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Original Article



Prevalence of Meningitis in First Episode of Febrile Seizure in Children Aged between 6 to 18 Months: A Cross-sectional Study

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ABSTRACT

Introduction: Febrile Seizures (FS) are the most common type of childhood seizures, affecting 2-5% of children older than one month and most commonly from six months to 5-year-old. It is a major cause of paediatric admissions worldwide. In India, American Academy of Paediatrics (AAP) 2010 guidelines are followed for performing Lumbar Puncture (LP) in first episode of FS, despite the fact that epidemiological differences exist between the two countries. The present study has been done to find out whether AAP guidelines are applicable in India.

Aim: To find out the prevalence and predictors of meningitis in first episode of FS in children aged 6-18 months.

Materials and Methods: This was a cross-sectional study carried out in 200 children, aged between 6-18 months admitted with first episode of FS in Paediatric Ward of tertiary care hospital New Delhi, India, over a period of 18 months (May 2018 to December 2019). The LP was performed and blood, Cerebrospinal Fluid (CSF), clinical parameters were analysed using Statistical Package for the Social Sciences (SPSS) version 21.0.

Results: The prevalence of meningitis in children aged 6-18 months presenting with first episode of FS was 16% (n=32). Bacterial Meningitis (BM) was seen in 3% (n=6) of cases. The independent predictors of meningitis were high Total Leucocyte Count (TLC) (>16500 cells/mm³) and positive C-Reactive Protein (CRP). Blood culture was positive in seven cases (three cases of *Streptococcus pneumoniae*, two MRSA, one each *Klebsiella pneumoniae* and *Neisseria meningitidis*). Most common type of cell seen was monocytes which was alone seen in 56.2% (n=18) of the meningitis cases.

Conclusion: India should have its own guidelines for performing LP in cases of first episode of FS as the prevalence of meningitis in children with first episode of FS in India is more than in the USA, and immunisation coverage for Haemophilus and Pneumococcal Vaccine (PCV) is very less as compared to USA. Meningitis can be predicted in those with high TLC (16500 cells/mm³) and CRP positive.

Keywords: C-reactive protein, Lumbar puncture, Total leucocyte count

INTRODUCTION

The most common type of childhood seizures is Febrile Seizures (FS). It affects 2–5% of children. Most common from six months to 5-year-old [1,2]. Worldwide, FS is a major cause of admissions [3]. Febrile seizures are defined as seizures accompanied by fever with no intracranial infection, history of previous afebrile seizures or metabolic disturbance [4].

Simple FS (typical) are generalised, usually tonic-clonic, last for a maximum of 15 minutes, not recurrent within a 24 hour period. Complex FS (atypical) are prolonged (more than 15 minutes), are focal and/or recur within 24 hours [4].

The first manifestation of meningitis in 16.7% of children is seizures, and in one-third of these patients, meningeal signs and symptoms may not be evident [5]. Therefore, excluding underlying meningitis is mandatory in children presenting with fever and seizure prior to making the diagnosis of FS [6]. Lumbar Puncture (LP) is an invasive procedure. Thus, it should be done only if indicated. Prevalence of meningitis in Indian population with FS is 18.6% [7] in six to 60 months age.

The most common cause of Bacterial Meningitis (BM) are *Streptococcus pneumoniae* and *Neisseria meningitidis* for those over one month of age [8]. Haemophilus influenza type b (Hib) vaccine coverage and Pneumococcal Vaccine (PCV) coverage in India is not known while in United States of America (USA), it is 82.4% and 84.1%, respectively, so the two countries cannot be compared in terms of prevalence for meningitis in FS [9,10].

As per current American Academy of Paediatrics (AAP) 2010 guidelines LP should be performed in:

(i) Children with FS and signs and symptoms of meningitis or if the patient history or examination suggests the presence of meningitis or intracranial infection; (ii) in infants 6-12 months of age with FS, LP is an option if they have not received recommended Hib or PCV, or if their immunisation status is unknown; (iii) LP is also considered an option in children with FS who are pretreated with antibiotics; (iv) children appearing very sick [11].

India is a developing country as compared to the USA where the immunisation rates are much better than India, so, to compare and use guidelines of a developed country with totally different socio-economic status, immunisation coverage, epidemiology of meningitis and higher rates prior antibiotic treatment in our country is not right, thus, creating a need for our own guidelines. The study was done to see whether the AAP guidelines (2010) for LP in patients with first episode of FS are applicable to the Indian scenario and also to find out the prevalence and predictors of meningitis in children aged 6-18 months presenting with first episode of febrile seizures.

MATERIALS AND METHODS

This was a hospital based cross-sectional study conducted for 18 months (May 2018 to December 2019) in the Paediatric Wards of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India. The study was conducted after obtaining Institutional Ethical Committee's approval (IEC/VMMC/SJH/ 2018/157A) and patients were enrolled after receiving the written consent of the parents/guardians.

Sample size calculation: The sample size was calculated based on a study by at Ali Asghar hospital in Iran (N=681). The prevalence

of meningitis reported was 4.5% [12]. Therefore, taking p=4.5% as the prevalence of meningitis in children presenting with first FS with 3% margin of error, the minimum required sample size at 5% level of significance and adding 10% for any losses the sample size came out to be 200.

Formula used:
$$n = \frac{Z_{\alpha_{j_2}}^2 pq}{d^2}$$

where, p is the observed prevalence

q=1-p

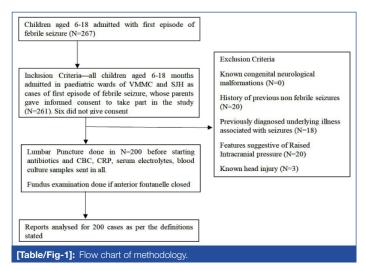
d is the margin of error

 $\textbf{z}_{_{\alpha\!/\!2}}$ is the ordinate of standard normal distribution at $\alpha\%$ level of significance

Inclusion and exclusion criteria: All children (aged 6-18 months) admitted with first episode of FS in hospital were included in the study (n=267), whereas parents/guardians not willing to participate in the study (n=6) or having known congenital neurological malformations or history of previous non FS (n=20) or a previously diagnosed underlying illness associated with seizures (n=18) or known head injury (n=3) or children with features suggestive of raised intracranial tension (bulging anterior fontanelle, papilloedema i.e., n=20) were excluded from the study , so final total cases included were 200.

Procedure

The participants were divided into two groups as per age; 6-12 months and more than 12 months to 18 months. All cases were examined in detail. Lumbar puncture was performed in all participants, after taking informed consent and CSF was collected in three sterile vials one was sent for cell count, second to biochemistry for sugar and protein and third for culture and CSF was analysed by standard laboratory methods. The following tests were also done by taking 8 mL of blood by venepuncture with all aseptic precautions- Complete Blood Count (CBC), serum electrolyte levels (sodium, potassium and calcium), C-Reactive Protein (CRP), blood culture and sensitivity and fundus examination if anterior fontenelle was closed. Summary of the methodology is given in [Table/Fig-1]. These results were analysed to find the prevalence of meningitis in children with first episode of FS and to find predictors of meningitis in these children.



Fever was defined as a temperature of >100.4°F in axilla.

Simple FS (typical) was defined as lasting for a maximum of 15 minutes and not recurring with in a 24 hour period [13]. Complex FS (atypical) was defined as seizures for more than 15 minutes, and/or recurs within 24 hours [13].

Meningitis was defined as having any of the following; CSF cells >5 (defined as CSF pleocytosis) and/or CSF protein >45 mg/dL and/or CSF sugar <50 mg/dL [8]. The WBC count for traumatised LP was determined by using the following corrections:

Corrected CSF WBC count={CSF WBC count- (CSF red blood cell count/500)}.

BM was defined as growth of a pathogen from CSF culture or one of the above criteria with growth of a pathogen from the blood culture. CSF pleocytosis with mononuclear cell dominancy and no growth of a pathogen from CSF or blood culture considered as aseptic meningitis if the patient was not pretreated with antibiotics during the previous week. In cases with CSF pleocytosis and history of pretreatment with antibiotics, if a diagnosis of BM was given on the side of caution and the patient was treated as having BM.

The CRP was done by immunoturbidimetry and more than 6 mg/L was taken to be positive. The FS were managed as per unit protocol.

STATISTICAL ANALYSIS

Statistical testing was conducted with the statistical package for the social science system (SPSS) version 21.0. Continuous variables were presented as mean±SD or median (IQR) for non normally distributed data. Categorical variables were expressed as frequencies (N) and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups were compared using chi-squared test or fisher's-exact test as appropriate. Non normal distribution continuous variables were compared using Mann-Whitney U test. Logistic regression was used to find the predictors of meningitis in children presenting with first FS. For all statistical tests, a p-value <0.05 was were taken to indicate a significant difference.

RESULTS

[Table/Fig-2] shows age characteristics of the cases taken and its relationship to meningitis. The cases taken were divided into two groups of 6-12 months and >12 to 18 months for comparison with the AAP guidelines for LP. Out of the 200 cases, 112 were in the age group of 6-12 months and 88 were in the 12 to 18 months age group. Meningitis was seen in 14 (12.5%) of the 112 in the 6-12 months age group as compared to 18 (20.4%) of the 88 in the 12 to 18 months age group. No significant relationship was found in the two age groups to meningitis (p-value=0.128). The mean age of the cases was 12.88 ± 4.37 months.

			Meningitis		
Variables		Absent (n,%)	Present (n,%)	p-value	
Age (months)	6-12	98 (58.3)	14 (43.7)	0.128¹	
	>12-18	70 (41.7)	18 (56.3)		
Febrile seizure type	Typical	75 (44.6)	4 (12.5)	0.0011	
	Atypical	93 (55.4)	28 (87.5)		
C-Reactive protein	Positive	3 (1.8)	14 (43.8)	<0.0012	
	Negative	165 (98.2)	18 (56.2)		
Sex	Male	122 (72.6)	13 (40.6)	<0.0011	
	Female	46 (27.4)	19 (59.4)		
Blood culture	Positive	1 (0.6)	6 (18.8)	<0.0012	
	Negative	167 (99.4)	26 (81.2)		
Prior antibiotics history	Present	2 (1.1)	2 (6.25)	0.121 ²	
	Absent	166 (98.9)	30 (93.75)		
Cerebrospinal fluid cell type	Polymorphonuclear (PMNL) leucocytes	3 (1.8)	1 (3.1)		
	Monocytes	5 (3.0)	18 (56.2)		
	Mostly PMNL	0	8 (25)		
	Mostly monocytes	0	5 (15.7)		
	None	160 (95.2)	0		

[Table/Fig-2]: Distribution and comparison of cases between meningitis and Non meningitis group with and their relationship with meningitis. p-value <0.05 statistically significant;1=Chi-square test; 2=Fischer's exact test

Of the 200 cases, 135 (67.5%) were male and 65 (32.5%) were female. The mean fever in the cases was 102.5±1.09°F with highest recorded fever of 105°F. Two had been vaccinated against *Haemophilus influenzae b* and none against *pneumocoocus*. Three had a family history (parent's or sibling) of seizure disorder but none had family history of FS. None of the LP was traumatic. All 200 were discharged with mean of hospital stay 4.75±1.06 days.

[Table/Fig-2] shows the comparison of typical and atypical FS. Total 39.5% (n=79) of the cases were typical FS and 60.5% (n=121) were of atypical FS. Furthermore, it shows that there was a significant difference in the prevalence of meningitis in the atypical FS group than the typical FS group (p-value=0.001).

Meningitis was seen in 16% of the cases (n=32), with BM seen in 3% (n=6), and the rest were aseptic meningitis (n=26). Total 17 cases had CRP positive (8.5%), out of 17 CRP positive cases, 14 had meningitis (82.3%) thus, showing a positive relation between CRP positive and meningitis (p-value <0.001), thus, positive CRP is a predictor of meningitis in first episode of FS children aged 6-18 months [Table/Fig-2].

Blood culture was positive in seven cases (three cases of *Streptococcus pneumoniae*, two MRSA, one *each Klebsiella pneumoniae* and *Neisseria meningitidis*) [Table/Fig-2]. Six of the 7 (81.2%) of the blood culture positive cases had meningitis and the other one had MRSA sepsis.

Monocytes were seen in CSF on microscopy in 18 of the 32 meningitis cases (56.2%) and were the most commonly seen cells [Table/Fig-2]. The mean CSF protein of the 200 cases was 55.1±70.57 mg/dL. Six (3%) of the cases had positive CSF culture (three cases of Streptococcus pneumoniae, one each *Klebsiella pneumoniae, Neisseria meningitidis* and MRSA). It was seen that 18.8% of the meningitis cases had positive CSF culture and the most

common organism isolated was *Streptococcus pneumoniae* in the CSF culture, it was isolated in 9.3% of the meningitis cases with the other three organisms isolated seen in 3.1% of the meningitis cases. Distribution of cases as per age, clinical and blood parameters and comparison between meningitis and non meningitis group with meningitis [Table/Fig-3].

The mean TLC of the study was 9947.3±4315.1 cells/mm³. The mean TLC of the non meningitis and the meningitis cases was 8659.1±2916.84 cells/mm³ and 16715.62±4171.49 cells/mm³ respectively. A significant relationship was found between high TLC and meningitis, thus, making it (TLC >16500/mm³) a predictor of meningitis (p-value <0.001) in cases with first episode of FS aged 6-18 months [Table/Fig-4].

DISCUSSION

The FS is one of the most common types of childhood seizure, affecting 1-5% children in the age group of six months to five years. This study was done to see whether the AAP guidelines for LP in patients with first episode of FS are applicable to the Indian scenario also and to find out the prevalence of meningitis in children aged 6-18 months presenting with first episode of FS.

The present study also aimed at finding the predictors of meningitis children aged 6-18 months presenting with first episode of FS. Various other studies across the globe have been done to find out the prevalence of meningitis in children with first episode of FS but only a few studies [7,14] have been done to find out the predictors of meningitis in these children.

In the present study, the prevalence of meningitis and BM was found to be 16% and 3%, respectively, independent risk factors for predicting meningitis in children presenting with first episode of FS aged 6-18 months were CRP positive and high TLC. A retrospective study was done in Iran by Tavasoli A et al., in the

	Meningitis					
		Absent	Pre	p-value		
Variables	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	(student t-test)	
Age (months)	12.9±4.38	12.00 (9.00-18.00)	12.72±4.36	14.00 (10.00-17.25)	0.128	
Haemoglobin (gm%)	12.06±1.77	12.30 (11.12-13.10)	11.39±1.86	11.25 (10.00-13.00)	0.58	
Total Leucocyte Count (cells/mm³)	8658.1±2916.84	7800 (7000-9575) 16715.62±4171.49 16850 (14625-1		16850 (14625-18975)	<0.001	
Platelet count (cells/mm³)	304636.9±114677.49	3000000 (230000-400000) 255937.5±160810.84 300000 (80500-3		300000 (80500-350000)	0.132	
Mean corpuscular volume (fL)	77.21±8.76	77.00 (72.00-81.00)	73.22±6.61	73.00 (71.00-76.75)	0.006	
Postictal state duration (min)	8.34±7.55	5.00 (2.00-10.00)	14.53±11.98	15.00 (5.00-150.00)	0.002	
Fever duration (days)	2.63±1.16	2.00 (2.00-3.00)	3.16±1.65	3.00 (2.00-4.00)	0.094	
Dextrose (mg/dL)	94.92±24.55	90.00 (78.00-105.75)	96.56±21.63	91.00 (82.25-10.00)	0.446	
Serum Calcium (mg/dL)	9.57±7.61	9.20 (8.60-9.50)	9.07±1.01	9.30 (8.92-9.60)	0.372	
Serum sodium (Meq/L)	139.38±5.92	138 (135-144)	140.00±6.26 0.592	136 (134-143)	0.592	
Serum potassium (Meq/L)	4.42±0.69	4.3 (4.0-5.0)	4.38±0.71 0.768	4.6 (4.1-5.0)	0.768	
CSF cytology(cells/mm³)	0.21±0.98	0	74.19±119.91	35.00 (10.500-87.50)	0.458	
CSF protein (mg/dL)	47.73±61.15	37.00 (31.00-41.00)	93.75±99.96	43.00 (34.25-98.50)	0.003	
CSF sugar (mg/dL)	62.70±17.87	60.00 (55.00-68.00)	58.84±25.47	63.00 (52.75-71.75)	0.665	
Seizure duration (min)	6.32±5.76	35 (2.00-100)	12.62±8.83	10.00 (5.50-15.00)	<0.001	

[Table/Fig-3]: Distribution of cases as per age, clinical and blood parameters and comparison between meningitis and non meningitis group. CSF: Cerebrospinal fluid; p-value <0.05 statistically significant

							95.0% C.I. for EXP(B)	
Variables	В	S.E.	Wald	Df	p-value	Exp(B)	Lower	Upper
C-Reactive Protein (CRP)	5.56	1.434	15.032	1	<0.001	259.939	15.635	4.32E+03
Total Leukocyte Count	0	0	17.793	1	<0.001	1	1	1.001
Constant	2.511	2.84	0.782	1	0.377	12.32		

[Table/Fig-4]: Independent predictors for meningitis in first episode of febrile seizure in children aged 6-18 months. B-unstandardised regression weight; S.E.-Standard Error; C.I.-Confidence Interval; EXP(B)-Exponentiation of B coefficient

age group of one month to six years showed the prevalence to be 4.5%, which was lower than this study. The LP was done in 22 of the children taken [12].

An evidence based review by Horn J and Medwid K from USA in which Cochrane, Medline, Embase library databases were searched and cases in the age group of 6-18 months with simple FS searched in whom LP was performed. It was seen that 0% had meningitis and CSF pleocytosis was seen in 2.5% which in comparison to this study is very less [2].

Another retrospective study done in USA by Kimia A et al., on 340 children aged six months to six years with atypical FS showed CSF pleocytosis in 2.7% and ABM in 0.9%. It also showed that the meningitis prevalence in USA is very less in children with first episode of FS as compared to this study [1].

A retrospective study done in France by Casasoprana A et al., to see whether AAP guidelines for LP in first episode of FS are applicable in France, showed that meningitis was seen in only 5% of the cases. A 157 cases were taken LP was done in 63. Three cases of viral meningitis, three BM (*Streptococcus pneumoniae*) and two non herpetic viral encephalitis were found. The incidence of Acute Bacterial Meningitis (ABM) in the study was 1.9% [14].

The study done in Tunisia by Tinsa F et al., in 106 infants (<12-month-old), to assess the risk factors for meningitis in infants presenting with first episode of FS, found prevalence of meningitis in these cases to be 10% which is lesser as compared to this study but more if compared to studies done in developed countries as stated above. The risk factors found were age less than seven months, duration of seizure more than 5 minutes, recurrence of seizure in the same day, high CRP (>20 mg/L), less sodium (< or = 125 mmol/L) and neurological abnormalities [15].

Another retrospective study done in Turkey by Kanik A et al., on 564 children aged 6 to 24 months presenting with first episode of FS with LP done in 135, showed no CSF abnormality and no cases of BM.CSF pleocytosis was seen in 10 (1.7%) out of which seven were in the complex FS group and 3 in the simple FS group. CSF pleocytosis was defined as more than 10 cells/mm³, which is more than the cut off taken in this study which could be a reason for the low rates of CSF pleocytosis [16].

A retrospective study done in southern India by Reddy DS et al., on 105 children aged six to 60 months presenting with first episode of FS reported BM in 18.6%, which is comparable to this study. The LP was done only in 43 cases out of which BM was seen in eight. None of these cases had any growth in culture but had CSF pleocytosis [7].

A cross-sectional study done in Pakistan by Siddiqui HB et al., on 157 children aged six to 60 months showed that 12 cases (7.6%) had ABM of which 7(58.3%) had positive culture. These results were lesser than this study probably due to the different diagnostic criteria taken in the study for ABM. In the age group of 6-12 months, 2(1.3%) cultures were positive for *Streptococcus pneumoniae*, 1(0.6%) for *Haemophilus influenzae* and there was no growth on 2(1.3%) samples of CSF. In the age group of 13-18 months, 2(1.3%) cultures were positive for *Streptococcus pneumoniae*, 1 for *Haemophilus influenzae* and no growth on 1(0.6%) sample [17].

A study done in Nepal by Shrestha SK showed that 14.5% of 110 cases from five months to six years taken had meningitis. Six (21.4%) of these were in the 6-12 months age group (total cases 28) compared to 12.5% (N=14) in this study, six of 31 in the 12 to 18 months age group had meningitis (19.3%) compared to 20.4%

(N=18) in this study and in the more than 18 months age group only 4(7.84%) of the 51 cases had meningitis [18].

After comparing all the above studies from all over the world, it, was seen that the prevalence of meningitis in the first episode of FS in the developing country like India is much more than the developed countries. There is no significant difference between prevalence of meningitis between age groups 6-12 months and 12-18 months, so as per the AAP guidelines doing LP in children >12 months only if certain criteria are met will be wrong. Immunisation coverage for the most common organisms causing BM i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae* is much lower in India than The USA. So considering all the above, authors would suggest Indian guidelines for LP in children with first episode of FS. The strength of the study were larger sample size, study being cross-sectional and predictors of meningitis were assessed.

Limitation(s)

Limitations were sample taken from hospital only, single site study and memory/recall bias in terms of the seizure duration, postictal state.

CONCLUSION(S)

The prevalence of meningitis in children aged 6-18 months presenting with first episode of FS in this study (16%). This study also adds that meningitis can be predicted in those with high TLC (16500 cells/mm³) and CRP positive. Prior history of antibiotics in the past one week could have altered our results by making the CSF results negative but it was seen only in 2% of the cases. The authors would suggest to confirm these findings through bigger prospective trials and considers for Indian guidelines to substitute or replace the AAP guidelines.

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