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Research Paper

A long-term (7-years) follow-up of Cerebrospinal fluid analysis in the first simple febrile seizure; an Iranian children›s therapeutic center-based study

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ABSTRACT

Febrile seizure (FS) is the most common manifestation of neurologic disease in infants who referred to hospital. Because of pneumococcal and Haemophilus influenzae vaccination, cerebrospinal fluid (CSF) perforation is not necessary in infants 6 to 12 months of age with simple FS. This study aimed a 7-years follow-up of CSF analysis in infants 1-6 and 6-12 months of age with the first simple of FS. This retrospective analytical cross-sectional study was conducted in infants 1 to 12 months of age with simple FS who hospitalized in Amirkola pediatric's hospital in Babol (north of Iran) from 2013 to 2019. CSF parameters and type of meningitis were divided into two groups: 1-6 and 6-12 months. Also, CSF analysis, white blood cell count, CSF protein concentration and CSF glucose was considered to differentiation bacterial meningitis and aseptic meningitis. A total of 106 infants (mean age of 7.94 ± 2.60 months) participated in this study. The prevalence of meningitis in infants with first simple FS was 4.7% (n= 5 of 106), which 80% (n= 4 of 5) of meningitis occurred in infants under 6 months and 75% (n=3 of 4) in infants under 6 months had aseptic type. Bacterial meningitis was significantly higher in infants younger than 6 months (P <0.001). The prevalence of bacterial meningitis in infants with 1-6 months was partially higher than 6-12 months of age and our results suggest that performing LP among infants aged 6 to 12 months with the first FS should be performed more cautiously.

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1. Introduction

Febrile seizure (FS) is the most common neurologic manifestation in 2% to 5% of infants [1]. FS is described as a seizure happening in infants aged 5-10 years, with a temperature ≥ 38ºC, without any evidence of CNS infection, metabolic disorder and trauma [2, 3]. Febrile seizures are classified into two categories, simple and complex. Simple FS is defined by generalized tonic- colonic convulsion with a fever ≥38ºC, lasting less than 15 min without recurrence during 24 h. Complex FS is defined with focal symptoms; it lasting more than 15 min with a recurrence in 24 h. Epilepsy will occur in 2-7% of infants with FS [4]. In generally, prognosis of FS is benign but, there is no consensus in CNS infection management. So, FS is an emergency state for physicians because management of bacterial meningitis is different [5]. Because, meningitis in infants younger than 18 months is usually without focal neurological signs such as stiff neck, Kernig's or Brudzinski's sign, it is recommended that lumbar puncture (LP) be performed for CSF analysis [6]. Group B streptococci (GBS or Streptococcus agalactiae) and Escherichia coli (especially serotype K1) are the most common neonatal meningitis-causing microorganisms, with a mortality rate of > 60% [7, 8]. But, in children, Neisseria meningitidis, Streptococcus pneumonia and Haemophilus influenzae (especially capsular type b-HiB) are the most common causes of meningitis [9, 10]. According to the American Academy of Pediatrics (AAP), CSF analysis for all infants younger than 6 months with FS is necessary. Also, LP is recommended for infants 6 to 12 months with FS who haven't received H. influenzae and pneumococcal vaccines and those who have taken antibiotics due to hide meningeal signs [11, 12]. Early diagnosis and timely treatment of meningitis can prevent neurological complications such as septic shock, persistent fever, acute respiratory distress syndrome (ARDS), seizures, subdural effusion, hydrocephalus, cerebral palsy, mental retardation, hearing loss and blindness. On the other hand, the only definitive diagnosis is LP and CSF culture [13, 14]. In CSF analysis, bacterial meningitis defined as follows, WBC count > 100 mm3 (PMN), glucose < 40% (< 2.2 mmolL-1) and protein level > 1gL-1 [12, 13]. WBC count < 100 mm3 preferably lymphocyte, glucose ratio > 60% of serum (> 2.5 mmolL-1) and protein level < 1gL-1, considered aseptic meningitis [15].

Because of the importance of seizures and the prevention of neurological complications, we examined 109 children with the first simple FS aged 1 to 12 months over a 7-year period (2013 to 2019). Therefore, the aim of this study was to evaluate the CSF analysis in infants with first simple FS admitted to the Amirkola pediatric hospital, Babol, north of Iran.

2. Materials and Methods

2.1 Study Design

This retrospective analytical cross-sectional study was approved by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.HRI.REC.1399.103). In a period of 7-years (2013-2019) CSF analysis of all patients who experience a first simple FS were recorded in this study. The Amirkola Children's hospital is a referral children hospital in the north of Iran with a110-registered bed and is one of the most equipped teaching hospital affiliated to the Babol University of Medical sciences.

2.2 Patients

All infants 1 to 12 months with central fever > 38 ° C, which lasts less than 15 minutes and does not recur in 24 hours, are included in the study [15, 16]. Patients younger than 1 month and older than 1 year, recent history of antibiotic use, history of nonfebrile seizure, neurodevelopment delayed disease (NDD), neurologic disease, immunodeficiency, electrolyte and metabolite disorders, focal seizure, seizure longer than 15 minutes which were repeated in 24 hours, clinical signs for meningitis and CNS infections such as Kerning, Brudzinski's signs and stiff neck, were considered as a exclude criteria.

2.3 CSF analysis

LP was performed by a pediatrician before prescription of antibiotic and CSF was collected between the 3rd and 4th lumbar vertebrae for further tests. The patient's information was collected from the archived files of patients. In the CSF analysis, white blood cell count <5 /mm3 was considered as normal, > 100 /mm3 were bacterial meningitis and 5-100 /mm3 showed aseptic meningitis. The cutoff for normal CSF protein concentration was 18- 58 mgdl-1 that > 100 mgdl-1 showed a bacterial meningitis. CSF glucose < 40% and/or lower than 40 mgdl-1 (2.2 mmolL-1) was considered as a bacterial meningitis and a normal glucose level considered as aseptic meningitis.

2.4 Statistical analysis

CSF Analysis parameters and meningitis cerebral infection were assessed in two groups, 1- 6 and 6- 12 months. Data have compared according to the age, sex and type of meningitis. A P-value less than 0.05 was considered as a significance. All statistical analyses were performed by SPSS 17 (SPSS Inc., Chicago, Ill., USA). The results were analyzed using the Chi-square and Kruskal-Wallis tests.

3. Results

In total, 106 infants including, 44.3% (n= 47) male and 55.7% (n=59) female with an experience of first simple FS were participated. The mean age of patients was 7.94± 2.60 months. Descriptive characteristics of quantitative variable were shown in table 1. Age distribution showed that, 16% (n=17) infants were younger than 6 months and 84% (n= 89) were 6 - 12 months (table 1). All of CSF smear and culture were negative. Only, 0.9% (n=1) and 3.8% (n=4) of patients have a bacterial and aseptic meningitis, respective-

ly. Also, 95.3% (n=101) of infants were diagnosed normal (Table 2). CSF white blood cell count in 96.3% (n= 102) infants were > 5/mm3 (normal range), 2.8% (n= 3) infants was 5- 100/mm3 (aseptic meningitis) and in 0.9% (n=1) of child was < 100/mm3 (bacterial meningitis). In 99.1% infants (n= 105) CSF glucose was more than 40 mgdl-1 in favor to aseptic meningitis and 0.9% child (n= 1) was lower than 40 mgdl-1 that was considered as bacterial meningitis. In 95.3% infants (n= 101), the ratio of CSF to serum glucose was higher than 40%, which was considered normal or in favor of aseptic meningitis, and in 5 infants it was less than 40% that reported bacterial meningitis. CSF protein was typically measured 18- 58 mgdl-1 in 96.2% infants (n= 102) and in 3.8% infants (n=4) CSF protein had abnormal range. Protein level greater than 100 mg/dl was not detected (Table 3). In comparison of WBC, CSF glucose, CSF to serum glucose ratio were detected significantly differences in infants younger than 6 months and 6- 12 months; but median of CSF protein level in infants younger than 6 months significantly was detected greater than 6- 12 months' infants (P= 0.02). In comparison of WBC, glucose, CSF protein, CSF to serum glucose ratio, significant difference not observed; but girls' serum glucose was detected more than boys significantly (P= 0.003) (Table 4). As shown in table 5, 75.0% (n= 3) infants younger than 6 months and 25.0% (n= 1) children aged 6 to 12 months of age had aseptic meningitis. 100% (n= 1) of child younger than 6 months was reported bacterial meningitis.

In this study, bacterial and aseptic meningitis were significantly higher in infants younger than 6 months (P< 0.001). Also in infants younger than 6 months, CSF WBC count was 11.8 % which was in favor of aseptic meningitis and 5.9% in favor of bacterial meningitis. In other hand, there was significant correlation between CSF WBC count and age less than 6 months (P= 0.003). In children aged 6 to 12 months, total CSF glucose was detected aseptic meningitis/ normal; and in infant younger than 6 months, 94.1% were detected aseptic meningitis/ normal. Significant correlation younger than 6 months groups between CSF glucose in bacterial meningitis and age was showed (P= 0. 02). Among 17 infants younger than 6 months, 23.5% (n= 4) infants had abnormal protein level and relationship between abnormal protein and age< 6 months was significant (P<0.001). Positive significant correlation between CSF WBC counts and protein was shown. There was a positive meaningful correlation between CSF to serum glucose ratio (r = 0.55 and P< 0.001). Negative meaningful association between CSF to serum glucose ratio was showed (r =0.64 and P< 0.001).

4. Discussion

The most important finding was prevalence of meningitis in infants younger than 6 months with the first simple FS was partially higher than 6- 12 months significantly. This finding showed that LP in infants younger than 6 months with first simple FS is important, to diagnose and treatment of meningitis. However, in children aged 6 to 12 months with the first simple FS without recent antibiotic use, immunodeficiency and no clinical findings for meningitis, LP is not necessary. Other findings included, CSF protein level among infants younger than 6 months was reported higher than 6- 12 months and it used to diagnose bacterial meningitis.

Table 1: Descriptive statistical analysis in patients enrolled to this study

Variables	Mean	Inclusion criteria	Minimum	Maximum
Age(month)	7.94	2.60	2	11
WBC Count (mg/dl)	1.75	11.00	0	102
CSF glucose (mg/dl)	60.61	11.38	38	100
Serum glucose (%)	101.59	19.86	61	159
CSF to serum glucose ratio	61.32	13.57	32.43	94.29
CSF protein	33.49	8.17	21	82

Table 2: No [(%)] of frequency distribution of CSF parameters in this study

Variables	Frequency	Percentage (%)
CSF WBC count (MM3)		
<5	102	96.3
5-100	3	2.8
≥100	1	0.9
CSF glucose (mg/dl)		
<40	1	0.9
≥40	105	99.1
CSF to serum glucose ratio (%)		
<40	5	4.7
≥40	101	95.3
CSF protein(mg/dl)		
18-58	102	96.2
58-100	4	3.8

Table 3: Quantitative variables comparison of WBC count, glucose, CSF, serum glucose and cerebrospinal fluid glucose to serum glucose ratio based on age of infants

Variables	Less than 6 months criterion deviation± mean	6- 12 months criterion deviation± mean	P value*
CSF WBC count (MM3)	9.47±26.74	0.27±0.83	0.20
CSF glucose (mg/dl)	60.64±12.69	60.60±11.20	0.87
Serum glucose (mg/dl)	103.88±21.45	101.15±19.64	0.73
CSF to serum glucose ratio (%)	60.52±16.01	61.41±13.15	0.93
CSF protein(mg/dl)	42.35±16.57	31.79±3.41	0.02

Table 4. Comparison of WBC count, glucose, CSF, serum glucose and CSF glucose to serum glucose ratio based on sex of infants

Variables	Boy Inclusion criteria± mean	Girl Inclusion criteria± mean	P value*
CSF WBC count (MM3)	2.38± 14.86	1.23±6.57	0.54
CSF glucose (mg/dl)	5.59±11.06	61.16±11.70	0.67
Serum glucose (mg/dl)	95.17±17.03	106.71±20.59	0.003
CSF to serum glucose ratio (%)	64.50±14.17	58.78±12.62	0.06
CSF protein(mg/dl)	34.87±10.37	32.39±5.74	0.02

*Using the test of Mann-Whitney

Table 5: Comparison of WBC count, glucose, CSF protein and CSF to serum glucose ratio by age

Variables	Less than 6 months	6- 12 months	P value*
Sex Girl Boy	 (41.2)7 (58.8)10	 (58.4) 52 (41.6)37	0.19
Type of meningitis Bacterial Aseptic Without meningitis	 (5.9)1 (17.6) 3 (76.5)13	 - (1.1)1 (98.9)88	<0.001
referral season Spring Summer Autumn winter	 (35.3)6 (29.4)5 (5.9)1 (29.4)5	 (43.8)39 (29.2)26 (12.4)11 (14.6)13	0.52
WBC count (mm3) Normal Aseptic meningitis Bacterial meningitis	 (82.4)14 (11.8)26 (5.9)1	 (98.9)88 (1.1)1 -	0.003
Serum glucose (mg/dl) Bacterial meningitis Aseptic meningitis/ Normal	 (5.9)1 (94.1)16	 - (100)89	0.02
CSF to serum glucose ratio (%) Bacterial meningitis Aseptic meningitis/ Normal	 (11.8)2 (88.2)15	 (3.4)3 (96.6)86	0.13
CSF protein (mg/dl) Normal Abnormal	 (76.5)13 (23.5)4	 (100)89 -	<0.001

*Using the test of Chi-Square

In our study, the frequency of meningitis in infants with first simple FS was 4.7% (5/106). 80% (4/5) of meningitis occurs in infant younger than 6 months, of which 75% (3/4) was aseptic. In concordance with our data, Carroll et al (2002), reported that infants younger than 12 months who referred with FS had meningitis less than 1% and 99% had FS. They reported performing LP is not necessary in this group [17]. Similar to our study, Golestan et al (2009), the prevalence of bacterial meningitis was low [18].

In Guedj et al (2015), infants with 6-11 months of age with the first simple of FS, risk of bacterial meningitis is low and these findings should be encouraging national and international communities that limited LP [19]. Tavasoli et al, (2014), showed that the prevalence of meningitis in children aged 1 month to 6 years was 4.5 %, of which 63.2% were aseptic [20]. Eldardear et al, (2020), reported that in 108 infants (mean ages of 13 months) with meningitis, 11.1% was observed in infant younger than 6 months [21]. In present study, prevalence of meningitis was 4.7% (5 cases from 106).

The reason of difference between two studies can be due to the difference in the mean age and small sample size. Kimia et al, (2009), declared that risk of bacterial meningitis with the first simple of FS at the age of 6- 18 was very low and LP should be revised [22]. In contrast with the present study, Son et al, (2018), reported that all vaccinated infants with FS younger than 12 months LP must be done [23]. In our experience, we compared before and after vaccination in infants that showed vaccination will reduce risk of bacterial meningitis. The result of Siddiqui et al, (2017), in infants with FS the main cause of the fever should be identified and this study suggested LP should be done [24]. These results were not similar to our data which can be due to ages, sampling size and geographic and genetic differences. The result was shown that serum glucose ratio in girls with first simple FS was more than boys. We found that the prevalence of febrile seizures among boys and girls is similar to the Golestan et al, [18]. Increased CSF WBC in infants younger than 6 months was related to meningitis. As expected, abnormal CSF protein level and other variables were shown in infants younger than 6 months with first simple FS was related to meningitis. In 2005, Ehsanipour et al, showed that bacterial meningitis with FS was common in infants younger than 18 months [25]. Also, they had not signs and symptoms of meningitis. Contradictory result between this study and our findings was different by age distribution. The result of this study showed that admitted infants require LP; because prevalence of meningitis was common in children aged 6 to 12 months. Studies have shown that LP in infants older than 2 years with the first attack seizure was limited [23]. In the present study, infants younger than 12 months divide into two groups and importance of LP was investigated; that is first studies in this field. One of the goals of our study was investigation of the frequency of referral in different seasons which is not statistically significant. Although different analysis result showed, that was not significant but this finding is important practically. Tinsa et al, (2010), showed that the prevalence of meningitis in infants older than 7 months without H. influenzae and pneumococcus vaccinations and without neurologic disorders was low and recommended infants monitored for 24 hours and considered avoiding the early LP [26].

The present study had some limitations. First, this was a center study; therefore, generalization of the results to other regions requires further investigations. Second, we couldn't perform bacterial culture and microbiological analysis.

In this study, prevalence of meningitis was reported 4.7% that infants 6- 12 months had not bacterial meningitis. Seizure etiology in infants younger than 12 months without signs and symptoms of meningitis is important; because there is no correlation between age and CSF analysis, so suggested these infants to be hospitalized and monitored. Our result showed CSF analysis (WBC and protein level) among infants younger than 6 months with first simple FS was favor to meningitis. LP is painful and it causes anxiety for parents; so, LP in infants 6-12 months with first simple FS without recent history of antibiotics, immune deficiency, history of diseases of the CNS and physical examination, routinely is not necessary. These infants should be hospitalized and carefully monitored for evidence of clinical meningeal signs.

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Authors' contributions

All authors have cooperated in conception and design, or analysis and interpretation of the data for this study; drafting the article or revising it for important content and they approved the final version.

Conflict of interests

The authors declare that there is no conflict of interest.

Ethical declarations

This study was approved by the Research Ethics Committee of Babol University of Medical Sciences; Babol, Iran with code number IR.MUBABOL.HRI.REC.1399.103.

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