ORIGINAL ARTICLE

Clinical Significance of Lumbar Puncture in Children with First Febrile Seizures

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ABSTRACT

Objectives

To evaluate the need for lumbar puncture (LP) in children aged 6 to 60 months experiencing their first febrile seizure, regardless of seizure type, and to determine if LP is particularly beneficial for those under 12 months old.

Materials & Methods

In this retrospective study, data from 253 children who presented with first febrile seizure were analyzed. All patients in this study underwent LP and were divided into two groups based on their cerebrospinal fluid (CSF) results: non-pleocytosis and pleocytosis. Patients were evaluated for age, sex, familial history of seizure, and type and duration of seizures. They were also evaluated based on laboratory results, including blood tests, CSF analysis, and electroencephalography.

Results

Sixty-seven (25.9%) of the 253 patients were under 12 months of age, and only two of the 67 patients (2.8%) had pleocytosis. Patients younger than 12 months did not have a higher rate of complex febrile seizure or pleocytosis than those over 13 months of age. None of the patients had bacterial meningitis. Regarding viral meningitis, seven patients (5.3%; age mean SD, 12.3±1.8 months) were diagnosed with enteroviral meningitis, though only one of them had pleocytosis. When compared to the non-pleocytosis group, the pleocytosis group showed no differences in clinical characteristics (age, sex, familial history of seizure, type, and duration of seizure), laboratory results, or the use of antiepileptic drugs.

Conclusion

The present study suggests that LP should be carefully considered in children with first febrile seizure, including children under 12 months of age.

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Introduction

A febrile seizure (FS) is accompanied by a fever, without central nervous system infection, often occurringin infants and children between six and 60 months of age (1). FS are the most common type of childhood seizures, specifically in children under 60 months of age, affecting 2–5% of all children (2). The 1996 clinical guidelines of the American Academy of Pediatrics (AAP) for the neurodiagnostic evaluation ofa child with simple febrile seizures (SFS) recommended routine lumbar puncture (LP) to exclude underlying bacterial meningitis in children less than 12 months. However, the introduction of the *Haemophilus influenza* type b and pneumococcal conjugate vaccines dramatically decreased in the incidence of bacterial meningitis, leading to questions about the necessity of routine LP in children of this age. According to the revised AAP guidelines of 2011, LP is currently recommended if there are clinical signs or symptoms of meningitis and if the child is considered to have incomplete *H. influenza* type b or *Streptococcus pneumoniae* immunizations (3). The AAP guidelines are limited to SFS, without a consensus regarding the need for LP in complex febrile seizures (CFS).

This study aimed to examine LP's clinical significance and necessity in children presenting with a first febrile seizure (FS) between six and 60 months of age without conspicuous signs of meningitis. Both simple and complex types of FS were assessed, and the results of cerebrospinal fluid (CSF) tests were analyzed. The study also aimed to determine whether LP was needed, specifically in those patients with a first FS before 12 months of age.

Materials & Methods

Study Population

The medical records of 264 pediatric patients admitted to the pediatric department of Kyung Hee University Hospital between September 2004 and September 2019 were retrospectively reviewed. Patients who presented with a first FS and underwent LP were included. Since the *H. influenza* type b vaccine and the pneumococcal conjugate vaccine were implemented into South Korea's national immunization program in 2014, most young children with FS who were hospitalized before this period underwent routine LP. Since 2015, our institution has selectively performed LP according to the revised AAP guidelines of 2011. In addition, our institution routinely recommended LP testing for patients with CFS except in cases where testing was strongly refused. Those patients with known neurologic disorders and/or developmental delay, previous antiepileptic drug (AED) treatment, or at an age less than six months or greater than 60 months were excluded. This study was approved by the institutional review boards of the hospital (IRB No. 2021-03-008). Due to the study's retrospective nature, the institutional review boards waived need for written informed consent. The following clinical data were collected: age, sex, type of seizure, seizure duration, familial history of FS, and use of AEDs. Laboratory results, including blood tests (complete blood counts, C-reactive protein [CRP]), CSF analyses, including herpes simplex virus (HSV) and enterovirus polymerase chain reaction (PCR), and electroencephalogram (EEG) results, were also collected.

Patients were grouped based on their CSF analysis results: the non-pleocytosis or pleocytosis groups. CSF pleocytosis was defined as having five or more corrected white blood cells (WBCs) per microliter. Bacterial meningitis was confirmed

if the CSF culture results were positive. This research also divided the subjects into three subgroups by age: 6-12 months, 13-18 months, and 19-60 months. Demographic and clinical characteristics, laboratory findings, EEG results, and the rates of subsequent prescriptions of AEDs were compared between children aged 6-12 months and those 13 months and older.

SFS was defined as a generalized seizure lasting less than 15 minutes that did not recur within 24 hours. CFS was defined as a seizure with focal features, prolonged duration (≥15 minutes), or recurrence within 24 hours.

Data Analysis

Comparisons between groups were performed using the chi-square test, Fisher's exact test, or Wilcoxon rank sum test using SAS version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was set at $p < 0.05$.

Results

Of the 264 patients whose medical records were reviewed for this study, 11 patients were excluded (six patients with previous diagnoses of developmental delay and five patients discharged against medical advice) to include 253 patients in the analyses. The mean age was 18.3 ± 10.1 months (7 to 60 months), with 67 (26.5%) patients under 12 months of age. Among the population, 187 (73.9%) had SFS and 66 (26.1%) had CFS.

Results of CSF analysis and identification of causative organisms

This study showed that 10 of 253 patients (3.9%) had CSF pleocytosis. The proportion of patients with pleocytosis was 3.7% for those with SFS and 4.5% for CFS. When comparing age groups, the proportions of patients with pleocytosis showed no significant differences: 3.0% for 6-12 month-olds, 4.6% for 13-18 month-olds, and 3.9% for those 19 months and older (Figure 1).While there were no reported cases of bacterial meningitis, seven cases of enteroviral meningitis were identified, with only one patient demonstrating CSF pleocytosis. The clinical and laboratory

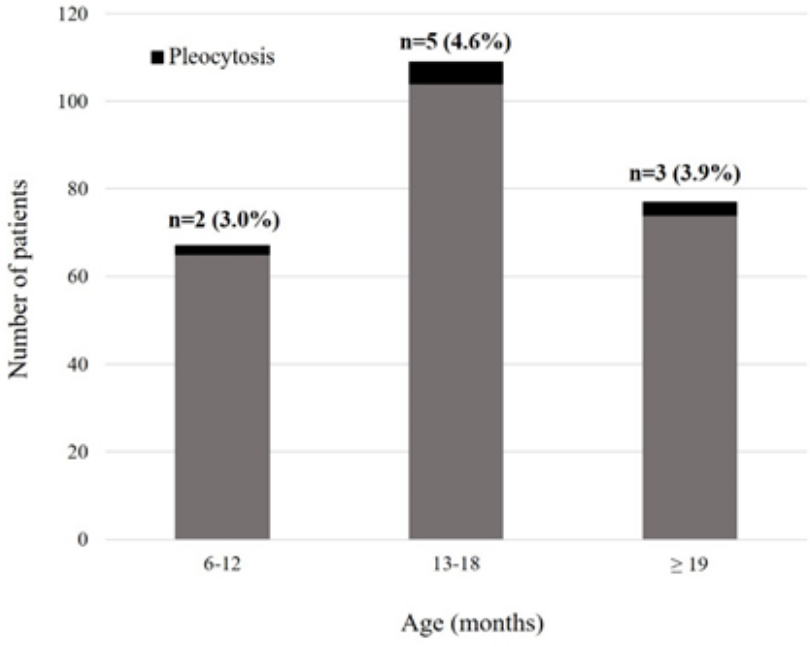

Figure 1. The proportion of patients with pleocytosis in each age group: 6-12 month olds, 13-18 month olds, and ≥19 month olds

Table 1. Clinical and laboratory finding of patients positive for enterovirus in the cerebrospinal fluid

	Sex	Age (months)	Seizure type	Laboratory findings			CSF study			
				WBCs (10^3/μL)	CRP (mg/dL)	Corrected WBCs (cells/mm3)	Protein (mg/dL)	Glucose (mg/dL)	Culture	Enterovirus PCR
Case 1	M	11	CFS	11,760	<0.3	1	8.9	76.8	Negative	Positive
Case 2	M	11	CFS	16,620	<0.5	0	30.8	73.6	Negative	Positive
Case 3	M	11	CFS	19,870	0.52	2	9.3	68.5	Negative	Positive
Case 4	M	12	CFS	21,460	3.94	3	7.9	74.1	Negative	Positive
Case 5	M	15	CFS	5,690	0.92	0	9.9	61.2	Negative	Positive
Case 6	M	16	CFS	25,350	0.41	0	9.3	88.9	Negative	Positive
Case 7	M	14	CFS	15,550	2.12	9.7	15.9	68.4	Negative	Positive

characteristics of the patients with enteroviral meningitis are summarized in Table 1. Patients' median age was 12.3±1.8 months, and three (39.4%) patients had CFS. None of the patients were positive for HSV 1 or 2 on PCR.

Clinical characteristics of patients with CSF pleocytosis

Table 2 shows the clinical characteristics of the ten patients with CSF pleocytosis. All patients had normal consciousness and normal findings on the neurologic examination. Seven patients had SFS, whereas three had CFS. Nine patients were administered intravenous antibiotics after hospitalization, while one (Case 8) was treated with oseltamivir instead of antibiotics for influenza A infection. Three patients with corrected WBC above five had taken antibiotics prescribed by a primary hospital prior to admission.

Table 3 lists the demographic characteristics of patients with SFS. Comparing the groups with and without pleocytosis among patients

Table 2. Clinical and laboratory finding of patients with first f ebrile seizure with pleocytosis

	Sex	Age (months)	Seizure type	Neurologic deficit	Dec. mental status	Laboratory findings			CSF study				
						WBCs (10^3/μL)	CRP (mg/dL)	Corrected WBCs (cells/mm3)	Protein (mg/dL)	Glucose (mg/dL)	Culture	Enterovirus PCR	HSV PCR
Case 1	F	10	SFS	-	-	30.770	1.48	5	15.7	77.1	Negative	Negative	Negative
Case 2	M	14	SFS	-	-	23.880	4.62	5	9.6	75.6	Negative	Negative	Negative
Case 3	M	18	SFS	-	-	12.160	<0.3	5	10.1	78.9	Negative	Negative	Negative
Case 4	F	15	SFS	-	-	8.880	1.43	5	34.1	64	Negative	-	-
Case 5	M	21	SFS	-	-	8.450	2.2	5	11	77	Negative	-	-
Case 6	M	29	SFS	-	-	12.770	1.7	30	22.9	70	Negative	-	-
Case 7	M	40	SFS	-	-	16.050	0.48	54.04	22.6	63	Negative	-	-
Case 8	M	6	CFS	-	-	3.920	1.97	8.9	33.5	64.1	Negative	Negative	Negative
Case 9	M	15	CFS	-	-	19.790	2.5	5	9.2	66.2	Negative	Negative	Negative
Case 10	M	14	CFS	-	-	15.550	2.12	9.7	15.9	68.4	Negative	Negative	Negative

Abbreviation: CFS, Complex Febrile Seizure; CRP, C-Reactive Protein; CSF, Cerebrospinal fluid; HSV, Herpes, Simplex Virus, PCR, Polymerase Chain Reaction; SFS, Simple Febrile Seizure; WBC, White Blood Cells

Table 3. Demographic and clinical characteristics of patients with simple febrile seizure

		Non pleocytosis (n=180)	Pleocytosis (n=7)	*P*-value
Sex	Male	104 (57.8%)	5 (71.4%)	0.7011
	Female	76 (40.6%)	2 (28.6%)	
Age	6–12 months	52 (98.1%)	1 (1.9%)	0.4824
	13–18 months	84 (96.6%)	3 (3.4%)	
	≥19 months	44 (93.6%)	3 (6.4%)	
Familial history of febrile seizure	Yes	52 (28.9%)	3 (42.9%)	0.4214
Seizure duration (minutes)		3.4±3.3	2.5±1.9	0.4402
Total febrile day (day)		3.5±1.9	2.9±1.0	0.2874
Laboratory findings	WBCs (10^3/μL)	13,100.2±6,426.4	16,125.7±8,308.8	0.3308
	Segmented neutrophils (%)	64.3±12.9	70.9±5.88	0.1433
	CRP (mg/dL)	1.3±1.7	1.7±1.4	0.2592
EEG	Normal	145 (94.8%)	6 (5.2%)	1.0000
	Abnormal	14 (100%)	0 (0%)	
AED	Yes	0 (0%)	0 (0%)	

Abbreviation: AED, Anti-Epileptic Drugs; CRP, C-reactive protein; EEG, Electroencephalogram; WBC, White Blood Cells

with SFS showed no differences in seizure duration, total febrile days, or laboratory findings (WBC, segmented neutrophils, and CRP). EEG was performed in 165 patients (88.2%), and abnormalities were found in 14 (7.5%) of the non-pleocytosis group. None of the patients were prescribed AEDs because EEG results mostly showed postictal slow-wave discharges.

In patients with CFS, no differences were found in the total number of febrile days or laboratory findings (WBC, segmented neutrophils, CRP). However, the median seizure duration was longer in the non-pleocytosis group than in the pleocytosis group (10.2 minutes vs. 1 minute, $p = 0.0336$; Table 4). No patients with prolonged seizures (≥15 minutes) had pleocytosis. The three patients with pleocytosis had CFS with repeated convulsions within 24 hours. EEGs were performed in 58 patients (87.9%), and abnormalities were found in three patients (4.5%) in the non-pleocytosis group. One had postictal slow waves, and the other two patients had epileptiform discharges and background asymmetry, leading to the prescription of AEDs. Another patient with a prolonged seizure (20 minutes) had a normal EEG but was prescribed an AED for prophylactic reasons.

Comparison of demographic and clinical characteristics between different age groups

The present study sought to investigate the clinical significance of LP in children ≤12 months of age when FS first occurred. Thus, this study compared clinical and laboratory findings between patients aged 12 months or younger and those aged 13 months or older (Table 5). No differences

Table 4. Demographic and clinical characteristics of patients with complex febrile seizure

		Non pleocytosis (n=63)	Pleocytosis (n=3)	*P*-value
Sex	Male	37 (58.7%)	3 (100%)	0.2727
	Female	26 (41.3%)	0 (0%)	
Age	6–12 months	13 (92.9%)	1 (7.1%)	0.2157
	13–18 months	20 (90.9%)	2 (9.1%)	
	≥19 months	30 (100%)	0 (0%)	
Familial history of febrile seizure	Yes	18 (29.0%)	2 (66.7%)	0.2218
Seizure duration (minutes)	Median	10.2±10.1	1.0±0	0.0336*
	<15 minutes	39	3	
	15–30 minutes	16	0	
	≥30 minutes	8	0	
Total febrile day (day)		3.0±1.4	4.3±0.6	0.0719
Laboratory findings	WBCs (10^3/μL)	12,229.7±7,238.0	13,086.7±8,216.8	0.6679
	Segmented neutrophils (%)	67.9±14.6	66.4±9.8	0.7220
	CRP (mg/dL)	1.9±2.3	2.2±0.27	0.2086
EEG	Normal	52 (94.5%)	3 (5.5%)	1.0000
	Abnormal	3 (100%)	0 (0%)	
AED	Yes	3 (4.8%)	0 (0%)	

Abbreviation: AED, Anti-Epileptic Drugs; CRP, C-reactive protein; EEG, Electroencephalogram; WBC, White Blood Cells

* Significant *p-value*

were observed in the seizure type or the febrile illness's total duration. In laboratory tests, while no significant differences were found in WBCs, the segmented neutrophil count ($p = 0.0065$) and CRP levels ($p = 0.0173$) were higher in the group aged 13 months or older. No differences were observed in the rate of CFS or pleocytosis among patients aged 12 months or younger.

Discussion

In this study, no cases of acute bacterial meningitis were found in children aged 6 to 60 months who experienced a first SFS or CFS. Although ten of 253 patients (3.9%) had pleocytosis, no statistical differences were found in demographic features or clinical characteristics between children with and without CSF pleocytosis.

FS is the most common type of childhood seizure, and it is of utmost importance to rule out acute bacterial meningitis, which may present similarly with seizures and fever but has far more severe, potentially fatal consequences. *H. influenza* type b and *S. pneumoniae* were previously the most common causes of bacterial meningitis in infancy. However, the incidence of both has decreased dramatically with the implementation of vaccines in many countries (4, 5). Despite such declines in the prevalence of bacterial meningitis in the post-vaccination era, concerns remain, especially since a seizure with fever is a significant symptom

Table 5. Comparison of demographic and clinical characteristics of patients aged 6–12 months and ≥13 months patients

		6-12 months (n=67)	≥ 13 months (n=186)	*P*-value
Sex	Male	38 (56.7%)	111 (59.7%)	0.6728
	Female	29 (43.3%)	75 (40.3%)	
Familial history of febrile seizure	Yes	17 (25.8%)	58 (31.2%)	0.4076
Seizure type	Simple	53 (79.1%)	134 (72.0%)	0.2590
	Complex	14 (20.9%)	52 (28.0%)	
Seizure duration (minutes)		5.4±7.5	4.9±6.1	0.7470
Total febrile day (day)		3.4±1.3	3.3±1.9	0.3694
Laboratory findings	WBCs ($10^3/\mu L$)	12,438.8±6,419.6	13,157.3±6,799.0	0.4755
	Segmented neutrophils (%)	61.9±11.5	66.6±13.6	0.0065*
	CRP (mg/dL)	1.0±1.1	1.7±2.0	0.0173*
CSF	Non pleocytosis	65 (97.0%)	178 (95.7%)	1.0000
	Pleocytosis	2 (3.0%)	8 (4.3%)	
EEG	Abnormal	7 (11.9%)	10 (6.1%)	0.1607
AED	Yes	0 (0%)	3 (1.61%)	0.5678

Abbreviation: AED, Anti-Epileptic Drugs; CRP, C-reactive protein; CSF, Cerebrospinal fluid; EEG, Electroencephalogram; WBC, White Blood Cells

* Significant *p-value*

of bacterial meningitis in children. However, previous reports have shown minimal risk of bacterial meningitis in children with FS without obvious neurologic signs. Guedj et al. (6) reported that the risk of bacterial meningitis was extremely low (no bacterial meningitis was found among 168 patients; 95% CI, 0–2.2%) in children aged 6-11 months with a first SFS. In another retrospective review by Kimia et al. (7), among children aged 6-18 months with a first SFS, 3.5% (10 out of 260 cases; 95% CI, 1.9–6.9%) presented with CSF pleocytosis, but no patients had bacterial meningitis (0 of 260 cases; 97.5% CI, 0–1.4%). Other studies reported that neurological deficits seemed to be the best clinical predictor of bacterial meningitis, with good sensitivity, specificity, and positive predictive value (8, 9). Bacterial meningitis was uncommon without clinically relevant signs (lethargy, abnormal mental status, and/or nuchal rigidity, bulging fontanelle, and irritability).

The latest AAP guideline for LP in patients with FS applies only to those with SFS (3). Currently, no consensus exists regarding the need for LP in patients with CFS, with diagnostic and treatment plans for this particular population varying among pediatric physicians (10). At present, numerous research projects are underway to determine the importance of LP in an initial CFS diagnosis. Kimia et al. (11) assessed the rate of acute bacterial meningitis among children aged 6-60 months who presented with a first CFS. Only 3/14 cases (0.9%; 95% CI, 0.1-0.8%) with CSF pleocytosis had acute bacterial meningitis. Two patients (both

S. pneumoniae) presented before introducing conjugated pneumococcal vaccines. Fletchet et al. (12) claimed that acute bacterial meningitis is uncommon in patients experiencing their first CSF examination. They suggested that an LP might not be necessary if no clinical symptoms of neurological disease exist. The evidence suggests that acute bacterial meningitis is rare in patients with a first CFS without accompanying neurologic symptoms. Thus, LP testing may not be necessary in these cases.

Regarding viral meningitis, the significance and necessity of LP are also dubious. Epidemiological studies have shown that is enterovirus the most common cause of viral meningitis. Despite a risk of severe complications and long-term disability, the treatment for enteroviral meningitis is usually conservative management (13, 14). Hudson et al. (15) reviewed several studies to describe common, clinical, post-discharge sequelae in infants and children with viral meningitis. According to this systematic review, good clinical outcomes were demonstrated in the majority of cases. Moreover, in other studies, most cases were positive for enterovirus, and human parechovirus (HPeV) who had severe infections were under six months old (16-18). Overall, the risk of severe complications and long-term disability in viral meningitis seems to be low in most pediatric patients older than six months. However, the risk is increased in young infants, along with the possibility of CSF non-pleocytosis in the early stage of bacterial meningitis in neonates (19). Therefore, undoubtedly, LP should be performed for patients with FS under six months of age.

This study found no significant differences between the non-pleocytosis and pleocytosis groups regarding clinical symptoms, medical history, or laboratory results, regardless of the seizure type. Moreover, little correlation was found between using anticonvulsants during hospitalization and CSF pleocytosis. In this post-vaccination era, comparisons between the different age groups showed that the prevalence of bacterial meningitis or pleocytosis was not increased, even among infants 12 months old or younger. In terms of seizure type, despite brief durations, patients with CFS with repeated convulsions within 24 hours were observed to have a higher rate of pleocytosis. The clinical significance of this finding remains to be determined.

The main limitation of this study was that the medical records were reviewed retrospectively in a single institution with a small sample size. The current study was a single-center study conducted in a tertiary care setting. Hence, the study results may not be applicable to other settings. The high vaccination rates in this study population may also limit generalizability to patient populations, primarily developing countries with low vaccination rates.

In conclusion

Since the introduction of the *H. influenza* type b and the pneumococcal conjugate vaccines in South Korea, the incidence of bacterial meningitis has dramatically decreased. In general, clinical symptoms, including decreased mental status, likely appear before CSF pleocytosis in bacterial meningitis. This means that LP itself may not provide much information in patients with normal consciousness having a first FS. The current study suggests careful deliberation of whether an LP should be performed in children with first FS who do not have neurological defects, including children under 12 months of age, although more extensive prospective studies are needed to confirm the obtained results. Nevertheless,

emphasizing the significance of aggressive testing is vital for individuals with reduced consciousness, neurological symptoms, and for those who are either younger than six months old or older than six years of age. LP remains an absolute indication when clinical symptoms are suggestive of a central nervous system infection.

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Authors' Contribution

Yoon Zi Kim: Contributed to conception and design; contributed to analysis; drafted the manuscript; revised the manuscript; gave final approval as submitted; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Hae Woon Jung: Contributed to conception and design; revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Eun Hye Lee: Contributed to conception and design; contributed to analysis; drafted the manuscript; revised the manuscript; gave final approval as submitted; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of Interest

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

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