

Meningitis after MMR vaccination in Mashhad, Iran

*Mohamad Saeed Sasan¹, Saeid Amel Jamedar², Nahid Donyadide³

¹ MD, Subspecialty in Pediatric Infectious Diseases, Associated Professor, Department of Pediatrics, Mashhad University of Medical Sciences, Akbar Hospital, Mashhad, Iran.

² PhD, Assistant Professor, Department of Microbiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

³ MD, subspecialty in Pediatric neurologic Disease, Department of neurology, Mashhad University of Medical Sciences, Ghaem Hospital Mashhad, Iran.

Abstract

Background: More than 20 years after the introduction of the mumps vaccine in the Iranian national vaccination program, there are concerns about meningitis induced by the Measles, Mumps, and Rubella (MMR) vaccine. The aim of this study is to virologically determine the incidence of MMR-induced meningitis in Mashhad, Iran.

Method: This is an observational prospective study during which all children who were admitted (in all hospitals of Mashhad) under the clinical suspicion of meningitis and had a history of MMR vaccination during the past 45 days were included. A polymerase chain reaction (PCR) test for mumps virus and enterovirus (EV) was done on cerebrospinal fluid (CSF) samples with pleocytosis.

Results: During 13 months of study, 55 children were hospitalized for suspicion of meningitis and had a history of recent MMR shots (94% presented with a febrile seizure). Meningitis was confirmed by CSF pleocytosis in 23 (2 bacterial and 21 aseptic) cases (44.2%). All incidents of meningitis had occurred after the first MMR. The incidence of any kind of aseptic meningitis, EV meningitis, and mumps meningitis during 45 days after the first MMR was, respectively, 19.9, 5.71, and 1.9 per 100,000 cases. The number of meningitis cases during the first 3 months after MMR was, respectively, 4.5 and 2 times more than the cases that occurred during the 3 months before and 3-6 months after MMR.

Conclusion: Around 40% of all cases of meningitis (between 4 and 43 months of age) occur during the first 3 months after the first MMR vaccination (12-15 months). The disproportionate increase of aseptic meningitis after the first MMR is strong epidemiologic evidence in favor of mumps vaccine induced meningitis.

Key Words: Febrile convulsion, Meningitis, Mumps, Vaccine, Iran.

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*Corresponding Author:

Mohamad Saeed Sasan, MD, Subspecialty in Pediatric Infectious Diseases, Associated Professor, Department of Pediatrics, Mashhad University of Medical Sciences, Akbar Hospital, Mashhad, Iran. Email: sasanms@mums.ac.ir

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1- INTRODUCTION

Aseptic (viral) meningitis is by far the most common type of meningitis in Iranian children (1, 2). Aseptic meningitis during the first month after MMR vaccination is a leading type of viral meningitis in our daily clinical experience in children's hospitals of Mashhad. Meningitis induced by the mumps vaccine has been reported in several countries (3, 4). In Japan, MMR-induced meningitis has led to the exclusion of mumps from the routine immunization program (5). Vaccination for mumps in Iran was started in 2003. During the past decade, several reports have been published in Iran about aseptic meningitis associated with the mumps vaccine (6-9).

This study aims to further evaluate the association of the mumps virus with meningitis in children, within 45 days after MMR vaccination.

2- MATERIALS AND METHODS

This is an observational prospective study (December 2011 to December 2012) focusing on meningitis during 45 days after MMR vaccination. All children who were admitted to Mashhad hospitals with a pediatric ward (Imam Reza, Ghaem, Dr. Sheikh, Hashemi Nejad, and 17 Shahrivar) were included in the study. We also collected data on all cases of meningitis (regardless of the etiology) in the age range of 4 to 43 months, to evaluate if there is any disproportionate higher rate of meningitis after MMR vaccination, compared to the rest of the study population. All cases of post-surgical, post-traumatic, and carcinomatous meningitis were excluded from the study. We also met all pediatricians and residents of the five mentioned hospitals and provided them with information about MMR-induced meningitis. In this study, there was no other intervention besides the routine care of patients.

The definition of meningitis in this study is based on cerebrospinal fluid (CSF)

pleocytosis as $WBC > 5/mm^3$. Clinical data were gathered directly from the parents, patients, and hospital files. Besides routine CSF analysis (culture, cell count, sugar, and protein), PCR for enteroviruses (EV) and mumps was done on all frozen CSF samples. Nucleic acid extraction was performed by the High Pure Viral RNA kit (Roche Diagnostics GmbH, Germany) according to the manufacturer's instructions. Real-time reverse transcription PCR (RT-PCR) was carried out on a Rotor-Gene 6000 instrument using mumps virus and enterovirus real-time RT-PCR kits (Liferiver, Shanghai ZJ Bio-Tech Co., Ltd., China) in a 25 μ l total volume according to the manufacturer's instructions. These kits contain a specific ready-to-use system for the detection of mumps and EV by RT-PCR within the real-time PCR system. The reaction is carried out in one step real-time RT-PCR. The detection of amplified mumps and enteroviruses DNA fragments is done in fluorimeter channel FAM with the fluorescent quencher BHQ1. Reactions were performed along with positive and negative controls.

According to the Iranian national immunization program of immunization, MMR is administered at 12 and 18 months of age since 2008, but before that, it used to be given at 12 months and 4-6 years; therefore, in the study period, there were still some preschool children who were receiving their second MMR shot.

3- RESULTS

During the 13 months of study, 105,046 and 168,616 children received their first and second dose of MMR vaccine, respectively, in the city of Mashhad. As **Fig. 1** shows, except for a peak in June and July 2012 which was due to the second dose MMR vaccination for school entrance, the rate of MMR vaccination was similar throughout the year.

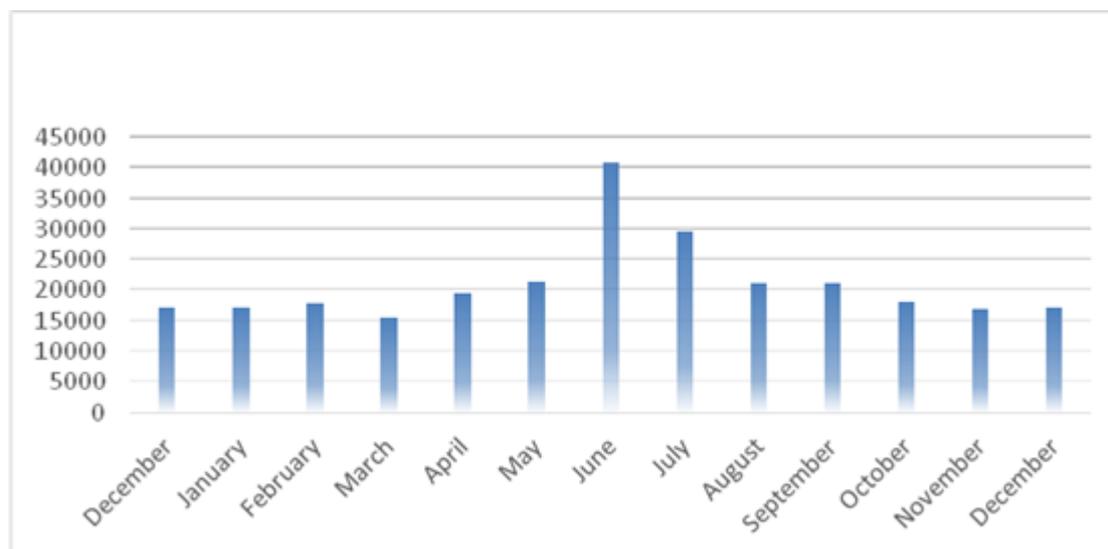


Fig. 1: The number of monthly doses of MMR vaccine administered in Mashhad during the study period (Dec 2011 – Dec 2012)

The mean rate was 19600/month. In this period, we had 52 suspected cases of meningitis that occurred within 45 days after the MMR vaccination, where 49 (94%) presented with febrile seizure and 3 (6%) with fever and vomiting. A Lumbar

puncture (LP) was performed for 40 (76.9%) children. In the other 12 cases, the parents refused it. CSF analysis confirmed meningitis ($WBC > 5/mm^3$) in 23 (57.5%) of these cases, with two bacterial and 21 aseptic meningitis (**Table 1**).

Table 1: Clinical and laboratory data of children with mumps vaccine associated meningitis In Mashhad (Dec 2011-Dec 2012)

Item	Number (%)
Total cases	52
Presented with fever and seizure	49 (94%)
Presented with fever and vomiting	3 (6%)
Lumbar puncture was performed	40 (76.9%)
Normal CSF	23 (/40) (57%)
Bacterial meningitis	2
Aseptic meningitis	21 (/40) (52.5%)
Enteroviral meningitis	6
Mumps meningitis	2

The manufacturer of the MMR vaccine that the 21 children with aseptic meningitis had received in 57.7% of the cases was Iranian (Zagreb strain, Razi Institute of Serum and Vaccine) and in the rest (42.3%) Indian (Hushinoo strain, Serum Institute of India, Ltd.). PCR for mumps

and enteroviruses was performed for 19 CSF samples with pleocytosis, which was positive in 2 and 6 patients, respectively. Therefore, in this study, the cause of aseptic meningitis was found in 42.1% of cases (8 out of 19) (**Table 1**).

All these 23 cases of meningitis were first-time vaccine receivers. The incidence of any kind of meningitis during the first 45 days after MMR vaccination was 21.8/100,000 and zero, respectively, for the first and second dose of the vaccine. The incidence of any kind of aseptic meningitis, EV meningitis, and mumps meningitis during the 45 days after the first MMR dose was 19.9, 5.71, and 1.9 per 100,000 cases, respectively. The mean interval between the first MMR dose and any kind of aseptic meningitis and EV negative aseptic meningitis was,

respectively, 23 ± 8 days and 20 ± 9 days. Moreover, the mean duration of hospitalization was 3 ± 2 days for all 21 aseptic meningitis cases.

The incidence of febrile seizure (FC), with normal CSF, during the first 45 days after the MMR vaccination was 14.2 and 4.7 per 100,000 cases, for the first and second dose of the vaccine, respectively. The mean interval between vaccination and FC was 25 ± 6 days and 11 ± 9 days, respectively, for the first and second MMR shots (**Table 2**).

Table 2: Comparison of neurologic adverse reactions of the first and second MMR

Item	First MMR	Second MMR
Meningitis incidence	19.9/100,000	0/100,000
Febrile seizure incidence (Normal CSF)	14/100,000	4/100,000
Interval between FCs and MMR vaccination	25 ± 6 days	11 ± 9 days

The shortest observed interval between vaccination and FC was, respectively, 16 days and 1 day for the first and second dose of the vaccine. However, the second MMR shot is often accompanied by the DPT vaccine (diphtheria, pertussis, and tetanus); and FC on the first day after this combined vaccination is almost always due to DPT.

We had 16 children with EV negative aseptic meningitis, which could be meningitis induced by mumps vaccine. The MMR manufacturer was Iranian in 53.3% of the cases and Indian in the rest. The mean length of hospital admission in this group was 3 ± 3 days. A mumps virus PCR was performed on 13 (81%) of these samples which was positive in 2 cases (15.3%). The MMR brand was Iranian in one and Indian in the other case of mumps meningitis. As shown in **Fig. 2**, 43.8% of these cases (7 of 16) occurred in autumn, and the seasonal distribution of these cases is in favor of EV meningitis.

To find the relative frequency of post MMR meningitis in comparison to all

cases of meningitis, we collected the data of all 4-to-43-month-old children with meningitis, from the major pediatrics wards of the city. As demonstrated in **Fig. 3**, 40% of all meningitis cases occurred between 12 to 15 months of age ($P < 0.05$). The number of meningitis cases during the first 3 months after MMR was, respectively, 4.5 times and 2 times more than the meningitis cases that occurred 3 months before and 3-6 months after the MMR vaccine.

4- DISCUSSION

According to the American Academy of Pediatrics (AAP), aseptic meningitis after the mumps vaccine (Jeryl Lynn strain) is rare in the USA, and causality has not been established (10). In Japan, the incidence of meningitis induced by mumps vaccine (Urabe strain) (confirmed by PCR of CSF) was 15/100,000 in a nationwide surveillance study for MMR neurologic complications, which is much higher than 1.9 per 100,000 cases in our study (3) (11). If we consider all EV negative aseptic meningitis cases of our study as mumps

meningitis, the incidence of meningitis after the first MMR dose will be 14.2 per

100,000 cases, which is close to the Japanese report (5).

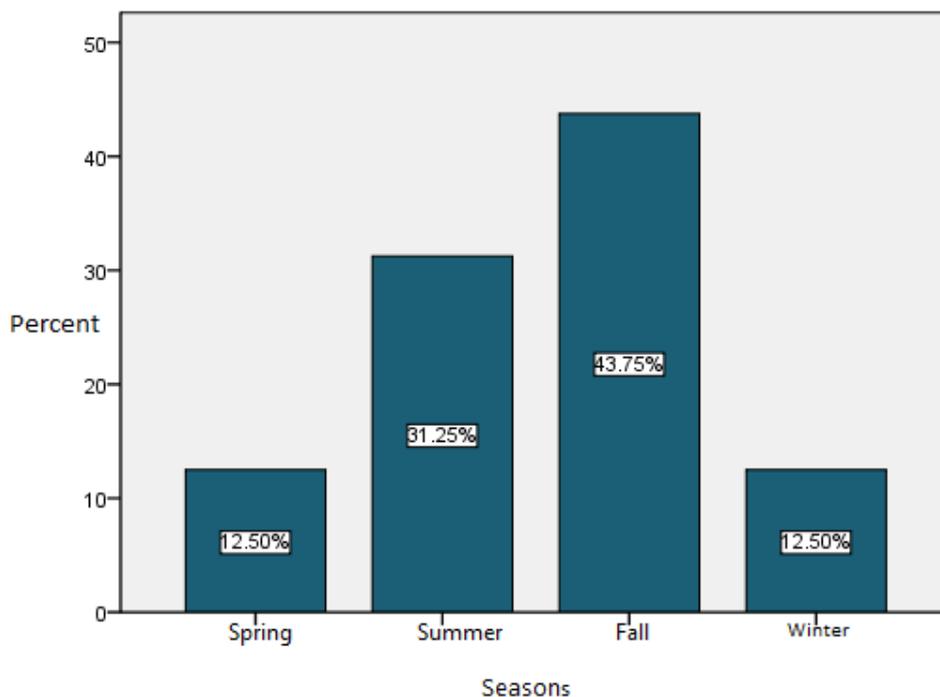


Fig. 2: Seasonal distribution of EV negative aseptic meningitis, 45 days post MMR vaccination in Mashhad

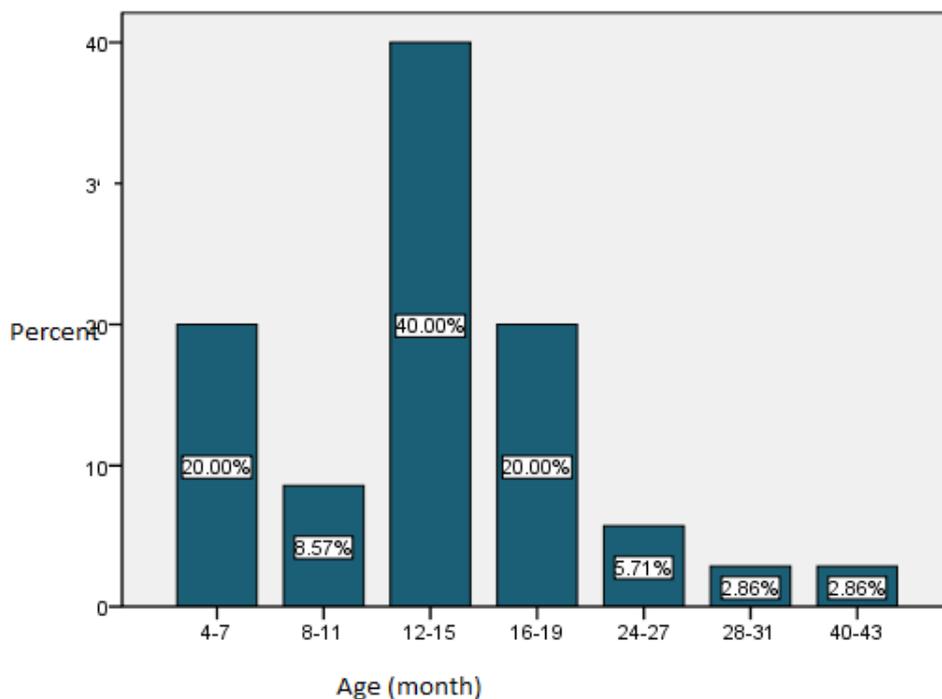


Fig. 3: Age distribution of meningitis cases (in the age range of 4-43 months) in Mashhad (Dec 2011-Sep 2012)

The only published study about virologically confirmed MMR meningitis in Iran is a retrospective study by Mamishi, conducted in Children's Medical Center (Tehran) (12). They had 481 cases of meningitis during 7 years (2006-2012), where 125 (27%) of them were aseptic, and in 49 out of 125, PCR of CSF was positive for the mumps virus. The onset of post MMR meningitis was from 10 to 33 days after the vaccination. The incidence of MMR-associated aseptic meningitis in that study varied between 0.2/1,000 and 1/1,000 in different years (12).

A recent case-control study in Egypt among 453,119 children who received the MMR vaccine manufactured by Serum Institute of India, which is the same vaccine used in Iran, did not show any case of aseptic meningitis, encephalitis, or convulsions. The study design was based on parents recording adverse events for up to 42 days post-vaccination. The correspondent of the article, who is also a member of the vaccine manufacturing company, believes that the Leningrad-Zagreb (L-Z) mumps vaccine strain used by different manufacturers might have changed over the years. This perspective may explain the contrast between these recent findings in Egypt and older studies (1990 and before) which reported the incidence of post L-Z vaccine meningitis to be from 1 case per 900 doses (Japan) up to 1 per 120,000 (France) (13-16).

In Brazil, two separate studies have compared the incidence of hospitalization for aseptic meningitis in children aged 1 to 11 years, before and after a mass MMR (L-Z strain) vaccination campaign. In both studies, the incidence of aseptic meningitis significantly increased after the mass immunization. This difference was observed 2 weeks after the beginning of the campaign (RR 5.6), peaked at the 3rd week (RR 14 and 22), and was present up to the 6th week after the MMR (17-19).

In the current study, the fact that the incidence of aseptic meningitis during the first 45 days after the first dose of MMR is incomparable to the incidence after the second dose ($P < 0.0001$) and that 40% of all meningitis cases in the age range of 4 to 43 months occurred during 12-15 month of age (3 months after the age of receiving the first MMR) indicate that the first dose of MMR vaccine is responsible for meningitis. On the other hand, the seasonal increase of post MMR meningitis cases in autumn and summer and the fact that the mumps virus PCR was negative for most cases are against this theory. So, what can be the cause of this significant increase in the incidence of meningitis around the age of 13 months?

The most acceptable explanation is coincidental enteroviral meningitis, which is seasonally compatible with our findings and is the most common type of aseptic meningitis in children. However, EV PCR was negative in most cases, so this assumption cannot justify the disproportionate rise of meningitis during the 2 months after the first MMR. The alternative explanation is that mumps PCR was false negative in most cases of post MMR meningitis. This explanation is compatible with the high incidence of meningitis in the post MMR weeks but does not justify the seasonal increase of the cases.

The sensitivity of CSF PCR for the diagnosis of mumps meningitis is poor. In the Virology Center of Edinburgh (UK), real-time PCR for mumps virus was positive in just 5.7% of 88 CSF samples sent for mumps diagnosis. In the same study, oral samples had the best sensitivity (66.1%) followed by urine RT-PCR (29.8%) (20). Further, the sensitivity of CSF PCR is much lower in mumps than in enteroviral meningitis. For enteroviruses, PCR can detect 10^{-10} diluted viruses, in comparison to 10^{-1} to 10^{-5} dilutions for the mumps virus. Even for enteroviruses,

simple RT-PCR misses 34% of meningitis cases (19).

Febrile seizure is a relatively common adverse effect of the MMR vaccine (21, 22). In Denmark, MMR vaccination significantly increased the risk of febrile seizure (RR 1.10), the highest incidence of which was within the two weeks after the immunization (RR 2.75) (23). In the UK, the relative incidence of encephalitis or severe illness with convulsions and fever increased up to 5.68 times the normal rate during 6–11 days after the MMR vaccine (24). Esteghamati et al. reported the adverse effects of MMR vaccination in 43,447 Iranian children. Their method was weekly examinations, up to one month after the shot. The incidence of febrile convulsion was 29.9/100,000 (56.7 per 100,000 for 1-year old and 17.0 for 4- to 6-year old children), which is much higher than in our study (14.2 and 4.7 per 100,000 for the first and second dose of vaccine, respectively). However, if we add the aseptic meningitis cases with seizure to the number of febrile seizures, the incidence of FC after the first MMR in our study would be 40 per 100,000 cases (7).

A recent systematic review about the safety of routine vaccination of American children supported the causal relationship between MMR and febrile seizures within 2 weeks post MMR but didn't show any link between Jeryl Lynn strain of the mump vaccine and aseptic meningitis (25).

4-1. Limitations of the study

The most important limitation of this study is the method that we used for the confirmation of enterovirus and mumps meningitis. We should have used stool and saliva samples besides CSF to increase the diagnostic yield of virology. The other limitation is that we didn't plan to differentiate between the wild-type mumps and the vaccine virus. We didn't also perform PCR of CSF for all children suspected of meningitis after MMR, partly

because we had planned to limit the PCR to CSFs with pleocytosis and partly because of inadequate CSF samples or parental refusal for a Lumbar puncture.

5- CONCLUSION

In sum, this study confirms the presence of mumps vaccine induced meningitis (by PCR) in Iranian children. We also reported a disproportionately high incidence of PCR negative aseptic meningitis in 12- to 15-month children, which is the age of the first MMR. The disproportionate increase of aseptic meningitis after the first MMR is strong epidemiologic evidence in favor of mumps vaccine induced meningitis. Further studies are required to clarify the incidence of post MMR meningitis in Iran. We recommend that future studies use samples of oral secretions besides CSF, for a better diagnosis of mumps meningitis.

6- ETHICAL CONSIDERATIONS

The study was approved by the ethics committee of the Mashhad University of Medical Sciences (MUMS) and has been registered by the number 900271 in the research affairs of the school of medicine of MUMS.

7- ACKNOWLEDGMENTS

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8- CONFLICTS OF INTEREST

None.

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