antibiotics that were tested included penicillin and other beta lactams, cefepime, ceftazidime, ceftriaxone, linezolid, vancomycin, gentamycin, cotrimoxazole, chloramphenicol, ciprofloxacin, meropenem. The appropriate antimicrobial-impregnated disks were placed on the

surface of the agar using a pair of sterile forceps. Each disc was gently pressed down ensuring complete contact with agar surface.

- After incubation, the diameter of each zone (including the diameter of the disc) was measured and recorded in millimeters using a ruler or caliper
- The results of antibiotic susceptibility were interpreted according to the Clinical and Laboratory Standards Institute to determine the susceptibility or resistance of the organism to each drug tested. For each drug, it was indicated on the recording sheet whether the zone size was susceptible (S), intermediate (I), or resistant (R) based on the interpretation chart.(39)

v) Infection control

- Sterile gloves were used during CSF sample collection.
- Clean gloves were used during the random blood sugar check.
- The skin on the patient's back was cleaned using povidone iodine before the LP was performed to prevent contamination by skin flora.
- The skin on the patient's finger-tip was wiped using spirit swabs before the needle prick to check the random blood sugar.
- The needles used were discarded into a sharps container after CSF and random blood sugar sample collection.
- The biological specimens were disposed and international standard operating procedures were followed. Immediately after analysis of the specimen, the specimen containers with the CSF specimen were decontaminated using 10% sodium hypochlorite solution (bleach) for twenty minutes. The containers bearing the biological specimen were then wrapped in appropriate biohazard bags and incinerated. The chief laboratory technologist was responsible for the processing and disposal of the biological specimens

6. DATA MANAGEMENT AND ANALYSIS

A data collection form was used to record information on the child's socio demographics, history and physical examination findings (Appendix 2). A predesigned form was used to record the CSF results (Appendix 7). The categorical data assessed was the patient's sex, residence, immunization and referral status, clinical symptoms and physical examination

findings of the child, education level of mother and child's HIV status. The continuous data assessed was the patient's age, duration of clinical symptoms and number of people in the household. It was coded and keyed into a computer using Statistical package for Social Science (SPSS) windows version 23. Final analysis was done using SPSS and STATA version 12. Descriptive statistics were used to summarize data on mean, median and standard deviation of continuous variables.

Primary analysis was done for the proportion of CSF samples with normal or abnormal findings specifically focusing on the CSF microscopy, biochemistry and culture. Associations of abnormal CSF findings with specific symptoms, signs or socio demographic information were analyzed and summarized using odds ratios.

7. CONTROL OF ERRORS AND BIASES

1. The questionnaire was pretested on a sample population to ensure validity before commencement of the study

2. The research assistant was trained and provided with standard definitions of terminologies used in the questionnaire to ensure uniform interpretation and reduce outcome ascertainment bias. Selection bias was addressed by recruiting all patients who fulfilled the inclusion criteria on all days including weekends.

8.DISSEMINATION OF RESULTS

The results of this study were be submitted to the Department of Paediatrics and Child Health and results presented as a poster presentation in May 2017. The completed thesis will be submitted for marking at the Department of Paediatrics and Child Health and then submitted for publishing in a peer reviewed journal.

The results of the study will also be presented as a poster presentation in local scientific conferences for instance the Kenya Paediatrics Association annual conference.

9. ETHICAL CONSIDERATIONS

Ethical approval was sought from the KNH/UON ethics research committee.

Informed consent

The procedures of the study were explained in full to the caregivers of the children. A written consent form (Appendix 1) was provided to the caregivers. Those who consented to participation in the study appended their signatures on the consent form.

Risks

The common risks of post lumbar puncture headache and pain on the lumbar puncture site were communicated to the caregivers prior to conducting the procedure. Other risk factors such as shooting pain down the legs, bleeding at the site of needle insertion or into the spinal canal, lower limb weakness or numbness, double vision, infection at the needle site or in the spinal fluid, dermoids at the needle site, brain herniation or coning, physical disability or death as a result of brain herniation were also explained to the caregivers prior to conducting the procedure.

Benefit

Any abnormal CSF result that warranted treatment was communicated to the doctor at the ward. The caregiver was also informed on abnormal CSF results that required treatment.

Autonomy

The participants were free to choose whether to participate in the study. They were free to pull out from the study at any time without any penalty on their part. Their child received treatment at the hospital whether they choose to participate in the study or not.

Cost

The principle investigator covered the cost of the cerebrospinal fluid tests.

Confidentiality

The data collected was coded and handled confidentially. The questionnaires contained study numbers which dissuaded use of patients' names. Written data was stored in a locked cupboard whose key was only be accessible to the principal investigator and the research assistants. Data entry was done daily using SPSS Windows version 23 into a computer which was password protected to restrict access.

10.RESULTS

A total of 84 children who presented with fever and convulsions were recruited into the study. The baseline demographics of the children are shown in Table 4. The median age of the children was 16 months (IQR 9-36.5 months). Children aged less than 35 months accounted for the majority of the participants. The male-to-female ratio was 5:4. Only 8(9.5%) mothers had attained tertiary education.

Table 4: Characteristics of children with fever and convulsions in KNH

Patient characteristics	Frequency (n)	Percent (%)
Age		
3-11 months	28	33.3
12-35 months	34	40.5
36-59 months	12	14.3
5 to 12 years	10	11.9
Sex		
Male	47	56
Female	37	44
Appropriately immunized for age (Pentavalent and PCV)		
Yes	80	95
No	4	5
Maternal education		
Primary and below	31	36.9
Secondary	45	53.6
Tertiary	8	9.5
Patient referred to KNH		
Yes	34	40.5
No	50	59.5
Patient re admitted in last one month		
Yes	14	16.7
No	70	83.3

Interpretation of laboratory results

Normal CSF was described as CSF white cell count of less than 5/mm^3, CSF glucose of >2.7 mmol/L, CSF protein of 20-45mg/dl and absent organisms on gram stain and

culture. Abnormal CSF was described as CSF white cell count of more than 5/mm^3, CSF glucose <2.7 mmol/L, CSF protein of >45mg/dl and organisms isolated on gram stain and culture. A summary of the CSF results is found in Table 5.

Table 5: CSF results of children with fever and convulsions at KNH

CSF results	Frequency (n)	Percent (%)
CSF appearance		
Clear	78	92.9
Turbid	4	4.8
Straw coloured	2	2.4
CSF protein (mg/dl)		
Normal (<45)	74	88.1
Abnormal (> 45)	10	11.9
CSF WBC		
Normal (< 5 cells/mm^3)	79	94
Abnormal (> 5 cells/mm^3)	5	6
CSF glucose(mmol/l)		
Normal (> 2.7)	77	91.7
Abnormal (< 2.7)	7	8.3
CSF gram stain		
No organism seen	81	96.4
Organism identified	3	3.6
CSF culture		
No organism	81	96.4
Organisms isolated	3	3.6

An overall 69(82.1%) patients had normal CSF results while 15(17.9%) patients had abnormal CSF results. Four (4.8%) CSF samples had abnormal CSF protein. Three (3.6%) CSF samples had abnormal CSF glucose (their respective random blood sugars were above 4 mmol/l). Two (2.4%) CSF samples had abnormal CSF WBCs. One (1.2%) CSF sample had a combination of abnormal CSF protein and glucose. Five (5.9%) CSF

samples had a combination of abnormal CSF protein, glucose, CSF WBCs and isolated organisms. The median CSF protein was 18mg/dl (IQR 14 to 29.5mg/dl). The median CSF glucose was 3.8mmol/l (IQR 3.4 to 4.5mmol/l). Five (6%) patients had more than 5 white blood cells counts seen in their CSF. In total 5(5.9%) CSF samples had organisms identified either on gram stain or culture.

Two CSF samples had gram positive cocci identified and one CSF sample had gram negative rods identified. The CSF sample with gram negative rods was the only one that had an organism identified (*Haemophilus influenzae*). The other organisms identified on CSF culture were *Enterococcus and Escherichia coli.* The antimicrobial susceptibility of the isolated organisms is displayed on Table 6.

Table 6: Antimicrobial susceptibility of isolated organisms

Antimicrobial	*Haemophilus influenzae* (n=1)	*Enterococcus* (n=1)	*Escherichia coli* (n=1)
Ceftriaxone	R	-	S
Cefepime	-	-	S
Meropenem	S	S	S
Amikacin	-	-	S
Gentamycin	-	R	S
Chloramphenicol	S	-	-
Ciprofloxacin	-	-	R
Ampicillin/amoxicillin	R	S	-
Vancomycin	-	S	-
Linezolid	-	S	-

Comparison of normal and abnormal CSF according to patient characteristics

Children aged 12-25months had 80% lower odds of having abnormal CSF when compared to children aged 3-11 months. This association however was no longer

significant with increasing age. As shown on table 7, the sex, immunization and referral status of the patient were not significantly associated with abnormal CSF findings.

Table 7: Comparison of patients with normal and abnormal CSF according to patient characteristics

	Prevalence of normal CSF n=69 (%)	Prevalence of abnormal CSF n=15 (%)	OR(95% CI)	p value
Age				
3-11 months	20(29.0)	8(53.3)		
12-25 months	32(46.4)	2(13.3)	0.2(0.03-0.8)	0.027
36-59 months	11(15.9)	1(6.7)	0.2(0.03-2.1)	0.2
5 to 12 years	6(8.7)	4(26.7)	1.7(0.4-7.5)	0.5
Sex				
Male	40(58.0)	7(46.7)	1.6(0.5-4.8)	0.4
Female	29(42.0)	8(53.3)		
Appropriately immunized for age (pentavalent and PCV)				
Yes	66(95.6)	14(93.3)	0.6(0.1-6.6)	0.7
No	3(4.3)	1(6.7)		
Referral				
Yes	28(40.6)	6(40.0)		0.97
No	41(59.4)	9(60.0)	0.98(0.3-3.0)	
Patients admitted in the last one month				
Yes	10(14.5)	4(26.7)	2.2(0.6-8.1)	0.3
No	59(85.5)	11(73.3)		

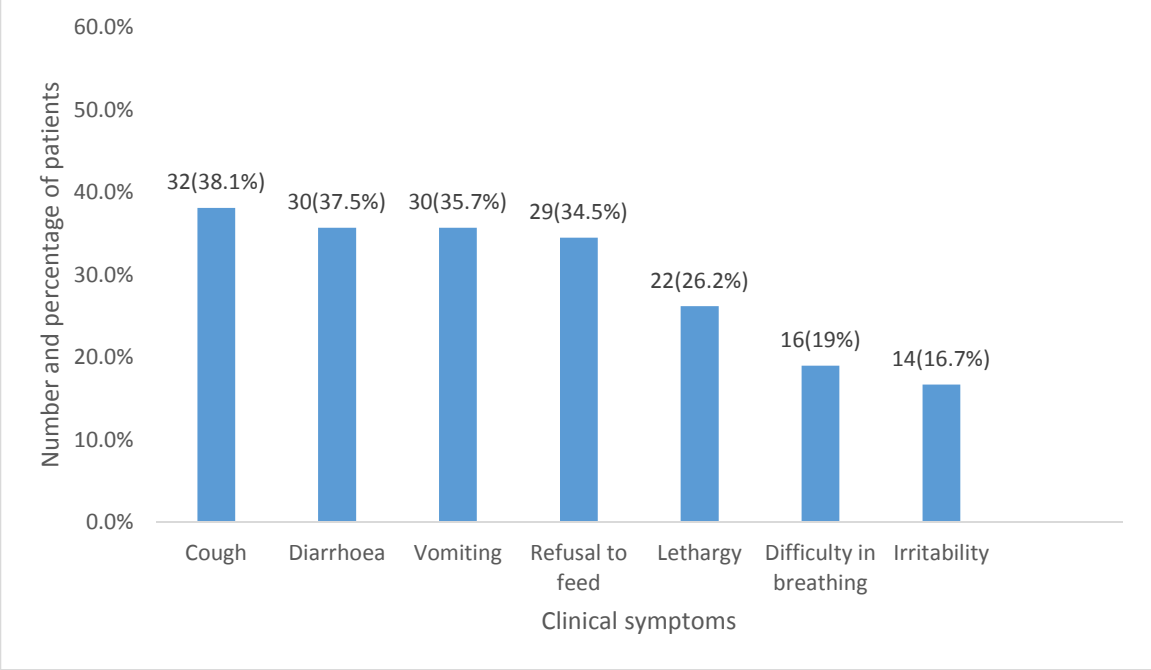

Figure 2: Other symptoms in children presenting with fever and convulsions

Figure 2 shows the other symptoms that were documented on admission for children with fever and convulsions. Cough, diarrhea and vomiting were other leading symptoms in children with fever and convulsions. Headache was present in 9 (40.9%) of 22 patients who were above 3 years of age. Presence of headache was not inquired about in children less than 3 years.

Comparison of normal and abnormal CSF according to clinical presentation

A comparison of clinical symptoms with normal and abnormal CSF results was made as shown on table 8. The median temperature of the children was 38.3℃ (IQR 38-39℃). Children with abnormal CSF findings had higher likelihood of having fever lasting more than 24 hours'; 12(80%) of 15 versus 32(43%) of 69 respectively; (OR=4.6, 95% CI 1.2-17.9, p=0.03). The presence of irritability increased the odds of having abnormal CSF (OR=5, 95% CI 1.4-18, p=0.012). Children with lethargy had higher likelihood of having abnormal CSF (OR= 4.5, 95% CI 1.4-14.5, p=0.012).

Children with abnormal CSF findings had higher likelihood of having neck stiffness; 10(66.7%) of 15 versus 14(20.2%) of 69; (OR=7.9, 95% CI 2.3-26.7, p=0.001). A

positive kerning sign significantly increased the odds of having abnormal CSF; (OR=11.4, 95% CI 3.2-40.7, p=<0.001). Children with abnormal and normal CSF findings did not differ in prevalence of length, past history or duration of convulsions. Diarrhea, vomiting, cough and difficulty in breathing were not associated with abnormal CSF. Headache was present in 3 (60%) of 5 patients with abnormal CSF versus 6(35.3%) of 17 patients with normal CSF; (OR=2.75, 95% CI 0.4-21.3, p=0.3). Presence of bulging fontanelle was found in 3(0.06%) of 45 children aged below 18months. Of those with bulging fontanelle, only 2 had abnormal CSF.

Six (7.1%) children were HIV positive. Nine (10.7%) patients had a positive blood slide for malaria parasites. Children with positive malaria blood slide had significantly reduced risk of having abnormal CSF findings. HIV status was not significantly associated with abnormal CSF findings. Three (3.6%) patients had organisms isolated from blood culture. The organisms were Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus *faecium.* Two of the patients with positive blood culture also had positive CSF culture. The third patient with positive blood culture had abnormal CSF biochemistry.

Table 8: Comparison of patients with normal and abnormal CSF according to clinical presentation

CLINICAL PRESENTATION	Prevalence of normal CSF n=69(%)	Prevalence of abnormal CSF n=15(%)	OR (95% CI)	p value
Duration of fever				
Less than 24 hours	37(53.6)	3(20.0)		
More than 24 hours	32(46.4)	12(80.0)	4.6(1.20-17.85)	0.03
Past history of convulsions	17(24.6)	1(6.7)	0.2(0.03-1.7)	0.14
Duration of convulsions				
Less than 24 hours	56(81.2)	10(66.7)		
More than 24 hours	13(18.8)	5(33.3)	2.2(0.6-7.4)	0.22
Number of convulsions				
Once	32(46.4)	6(40.0)		
More than once	34(49.3)	5(33.3)	0.8(0.2-2.8)	0.7
Uncertain	3(4.3)	4(26.6)	7.1(1.3-40.2)	0.026
Length of convulsions				
Less than 15 minutes	59(85.5)	10(66.7)		
More than 15 minutes	4(5.8)	2(13.3)	2.9(0.5-18.3)	0.2
Not sure	6(8.7)	3(20.0)	2.9(0.6-13.8)	0.2
Refusal to feed	21(30.4)	8(53.3)	2.6(0.8-8.1)	0.1
Irritability	8(11.6)	6(40.0)	5.1(1.4-18.1)	0.012
Lethargy	14(20.3)	8(53.3)	4.5(1.4-14.5)	0.012
Level of consciousness				
Alert (A)	54(78.3)	11(73.3)		0.7
Altered consciousness (VPU)	15(21.7)	4(26.7)	1.3(0.4-4.7)	
Neck stiffness	14(20.2)	10(66.6)	7.9(2.3-26.7)	0.001
Kerning sign positive	8(11.6)	9(60.0)	11.4(3.2-40.7)	<0.001
Opisthotonus	1(1.5)	0(0.0)	1.0(1.0-1.0)	-
Spastic tone	4(5.8)	3(20.0)	4.1(0.8-20.5)	0.1
Reduced tone	7(10.1)	1(6.7)	0.6(0.1-5.6)	0.7
Positive blood slide for malaria parasites	9(13.0)	0(0.0)	1.0(1.0-1.0)	-
HIV Positive	4(5.8)	2(13.3)	2.5(0.4-15.1)	0.3

Multivariable analysis of factors associated with abnormal CSF

The multivariable logistic regression model showed that neck stiffness was the only factor that was independently associated with abnormal CSF. This was after adjusting for age, presence of lethargy, fever duration, irritability and spastic tone as shown on table 6. The odds of having abnormal CSF was eight fold higher (OR = 8, 95% CI 1.6-40.62) among children who had neck stiffness compared to those who did not have this sign. This association was significant with a p value of 0.012.

Table 9: Multivariable analysis of factors associated with abnormal CSF in children with fever and convulsions

	OR (95% CI)	P value
Age		
3-11 months	1	
12-25 months	0.2(0.03-2.1)	0.2
36-59 months	1.3(0.1-19.2)	0.85
5 to 12 years	2.5(0.3-19.5)	0.39
Lethargy	3.9(0.9-17.5)	0.07
Neck stiffness	8(1.6-40.6)	0.012
Fever duration > 24 hours	3.1(0.5-19.3)	0.23
Irritability	0.2(0.03-1.1)	0.07
Spastic tone	1.9(0.2-21.1)	0.59

11. DISCUSSION

Our primary objective was to describe the profile of CSF findings (microscopy, biochemistry, culture and sensitivity) in children aged 3 months to 12 years presenting with fever and convulsions at KNH. In our study,69(82.1%) children had normal CSF findings while 15(17.9%) children had abnormal CSF.

Sadek et al (37) in a study in Egypt reported that 20(23.5%) of 85 children with fever and convulsions had abnormal CSF. Three (3.6%) cases in our study had positive CSF cultures of *H. influenzae*, Enterococcus and *Escherichia coli* which was almost similar to Sadek's study whereby three (3.5%) cases had positive CSF culture. The organism isolated in Sadek's study was *Streptococcus pneumoniae.* Gichina's study at KNH reported a higher culture positive rate of 6.7%(11 of 163 CSF samples). (5)The organisms isolated in his study were *S.pneumoniae*, Enterococci, Group B streptococci and *Staphylococcus aureus.* Njuguna's study at KNH reported positive CSF cultures in 3 of 56 (5.4%) specimens and the organisms isolated were *Haemophilus influenzae* and *S. pneumoniae*. (4)

The median CSF glucose in our study was 3.4mmol/L and median CSF glucose was 18mg/dl. This was slightly lower compared to Gichina's study where the median CSF glucose was 4 mmol/L and median CSF protein was 100mg/dl.(5) Our study reported 5(6%) CSF specimens with CSF white cell counts of above 5. This was slightly lower than what Njuguna reported; four (7.3%) of 56 CSF samples with white cell counts above 5. (4)

The three bacterial organisms isolated in our study were all sensitive to meropenem which is considered a reserve drug. Our study reported that *H. influenzae* was sensitive to chloramphenicol and amoxicillin/ampicillin but resistant to ceftriaxone. Berkley's study (20) done in 1999 involving 905 children with lumbar punctures performed reported that in 45(5%) CSF samples, the organisms isolated on culture were *S.pneumoniae,* non typhi salmonellae, *H. influenzae,* group A and B streptococcus and *Pseudomonas aeroginosa*,. *H influenzae* isolates showed resistance to both penicillin and chloramphenicol and were

sensitive to cefotaxime. Antibiotic sensitivity of the other isolates was not mentioned. In Kuti's study involving 81 children, the predominant bacterial isolates were *S. pneumoniae* and *H. influenzae* in children less than 5 years of age and *N. meningitidis* found in those more than 5 years. *H. influenzae* was sensitive to ceftriaxone and ciprofloxacin. *S. pneumoniae* was sensitive to ciprofloxacin, ampicillin and ceftriaxone. (25)

In our study, it was worrying to note that *H. influenzae* was resistant to ceftriaxone which is the first line treatment for bacterial meningitis in our Kenyan basic paediatric protocols. (40) There is a possibility that increased pre admission use of ceftriaxone even for minor illnesses may contribute to increased resistance of bacterial organisms to ceftriaxone. It should however be noted that KNH is a referral center that tends to receive very sick children who may have been managed in peripheral hospitals with ceftriaxone. Antibiotic stewardship is still needed to ensure that these drugs are used in a rational manner.

The median age of children who presented with fever and convulsions in our study was 16 months. This was slightly lower compared to Sadek's study where the median age was 19.9 months. (37)In our study, the age of less than 2 years was found to be significantly associated with abnormal CSF results (p=0.027). Similarly, Batajoo et al reported that children less than 1 year were more likely to have bacterial meningitis (p=0.001). (34)

According to other symptoms that were present in children with fever and convulsions, 32 (38.1%) children in our study had cough while thirty (35.7%) children had associated symptoms of gastroenteritis. There was no statistical significant association with abnormal CSF. Sadek et al reported 37.6% with diarrhea and 8% with respiratory symptoms but there was no statistically significant association of abnormal CSF with these symptoms (p=0.46).(37)

Our study reported that presence of fever for more than 24 hours, neck stiffness, irritability, lethargy and positive kerning sign were associated with abnormal CSF and this was statistically significant ($p<0.05$).

A systematic review published by Curtis et al (24) in 2010 reported that the following clinical signs increased the likelihood ratio of bacterial meningitis; history of neck stiffness by 7.70 [95% CI:3.2–19]), irritability by 1.3 [95% CI:1.10–1.50), kerning sign by 3.50 [95% CI:2.1–5.7]), lethargy by 1.9 [95% CI:1.30–2.90]) and fever of more than 40 . In 1999, Berkley reported that neck stiffness was strongly associated with evidence of bacterial meningitis, 40 of 76 children (40%) with neck stiffness on admission had proven or probable acute meningitis compared with 41 of 829(5%) children without neck stiffness (odds ratio of 12.5(95% CI 6.9-22.8). (20) Sadek et al also reported that presence of neck rigidity was significantly associated with abnormal CSF ($p=0.01$). Kuti in his study reported that irritability was significant in 21(30.9%) of 68 children aged less than 5 years who presented with bacterial meningitis. ($p=0.04$). Neck rigidity was present in 12(92.3%) of 13 children aged more than 5 years with bacterial meningitis ($p<0.001$).(25)

Suresh et al in his study of 120 children aged 6-18 months with fever and convulsions, reported 5(4.2%) children with confirmed acute bacterial meningitis on CSF analysis but notably, these children did not have any meningeal signs.(35) Similarly, in our study, one of the children who had a positive CSF culture growth of *Escherichia coli* was 9 months old but did not present with other meningeal signs.

Study Limitations

The following study limitations were encountered.

1. CSF pressure was not measured objectively as we did not have a manometer to do so. We however noted whether the CSF gushed out during the lumbar puncture procedure.
2. Polymerase chain reaction tests on CSF to diagnose viral agents and tests to check for fungal or mycobacterial organisms were not carried out due to financial constraints.

12. CONCLUSION

High index of suspicion for abnormal CSF is needed in children less than 2 years presenting with fever and convulsions especially if they have a stiff neck.

13. RECOMMENDATIONS

1. It is important to carry out a lumbar puncture in children aged less than 2 years who present with fever and convulsions.
2. Further studies on antibiotic sensitivity patterns for isolated microorganisms need to be carried out.

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12. APPENDICES

APPENDIX 1:CONSENT FORM TO PARTICIPATE IN THE STUDY

STUDY TITLE: PROFILE OF CEREBROSPINAL FLUID FINDINGS IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH FEVER AND CONVULSIONS AT KENYATTA NATIONAL HOSPITAL

Investigator: Dr. Jemimah K. Mugo (MB Ch.B), Peadiatrics Registrar,
University of Nairobi
Tel 0720201171

Supervisors: Professor Francis Ephraim Onyango (M.B.Ch.B, M.Med. M.P.H., FCP, F. Clin Epid, CTM)
Associate Professor,
Department of Paediatrics and Child Health, University of Nairobi

Dr Jacqueline Oliwa (M.B.Ch. B, M. Med, Msc.Epidem)
Lecturer
Department of Paediatrics and Child Health, University of Nairobi

Dr. Marianne Mureithi (BSc, Ph.D.)
Lecturer,
Department of Medical Microbiology, University of Nairobi

Background:

Thank you for taking your time to read this form. This form provides information about the purpose and procedures of the study. Please read this consent form carefully. You may seek clarification on any matter pertaining to the study. The purpose of the study is to investigate the profile of cerebrospinal fluid findings in children aged 3months to 12 years who present with fever and convulsions at Kenyatta National Hospital. This study will involve being asked some questions about your child and it will also mean that a lumbar puncture will be performed for your child. A lumbar puncture is a procedure that involves putting a needle onto the lower backbone of the child to obtain cerebrospinal fluid. Cerebrospinal fluid is the normal clear fluid that is found in the brain and around

the spinal cord. This fluid may be affected when a child has a disease involving the brain or nerves. A few examples of these diseases are meningitis, encephalitis, febrile convulsions and others. The cerebrospinal fluid will then be taken to the laboratory for various tests. About 1 ml of cerebrospinal fluid is enough for these tests.

Benefits

The cerebrospinal fluid results will be relayed to the doctors involved in the care of your child and appropriate treatment will be prescribed for the child in the case of abnormal cerebrospinal fluid results.

Compensation

There will be no monetary compensation for participating in the study. Participation is on voluntary basis.

Cost

The principal investigator will cover the cost of doing the cerebrospinal fluid tests.

Risk

- Backache is common especially at the site of the lumbar puncture. The child may also experience headache. In the event of this, painkillers like panadol will be administered to the child.
- The child may experience some shooting pain down the legs as the procedure is being done; this usually resolves when the needle is removed.
- The child may bleed at the site of needle insertion or into the spinal canal. This is experienced especially if the child is on blood thinning drugs for example warfarin, heparin or aspirin.
- Lower limb weakness or numbness is an uncommon complication.
- Other neurological problems such as double vision are rare.
- Very rarely may infection at the needle site or in the spinal fluid occur.
- Local lumps (dermoids) at the needle site may occur as a result of occasional implantation of skin cells.
- Brain herniation or coning (some movement of part of the brain) may occur very rarely. Physical disability or death may be an end result if brain herniation takes place.

Voluntariness

Your participation in this study will be on voluntary basis. You may refuse to consent or withdraw your consent at any point in the study and this will not affect the care that the child receives at the hospital.

Request to access medical records

The principle investigator will request access to laboratory results as recoded in the patient's file. The abstraction of these results from the file will be done from the second day of admission as this allows time for the results to be filed by the records clerk. These results will mostly constitute routine blood tests that will be taken at the Paediatric Emergency Unit on the day of admission (Taking of blood tests is a routine admission procedure that is done for all patients being admitted).

Confidentiality:

The information obtained about your child will be confidential. No specific information regarding you or your child will be released to any person without your written permission.

Results Sharing:

The results of the study will be published and may be used for teaching purposes but no published information will be linked to your child. The results will be in regards to all children who participate in the study.

If you have any questions pertaining to the study, you may contact me on the following addresses;

DR. JEMIMAH K. MUGO,

DEPARTMENT OF PAEDIATRICS & CHILD HEALTH

UNIVERSITY OF NAIROBI
P.O.BOX 19676-00200,
PHONE NO.0720201171

THE SECRETARY
KNH/UON ETHICS & RESEARCH COMMITTEE
P.O.BOX 20723-00202, NAIROBI
TEL. 020 2726300-9
EMAIL: KNHplan@ken.Healthnet.org

CONSENT FORM FOR PARENT/GUARDIAN

The above study has been explained to me. I have understood the aim of the study and my rights as a parent/guardian to the participant. The risks of the lumbar puncture procedure have also been explained. I have been informed that I can ask questions and terminate my participation in the study whenever I choose. I voluntarily accept to be part of the study.

Signed(parent/guardian) ……

Signed (principle investigator) ……

Date……

MAELEZO KWENYE CHETI CHA RIDHAA

Mtafiti: Daktari.Jemimah K.Mugo(Chuo Kikuu cha Nairobi)

Asante kwa kuchukua muda kusoma maandishi haya. Maandishi haya ni kukueleza juu ya utafiti huu.Tafadhali soma kwa maakini. Unaruhusiwa kuuliza maswali.

Watoto wachanga wanaweza kupatwa na ugonjwa wa homa ya uti wa mgongo ama ugonjwa ambao unadhuru ubongo. Watoto wanaopatwa na joto ya mwili na kifafa wanahitaji kuletwa hospitali ili kufanyiwa vipimo na kupata matibabu.Utafiti huu unahusu upimaji wa maji kutoka kwa uti wa mgongo kwa watoto wa umri wa miezi tatu hadi maika kumi na mbili ambao wanaletwa hospitali ku ya Kenyatta wakiwa na joto ya mwili na kifafa. Utafiti huu utahusu kuulizwa maswali kadhaa kuhusu mtoto wako na pia kuna kipimo ambacho kitafanywa. Mtoto atadungwa sindano ndogo kwa uti wa mgongo ili kupata maji ambayo huwa kwa ubongo na ambayo huzunguka ubongo. Kipimo hiki kinahitaji mililita moja ya maji hayo ambayo yatatumwa kwa maabara.

Kujitolea kushiriki

Kukubali mtoto kushiriki kwa utafiti huu ni kwa hiari yake mtu mwenyewe.Hakutakwepo na

kulazimishwa.

Faida

Madaktari wanaotibu mtoto wako wataelezwa kuhusu matokeo ya kipimo cha maji hayo ya mgongo na itawasaidia kubadilisha matibabu kulingana na majibu.

Malipo.

Mtafiti atalipia kipimo cha kutolewa maji ya mgongo na vipimo vitakavyofanywa maabarani kwa maji haya.

Madhara

Mtoto atahisi uchungu akidungwa sindano hiyo kwa mgongo. Kuna uwezekano wa kuumwa na kichwa kwa muda mfupi.Hiyo ikitokea,mtoto atapatiwa dawa ya kumaliza uchungu .Anaweza kuhisi uchungu unaoenda mpaka kwa mguu. Kuna uwezekano wa kutoka damu pahali ambapo atadungwa kutoa maji hayo na kukosa nguvu kwa miguu kwa muda mfupi.

Hakikisho la siri kwa mhusika

Yale yote ambayo yatanakiliwa kuhusu mtoto wako yatabaki kuwa siri na hakuna majina ambayo yatatumika ambayo yanaweza kukutambulisha wewe ama mtoto wako.

Utumizi wa matokeo ya utafiti huu:

Matokeo ya utafiti huu yanaweza kuchapichwa kwa majarida ya kisayansi lakini siri ya mshiriki
itadumishwa.

Haki yako ya kujiondoa kwa utafiti huu:

Una haki ya kujiondoa kwenye utafiti huu wakati wowote ule.Hiyo haitadhuru matibabu amabyo mtoto atahitaji.

Ukiwa na maswali yoyote kuhusu utafiti huu,unaweza kutumia nambari hizi.

DR.JEMIMAH K.MUGO
DEPARTMENT OF PAEDIATRICS & CHILD HEALTH
UNIVERSITY OF NAIROBI
P.O.BOX 19676-00200,
NAIROBI
PHONE NO.0720201171

THE SECRETARY
KNH/UON ETHICS & RESEARCH COMMITTEE
P.O.BOX 20723-00202, NAIROBI
TEL. 020 2726300-9
EMAIL: KNHplan@ken.Healthnet.org

Cheti cha ridhaa:

Nimeelezwa kuhusu utafiti huu. Nimeelewa kanuni zote zinazohusu utafiti huu na pia nimeelezwa madhara ambayo yanaweza kutokea. Ninaelewa kuwa ninaruhusiwa kuuliza maswali ambapo nitakuwa nayo.Ninaelewa kuwa ninaweza kukataa kuendelea na utafiti huu wakati wowote na hiyo haitadhuru matibabu ambayo mtoto anapata. Nimejitolea kutoa idhini kwa niaba ya mtoto wangu.

Sahihi ya mzazi ……Sahihi ya mtafiti ……..Tarehe ……

APPENDIX 2: STUDY QUESTIONNAIRE

STUDY TITLE: <u>PROFILE OF CEREBROSPINAL FLUID FINDINGS IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH FEVER AND CONVULSIONS AT KENYATTA NATIONAL HOSPITAL.</u>

<u>Kindly read the questions and answer appropriately:</u>

Principal Investigator: Dr. Jemimah K. Mugo

Study ID: _____

Date of data collection: _____

<u>DEMOGRAPHICS</u>

1. Age of child: _____ (months / years)
2. Sex of child:

   1.Male 2.Female

3. Residence:
   1. Town_____
   2. Neighborhood/estate:_____
4. Immunization status (provide card if available):
   1. Pneumococcal (number):_____
   2. Pentavalent (number):_____
5. Education level of mother
   1. Less than primary school
   2. Secondary school
   3. Tertiary education
6. Was this child referred from another health facility?
   1. No
   2. Yes (specify):_____
7. Was this child admitted in the last 1 month at a health facility?
   1. No
   2. Yes(specify):_____

<u>CLINICAL PRESENTATION</u>

8. Did the child have fever?
   1. Yes
   2. No
9. How long has the fever lasted?
   1. Less than 24 hours
   2. 24 – 48 hours
   3. 48-72 hours

4. Greater than 72 hours (specify): _____ days

10. Any history of travel to a malaria endemic area? (Coast, Nyanza or Western regions)
    1. No
    2. Yes (specify):
        i. Location _____
        ii. Last potential exposure _____ days/months before presentation
    3. Unsure
11. When did the convulsions start?
    1. Less than 24 hours ago
    2. 24 – 48 hours ago
    3. 48-72 hours ago
    4. Greater than 72 hours (specify): _____ days
12. How many separate times in the last 24 hours did the child convulse?
    1. One
    2. More than one (specify): _____
    3. Not sure
13. How long did the convulsion last?
    1. Less than 15 minutes
    2. More than 15 minutes (specify): _____
    3. Notsure
14. What was the pattern of the seizure (ask parent to describe)?
    1. Focal
    2. Generalized
    1. Other (specify): _____
    2. Unsure / unclear
15. Has the child ever had a convulsion in the past?
    1. No
    2. Yes .3. Unsure
16. Is the child taking any medication to control convulsions?
    1.Yes
    2. No
    3.Unsure

Did the child have any other symptoms apart from fever and convulsions? (read list)

16. Diarrhea	(Yes/No)	Duration (if yes): _____ days
17. Vomiting	(Yes/No)	Duration (if yes): _____ days
18. Cough	(Yes/No)	Duration (if yes): _____ days
19. Refusal to feed	(Yes/No)	Duration (if yes): _____ days
20. Difficulty breathing	(Yes/No)	Duration (if yes): _____ days
21. Irritability	(Yes/No)	Duration (if yes): _____ days

22. Lethargy / weakness (Yes/No) Duration (if yes): _____ days
23. Headache (Yes/No) Duration (if yes): _____ days

PHYSICAL EXAMINATION

VITAL SIGNS

24. Temperature: _____C (axillary)
25. Respiratory rate: _____
26. Pulse: _____

Neurologic examination

27. State of consciousness(AVPU scale)
    1. Alert
    2. Responds to voice
    3. Responds to pain
    4. Unresponsive/unconscious

28. Bulging fontanelle: Yes / No
29. Neck stiffness: Yes/No
30. Kerning's sign: Yes/No
31. Opisthotonous: Yes/No
32. Unequal pupils(anisocoria): Yes/No
33. Spastic tone across all limbs: Yes/No
34. Reduced tone across all limbs: Yes/No
35. Reduced tone/weakness of one limb: Yes/No

LABORATORY RESULTS

The following laboratory tests will be done by the principle investigator. Record the results below.

CSF appearance

1. Clear
2. Turbid
3. Other:specify_____

CSF biochemistry

1. CSF protein _____g/dl
2. CSF glucose _____mmol/L

CSF microscopy

3. CSF gram stain
    1. No organisms seen
    2. Gram positive organisms. Specify_____
    3. Gram negative organisms. Specify_____

CSF cytology

4. CSF red blood cell count_____ cells/mm^3
5. CSF white blood cell count _____cells/mm^3
6. *CSF culture results:*
    1. No organisms isolated
    2. Organisms isolated. Specify_____

Blood glucose

7. Random Blood Sugar: _____ mmol/L

The following laboratory results may be abstracted from the patient's file:

Full Hemogram:

8. Hemoglobin: _____ g/dL(or *not available*)
9. RBC:_____(*or not available)*
10. WBC: _____ (or *not available*)
11. Platelets: _____ (or *not available*)

BS for MPS

1.No MPS seen

2.MPS seen _____

HIV test

1.Negative

2.Positive

UEC:

12. Sodium(Na): _____mmol/L(or *not available*)
13. Potassium(K): _____mmol/L(or *not available*)
14. Creatinine: _____(or *not available*)
15. Urea: _____ (or *not available*)

Other chemistries:

16. Calcium: _____(or *not available*)
17. Blood culture results: _____(or *not available)*
18. Urine culture results: _____ (or *not available)*

APPENDIX 3:SCREENING FORM

PROFILE OF CEREBROSPINAL FLUID FINDINGS IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH FEVER AND CONVULSIONS AT KENYATTA NATIONAL HOSPITAL.

1. Age (3 months to 12 years): _____

2. Child presenting with fever (38ºC and above) and convulsions: _____

3. Signs of contraindication of Lumbar Puncture (exclude these patients)

- Anisocoria (unequal pupils)
- Signs of raised intracranial pressure (Irregular breathing, bradycardia and hypertension).
- Skin infection at the lower back
- Focal neurological signs: paralysis of any limb
- Cardiopulmonary compromise requiring resuscitation.
- Coagulopathy and thrombocytopenia (platelet count of less than 50).

4.Exclude patients with known history of

- Epilepsy (two or more unprovoked seizures in the past)
- History of head injury
- Cerebrovascular accident (stroke)
- Hydrocephalus

APPENDIX 4: TIME FRAME

The following is the expected time frame of the study process

No	Activity	Estimated time
1.	Proposal development and presentation	January to April 2016
2.	Proposal submission	May 2016
3.	Data collection	September to April 2017
4.	Data analysis	April 2017
5.	Thesis writing	June 2017
6.	Poster presentation	May 2017
7.	Thesis submission	July 2017

APPENDIX 5: STUDY BUDGET

The following is the estimated budget cost for the study.

Category	Remarks	Units	Unit Cost	Total (Ksh.)
Proposal preparation	Proposal copies	6 copies	300.00	1,800.00
Data Collection	Stationery pack (Pens, paper etc)	10	100.00	1,000.00
	Training research assistants	1	1,000.00	1,000.00
	Research Assistants	1	15,000.00	15,000.00
	Laboratory cost	84	1800.00	151,200.00
Data Analysis	Statistician	1	30,000.00	30,000.00
Thesis Write up	Printing drafts	500pages	5.00	2,500.00
	Printing Thesis	10 copies	1,500.00	15,000.00
Contingency fund				6,000
Total				**234,400.00**

APPENDIX 6: CSF RESULTS DISPATCH FORM

STUDY TITLE: PROFILE OF CSF FINDINGS IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH FEVER AND CONVULSIONS AT KENYATTA NATIONAL HOSPITAL.

1. Study ID No: _____

2. Age: _____

3. Sex: _____

4. Date of sample collection: _____

5. Date of results dispatch: _____

Test	Results
CSF appearance	
CSF glucose	
CSF protein	
CSF WBC cell count	
CSF Gram stain	
CSF culture	
Organisms isolated in CSF positive culture	
Sensitive antibiotics to organisms isolated on CSF Positive cultures	