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Change in Prevalence of Meningitis among Children with Febrile Seizure after the Pentavalent Vaccination

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Abstract

Introduction: One of the most significant current discussions in pediatrics is whether lumbar puncture (LP) should be performed in children with febrile seizure (FS) as in the past.

Objectives: We compared the prevalence of meningitis among FS children before and after the pentavalent vaccine to determine the importance of the LP in these children

Methods: We performed a retrospective cross-sectional study on the prevalence and etiology of bacterial meningitis (BM) in 1314 children with FS before and after pentavalent vaccination.

Results: We found that complex FS was more prevalent in patients aged under 12 months compared to other patients. The peak incidence of aseptic meningitis and BM was in the age group of 12- to18- and 18- to 36-month-old, respectively (P value <0.001 and <0.05, respectively). Children with complex FS had a significantly higher rate of BM and a lower rate of seizure recurrence than those with simple FS (P value <0.05). There was a significant relationship between getting the pentavalent vaccine and reducing the prevalence of BM and Hib-induced BM, but no SP-induced BM (P value <0.05 and 0.05 and 0.104, respectively). **Conclusion:** This study offers some insights into the effectiveness of the pentavalent vaccine. In addition, the low prevalence of BM in vaccinated FS cases does not support strong recommendations for LP in FS children.

Keywords: Meningitis, Febrile seizure, Pentavalent vaccine, Lumbar puncture, Children

Introduction

Febrile seizure (FS) is defined as a seizure associated with febrile diseases in the absence of a central nervous system infection, acute electrolyte imbalance, or prior afebrile seizures in children older than one month of age [1]. It is the most prevalent class of childhood seizures. The A study revealed that the incidence rate of febrile seizures in Zahedan, a city in the southeastern part of Iran, was noted as 3.5% [2]. Two to five percent of children older than one month and most commonly from six months to five years old are affected by this disease [3,4]. Approximately one-third of these children experience recurrent FS [5]. So, it is a major public health problem and the leading cause of admission of children worldwide [6]. FS is categorized into two types: simple and complex. A simple febrile seizure typically manifests as a generalized seizure, characterized by tonic-clonic movements and the rolling back of the eyeballs. These seizures have a brief duration, lasting from a few seconds to a few minutes, and are followed by a short period of drowsiness known as the postictal phase [7]. Complex seizures typically have a duration exceeding 15 minutes, are localized (focal), have the potential to occur multiple times within a day, and can be accompanied by either an extended period of postictal drowsiness or the presence of postictal neurological abnormalities [7].

Most FS is considered simple, although those with focal onset, prolonged duration, or occur more than once within the same febrile illness (multiple seizures) are considered complex [1]. There was a significant relationship between FS and bacterial meningitis (BM) [8,9]. BM is a life-threatening disorder that may be presented only by seizures, spatially complex seizures [4,10,11], and is often caused by *Streptococcus pneumonia* (SP), *Neisseria meningitis*, and *Hemophilus influenza* type b (Hib) [12]. Between the time period of 1989-1993 and 2014-2019, there has been a significant decline in the occurrence of *N. meningitidis* meningitis cases, with the incidence dropping from 2.87 per 100,000 population to 0.20 per 100,000 population. The introduction of MenC vaccination in 2002, in response to the outbreak that occurred from 1999-2001, played a crucial role in reducing the incidence of MenC meningitis, which accounted for 27.4% of all *N. meningitidis* meningitis cases during that period [13]. The primary cause of the significant decline in meningococcal meningitis cases is attributed to the decrease in serogroup B infections. It is important to note that no conjugate vaccine specifically targeting serogroup B has been implemented thus far [14].

According to the high prevalence of meningitis and its serious complications, including death, subdural effusion, hemiparesis, hydrocephalus, infarcts, ventricular abscess, cranial nerve palsy, persistent seizures, isolated hearing loss, hemiparesis, and moderate to severe developmental delay, the World Health Organization (WHO) has recommended induction of the Hib vaccine to children around the world, aiming to reduce the number of patient with pneumonia, meningitis, and subsequent seizures. So, in Iran, the pentavalent vaccine acts against Hib, Hepatitis B, Diphtheria. Tetanus and Pertussis have been added to the routine vaccination program at 2, 4, and 6 months old since 18th November 2014 [15-20]. The pentavalent vaccine functions by stimulating the immune system to generate antibodies that specifically target and counteract the disease-causing agents [21]. The pentavalent vaccine is widely regarded as safe and has not been linked to any significant adverse effects. However, minor side effects like swelling, localized redness, and discomfort at the site of injection may occur [22].

A considerable amount of literature has been published on the effectiveness of the pentavalent vaccine. These studies showed that the vaccine is effective above 90% [23-26]. Furthermore, a study demonstrated that the implementation of the pentavalent vaccine resulted in a 46.2% reduction in the occurrence of meningitis across all age groups. Moreover, there was a notable 57% decrease in children under the age of five specifically attributed to the vaccination against *H. influenzae* [27]. Despite the high efficacy of the vaccine, the etiology of FS in some children is still recognized as meningitis. So it is crucial to exclude meningitis in children with FS [28] using lumbar puncture (LP). However, it is an invasive procedure with serious complications, including headaches lasting from 8 days to 1 year, cranial neuropathies, chronic backache, and nerve root injury. Also, LP can cause meningitis by itself [28,29]. Given the recent decrease in the prevention of bacterial meningitis due to the pentavalent vaccine and according to serious complications of LP, one of the most significant current discussions in pediatrics is that LP should be performed in children with FS as in the past. Determining the prevalence of meningitis in children with FS make clinicians able to make appropriate decisions for these patients [28]. Although extensive research has been carried out on the prevalence of meningitis in the general population in the era of vaccine implementation, implying the effectiveness of this vaccine, no single study exists which compares the prevalence of meningitis among FS children before and after the pentavalent vaccine to determine the importance of the LP in these children. For this reason, we performed an epidemiological study on the prevalence and etiology of meningitis in children with FS before and after vaccination in northwest Iran.

Methods

In this retrospective cross-sectional study, we reviewed the medical records of all children aged six months to six years with FS, who were admitted to Farmanfarmayan Children's Hospital, a tertiary care center in Tabriz, Iran, between October 2011 and August 2020. Both urban and rural patients are referred to this hospital. The inclusion criteria were as follows: (i) 6-month to 6-year-old children and (ii) developing the first episode of FS. The exclusion criteria were as follows: (i) history of neurological and metabolic disorders, (ii) previous non-febrile seizures, (iii) antibiotics use during the previous week, and (iv) immune-suppressed condition.

Collected data were age, gender, type of seizure, signs of meningeal irritation (neck stiffness, Kerning's or Brudzinski's Signs), results of LP and cerebrospinal fluid (CSF) culture, and history of taking the pentavalent vaccine. We categorized the patients into two groups: simple and complex FS, using medical records and the description given by the American Academy of Pediatrics [30]. Then we compared the recurrence rate of each group. Then, we categorized the patients into four groups intending to compare the prevalence of BM and aseptic meningitis among different age groups, including (i) 6 to15-month-old, (ii) 16to30-month-old, (iii) 31to45-month-old, and (iv) 46to60-month-old. Also, we classified patients into two groups: children immunized by the pentavalent vaccine and children not immunized. This classification was conducted to compare the prevalence of meningitis and its bacterial cause between the two groups. CSF pleocytosis was described as a white blood cell (WBC) count ≥ 6 μL presented in the CSF. Bacterial meningitis (BM) was defined as A positive CSF culture.

Aseptic meningitis was diagnosed based on CSF pleocytosis with mononuclear cell domination and negative CSF culture. Developmental delay was defined as a development level of 2 standard deviations (SD) lower than the cut of point, described in the Ages and Stages Questionnaires (ASQ) [31]. Data were analyzed using the SPSS version 16. We used the Chi-square test to compare the qualitative variables among two or more groups. Data are presented as mean ± SD or number(percent). A P value of <0.05 was considered statistically significant. The patients' parents gave informed consent before LP. The ethical committee of Tabriz University of Medical Sciences approved our study.

Results

The general characteristics of included patients are shown in **Table 1**. A total of 1314 patients diagnosed with FS were identified, of which 1037 cases (78.91%) received the pentavalent vaccine. The mean age of patients was 24.06 ± 12.8 months. The number of boys (793, 60.3%) was more than girls (521, 39.7%). Sixty-seven patients (5.1%) had developmental delays, and 60 patients (4.5%) had a positive family history of FS. None of our patients showed signs of meningeal irritation. With regards to FS type, 1033 patients (78.6%) presented with simple FS, 281 patients (21.4%) with complex FS, of which 209 patients (74.4%) presented with multiple seizures, 67 patients (23.8%) presented with the prolonged seizure (>15 minutes) and five patients (1.8%) presented with the focal seizure.

The seizure recurrence rate was significantly higher among simple FS (176 cases, 17%) compared to complex FS (32 cases, 11.3%) (P value <0.05). Two hundred eighty-two patients aged under 12 months and 1032 up to 12 months. Complex FS was more prevalent in the patients aged under 12 months compared to another group (23.7% and 20.7%), and it was statistically significant (P value <0.05). In total, 1189 patients (90.4%) underwent LP. Forty-six patients had BM, and 176 had aseptic meningitis. The prevalence of aseptic meningitis in the age group of 12- to18-month-old (32.4%) was more than other groups (**Table 2**), and it was statistically significant (P value <0.001). The prevalence of BM in the age group of 18- to 36-month-old (5.3%) was more than in other groups **(Table 2)**, and it was statistically significant (P value <0.05). Of 46 patients with BM, 12 (27%) were female, and 34 (73%) were male. However, this difference was not statistically significant (P value=0.056). Children with complex FS had a significantly higher rate of BM in LP results than those with simple FS (12.4% versus 1%, P value < 0.05). **Table 3** Compares the prevalence of BM between vaccinated and unvaccinated children with FS. Of 277 unvaccinated cases, 17 patients (6.1%) were diagnosed with BM, of which eight cases (47%) were due to Hib, six cases (35%) were due to SP, and 3 cases (17%) were due to other organisms. Of 1037 vaccinated patients, 29 cases (2.8%) were presented with BM, of which eight cases (27.5%) were due to Hib, 12 cases (41.3%) were due to SP, and nine cases (31%) were due to other organisms. So, the proportion of BM and particularly Hib-induced BM in children with FS

Table 1. General characteristics of included patients (n=1314).

Age (month)	24.06 ± 12.8
Male gender	793 (60.3%)
Developmental delay	67 (5.1%)
Signs of meningeal irritation	60 (4.5%)
Simple FS	1033 (78.6%)
Complex FS	281 (21.4%)
Multiple seizure	209 (74.4%)
Prolonged seizure	67 (23.8%)
Focal seizure	5 (1.8%)
Patients undergoing lumbar puncture	1189 (90.48%)
Bacterial meningitis	46 (3.5%0
Hib-induced meningitis	16 (34.78%)
SP- induced meningitis	18 (39.13%)
Meningitis due to other organisms	12 (26.08%)
Aseptic meningitis	176 (13.39%)
Patients receiving pentavalent vaccine	1037 (78.91%)

FS: Febrile Seizure; SP: *Streptococcus pneumonia*; Hib: *Hamophilus influenza* type b

Data are presented as mean ± SD or number(percent)

Table 2. The prevalence of bacterial and aseptic meningitis among distinct age groups.

Age group	Number of patients	Aseptic meningitis	Bacterial meningitis
One-day- to 12-month-old	282	37 (13.12%)	2 (0.07%)
12- to18-month- old	271	88 (32.47%)	4 (1.4%)
18- to 36-month-old	445	24 (5.3%)	24 (5.3%)
36-month- to six-year-old	316	27 (8.5%)	16 (5.0%)
All patients	1314	176 (13.39%)	46 (3.5%)
P value	-	<0.001	<0.05

Table 3. Comparison of prevalence of BM between vaccinated and unvaccinated children with FS.

Diagnosis / Vaccination status	BM	Hib-induced BM	SP-induced BM	BM due to other organisms
Vaccinated (n=1037)	29 (2.8%)	8 (27.5%)	12 (41.3%)	9 (31%)
Unvaccinated(n=277)	17 6.1	8 (47%)	6 (35%)	3 (17%)
P value	<0.05	<0.05	0.194	-

BM: Bacterial Meningitis; SP: *Streptococcus pneumonia*; Hib: *Hamophilus influenza* type b

decreased after vaccination. In contrast, the proportion of SP-induced BM increased after vaccination. Then, we analyzed the relationship between vaccination and BM, Hib-induced BM, and SP-induced BM. There was a statistically significant relationship between getting the pentavalent vaccine and reduction of BM (P value <0.05) and Hib-induced BM (P value <0.05), but no SP-induced BM (P value=0.194).

Discussion

Our study had four main findings. First, complex FS was more prevalent in patients aged under 12 months compared to other patients. Second, the peak incidence of aseptic meningitis and BM was 12 to 18 months and 18 to 36 months, respectively. Third, children with complex FS had a significantly higher rate of BM in LP results than those with simple FS. Fourth, there was a statistically significant relationship between getting the pentavalent vaccine and reducing BM and Hib-induced BM, but no SP-induced BM.

The effect of gender on FS development was also studied. Our results showed a higher incidence of FS among boys than girls. It was parallel with other studies [32-34]. On the other hand, some studies showed no significant difference based on gender [35,36]. The reason for different FS incidences in our study is not clear.

In our study, 5.1% of patients were presented with developmental delay. The correlation between growth and risk of FS is well known. Numerous studies showed that growth retardation due to deficiency of vitamin B12, folic acid, selenium, calcium, magnesium, and zinc, and intrauterine growth retardation, increase the risk of FS [37-41].

In our study, 4.5% of affected children had a positive family history of FS, while other studies concluded differently [42,43]. This could be affected by genetic variation and the size of population studies. Specific genetic mutations, such as SCN1A mutations linked to conditions like Dravet syndrome and Generalized Epilepsy with Febrile Seizures Plus (GEFS+), have been detected in certain populations of children who are inclined to experience recurring febrile seizures. While there is indeed a genetic predisposition to febrile seizures, the precise pattern of inheritance remains unknown [44]. Besides genetic predisposition, there are additional risk factors for febrile seizures. These include neurological disorders, imbalances in electrolytes, viral infections, developmental delays, and elevated levels of cytokines [2].

Similar to Joshi-Batajoo et al. [35], Laditan et al. [45], and Tavassoli et al. [36], none of the patients with BM had meningeal irritation signs in our study, implying that the lack of these signs does not exclude BM in children. Clinicians should not rely solely on physical signs in this regard. Similar to previous studies [46-48], most patients presented with simple FS. The diagnostic accuracy of physical signs in identifying bacterial meningitis in children with febrile seizures has been the subject of several studies. However, the results suggest that these physical signs are not reliable enough to accurately determine whether meningitis is present or not [49,50]. In a comprehensive study that followed 696 cases of bacterial meningitis in adults, it was discovered that only 95% of the patients exhibited two out of the four common symptoms: headache, fever, altered mental status, and stiff neck [51]. While the classic triad of meningitis typically includes nuchal rigidity (stiff neck), fever, and altered mental status, it is important to note that not all patients with meningitis will display these specific symptoms [51]. A definitive diagnosis of meningitis is typically achieved by performing LP and analyzing cerebrospinal fluid (CSF). However, it is important to acknowledge that this method is relatively invasive [52].

Most patients with complex FS were presented with multiple seizures, while focal seizures had the least prevalence. It was similar to Berg et al. study [46]. Berg et al.'s study revealed that 35% of initial febrile seizures and 33% of recurrent febrile seizures presented with one or more complex features, such as a duration of 10 minutes or longer, focal onset, or multiple seizures during the illness episode. Additionally, significant associations were observed between focality and prolonged duration in both first-time and recurrent febrile seizures [46].

We found that children with simple FS were most predisposed to recurrent FS. In contrast, some previous studies concluded differently and showed that the type of FS was not the predictor of FS recurrence [53,54]. It could be due to the low number of cases in those studies.

Our results showed that complex FS was more prevalent in patients under 12 months old. This is in parallel with other studies that reported that age <12 months was associated with a slightly increased risk of FS, spatially complex [55], and prolonged FS [56,57]. The heightened susceptibility to complex features in febrile seizures, particularly in infants and young children, is potentially attributable to the immaturity of their brain and their developing immune system [58].

Aseptic meningitis in 12 to 18-month-old was more prevalent in other groups. It may be due to the fact that the MMR vaccine, which induces aseptic meningitis, is generally given to children around this age. Aseptic meningitis refers to the inflammation of the protective membranes (meninges) surrounding the brain and spinal cord. It is typically caused by various factors such as mycobacteria, viruses, fungi, spirochetes, cancerous tumors, and certain medications [59,60]. The MMR (measles, mumps, and rubella) vaccine has been linked to a rare occurrence of aseptic meningitis, although the occurrence is uncommon. The precise mechanism behind how the MMR vaccine can trigger aseptic meningitis is not yet comprehensively understood. Nonetheless, it is believed that the mumps component of the vaccine is the primary contributor to this potential adverse reaction [61-63]. In addition to the MMR vaccine, several other factors may contribute to the occurrence of aseptic meningitis among children aged 12 to 18 months. These factors include: 1) infections caused by enteroviruses, 2) seasonal variations, 3) exposure to ill patients, and 4) a history of traveling [59].

Numerous studies on FS have reported that BM is more common in younger children [11,32,35,64,65]. Surprisingly, in our study, BM was significantly more prevalent in the 18- to 36-month-old age group than in other groups. This may be because some children did not undergo LP in our study, of which the majority were neonates and very young children. LP plays a crucial role in assessing the prevalence of bacterial meningitis as it serves as a diagnostic procedure that confirms the presence of the infection by analyzing CSF obtained through the procedure. The results obtained from LP can guide the appropriate treatment and management of bacterial meningitis [66]. In fact, parents of such children were more anxious about the side effects of LP than those of other children due to their children's low age, so they did not give informed consent for LP. Parents may be anxious about the possible adverse effects of LP on their children, including 1) backaches, 2) headaches, 3) vomiting, 4) difficulty sleeping, and 5) uncommon complications like infection or bleeding [67,68]. Consequently, the BM prevalence was underestimated in young children.

We did not find any significant correlation between gender and BM. This was similar to the results of other studies [35,36,64,69].

Our results showed that the majority of children with BM had complex FS. This is similar to the results of Ham et al. [4] and Casasoprana et al. [11], showing that BM and encephalitis are rare among patients with simple FS and a normal physical examination. Rossi et al. revealed that in children less than 3 years old without neurological signs, a complex FS can distinguish between cases with and without BM [70]. Najaf-Zadeh et al. reported a 0.6% prevalence of BM among children with complex FS versus 0.2% in simple FS [28]. Al-Eissa et al. reported that all patients with BM had complex FS [32]. Other studies have reported similar results [4,11,35,65,69].

Our study showed that 6.1% of unvaccinated children with FS were diagnosed with BM. Some other researchers have studied the prevalence of BM in Iranian children with FS before immunizing children with the pentavalent vaccine in Iran (before 2014). Ghotbi et al. conducted a four-year study from 2002 to 2006 in Iran and reported that 4.7% of children with FS were diagnosed with meningitis [35]. Ehsanpour et al. revealed that 3.6% of 6-month- to 5-year-old children with FS were diagnosed with meningitis and 1.6% with BM from 1997 to 2002 [69]. On the other hand, the results were completely different in vaccinated children. We showed that only 2.1% of vaccinated FS patients were diagnosed with BM. To the best of our knowledge, this is the first study investigating the prevalence of BM in FS patients after the implication of the pentavalent vaccine in Iran. However, in other countries, such studies were conducted. Caroll et al. showed a 0.23% rate of BM in children with simple FS after the implementation of immunization in the UK [71]. Our results showed a reduction of 4.6% in the prevalence of BM and 14% in Hib-induced BM in children with FS after implementing the vaccine. This result was due to our country's high effectiveness of the pentavalent vaccine. Numerous studies were conducted on the efficacy of the pentavalent vaccine. A study conducted in Iran by Heidari et al. showed a 57% reduction in the prevalence of Hib-induced BM among children under five after the pentavalent vaccine [72]. Lee et al. showed that the number of BM cases caused by Hib in children under 5 years old was reduced by 65% following the implementation of the pentavalent vaccine [24]. Another study conducted in Uganda by Lewis et al. on 0- to 59-month-old children reported a 93% efficacy of the pentavalent vaccine in reducing the prevalence of meningitis [25]. Results of other studies in Kenya and India also reported vaccine effectiveness of 89% and 94%, respectively [26]. In addition, we found that the proportion of SP-induced BM in vaccinated cases was higher than that in unvaccinated patients. It was similar to McCormick et al.'s results, which show that the proportion of patients confected with pneumococcal meningitis increased from 41.5% in 1997-2002 to 49.6% in 2003-2009 [73]. This result is likely due to the fact that the proportion of Hib-induced BM decreased after vaccination, so the proportion of SP-induced BM increased. Our results showed that SP caused 63% of BM after implementing the vaccine, and it was the leading cause of BM. Other studies have reported similar results [74-76]. The findings in this report are subject to at least three limitations. First, these findings are limited by the use of a cross-sectional design. Another weakness in this study that could have affected the results was that some children did not undergo LP, so that the BM prevalence could be underestimated. Thirdly, the study focused on SP and Hib- induced BM. So, the effect of the pentavalent vaccine on the prevalence of BM caused by other organisms, such as Escherichia coli and Neisseria meningitis, was not reported. Finally, the adverse effects or complications of vaccination and LP were nor reported in our study. However, the key strengths of this study are its large sample size and long duration.

Conclusion

Notwithstanding the limitations, this study offers some insights into the effectiveness of the pentavalent vaccine. In addition, the low prevalence of BM in FS cases after a pentavalent vaccine does not support strong recommendations for LP in FS children. Further research in this field would greatly help determine the importance of LP in these patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Author's Contribution

Sh.Kh.: Conceptualization, the original draft writing, investigation, and formal analysis.

Sh.Sh.: Conceptualization, supervision, and project administration.

V.Sh.: Writing including reviewing and editing and investigation.

Ethical Issues

Not applicable.

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