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## The predictors of acute bacterial meningitis among children presenting as first complex febrile seizure

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### Abstract

The association between febrile seizure and bacterial meningitis is well established. Although FS induced by age related hyper-excitability of the brain to fever, determining the cause of the fever is critical in the evaluation of these children. It is therefore imperative to rule out BM prior to making the diagnosis of FS. However, the diagnosis of FS in certain subgroups of children with an apparent FS is a challenge: It is mandatory to look for signs of raised intracranial pressure i.e. bulging fontanel, papilloedema and signs of meningeal irritation to exclude meningitis. After approval from the institutional ethics committee, the study was initiated. The parents of children admitted to our institute who were fulfilling the inclusion criteria were informed about this study. Only those patients presenting as first complex febrile seizures are included in the study. Written informed consent from the parents of patients admitted in paediatric wards of Post Graduate Institute of Paediatric Sciences were taken. All cases of ABM had positive CRP compared to the 19% (n=22) cases without bacterial meningitis had positive CRP. Out of total 125 cases, 96.8% (n=122) had negative blood culture, 3.2% (n=4) had positive blood cultures and the blood culture was positive in 3 (33.3%) of ABM cases and 1 (0.8%) with NO ABM. This difference between positive blood culture and ABM was statistically significant.

**Keywords:** Febrile seizure, bacterial meningitis, CRP

### Introduction

Febrile seizures are defined as the seizures that occur between the ages of 6 months to 5 years with a temperature of 38 °C or higher, are not the result of central nervous system infection or any metabolic imbalance, and occur without a history of prior afebrile seizures.

Febrile seizures are the most common form of childhood seizures, affecting 2% to 5% of all children and these seizures are mostly self-limiting with no long-term sequelae however, about 1-6% of the patients develop epilepsy later in life, especially those with the history of complex febrile seizures [1].

Febrile seizures are classified as simple and complex and about 65-90% of febrile seizures are simple. The incidence of febrile seizure increases to four folds if history of febrile seizure present in the family, and about 31% in first-degree relatives. This also shows there is some genetic aetiology behind these seizures, but little is known about it. Other reasons of febrile seizures are increased electrical activity of heated neuron probably by altering the activity of ion channels; cytokines released during fever, specifically interleukin-1, and alkalosis induced by hyperventilation during fever increases neuronal excitability. A recent study has shown that the incidence of febrile seizures, especially the complex variety, has increased over the last decade. For simple febrile seizure, no long term treatment is required. But for febrile seizure lasting more than 5 minutes, acute treatment with diazepam, lorazepam and midazolam is needed. Besides treatment, parental counselling is another important aspect of management. In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long term benefits, even if recurrence rate of febrile seizure is expected to be decreased by these drugs. No mortality or morbidity is associated with febrile seizure, even with prolonged febrile seizures no motor or cognitive deficit has been reported. Febrile seizure is a diagnosis of exclusion. So, it is important to rule out all other causes of seizures [2, 3].

The association between febrile seizure and bacterial meningitis is well established. Although FS induced by age related hyper-excitability of the brain to fever, determining the cause of the fever is critical in the evaluation of these children. It is therefore imperative to rule out BM prior to making the diagnosis of FS. However, the diagnosis of FS in certain

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subgroups of children with an apparent FS is a challenge: It is mandatory to look for signs of raised intracranial pressure i.e. bulging fontanel, papilloedema and signs of meningeal irritation to exclude meningitis [4]. FS may be the sole manifestation of BM in infants; complex features of seizure can increase the risk of BM in others. Accordingly, when these children present with an apparent FS, clinicians may remain uncertain about the risk of BM. In acute situation, the most challenging issue is to make a decision whether a lumbar puncture (LP) is necessary to rule out BM. Knowledge of the prevalence of BM among various subgroups of children with FS can assist clinicians to make appropriate clinical decisions in such challenging situations. There are several clinical studies worldwide reporting the prevalence of meningitis among children with FS. Some of these studies suggest that in the absence of typical meningeal signs, an LP should be considered in children with complex seizures, prior antibiotic therapy, and age less than 12 months, or incomplete vaccination history [5].

With the increasing in vaccination against the causal agents of bacterial meningitis, the incidence of meningitis has been decreasing with time. Several investigations have been conducted and reported on the need for LP in febrile seizure cases. Because of the low meningitis incidence in these investigations, the rate of LP in febrile seizures has been declining so, there is a need to re-evaluate the recommendations of AAP. In 2011, the AAP evaluate the results of the intervening studies and reported new evidence based recommendations for simple febrile seizure (SFS). It focuses on identifying the source of fever rather than performing a standard seizure workup, and examining signs of encephalitis or meningitis by performing a lumbar puncture on children presenting with clinical signs of neurological disease. However, to our knowledge there is no consensus as to the need for LP in complex febrile seizure (CFS). Medical providers often elect to perform lumbar punctures on these patients to rule out acute bacterial meningitis (ABM), although recent literature has shown that ABM is rarely diagnosed in the absence of other clinical signs and symptoms of serious neurological disease. Probability of acute bacterial meningitis (ABM) in children having fever with seizure varies from 0.6% to 6.7%. (28)ABM in early childhood has a considerable mortality, morbidity and serious long term sequels. Therefore early diagnosis and prompt treatment of ABM are essential and cerebrospinal fluid (CSF) examination helps in this objective [6].

The possibility that a febrile seizure may be the sole presenting sign of acute bacterial meningitis (ABM) remains a major concern, more so in cases of complex febrile seizures. It is essential to exclude underlying meningitis in all children presenting as CFS by lumber puncture (LP). The majority of such cases of meningitis are bacterial in origin, and delay in diagnosis can result in serious neurologic morbidity, and even death. There are few studies in our

country in this aspect.

**Methodology**

The study includes the children between the ages of 6 months to 5 years admitted as first complex febrile seizure in the department of pediatric medicine, at a Tertiary care hospital.

After approval from the institutional ethics committee, the study was initiated. The parents of children admitted to our institute who were fulfilling the inclusion criteria were informed about this study. Only those patients presenting as first complex febrile seizures are included in the study. Written informed consent from the parents of patients admitted in paediatric wards of Post Graduate Institute of Paediatric Sciences were taken. After obtaining informed consent, demographic details, details of current illness like fever-type, duration and grading (High-grade fever was defined as the temperature >104°F), convulsions-type, duration and number of episodes, any prior hospitalization and medication, co-morbid diseases, past history of convulsions, birth and developmental history, immunization history and family history of febrile seizure was elicited. A thorough clinical examination was performed and observations were noted on the study Performa. Laboratory investigations including CSF analysis were done in all children. Lumbar puncture for CSF analysis was done after stabilizing the patient in less than 24 hours of admission. EEG was done in all patients after 2 weeks of febrile seizure to identify the nature of underlying cerebral pathology and predict the risk of future seizures. CT scan brain was done in patients who presented with febrile status epilepticus and having abnormal neurological examination before performing lumbar puncture.

**The following definitions are used in our study**

A complex febrile seizure is more prolonged (>15min), is focal, and/or reoccurs within 24 hr. In the presence of any one of these features, the febrile seizures is considered complex.

Bacterial meningitis was defined by positive cerebrospinal fluid (CSF) culture results for a relevant bacterial pathogen, positive Gram’s staining of CSF with a negative CSF culture, CSF pleocytosis with positive blood culture of a relevant bacterial pathogen, with CSF protein >00mg% and glucose <40mg/dl. Pleocytosis was defined by ≥5 white blood cells per Ml.

Based on the above mentioned criteria, study subjects were divided into two groups, -children with acute bacterial meningitis (ABM) and-children with no acute bacterial meningitis (NO ABM) Clinical, demographic and laboratory features were analyzed and compared between the two groups.

**Results**

**Table 1:** Association between abnormal neurologic examination and acute bacterial meningitis

Neurological examination	Etiology				Total		P Value
	ABM	%	NO ABM	%	Number	%	
Abnormal	2	22.2	0	0	2	1.6	0.0046
Normal	7	87.8	116	100	123	98.4	
Total	9	100	116	100	125	100	

Among 9 ABM cases, 2(22.2%) had abnormal neurological examination at the time of admission and none of the patients without acute bacterial meningitis had abnormal neurological examination. This association between abnormal neurological examination and ABM was found to be statistically significant.

**Table 2:** Association of Anemia with ABM

Hemoglobin	Etiology				Total		P value
	ABM	%	No ABM	%	Number	%	
Anemia	7	77.7	42	36.2	49	39.2	
No Anaemia	2	22.2	74	63.8	76	60.8	0.00001
Total	9	100	116	100	125	100	

Out of total 125 subjects, 39.2% (n=49) of them had anaemia and 60.8% (n=76) had normal Haemoglobin level. 7(77.7%) cases of ABM had anaemia compared to 36.2% without acute bacterial meningitis had anaemia. This association between anemia and ABM was significant.

**Table 3:** Association between increased total leucocyte count and acute bacterial meningitis

Total leucocyte count	Etiology				Total		P value
	ABM	%	NO ABM	%	Number	%	
Increased	8	88.8	18	15.6	26	20.8	
Normal	1	11.1	98	84.4	99	79.2	0.0000001
Total	9	100	116	100	125	100	

Df-1, P value -0.0000001

Among 9 meningitis patients, 88.8% (n=8) had increased Total leucocyte count while 11.1% (n=1) had normal Total leucocyte count. This difference between increased total leucocyte count and ABM was found to be statistically significant.

**Table 4:** Association between positive CRP and ABM

CRP	Etiology				Total		Fisher exact P value
	ABM	%	NO ABM	%	Number	%	
Positive	9	100	22	19	31	24.8	
Negative	0	0	94	81	94	75.2	0.0000001
Total	9	100	116	100	125	100	

All cases of ABM had positive CRP compared to the 19% (n=22) cases without bacterial meningitis had positive CRP. The association between positive CRP and ABM statistically significant.

**Table 5:** Association between hyponatremia and ABM

Hyponatremia	Etiology				Total		P value
	ABM	%	NO ABM	%	Number	%	
Yes	7	77.7	18	15.5	25	20	
No	2	22.3	98	84.4	100	80	0.0000001
Total	9	100	116	100	125	100	

Chi square -1.631, df-1 P value-0.0000001

Out of total 125 cases, 14.4% (n=18) had hyponatremia while 85.6% (n=107) had normal serum sodium level. Hyponatremia was found in 7 (77.7%) cases of ABM compared to 15.5% without bacterial meningitis. The association between Hyponatremia and ABM was statistically significant.

**Table 6:** Association between blood culture and ABM

Blood C/S	Etiology				Total		Fisher exact P value
	ABM	%	No ABM	%	Number	%	
Positive	3	33.3	1	0.8	4	3.2	
Negative	6	66.7	115	99.2	121	96.8	0.0000001
Total	9	100	116	100	125	100	

df-1, Fisher exact P value-0.0000001

Out of total 125 cases, 96.8% (n=122) had negative blood culture, 3.2% (n=4) had positive blood cultures and the blood culture was positive in 3 (33.3%) of ABM cases and 1 (0.8%) with NO ABM. This difference between positive blood culture and ABM was statistically significant.

**Discussion**

In our study, 13 subjects (10.4%) had CSF pleocytosis (WBC>5). Among them, 9 patients met the criteria of acute bacterial meningitis and all the cases of ABM were having increased CSF protein with reduced CSF glucose. Out of 9 cases of ABM, 7 cases demonstrated bacteria by gram staining in CSF, 4 were gram positive and 3 were gram negative and 3 grew Streptococcus pneumonia in their CSF culture. Blood culture of 3 patients of bacterial meningitis demonstrated evidence of bacteremia with growth of Streptococcus pneumonia, E-coli and klebsiella in patients aged 18 months, 6 months and 7 months respectively. In our study, 3 cases of meningitis demonstrated Streptococcus pneumonia in CSF culture due to none of our study participants received pneumococcal vaccine however, didn't find any cases of Haemophilus influenza type b due to reduction of number of cases of Hib meningitis in India after the introduction of Hib conjugated vaccine in national immunization schedule.

CSF examination revealed patients who presented as febrile status epilepticus had increased risk of having bacterial meningitis. Similar case series were reported by RFM Chin [7], out of 49 children with convulsive status epilepticus with fever 4(17%) children aged 3 months, 9.5 months, 18 months, 26 months were confirmed to have ABM and was concluded that the risk of ABM in a convulsive status epilepticus with fever is much higher than that of short febrile seizures.

In a case control study done in India, it was seen that the iron deficiency anemia is the most important risk factor for febrile convulsion. No such data available for complex febrile seizures. In present study, we found that 39.2% of patients of complex febrile seizures were having haemoglobin level <11g/dl and classified as anemic according to WHO classification of anemia. In another study, it was also found to be a significant relationship between anemia and bacterial meningitis, also correlates in our study, haemoglobin level was marginally low in children with meningitis than the rest of the study population. It was because iron deficiency anemia is very much prevalent in Indian setup and might be due to a predisposition to infection in a nutritionally compromised child [8].

In laboratory parameters in study population about 20% cases of complex febrile seizure had hyponatremia and out of 9 cases of bacterial meningitis, 7 cases had hyponatremia which reveals 77.7%, this may be due to retention of water caused by increased secretion of antidiuretic hormone

(ADH) in patients with meningitis. Similar study conducted by F. Shann *et al*, 50% of patients with bacterial meningitis had hyponatremia<sup>[9]</sup>.

We found that postictal drowsiness, neurological deficit, body temperature >104°F, increased WBC count above the age wise reference range, positive CRP are the predicting factors for bacterial meningitis in our study. A study conducted in Iran also concluded that postictal drowsiness, neurological deficit, body temperature  $\geq 38.5$  °C, WBC count >15000/cumm and Hb <10.5g/dl were clinical and laboratory factors predictive of meningitis in cases with first attack of seizure and fever<sup>[10]</sup>.

In our study 28.8% of children who are presented as complex febrile seizure had abnormal EEG findings and among 9 cases of ABM, 8(88.8%) had abnormal EEG findings due to structural and functional alterations of the brain resulting from the meningitic process that may induce seizures include vasculitis and infarction, fever, electrolyte imbalances and metabolic changes. Neuroimaging was done in 6 patients who presented with febrile status epilepticus and having abnormal neurological examination, only one patient had diffuse leptomenigeal enhancement in the contrast enhanced CT scan of brain.

### Conclusion

In the laboratory findings, increased TLC, positive CRP, hyponatremia and Hb <11g/dl are more prevalent in meningitis patients. EEG findings were abnormal in 88.8% cases of ABM in the acute phase. Out of 6 patients in whom CT scan brain was done, only one had diffuse leptomenigeal enhancement.

We found that presence of high grade fever (>104°F), febrile status epilepticus, postictal drowsiness and abnormal neurological examination are the main clinical predictors of meningitis.

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