

## Evaluation of Aseptic Meningitis Following Measles-Mumps-Rubella Vaccine in Children Admitted due to Febrile Convulsion

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### Abstract

#### Background

Febrile convulsion (FC) is the most common neurological problem in children which can occur in 2 to 5% of this population. The most important issue is to identify the cause of fever and rule out bacterial meningitis. The purpose of this study was to evaluate the association of aseptic meningitis due to Measles-Mumps-Rubella (MMR) vaccine in admitted children with febrile convulsion.

#### Materials and Methods

This study was a retrospective cross-sectional. Children aged 6 months to 5 years old with FC that admitted to Mousavi Hospital in Zanjan, Iran, during one year (from 2016 to 2017) were enrolled. The demographic information of patients and laboratory parameters of meningitis in their CSF fluid were recorded in a researcher made questionnaire.

#### Results

A total of 275 children were admitted due to FC. Of these children, 36.3% had respiratory infections, 33.8% nonspecific febrile infections, 16% gastroenteritis, 5.8% urinary tract infection, 5.1% acute otitis media and 2.2% meningitis. All cases of meningitis were aseptic without evidence of bacterial compromise. There was a significant relationship between the age of febrile convulsion and meningitis ( $P=0.012$ ). The age of children with meningitis were between 385 to 395 days (equivalent one year and 20- 30 days), which coincide with 20 to 30 days after receiving the MMR vaccine.

#### Conclusion

In the study, all cases of meningitis occurred 20 to 30 days after the MMR vaccine at one year of age. It is strongly suspected the association between aseptic meningitis and the MMR vaccine. LP is recommended in children with febrile convulsions in this age range.

**Key Words:** Aseptic meningitis, Children, Febrile convulsion, Measles-Mumps-Rubella vaccine.

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## 1- INTRODUCTION

Fever-induced seizure or febrile convulsion (FC) includes seizures that occur in children aged 6-60 months old with a fever of 38 degrees centigrade or higher. On the other hand, these children should not have central nervous system infection or electrolyte disturbances or a history of seizures without fever (1). FC is divided into two types, simple and complex. Simple FC refers to a seizure that has been generalized, lasted less than 15 minutes, occurred only once within the first 24 hours, without any focal neurologic deficit. This type of FC usually stops spontaneously. Otherwise, it is called a complex FC (1, 2). The prevalence of simple FC is 2% to 5% in healthy infants and children (1). In children with FC, the most important actions are to diagnose the cause of fever and to treat it appropriately. Seizure is one of the primary manifestations of central nervous system (CNS) infection and then it is important to rule out meningitis. In FC children with generally poor condition, especially under the age of 12 months (if they have not received Haemophilus and Pneumococcal vaccine) as well as in children who have received antibiotics previously, a sample of CSF (cerebrospinal fluid) should be taken by LP (lumbar puncture) (1). FC can be triggered by some vaccines, including pertussis and Measles-Mumps-Rubella (MMR) (3). The seizure following pertussis vaccine usually occurs within 48-72 hours after injection (4). Cerebral involvement (including meningitis or meningoencephalitis) occurs during the third and fourth weeks after the first dose of the MMR vaccine, which can be manifested by febrile seizures. This condition is related to the mumps virus portion in the vaccine (4). Also, in 5 to 15% of children, fever may occur after 6-12 days of this vaccine and this could be associated with seizure. This condition is related to the measles virus portion in the

vaccine (4). Recently it has been recommended to routinely LP should not be performed in infants older than 1 year old with FC (1). However, LP may not be performed in patients with meningitis following MMR vaccine who present with FC at the age of 13 months, so the disease is not diagnosed. Therefore, performing LP in 13-month-old children with FC can help to diagnose meningitis following MMR vaccination. In most previous studies, association of MMR vaccine has been evaluated with the prevalence of aseptic meningitis. The purpose of this study was to evaluate the association of aseptic meningitis due to MMR vaccine in admitted children with febrile convulsion.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This study is a cross-sectional retrospective study. The data of children aged 6 months to 5 years old with febrile convulsion was collected.

### 2-2. Methods

They were admitted at the pediatric ward of Mousavi Hospital in Zanjan (Iran) during one year from March 2015 to February 2016. Demographic characteristics of patients including; age, gender, type of seizure, frequency of seizure, family history of FC, developmental status, history of antibiotic consumption, history of vaccination in a recent month and finally the parameters of meningitis in the cerebrospinal fluid (CSF) were evaluated and recorded in the questionnaire. The sampling method was Total Sampling. Aseptic meningitis was considered when inflammatory markers such as ESR and CRP were normal range, CSF with lymphocytic leukocytosis and normal protein, smear and culture of the fluid negative.

### 2-3. Inclusion criteria

The inclusion criteria included all children aged 6 months to 5 years who were admitted to the pediatric department due to convulsions with fever of 38 degrees centigrade or higher.

#### 2-4. Exclusion criteria

The exclusion criteria were incomplete data, history of developmental disorders, congenital neurological abnormalities, electrolyte disturbances, history of head trauma, focal deficit, anticonvulsants consumption and previous history of seizure without fever.

#### 2-5. Ethical consideration

Due to the retrospective nature of the study, it was not problematic for ethical considerations by maintaining privacy.

#### 2-6. Data analysis

The data were analysed using SPSS software version 18.0. The continuous quantitative data were expressed in the form of mean and standard deviation (SD) and the qualitative data were expressed in the form of percentage and frequency. P-value less than 0.05 were statistically significant.

### 3- RESULTS

A total of 275 patients were enrolled; 151 (54.9%) boys and 124 (45.1%) girls. Their mean age was  $1.48 \pm 1.12$  years (range from 6 months to 5 years). The most common age of FC was 1-2 years in about 40.4% of cases. Seizure was simple type in 86.2%. The most common cause of fever was summarized in **Table.1**. LP was performed in 22 (8%) patients; the

laboratory parameters of meningitis were observed in 6 cases in CSF specimens. All of these patients had Erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) normal, lymphocytic leukocytosis and normal protein in the CSF with smear (gram stain), and culture negative. CSF specimens were cultured on blood agar, chocolate agar and Eosin methylene blue (EMB) agar. According to these findings, all of them were aseptic meningitis without evidence of bacterial compromise. Table 2 summarizes the frequency distribution of demographic information of patients with meningitis in FC children. According to this table, there was a significant relationship between meningitis and age (*P*- value = 0.012). All cases of meningitis were in the age range of one year and 20 days (385 days) to one year and 30 days (395 days); they nearly 20 to 30 days after receiving the MMR vaccine. There was no significant difference in gender, season and type of seizure in the patients with meningitis. The mean of laboratory parameters for CSF samples in patients with meningitis was as follows: mean of white blood cells was 109.3 with 85.5% lymphocyte, glucose 46 mg/dl, and protein 34.5 mg/dl. The level of glucose in the CSF specimens in all cases was higher than 50% relative to the level of glucose in the blood. The characteristics of CSF with detail in these patients are shown in Table 3. Based on the table, none of the children had bacterial meningitis. It is noteworthy that none of these patients had a history of receiving antibiotics prior to admission.

**Table-1:** The distribution of cause of fever in FC patients

Cause of fever	Number	Percentile
Respiratory infections	100	36.3%
Non-specific febrile illness	93	33.8%
Gastroenteritis	46	16%
urinary tract infection	16	5.8%
Acute otitis media	14	5.1%
CNS infection	6	2.2%

CNS: Central nervous system; FC: Febrile convulsion.

**Table-2:** Frequency distribution of demographic data in children with meningitis in FC patients

Variables		Meningitis	P- value
Age	< 1 year	0 (00.0%)	0.012
	1-2 years	6 (5.4%)	
	2-5 years	0 (00.0%)	
Gender	Female	2 (1.6%)	0.560
	Male	4 (2.6%)	
Season	Spring	2 (3.8%)	0.807
	Summer	1 (1.9%)	
	Fall	2 (2.2%)	
	winter	1 (1.3%)	
Type of Seizure	Simple	4 (1.7%)	0.165
	Complex	2 (5.3%)	

**Table-3:** Laboratory parameters of cerebrospinal fluid in patients with meningitis

Patients	Age 1 Year +	WBC Lymp, Poly	Protein	Glucose	Smear	Culture
1	20 day	120 L: 95%, P: 5%	34	38	Not seen	No growth
2	21 day	35 L: 55%, P: 45%	59	45	Not seen	No Growth
3	24 day	80 L: 95%, P: 5%	33	59	Not seen	No Growth
4	30 day	140 L: 60%, P: 40%	24	40	Not seen	No Growth
5	30 day	96 L: 62%, P: 36%	59	40	Not seen	No Growth
6	30 day	185 L: 90%, P: 10%	32	50	Not seen	No Growth

WBC: White Blood Cell; Lymp: Lymphocytes; Poly: Polymorphonuclear.

#### 4- DISCUSSION

Simple febrile seizure is a common disease; it occurs in 2 to 5% of infants and children who are neurologically healthy. The most important point in management of FC is to identify the cause of fever and rule out meningitis and meningoencephalitis. There were no cases of bacterial meningitis in this study; this finding is similar to some previous articles (5), and contrasting with some other studies (6). Based on the recent children's references, the indications for performing LP in children with FC have been clearly limited and diminished. The main reason for this limitation is the administration of Haemophilus influenza and pneumococcal vaccines (1). The most common cause of bacterial meningitis in young children,

especially under age of one, is Haemophilus influenza. With routine vaccination against this organism, it is expected to reduce the incidence of bacterial meningitis. However, pneumococcal vaccine is not currently prescribed in our country. Another important point in our study was the significant incidence of aseptic meningitis, which occurred 20 to 30 days after the MMR vaccination. According to this fact (7), it can be concluded that the cause of aseptic meningitis in the study was related to the vaccine. Other study in our country also reported that the incidence of aseptic meningitis following MMR vaccination was higher than in other countries (8). It should be noted that in Iran, RS-12 is the main strain of mumps vaccine that used in

MMR vaccine. In the United States, this complication occur less than one, in every million children after receiving the MMR vaccine (4). Therefore, the prevalence of this complication is more than 400 times higher than in the United States. Based on this fact, the use of vaccines with lower rate of complications is mandatory. It should be noted that the quality of vaccines should be considered in addition to the good and extensive coverage of national vaccination (9). Overall, according to the results of the study, it can be concluded that in infants aged 13 months with febrile convulsion, aseptic meningitis caused by the MMR vaccine is strongly suggested, and LP in these cases is recommended for identifying of this complication. The present study has some limitations; the most important is the retrospective nature of the study and the absence of mumps virus *Polymerase chain reaction* (PCR) in the CSF.

It is recommended that a broad study with large sample size should be done on the children with FC presenting 2 to 6 weeks after MMR vaccination. Also, the PCR of the mumps virus should be performed on the CSF specimen. Health policymakers of the country should focus more attention on this issue. An important difference in this study with other studies is that FC can be a primary symptom of aseptic meningitis caused by MMR vaccine. Therefore it should be considered as one of the differential diagnoses of Herpes meningoencephalitis. Aseptic meningitis following the vaccine is often benign and does not lead to complications. But in children with FC and lymphocytic leukocytosis in CSF, it is very important to differentiate it from herpes meningoencephalitis. Measuring the PCR of mumps and herpes on the cerebrospinal fluid helps to differentiate them. At present, these tests are not performed in most cities, so most of these patients are hospitalized and treated with intravenous

acyclovir for at least two weeks, while they do not require the treatment.

#### **4-1. Limitations of the study**

From the most important limitations of our study were the retrospective nature of the study and the absence of the possibility of mumps virus PCR in the CSF for a definite confirmation of the cause of aseptic meningitis.

#### **5- CONCLUSION**

According to the study, all cases of meningitis occurred 20 to 30 days after the MMR vaccine at one year of age. It is strongly suspected the association between aseptic meningitis and the MMR vaccine. Therefore aseptic meningitis secondary to the MMR vaccine is the most common cause of meningitis in children with febrile convulsion. Consequently LP is recommended in children with FC in this age range.

**6- CONFLICT OF INTEREST:** None.

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