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Original Research Article

Etiology of viral meningitis in Aleppo-Syria: a retrospective study

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ABSTRACT

Background: Viruses are the most common causative agents of aseptic meningitis syndrome. This study aimed to identify the most common causes of viral meningitis (VM) by polymerase chain reaction (PCR) and study its relationship with age and seasonal variations.
Methods: During the study period, the records of 129 patients who had been discharged and diagnosed with VM were identified and reviewed. Cerebrospinal fluid (CSF) samples collected from these patients were tested by PCR using the Seeplex V1 AC meningitis detection kit that detects herpes simplex virus type 1 and type 2 (HSV1) and (HSV2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus type 6 (HHV6), and the Seeplex V2 AC meningitis detection kit that detects human enteroviruses (EV).
Results: VM was confirmed by PCR in 79 cases (61.42%). Most of the VM cases were reported in children younger than 6 years (72.15%; 57/79). EV were detected at the highest incidence of 60 cases (75.9%), followed by HSV1and EBV in 6 cases for each (7.6%, each), CMV in 3 cases (3.9%), VZV and HHV6 were detected in 2 cases for each (2.5%, each). VM cases were found to be more frequent during the spring season (64.6%; 51/79) and the peak incidence of enteroviral meningitis cases was during the spring season (68.4%; 41/60).
Conclusions: Our study showed that EV were the most common causative agent of VM in Aleppo-Syria. Genotype and serotype of identified viruses are recommended.

Keywords: VM, Enteroviruses, Herpesviruses, PCR, Syria

INTRODUCTION

Viruses are the most common causes of aseptic meningitis (AM) which is defined as acute inflammation of meningeal membranes with CSF pleocytosis and negative bacterial culture of bacteria routinely isolated from CSF in a patient who has not started antibacterial therapy prior to lumbar puncture.[1-7]

AM has many infectious and noninfectious causes. Viral meningitis (VM) is the most common clinical form of AM, which is why AM and VM are sometimes used synonymously.[1-8]

The enteroviruses (EV) are the most common causative agent of VM in populations immunized against mumps, accounting for 80-92% of cases in which a causative agent is identified followed by *herpesviridae* family viruses.[7,9-11]

The mumps virus is the most common causative agent of aseptic meningitis in unimmunized populations, occurring in 30% of all patients with mumps.[10]

EV belong to *Picornaviridae* family. EV are nonenveloped, single-stranded, positive-sense viruses that are further classified as follows: Poliovirus (3 serotypes),

coxsackievirus A (23 serotypes), coxsackievirus B (6 serotypes), echovirus (31 serotypes), newly recognized enterovirus serotypes 68-71.[10,12-14] Enteroviruses are primarily spread from person to person by the fecal-oral and respiratory routes.[10,13,14]

The *Herpesviridae* family consists of DNA-containing, large enveloped viruses. Eight members are known to cause human infections and all have been implicated in meningitis syndromes, except HHV-8 or Kaposi sarcoma-associated virus.[10-12]

Annually, the incidence rates of VM range from 10 to 20 cases per 100,000 children.[13] In the United States, VM causes approximately 26,000 to 42,000 hospital admissions each year.[13]

Most VM cases occur in children younger than one year, with a second peak in children older than five years.[13] Individuals under 15 years old are more susceptible to infection caused by enteroviruses with a peak in children less than one year.[10]

VM occurs worldwide in sporadic and epidemic forms.[6,15] The incidence during non-epidemic conditions is rarely known because of underreporting of VM cases.[6] Seasonal variations can be observed and depend on the causative agent.[6] Enteroviruses are the most common cause of epidemics of VM and they occur in general in late summer or early winter periods.[6,15] EV infection rates vary according to age, socioeconomic status, and season of the year.[10]

VM is usually a benign disorder with very low morbidity and mortality.[16] Patients with VM characteristically have an acute onset of meningeal symptoms, fever, and CSF pleocytosis that is usually prominently lymphocytic.[10,16]

Although bacterial meningitis is usually more severe than VM, it is not always easy to differentiate between bacterial and VM based on clinical presentation since the signs and symptoms of bacterial and VM can be similar.[5,17] This will be resulting in the initiation of presumptive treatment and prolonged hospital stays until the diagnosis is made.[5]

Epidemiological data, history, clinical manifestations, clinical prediction tools, and CSF findings can help classify patients as probable of having VM.[1,2]

Examination of the CSF is the primary test that must be done to establish a diagnosis of meningitis.[1] A provisional diagnosis of bacterial or VM can be made depending on CSF analysis.[1] In most VM cases, the CSF profile has a lymphocytic pleocytosis, an elevated protein concentration, and normal glucose concentration.[18] However, CSF analysis is not always helpful in distinguishing between a viral or bacterial infection because there is significant overlap in the relevant findings.[1]

CSF viral culture is positive in less than 50% of cases and rapidly declines to less than 10% over several days.[18]

PCR has become the gold standard for diagnosing VM with high sensitivity and specificity.[1,19] Its result will be available in just a few hours which can help shorten the hospitalization period and avoid the unnecessary use of antibiotics.[1,20]

To the best of our knowledge, this is the first report about the aetiology of VM in Aleppo-Syria.

METHODS

Patient group

This retrospective study was conducted at laboratory medicine department, Aleppo university hospital-faculty of medicine, Aleppo-Syria. From November 2011 to November 2013, the medical records of the patients who had been discharged and diagnosed with VM based on either detection of virus in CSF sample by PCR or physician's clinical diagnosis were identified and reviewed. All patients who enrolled in the study had met the following criteria: Had acute onset of meningitis-like symptoms and fever, CSF leukocyte count >5 nucleated cells/mm^3, absence of microorganisms on gram stain and routine bacterial culture, CSF PCR for EV, HSV1, HSV2, VZV, EBV, CMV, and HHV6 was done, didn't receive antibiotics before the lumbar puncture and had a clinical presumptive diagnosis of VM by the attending physician.

Based on the above criteria, cases were classified into two groups: 1. Confirmed VM cases (CVM): Viral agent was detected in the CSF sample by PCR and 2. Uconfirmed VM cases (UCVM): clinical VM cases diagnosed by a managing physician based on clinical manifestation and laboratory findings with a negative result of CSF PCR.

A questionnaire was used to collect information related to the date of birth, gender, date of onset of illness, clinical presentation, laboratory findings in blood and CSF, PCR results, and antimicrobial therapy.

The study approved by ethical and research committee boards of Aleppo university hospital, and due to the retrospective nature of the study informed consents were waived.

PCR test

CSF samples were collected from the patient at admission and sent by viral transport medium to the research laboratory of the faculty of medicine-Aleppo university for detection of the viral agent by PCR.

Viral DNA and RNA were extracted from CSF samples using a viral DNA mini kit (QIAGEN, Hilden, Germany) as per the manufacturer's protocol.

Complementary DNA (cDNA) was transcribed from enteroviruses RNA using RevertAid first strand cDNA synthesis kit (Fermentas, Germany) as per the manufacturer's protocol.

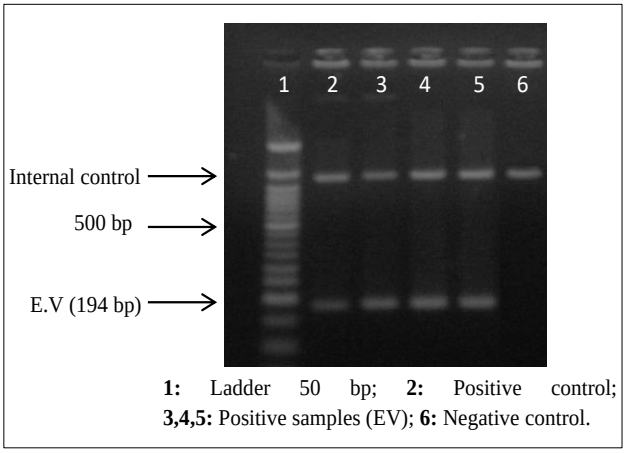
Amplification of extracted DNA and cDNA was performed using a Seeplex meningitis-V1 AC detection kit, which detects 6 herpesviruses (HSV1, HSV2, VZV, EBV, CMV, and HHV6); and Seeplex meningitis-V2 AC detection kit, which detects EV.

Multiplex PCR conditions

Each PCR amplification was performed using 5 µl of the isolated nucleic acid solution, 2 µl of 10×primer mixture, 10 µl of 2×Multiplex Master Mix (Seegene Inc.), and 3 µl of 8-MOP solution in a total volume of 20 µl.

The amplified PCR products were electrophoresed in 2% (w/v) agarose gels and stained with ethidium bromide.

An example of PCR positive sample is in Figure 1.



1: Ladder 50 bp; **2:** Positive control; **3,4,5:** Positive samples (EV); **6:** Negative control.

Figure 1: Amplification of standard DNA on a clinical sample.

All statistical analysis performed with SPSS version 13 (SPSS Inc, Chicago, IL, USA). The Chi-square test used to compare categorical variables whenever applicable, and $p<0.05$ was considered statically significant.

RESULTS

During the study period, 129 patients fulfilled the inclusion criteria and were enrolled in the study.

VM was confirmed by PCR in 79 cases (61.42%) while the remaining 50 cases with negative CSF PCR results were diagnosed as having VM by a managing physician based on clinical manifestation and laboratory findings in the inclusion criteria.

All PCR positive cases were caused by only one causative agent and no mixed infection was found.

Table 1 showed the demographic and laboratory characteristics of the patients.

Table 1: Demographic and laboratory characteristics of the patients.

Demographic and laboratory characteristics	CVM cases, (n=79)
Mean age, years (range)	5.9 (3 days-39 years)
Male (%)	62
Male/female ratio	1.63
Mean CSF leukocyte count, cells/mm^3 (range)	295 (10-2035)
Lymphocytes (%)	87.3
Mean CSF glucose, mg/dl (range)	46.9 (17-128)
Mean CSF protein, mg/dl (range)	76.7 (8-261)

Distribution of CVM cases according to age group

Among 79 CVM cases, the study population was divided into 3 age groups. The highest prevalence of VM cases was observed in the age group <6 years old (72.2%; 57/79), and the lowest prevalence was observed in the age group >17 years old (10.1%; 8/79) (Table 2).

Table 2: Distribution of CVM cases according to age group.

Age group (years)	<6	6-17	>17	Total
No. of CVM cases	57	14	8	79
Percentage (%)	72.2	17.7	10.1	100

Distribution of the detected virus by PCR in the different age groups

Among 129 patients who had been discharged and diagnosed with VM, PCR was positive in 79 cases (61.24%; 79/129). Among the PCR-positive cases, EV were the most common causative agent detected in 60 cases (75.9%; 60/79), and the highest incidence was shown in the age group <6 years (76.7%; 46/60), followed by the age group [6-17] years (20%; 12/60), and age group >17 years (3.3%; 2/60) (p=0.002). HSV1 was detected in 6 cases (7.6%; 6/79), 4 out of 6 cases (66.7%) were detected in the age group >17 years while the remaining two cases were detected in the age group <6 years (33.3%; 2/6) (p=0.000). EBV was detected in 6 cases (7.6%; 6/79), 4 out of 6 cases (66.7%) were detected in the age group <6 years while the remaining two cases were detected in the age group [6-17] (33.3%; 2/6) (p=0.454). CMV was detected in 3 cases (3.9%; 3/79), and all cases were in the age group <6 years (100%; 3/3) (p=0.548). VZV was detected in 2 cases (2.5%; 2/79), and both cases were in the age group >17 years (100%; 2/2) (p=0.000). HHV6 was detected in 2 cases (2.5%; 2/79), and both cases were in the age group <6 years (100%; 2/2) (p=0.673). HSV2 was not detected (Table 3) (Figure 2 and 3).

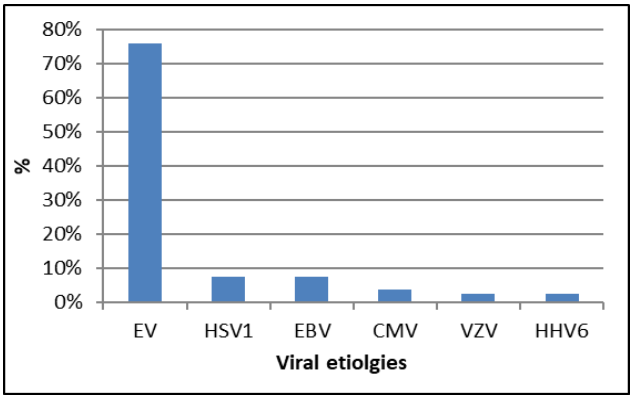


Figure 2: Distribution of viral etiologies detected by PCR.

Table 3: Distribution of the detected virus by PCR in the different age groups.

Viruses	Age group (years), N (%)				P value
	Total	<6	6-17	>17	
EV	60 (100)	46 (76.7)	12 (20)	2 (3.3)	0.002
HSV1	6 (100)	2 (33.3)	0 (0)	4 (66.7)	0.000
EBV	6 (100)	4 (66.7)	2 (33.3)	0 (0)	0.454
CMV	3 (100)	3 (100)	0 (0)	0 (0)	0.548
VZV	2 (100)	0 (0)	0 (0)	2 (100)	0.000
HHV6	2 (100)	2 (100)	0 (0)	0 (0)	0.673

Distribution of detected virus by PCR in each age group

In patients of the age group <6 years, EV were most common causative agent detected (80.7%; 46/57), followed by EBV (7%; 4/57).

In patients of the age group 6-17 years, EV were most common causative agent detected (85.7%; 12/14), followed EBV (14.3%; 2/14).

In patients of the age group >17 years, HSV1 was the most common causative agent detected (50%; 4/8), followed by VZV (25%; 2/8), and EV (25%; 2/8) (Table 4) (Figure 3).

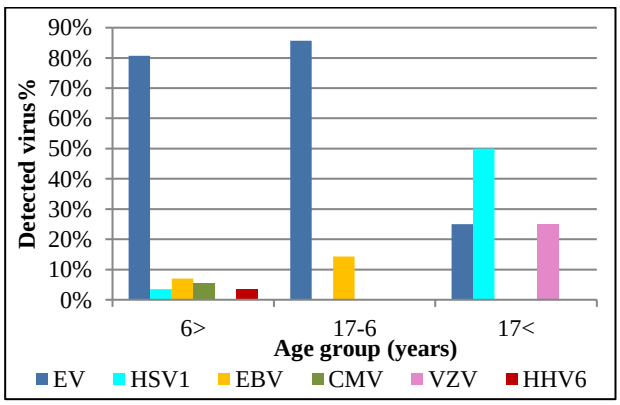


Figure 3: Distribution of the detected virus by PCR in the different age groups.

Table 4: Distribution of the detected virus by PCR in each age group.

Viruses	Age group (years), N (%)		
	<6	6-17	>17
EV	46 (80.7)	12 (85.7)	2 (25)
HSV1	2 (3.5)	0 (0)	4 (50)
EBV	4 (7)	2 (14.3)	0 (0)
CMV	3 (5.3)	0 (0)	0 (0)
VZV	0 (0)	0 (0)	2 (25)
HHV6	2 (3.5)	0 (0)	0 (0)
Total (%)	57 (100)	14 (100)	8 (100)

Distribution of the CVM cases according to seasonal variation

Although CVM cases occurred throughout the year during the study period, it was more common during the spring season (March to June) (64.6%; 51/79) (Figure 4 and 5).

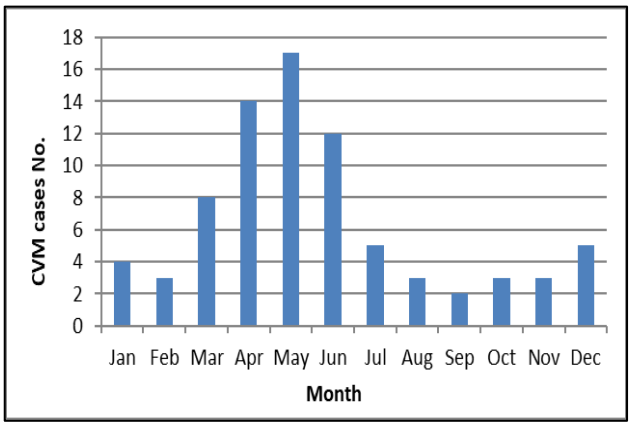


Figure 4: Monthly distribution of CVM cases.

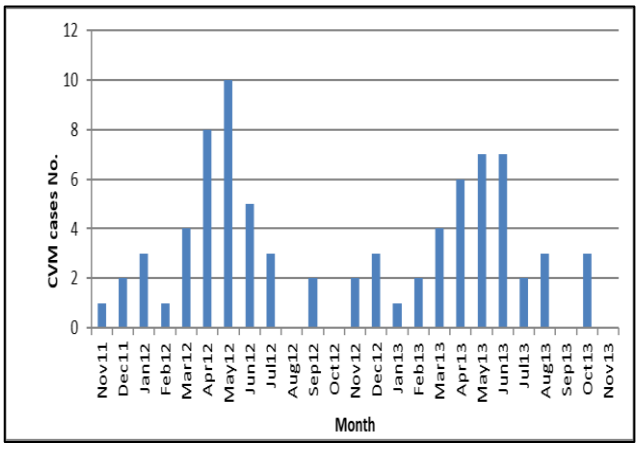


Figure 5: Monthly distribution of CVM cases.

Enteroviral meningitis cases were distributed throughout the year with a peak in the spring season (March to June) (68.4%; 41/60), while herpesviral infection doesn't show a seasonal distribution and occurred throughout the year (Figure 6 and 7).

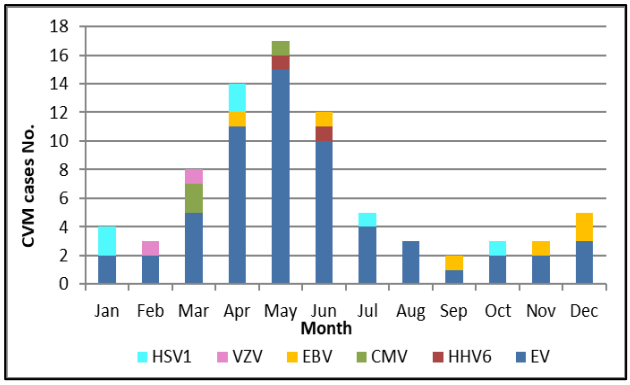


Figure 6: Distribution of the CVM cases according to seasonal variation.

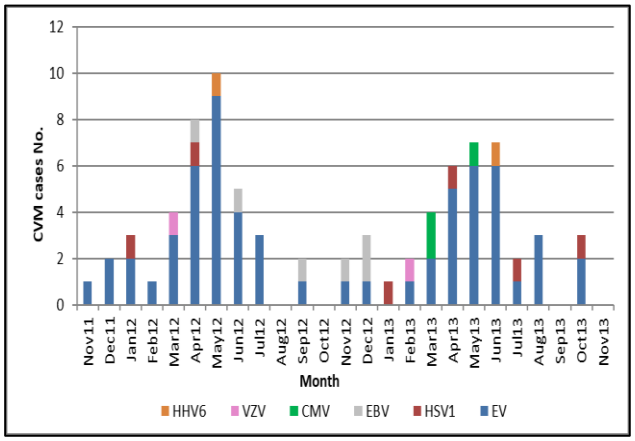


Figure 7: Distribution of the CVM cases according to seasonal variation.

Gender distribution of CVM cases

The infected male (62%; 49/79) outnumbered infected female (38%; 30/79) and the male to female ratio 1.63.

CVM cases caused by EV or HSV1 or CMV were detected more among males than females (35 vs. 25, 4 vs. 2, and 2 vs. 1, respectively). Interestingly, CVM cases caused by EBV and VZV comprised only males while that caused by HHV6 comprised only females (Figure 8).

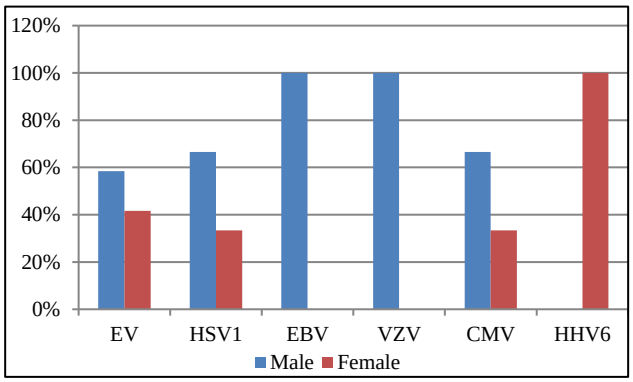


Figure 8: Gender distribution of CVM cases.

DISCUSSION

VM is the most common form of aseptic meningitis.[10,20,21] Although VM is usually a self-limited disease with a low rate of morbidity and mortality, death can occur in neonates with VM as a consequence of hepatitis or viral myocarditis.[1,16]

In the present study, among 129 who had been discharged and diagnosed with VM, viral etiology was detected by PCR in 79 (61.24%) cases. Similar findings were reported by De Ory et al (57.1%), and Hosseininasab et al (46.2%).[7,22] Also, different rates of VM cases were reported in many studies like studies by Soares et al (85%), Hydar et al (82.7%), Michos et al (48.9%), and Kumar et al (45.5%), Dash et al (37%), Vidal et al (12.8%), and Mathew et al (10.9%).[9,23-28]

Several factors influence PCR positivity rates such as the number of viruses detected by PCR, the presence of PCR inhibitor in CSF sample, and sample collection in the early stage of the disease.[7,9,29]

Concerning gender, CVM case rates were higher in males (62%) than in females (38%). A similar finding was reported by Mathew et al (60.9%), Vidal et al (57%), and Michos et al (57.4%).[9,25,28]

The present study demonstrated that the mean age of the infected patient was (5.9 years). Also, Jaïdane et al found that the mean age of infected patients with VM was (6.1 years), and the same finding was reported by Hosseininasab et al (5.52 years).[7,30]

Concerning age, most of the cases were reported between children less than 6 years old (72.2%; 57/79) which is consistent with studies of Hosseininasab et al (60%), and Michos et al (54.3%). Also, Vidal et al found that 56.9% of CVM cases were reported among patients less than 7 years old.[7,9,25]

Regarding the detected virus by PCR, EV were the most common causative agent detected in our study (75.9%). Also, EV were the most common causative agent in many studies like what was reported by Vidal et al (83%), De Ory et al (76.8%), Mathew et al (68.7%), Jaïdane et al (63.4%), Masri et al (60%), Soares et al (58.5%), Lee et al (54.3%), and Hosseininasab et al (43.3%). On the other hand, in some studies, EV were detected at a low rate compared to our study. This includes Dalwai et al (24%) and Vidal et al (12.8%).[7,9,22,23,28-32]

Viral etiology of VM varies from one geographical area to another and several factors influence its prevalence such as the age of the patient, methodologies, type of data (sporadic cases or outbreaks of aseptic meningitis), and country immunization program.[28]

Following EV, HSV1 was detected in 6 cases (7.6%). It was detected at different rates in other studies such as the

reports of Soares et al (17.6%), De Ory et al (1.6%), and Mathew et al (1.6%).[22,23,28]

Also, EBV was the causative agent in 7.6% of cases. Vidal et al found that EBV was the causative agent in 4% of cases and De Ory et al in 1.5% of cases.[9,22]

CMV was the causative agent in 3.8% of cases which was similar to the study of Hosseininasab et al (3.3%).[7] De Ory et al reported that CMV was the causative agent of VM in 1% of cases and Soares et al in 11.8% of cases.[22,23]

VZV was the causative agent in 2.5% of cases. De Ory et al reported that VZV was the causative agent of VM in 10.1% of cases and Hosseiniasab et al in 6.6% of cases.[7,22]

HHV6 was the causative agent in 2.5% of cases which is similar to what was reported by Hosseininasab et al (3.3%) and Vidal et al (3%).[7,9]

EV positive cases predominated mainly among children <6 years old (76.7%), followed by age group [6-17] (20%) and patients >17 years old (3.3%) (p=0.002). These results were consistent with what was reported by Mathew et al and Dumaidi et al.[28,33]

In comparison, HSV1 infection significantly predominated among patients>17 years old with 66.7%, and EBV infection significantly predominated among children < 6 years old with 66.7%.

Regarding the seasonal distribution of CVM cases in the present study, although the cases were observed throughout the year, most occurred during the spring (March to June) (64.6%; 51/79), which was similar to what was reported by Hosseininasab et al, and Mathew et al (47.8%).[7,28]

Enteroviral meningitis cases were distributed throughout the year with a peak in the spring season (March to June) (68.4%; 41/60) which is consistent with Soares et al study (60%) and Mathew et al study, while herpesviral infection doesn't show the seasonal distribution and occurred throughout the year. [23,28]

CONCLUSION

In conclusion, the present study demonstrated that EV were the most common cause of VM and was the main causative agent of VM among children less than 6 years old.

Understanding and knowledge of the causative agent of VM, its distribution, and its relationship with age and the season will help to develop VM's efficient control and prevention programs.

We recommend that genotyping and serotyping of the viruses detected in our study be performed to identify endemic serotypes that may emerge into new variants and cause epidemics periodically.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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