HK J Paediatr (new series) 2016;**21**:156-161

The Possibility of Bacterial Meningitis in First Simple or Complex Febrile Seizures among Children 6-24 Months of Age: An Evaluation of 564 Patients

A ***Kanik***, K ***Eliacik***, S ***Yesiloglu***, M ***Anil***,
DY ***Ciftdogan***, U ***Karadas***, B ***Sarioglu***, M ***Helvaci***

Abstract ***Purpose:*** The aim of this study was to assess the probability of bacterial meningitis presenting with a first simple febrile seizure or complex febrile seizure without any conspicuous signs of meningitis. ***Methods:*** This was a record based cross-sectional study of 564 patients of 6-24 months of age and was evaluated in a paediatric emergency department between 2007 and 2013 for their first febrile seizure. ***Results:*** In the study group 452 (80%) were diagnosed with simple febrile seizure and 112 (20%) with complex febrile seizure. In neither group was any patient diagnosed with bacterial meningitis. The number of children undergoing lumbar puncture was significantly higher in the complex febrile seizure group ($p<0.001$). ***Conclusion:*** The ratio of bacterial meningitis was not increased in patients with complex febrile seizure who otherwise appeared well and lacked clinical findings of meningitis like the patients with simple febrile seizure.

Key words Bacterial meningitis; Complex febrile seizure; Infant; Lumbar puncture; Simple febrile seizure

Department of Pediatrics, Tepecik Teaching and Research Hospital, Izmir, Turkey

A **Kanik** *MD*
K **Eliacik** *MD*
S **Yesiloglu** *MD*
U **Karadas** *MD*
M **Helvaci** *MD*

Department of Pediatric Emergency Medicine, Tepecik Teaching and Research Hospital, Izmir, Turkey

M **Anil** *MD*

Department of Pediatric Infectious Diseases, Tepecik Teaching and Research Hospital, Izmir, Turkey

DY **Ciftdogan** *MD*

Department of Pediatric Neurology, Tepecik Teaching and Research Hospital, Izmir, Turkey

B **Sarioglu** *MD*

Correspondence to: Dr A **Kanik**

Received October 25, 2015

**This study has been presented at the 57th Turkish National Pediatric Congress, Antalya, Turkey in 03 November 2013 and won the special award of oral presentation.*

Introduction

A febrile seizure is generally defined as a seizure concomitant with a fever and without central nervous system infection, occurring in children between 6 months and 5 years of age. According to the American Academy of Pediatrics (AAP) practice parameter in 1996, lumbar puncture (LP) was strongly recommended in infants up until 1 year of age because other symptoms of acute bacterial meningitis might not be present during this time. A child of 12-18 months of age should also be evaluated for signs of LP because clinical signs of meningitis may be vague in this age group.[1]

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 reevaluate the recommendations of AAP.[2] In 2011, the AAP evaluate the results of the intervening studies and reported new evidence-

based recommendations for simple febrile seizure (SFS).[3] However, to our knowledge there is no consensus as to the need for LP in complex febrile seizure (CFS). In this study our aim was to determine the ratio of meningitis and the need for LP in SFS and CFS patients of 6-24 months of age without any conspicuous signs of meningitis.

Materials and methods

This record based croos-sectional study was performed to evaluate patients 6-24 months of age who were admitted in the first 12 hours to a training and research hospital paediatric emergency department between March 2007 and April 2013 with first-time febrile seizures. The number of cases admitted to this emergency department is approximately 150,000 annually and six paediatricians work on a shift.

According to the descriptive criteria the patients were divided into groups of simple and complex febrile seizures. A complex febrile seizure was defined as the duration of more than 15 minutes, with a reoccurrence within 24 hours and focal seizures.[3] Cases were divided into two groups, with the first group comprising of patients between 6-12 months of age and the second group comprising of patients between 12-24 months. Age, gender, vaccination status, type of seizure, physical examination findings, and laboratory findings from all patients were analysed. The exclusion criteria included a prior history of seizures, lack of *Haemophilus influenzae* type b and *pneumococcal* vaccines, underlying neurological disease, the presence of a ventriculoperitoneal shunt, recent trauma and/or neurosurgical intervention, the presence of clinical findings of meningitis (e.g., bulging fontanelle, toxic appearance and lethargy), history of antibiotic usage before admission, and insufficient medical records.

The current study aims to detect the possibility of meningitis through a retrospective analysis of SFS/CFS charts. An analysis of emergency charts for a 72-month period (March 2007 to April 2013) was undertaken inorder to identify potential subjects. Data maintained through the retrieval of electronic medical records. Patients who were between 6 months and 2 years of age and who had the terms "febrile seizure" and "bacterial meningitis", according to the ICD-10 codes, were included in the study.

In all types of febrile seizure, patients with meningeal signs, a poor general condition and lack of vaccination and administration of antibiotics before admission were indicators. In cases without obvious clinical signs of meningitis of SFS cases the guideline of AAP was taken into consideration before performing LP. In practice, for CFS cases without these signs or symptoms, the decision to LP was tailored to each individual child's general condition.

Origin of fever as an ethiological factor for febrile seizures and the ratios of LP for any type of febrile seizure over the time were recorded.

A complete blood count, serum electrolytes, and C-reactive protein (CRP) measurements was taken and recorded with values of CRP over 5 mg/L and white blood cell (WBC) over 17,000/µL being deemed to be 'high'. Pleocytosis was defined as a cerebrospinal fluid (CSF) white cell count of 10/µL.[4] The diagnosis of bacterial meningitis was made with the CSF findings, where the CSF appearance may be cloudy, depending on the presence of significant concentrations of WBC, bacteria, and/or protein. The diagnostic tools used were elevated protein concentration, a ratio of CSF to serum glucose of <0.4, a neutrophil predominance in the CSF, a number of the WBC count is elevated, usually in the range of 1000-5000 cells/µL, although this range can be quite broad (<100 to >110,000 cells/µL), the presence of bacteria upon Gram staining, and a positive CSF culture.[5] Medical charts were monitored for the patients who were sent home without the need for LP.

The data was evaluated using the SPSS software (ver. 16.0 for Windows; SPSS, Inc., Chicago, IL, USA). Normally distributed data are presented as means ± standard deviations, whereas skewed data is presented as medians (interquartile ranges). Odds ratio (OR) and 95% confidence intervals (CI) were used to analyse the strength of the associations for the regression model output. For the evaluation of rational data, the χ^2 test was used. Differences between groups were calculated using independent samples of Student's *t*-test for normally distributed data and the Mann-Whitney *U*-test for non-normally distributed data. P values ≤0.05 were considered to indicate statistical significance.

Results

The study population consisted of 564 patients of which 295 (52%) were males. Among this population, 452 (80%) were SFS and 112 (20%) were CFS cases (Table 1). The ratio of lumbar puncture procedures, detection of pleocytosis and CSF culture results for both SFS/CFS patients are shown in Figure 1. All the patients were fully immunised against *pneumococcus* and *Haemophilus influenzae* type b. No biochemical CSF abnormality was detected in both SFS/

CFS patients. Moreover, no bacterial meningitis was detected. No pathogenic microorganism was detected in any of the CSF cultures in either group; in two cases the cultures were determined to be contaminants. Features of the cases with pleocytosis are shown in Table 2. In the follow-up period all of the CFS patients were hospitalised. In the SFS group none of the patients returned to the hospital with a diagnosis of bacterial meningitis who did not undergo LP.

The number of children undergoing LP was significantly higher in the CFS group. The ratios of LP in different age groups are shown in Table 1. The higher ratio was in the 6-12 month age group with the rate of LP significantly higher in CFS cases ($p<0.001$). It was detected that LP in SFS decreased over time. However, the rate of LP did not change for CFS patients over the years of this study.

Upper respiratory tract infection was detected as the most common aetioogical factor for the origin of fever (n=400, 71%). Others were fever of unknown origin (n=58, 10%), lower respiratory tract infections (n=39, 7%), acute gastroenteritis (n=35, 6%), urinary tract infections (n=26, 5%), roseola infantum (n=3, 0.5%), and chicken pox (n=3, 0.5%). However, no significant difference was detected in aetioogy between simple and complex seizures. The most common reason for LP was fever of unknown origin and the difference was significant versus the other aetioogical reasons (p<0.001). According to the age groups, fever of unknown origin was significantly higher in the 6-12 months age group (p<0.001).

For all cases, the average white blood cell count (WBC) was 13724±6265/μL (median, 12,700/μL). Evaluating WBC, 74.3% were in the normal range, 24.3% showed leukocytosis, and 1.4% was determined to be leukopenic. The average value of CRP was 12.91±20.29 mg/dL (median, 4 mg/dL); it was normal in 58.7% and high in 41.3%. When we compared SFS and CFS in terms of WBC and CRP parameters, no significant difference was found (p=0.736 and 0.950, respectively). The WBC and CRP values were not correlated with LP (p=0.830 and 0.546, respectively; Table 1).

Discussion

In infants with febrile convulsions, the risk of ABM had long been controversial. In the current study, no case of bacterial meningitis were determined among the 6-24 months old patients with SFS and CFS who did not receive antibiotics and who appeared well, with no clinical sign of meningitis.

The main limitations of the study are the reliance on a single referral centre and that it relies on a retrospective analysis of the data. The other limitation of the study is the lack of viral PCR examination of the CSF for the differential diagnosis of aseptic meningitis.

Table 1 Attributes of the patients with SFS/CFS with and without LP at baseline

Parameters	Total patients (n=564) N (%)	LP (+) (n=135) N (%)	LP (-) (n=429) N (%)	OR (95%CI)	*P*
*Age (month)	14.95 (5.51)	11.35 (4.7)	16.13 (5.3)		<0.001
Age groups					
<1 year	182 (32.3)	84 (62.2)	98 (22.8)	3.45 (2.56-4.66)	<0.001
>1 year	382 (67.7)	51 (37.8)	331 (81.2)		
Sex					
Female	269 (47)	61 (45)	208 (48)	0.90 (0.67-1.21)	0.504
Febril seizure					
SFS	452 (80)	70 (52)	382 (89)		<0.001
CFS	112 (20)	65 (48)	47 (11)	4.39 (3.18-6.06)	
WBC ($x10^3$/μL)*	13700 (6260)	13600 (7105)	13800 (5987)		0.814
CRP (mg/L)#	4 (15)	3.65 (13)	4 (15)		0.815
CRP group					
Normal	331 (58)	81 (60)	250 (58.3)	1.03 (0.76-1.39)	0.840

*Mean (SD); #Median (IQR)

Abbreviations: CI: confidence intervals; CFS: complex febrile sezure; CRP: C-reactive protein; LP: lumbar puncture; OR: odds ratio; SFS: simple febrile seizure; WBC: white blood cell

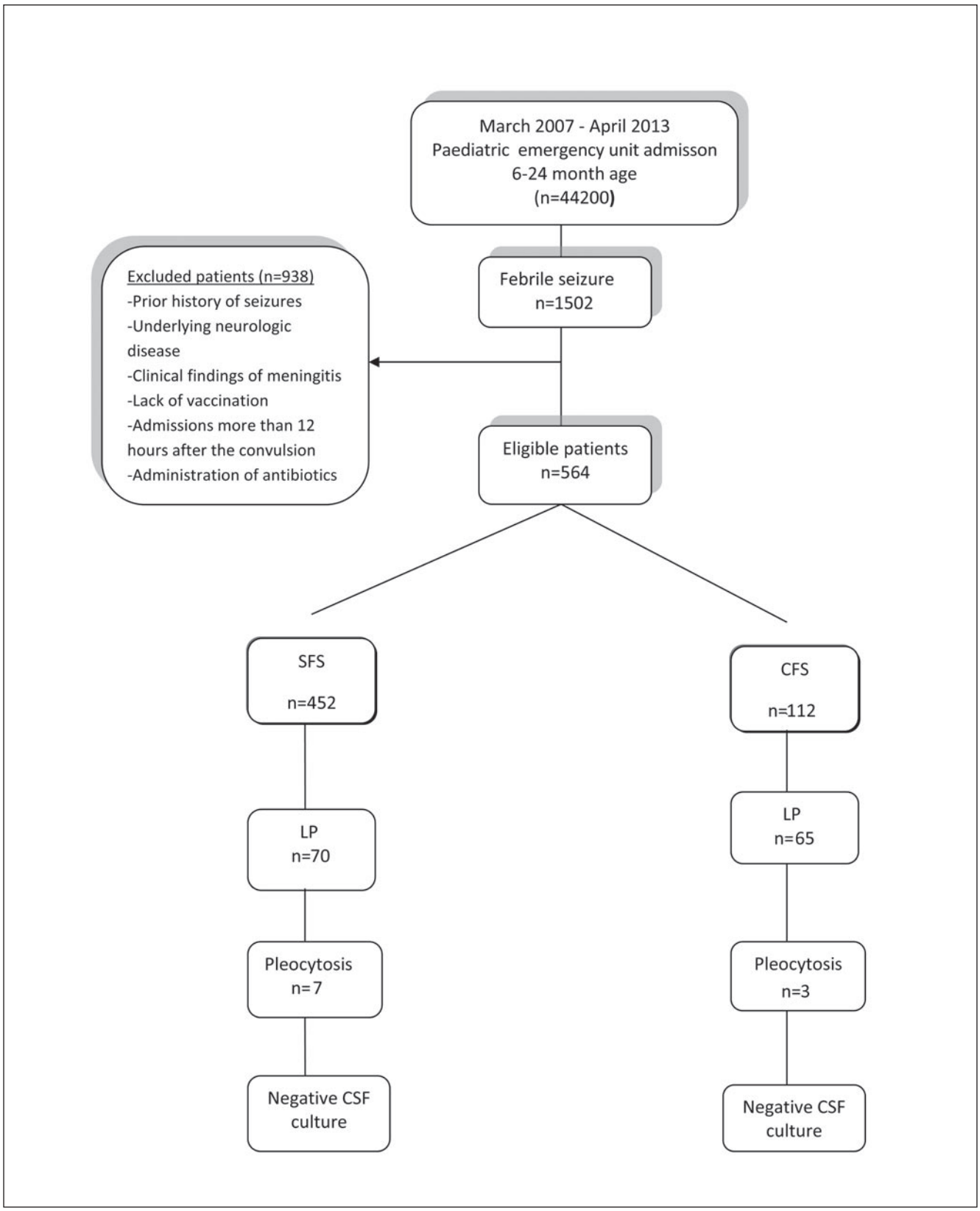

Figure 1 Study design, number of patients, and ratio undergoing lumbar puncture.

Many studies of the relationship between meningitis and febrile seizures have been conducted up until now. Given the changing results and literature, in 2011, the guidelines from the AAP regarding SFS recommend that LP is only used in the presence of clinical findings of meningitis.[3] However, today there is still no guideline for CFS cases. Since no case of bacterial meningitis was found in the series of SFS without the clinical findings of meningitis, the statement 'lumbar puncture rate decreased over the years for SFS but remained the same for CFS' might be due to the clinicians becoming less worried about SFS but remained to be concerned about CFS rather than based on evidence. In three studies, which includes CFS cases, no bacterial meningitis was determined.[6-8] In another study, LP was performed in 146 (37%) of 336 CFS cases and six cases of *Streptococcus pneumonia* meningitis were detected, all of which were reported to have abnormal mental status (1 drowsy, 1 decreased mental status, 3 lethargic, 1 somnolent cases).[9] Kimia et al,[10] performed LP in 64% of 526 CFS cases in the 6-60 month age group and detected two bacterial meningitis cases in patients with obviously abnormal neurological symptoms. Among these 2 patients, 1 was nonresponsive during presentation, and the other had a bulging fontanel and apnea. In a recent retrospective study of 193 CFS patients, LP was performed in 136 and pleocytosis was detected in 14 patients with only 1 case being diagnosed as ABM (this case had a total of 4 febrile seizures, one of which lasted 30 minutes and intubated after receiving anticonvulsants).[11] In a study which was conducted in India with 497 cases, LP was performed in 199 cases, ABM was found 0.5% in SFS and 2% in CFS. In the present study, both SFS and CFS cases under 2 years old were evaluated for bacterial meningitis.[12] However, no case of bacterial meningitis was found in both groups.

Among our cases, only 39% of patients between 6 and 12 months of age with first SFS underwent LP, despite the strong recommendation to perform LP by the AAP in 1996. The corresponding rate was 75% in CFS cases in this group. The reason is the belief for a higher potential risk of bacterial meningitis in CFS cases.

The present study is one of few in recent years that has evaluated the rate of bacterial meningitis in both SFS and CFS. According to the results, there was no increase in the risk of bacterial meningitis in CFS versus SFS. Moreover, the study group consisted of a population of patients under 2 years of age which are at a higher risk because of the obscure clinical findings of meningitis at this age.

For SFS cases, it is not recommended to perform total blood counts or serum electrolyte analyses.[3] In CFS cases, there is no recommendation for performing total blood counts and serum electrolytes. It was determined that neither origin of fever nor serum electrolytes were specific in SFS or CFS patients. Likewise, it was determined that for both SFS and CFS, there is no need to obtain total blood counts or serum electrolytes for the differential diagnosis.

Pleocytosis was detected in 10 (1.7%) of our cases. However, no biochemical or microbiological CSF abnormality was accompanied by a diagnosis of bacterial meningitis. In the cases with seizures, the reason for the pleocytosis remains unclear, but it has been suggested that there may be temporary impairment in the blood-brain barrier.[13] In another study it was stated that seizure-associated

Table 2 Clinical and laboratory findings of the 10 patients with pleocytosis

Case no.	Age (month)	Sex	Seizure type	WBC (mm^3)	CRP (mg/L)	CSF (cell)	CSF glucose (mg/dl)	CSF protein (mg/dl)	CSF culture	Aetiology of fever
1	21	Male	SFS	6300	18.0	20	76	23	Negative	Swine Flu
2	8	Female	CFS	9500	2.0	40	80	12	Negative	FUO
3	11	Female	SFS	16700	17.0	20	61	29	Negative	Pneumonia
4	13	Male	CFS	25700	16.7	20	76	23	Negative	FUO
5	13	Male	CFS	14500	1.0	30	68	37	Negative	AB
6	12	Male	SFS	11500	6.0	80	62	23	Negative	FUO
7	10	Male	SFS	16000	84	70	66	16	Negative	AGE
8	7	Male	SFS	40800	86	30	67	18	Negative	AOM
9	6	Female	SFS	16500	28	30	63	10	Negative	UTI
10	7	Female	SFS	4600	12	50	77	24	Negative	URTI

Abbreviations: AB: acute bronchiolitis, AGE: acute gastroenteritis, AOM: acute otitis media, CFS: complex febrile seizure, CRP: C-reactive protein, CSF: cerebrospinal fluid, FUO: fever of unknown origin, SFS: simple febrile seizure, URTI: upper respiratory tract infection, UTI: urinary tract infection, WBC: white blood cell.

CSF abnormality is rare in children, with postictal pleocytosis and increased protein levels occurring in only 5% and 10% of patients, respectively. They also found that the concept of postictal CSF abnormalities was of limited clinical value.[14]

In conclusion, in this study it was determined that in the cases of first febrile convulsion in patients who otherwise appeared well, the risk of bacterial meningitis was not increased if there was not a lack of vaccination or a history of antibiotic usage. The type of the seizure did not make a difference in terms of the possibility of bacterial meningitis. In cases that otherwise appear well with no sign of bacterial meningitis, LP should not be regarded as a mandatory rule in any type of febrile seizures.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice Parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Pediatrics 1996;97:773-5.
2. Hampers LC, Thompson DA, Bajaj L, Tseng BS, Rudolph JR. Febrile seizure: measuring adherence to AAP guidelines among community ED physicians. Pediatr Emerg Care 2006;22:465-9.
3. Subcommittee on Febrile Seizures; American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 2011;127:389-94.
4. Nigrovic LE, Kuppermann N, Macias CG, et al. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. JAMA 2007;297:52-60.
5. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39: 1267-84.
6. Teach SJ, Geil PA. Incidence of bacteremia, urinary tract infections, and unsuspected bacterial meningitis in children with febrile seizures. Pediatr Emerg Care 1999;15:9-12.
7. Watemberg N, Sarouk I, Fainmesser P. Acute meningitis among infants and toddlers with febrile seizures: time for a reappraisal of the value of a lumbar puncture. Isr Med Assoc J 2012;14:547-9.
8. Boyle DA, Sturm JJ. Clinical factors associated with invasive testing and imaging in patients with complex febrile seizures. Pediatr Emerg Care 2013;29:430-4.
9. Seltz LB, Cohen E, Weinstein M. Risk of bacterial or herpes simplex virus meningitis/encephalitis in children with complex febrile seizures. Pediatr Emerg Care 2009;25:494-7.
10. Kimia AA, Ben-Joseph E, Prabhu S, et al. Yield of lumbar puncture among children who present with their first complex febrile seizure. Pediatrics 2010;126;62-9.
11. Fletcher EM, Sharieff G. Necessity of lumbar puncture in patients presenting with new onset complex febrile seizures. West J Emerg Med 2013;14:206-11.
12. Batra P, Gupta S, Gomber S, Saha A. Predictors of meningitis in children presenting with first febrile seizures. Pediatr Neurol 2011; 44:35-9.
13. Siemes H, Siegert M, Hanefeld F. Febrile convulsions and blood-cerebrospinal fluid barrier. Epilepsia 1978;19:57-66.
14. Wong M, Schlaggar BL, Landt M. Postictal cerebrospinal fluid abnormalities in children. J Pediatr 2001;138:373-7.