Original Article

The Prevalence of Enteroviruses, Mumps virus, and Herpes Simplex Virus-1 in Cerebrospinal Fluid Samples of Children with Aseptic Meningitis

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ABSTRACT

Meningitis is defined as an inflammation of the meninges, which are the protective membranes surrounding the brain and spinal cord. Aseptic meningitis is the term used to describe all forms of meningitis that are not caused by pyogenic bacteria. Aseptic meningitis can be caused by a variety of etiological agents. Infectious agents include viruses, fungi, and parasites. Viruses are regarded as significant etiological agents of aseptic meningitis. The viral etiology of this disease exhibits variability across different age groups and countries. This study aimed to examine the prevalence of different viruses (enterovirus, mumps virus, and HSV-1) in cerebrospinal fluid (CSF) samples of children diagnosed with aseptic meningitis. A total of 58 cerebrospinal fluid (CSF) samples were obtained from patients suspected of having meningitis and admitted to Ali Asghar Hospital in Tehran during the 2019-2020 period. Nucleic acid extraction was conducted, and polymerase chain reaction (PCR) testing was performed to investigate the presence of various meningitis-causative viruses. A total of 32 patients (24 males and 8 females) were found to be infected with viruses. The most prevalent meningitis virus identified was enterovirus, accounting for 25.9% of cases (n=15). The mumps virus and herpes simplex virus (HSV) were identified in 11 (19%) and six (10.3%) patients, respectively. The most common clinical manifestations observed in children with aseptic meningitis were fever and vomiting. A statistically significant correlation was identified between term week and the occurrence of viral meningitis among patients infected with HSV and mumps (p-value = 0.04). Furthermore, a borderline relationship was observed between a history of surgery and viral meningitis. Enteroviruses represent a significant etiological agent of aseptic meningitis across a range of age groups. An accurate diagnosis of meningitis viruses, such as enteroviruses, will facilitate the implementation of appropriate and life-saving antiviral therapies, while reducing the overuse of antibiotics.

Keywords: Aseptic meningitis, CSF samples, Enteroviruses, HSV1, Mumps Virus.

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1. Introduction

Meningitis is defined as an inflammation of the meninges, which are the protective membranes that surround the brain and spinal cord. Aseptic meningitis is the term used to describe all forms of meningitis that are not caused by pyogenic bacteria (1). Aseptic meningitis may be caused by a variety of etiological agents. Infectious agents, including viruses, fungi (e.g., Candida and Histoplasma capsulatum), and parasites (e.g., Toxoplasma gondii and Naegleria), can also be responsible for aseptic meningitis. Non-infectious agents that may result in meningitis include systemic diseases (e.g., collagen vascular disorder, systemic lupus erythematosus), pharmaceuticals (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), amoxicillin, intravenous immunoglobulin), and neoplastic disorders . Additionally, leukemia, inflammation of neighboring structures (e.g., brain abscess, epidural abscess), and post-infectious/post-vaccine responses (e.g., rubella, varicella, variola, and influenza vaccines) have been identified as potential causes (1). Among the aforementioned etiological agents, viruses are the primary cause of aseptic meningitis. The most prevalent viruses that can induce aseptic meningitis include non-polio human enteroviruses (NPEVs) (23-66%), mumps virus (7.5-15.8%) (2), herpes simplex viruses (HSVs) (0.5-18%) (3), and lymphocytic choriomeningitis virus (LCMV) (1.9-9.7%) (4). The less common viruses that have been identified as causes of aseptic meningitis include flaviviruses (West Nile virus (WNV), Zika virus, Chikungunya virus, and Dengue virus (DENV)), as well as other members of the Herpesviridae family (Varicella-Zoster virus (VZV). Moreover, other viruses have been identified as potential causes of aseptic meningitis, including the Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus type 6 (HHV6), as well as the John Cunningham (JC) virus and human immunodeficiency virus (HIV) (5). To date, more than 110 genetically distinct enteroviruses have been identified. The Enterovirus species B, particularly echovirus 6 and 30, echovirus 9, 13, 14, and 16 (species B), echovirus A71 (species A), and coxsackievirus A9 and B5 (species B), have been identified in infected individuals (2). The incidence of viral aseptic meningitis is estimated to range between 10 and 20 cases per 100,000 children per year. The viral aetiology of this disease differs depending on the age group and country in question. The highest incidence of the disease has been documented in infants younger than one year of age and in children aged five years and older. In temperate climates, the incidence of viral meningitis is higher during the summer and autumn months, coinciding with the peak activity of enteroviral infections. A significant proportion of children with meningitis are hospitalized for a period of approximately one week or longer while receiving antibiotic treatment (7). Given that viruses are among the primary causes of aseptic meningitis, expeditious diagnosis and suitable treatment of the disease can forestall the unnecessary prescription of medications and/or the overuse of antibiotics, which may contribute to the emergence of drug-resistant pathogens. Given its reliability and rapidity, polymerase chain reaction (PCR) can be considered the optimal method for differential diagnosis. The objective of this study was to analyze the prevalence of different viruses (enterovirus, mumps virus, and HSV-1) in cerebrospinal fluid (CSF) samples of children referred to Ali Asghar Hospital in Tehran, Iran, during the 2019-2020 period. The proportion of viral etiology of aseptic meningitis is of paramount importance, as it can elucidate the necessity for the implementation of rapid diagnostic tools to curtail the inappropriate use of antibiotics.

2. Materials and Methods

2.1. Sample Collection

A total of 58 cerebrospinal fluid (CSF) samples were obtained from patients admitted to Aliasghar Hospital in Tehran during the 2019-2020 period. The patients were clinically examined by physicians, and cerebrospinal fluid (CSF) specimens were obtained by lumbar puncture. All 58 subjects were considered to be highly suspect of having either aseptic or bacterial meningitis, sepsis/icter, fever without a localizing sign (FWLS), or multisystem inflammatory syndrome in children (MIS-C). The patients exhibited a range of clinical symptoms, including fever, vomiting, malaise, hysteria, diarrhea, and a generalized rash. All CSF samples were subjected to investigation for the presence of common bacterial contaminants through cell culture and positive staining in the medical microbiology laboratory. Subsequently, the specimens were transferred on ice to the virology laboratory and stored at -70°C until utilization. The demographic data of the patients, including age, gender, weight, nationality, clinical manifestations, final diagnosis, vaccination status, primary immune deficiency, history of surgery, and history of blood transfusion, were obtained from the patient files.

2.2. Nucleic Acid Extraction

The nucleic acid (RNA/DNA) was extracted using a QIAamp virus kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's instructions. Subsequently, the quality and quantity of the genomic extracts were evaluated using the NanoDrop™ One spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Genomes with a 260/230 ratio of less than 2 and a 260/280 ratio of less than 1.8 were excluded from subsequent analysis. Subsequently, the elutions were stored at -70°C until required for further analysis.

2.3. The Complementary DNA (cDNA) Synthesis

The BioFact™ RT-Kit (BioFact, Daejeon, South Korea) was employed for the detection of mumps virus and enterovirus, with cDNA production conducted in accordance with the manufacturer's instructions. In brief, 25 µl of the purified extracted genome was combined with 24 µl of reverse transcriptase and 1 µl of random hexamer primers. Subsequently, the mixture was incubated for 40 minutes at 50°C, followed by 10 minutes at 95°C. The product was stored at -20°C for subsequent analysis.

2.4. Polymerase Chain Reaction (PCR)

The presence of herpes simplex virus (HSV), enterovirus, and mumps virus was determined in the samples through the use of the Roche-PCR Core Kit (Roche Diagnostics GmbH, Roche Applied Science, Mannheim, Germany). The PCR master mixture consisted of 25 µl of PCR 2X master mix, 1.5 µl of forward primer (10 pm), 1.5 µl of reverse primer (10 pm), and 18 µl of double-distilled water. For each sample, a volume of four microliters was added to the reaction mixture, resulting in a total volume of 50 microliters. The thermal cycling profile included a pre-denaturation step at 95°C for three minutes, 40 cycles of denaturation at 95°C for 30 seconds, annealing at 58°C for 40 seconds, and extension at 72°C for one minute. Additionally, a final extension step at 72°C for 5 minutes was conducted at the conclusion of the program. Subsequently, gel electrophoresis and sequencing were conducted to corroborate the identification of each specific virus.

2.5. Statistical Analysis

The data were analyzed using the statistical software package SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). The initial step involved investigating the normal distribution of the various variables. Subsequently, variables exhibiting a normal distribution were subjected to parametric testing, while non-parametric tests were employed for the remaining variables. All comparisons were conducted using the Chi-square test and t-test. Furthermore, the t-test and the chi-square test were employed to compare continuous variables and categorical variables, respectively. A p-value of less than 0.05 indicated a statistically significant difference.

3. Results

3.1. Clinical Features and Demographic Data

A total of 58 cerebrospinal fluid (CSF) specimens were obtained from children suspected of having aseptic meningitis and admitted to Ali Asghar Hospital in Tehran during the 2019-2020 period. Of the 58 patients, 41 (70.7%) were male and 17 (29.3%) were female. The mean age of the participants was 12.93 months (standard deviation ±3.32; range 0–26 months). Approximately 94.8% of the patients (55/58) were of Iranian nationality. The patients exhibited a range of clinical symptoms, including fever, vomiting, hysteria, malaise or lethargy, diarrhea, and a generalized rash, among others. The most prevalent clinical symptoms were fever (94.8%) and vomiting (56.9%) (Table 1). The mean temperature of fever in patients was 38.63±0.69℃ (ranging from 37 to 40℃). The final diagnosis was as follows: 53 cases (91.4%) were diagnosed with aseptic meningitis, one case (1.7%) was diagnosed with bacterial meningitis, one case (1.7%) was diagnosed with sepsis/icter, two samples (3.4%) were diagnosed with FWLS, and one case (1.7%) was diagnosed with aseptic meningitis in MIS-C. Additionally, patients were evaluated for their vaccination status, any history of medical surgery, any history of blood transfusion, and any underlying immune deficiency disorders. Among the 58 samples, 50 (86.2%) and 5 (8.6%) patients demonstrated complete vaccination coverage and a history of surgery, respectively. No patients had a history of blood transfusion or immunodeficiency disease. Additionally, the type of childbirth, whether preterm or full-term, the week of birth, and the birth weight were investigated. The data revealed that 13 cases (22.4%) had normal vaginal delivery (NVD), while 34 cases (58.6%) had cesarean delivery (S/C). The remaining 11 cases (19%) lacked sufficient information to determine the birth type. Preterm birth was identified in five cases, representing 8.6% of the total. The mean gestational age and birth weight of the participants were 37.5 ± 2.04 weeks (ranging between 29 and 41 weeks) and 3.14 ± 0.47 kg (1.35-3.90 kg), respectively. (Table 1).

3.2. Molecular Identification of Viruses

In the present study, cerebrospinal fluid (CSF) specimens were investigated for the detection of three viruses, including enterovirus, mumps virus, and herpes simplex virus type 1 (HSV-1), using polymerase chain reaction (PCR). Among the 58 samples from patients with aseptic meningitis, the viruses of interest were identified in 32 (55.17%) cases. The presence of enterovirus, mumps virus, and HSV-1 was identified in 15 (25.9%), 11 (19%), and 6 (10.3%) of the CSF samples, respectively. Approximately 75% (24/32) of virus-positive specimens were from male subjects, including enterovirus (12/15), mumps (8/11), and HSV-1 (4/6) samples. The mean age of children infected with different viruses was 12.47±0.51 for enterovirus, 12.73±0.64 for mumps, and 10.37±5 for HSV-1. With regard to the clinical manifestations of viral meningitis, fever was observed in 31 patients (96.8%), while vomiting was noted in 21 patients (65.6%). The mean temperature in cases of infection with enterovirus was 38.71±0.73℃, 38.78±0.69℃ in cases of infection with mumps, and 38.30±0.44℃ in cases of HSV-1 infection. Complete vaccination was documented in 90.6% (29/32) of the children infected with a virus, with enterovirus, mumps, and HSV-1 identified in 13 (86.7%), 11 (100%), and 5 (83.8%) CSF samples, respectively. A review of the patients' records revealed that four (26.7%) of the patients infected with mumps had a history of surgery, while none of them had a history of blood transfusion and/or any immunodeficiency disease. It was demonstrated that 56.2% (18/32) of patients infected with the virus were delivered via caesarean section. Only three cases, representing 20% of the total, were recorded as having been born prematurely. The mean gestational age of patients with viral meningitis was 37±1 (ranging from 36-38) in HSV-positive children, 36.8±3.25 (ranging from 29-41) in enterovirus-infected children, and 38.43±0.78 (ranging from 38-40) in mumps-positive patients. The mean weight of children who were virally infected was as follows: The mean weight of children with enterovirus infection was 2.97±0.64 kg, while the mean weight of mumps-positive children was 3.34±0.39 kg and the mean weight of HSV-positive cases was 3.21±0.34 kg. No significant statistical relationship was

identified between the demographic and clinical data of patients and the PCR results for the various viruses under study (Table 2). Nevertheless, a notable statistical correlation was observed between the gestational week and the occurrence of viral meningitis among patients with HSV and mumps infections (p-value = 0.04).

Table 1. Clinical and demographic data of patients.

	All patients N=58	Enterovirus N=15	Mumps N=11	HSV N=6
Sex				
Male	41 (70.7)	12 (80)	8 (72.7)	4 (66.7)
Female	17 (29.3)	3 (20)	3 (27.3)	2 (33.3)
Mean age(month)	12.93± 3.32	12.47± 0.51	12.73± 0.64	10.37± 5
Mean weight (Kg)	3.14 ± 0.47	2.97 ± 0.64	3.43 ± 0.39	3.21 ± 0.34
Delivery				
NVD	13 (22.4%)	3 (20%)	2 (18.2%)	1 (16.7%)
S/C	34 (58.6%)	8 (53.3%)	7 (63.6%)	3 (50%)
Indeterminate	11 (19%)	4 (26.7%)	2 (18.2%)	2 (33.3%)
Term week	37.5± 2.04	36.8± 3.25	38.43± 0.78	37± 1
Preterm birth				
Negative	46 (79.3%)	10 (66.7%)	10 (90.9%)	4 (66.7%)
Positive	5 (8.6%)	3 (20%)	0	0
Indeterminate	7 (12.1%)	2 (13.3%)	1 (9.1%)	2 (33.3%)
Final diagnosis				
Aseptic meningitis	53 (91.4%)	15 (100%)	11 (100%)	4 (66.7%)
Bacterial meningitis	1 (1.7%)	0	0	0
Sepsis/Icter	1 (1.7%)	0	0	1 (16.7%)
FWLS	2 (3.4%)	0	0	1 (16.7%)
Aseptic meningitis/ MISC	1 (1.7%)	0	0	0
fever temperature	38.63± 0.69	38.71 ± 0.73	38.78± 0.69	38.30 ± 0.44
Nationality				
Iranian	55 (94.8)	15 (100)	10 (90.9)	6 (100)
Afghan	1 (1.7)	0	0	0
Unknown	2 (3.4)	0	1 (9.1)	0
Vaccination				
Complete	50 (86.2%)	13 (86.7%)	11 (100%)	5 (83.8%)
Indeterminate	8 (13.8%)	2 (13.3%)	0	1 (16.7%)
History of surgery				
Negative	53 (91.4%)	11 (73.3%)	11 (100%)	6 (100%)
Positive	5 (8.6%)	4 (26.7%)	0	0

Table 2. Statistical relationship between demographic data of patients and viral meningitis

	PCR results (P-value)	HSV &Enterovirus (P-value)	Enterovirus & Mumps (P-value)	HSV & Mumps (P-value)
Age (month)	0.283	0.470	0.384	0.151
Gender	0.798	0.598	1	1
Ethnicity	0.373	-	0.423	1
Fever	0.305	0.168	0.959	0.163
History of Surgery	0.075	0.281	0.113	-
Preterm Birth	0.162	0.541	0.229	-
Delivery	0.864	1	1	1
Term Week	0.252	0.659	0.375	0.04
Birth Weight (Kg)	0.158	0.721	0.069	0.240
Current Weight (Kg)	0.509	1	0.343	0.202
Vaccination	0.409	1	0.492	0.313

4. Discussion

Meningitis is a severe neurological condition with a high morbidity and mortality rate in young children. In 2015, the Global Burden of Diseases study reported 8.7 million cases of meningitis and 379,000 deaths worldwide. Aseptic meningitis is diagnosed when meningitis is not caused by pyogenic bacteria (5). Aseptic meningitis can be caused by a variety of infectious and non-infectious agents, with viruses representing the primary cause. The most common groups of viruses that induce aseptic meningitis are enteroviruses, mumps, herpes simplex virus (HSV), and lymphocytic choriomeningitis virus (LCMV) (2, 3). Viral meningitis is frequently mild and devoid of significant clinical complications. As the initial clinical symptoms of various forms of meningitis are similar, it is challenging to distinguish between bacterial and viral meningitis. The most common treatment is antibiotics. The rapid diagnosis and appropriate treatment of viral meningitis can prevent the unnecessary prescription of antibiotics and the development of drug resistance. In the present study, the authors investigated the presence of three common meningitis viruses in 58 cerebrospinal fluid (CSF) specimens from patients admitted to a hospital in Tehran during the period between 2019 and 2020. Viral agents were identified in 55.17% of the samples. Our findings align with those of previous studies, which have identified viruses in 30–66% of patients with aseptic meningitis. Moghadam et al. conducted an investigation into the role of various meningitis viruses, including enteroviruses, herpes simplex virus (HSV), varicella-zoster virus (VZV), mumps, measles, and rubella, in a cohort of 104 children younger than 14 years old who were admitted to the hospital in Yasuj, Iran. As in the present study, the most commonly detected viruses were enterovirus (53/104), mumps (6/104), and HSV (4/104) (10). In another study, Sanaei Dashti et al. employed real-time PCR for the detection of viruses in 56 children aged between one month and 16 years with suspected viral meningitis admitted to the pediatric wards at Nemazee Hospital from March 2014 to February 2015. As with the findings of the present study, the results demonstrated that enterovirus (42.85%) and mumps (38.1%) were the most prevalent causes of viral meningitis in children (11). Additionally, enteroviruses, with an incidence of 20-59% in Iran and 51.1% globally, have been identified as the primary etiological agent of aseptic meningitis (12, 13). In the present study, the patients infected with the virus-caused meningitis were within the age range of 0 to 14 months. The youngest age group consisted of patients with HSV-induced meningitis (0-13 months old), while the oldest age group was comprised of patients with mumps-induced meningitis (12-14 months). Furthermore, in accordance with the findings of previous studies, children infected with enterovirus were over the age of one year (14). The majority of patients diagnosed with viral meningitis (24/32) were male. Despite the absence of a notable correlation between gender and the incidence of viral meningitis, male patients appeared to demonstrate a heightened susceptibility to viral meningitis infections compared to their female counterparts (15). Despite the lack of clarity regarding the primary mechanism involved, it appears that the X chromosome may confer a protective effect against this disease in females (16).The current research findings indicate that the most prevalent clinical manifestations among patients are fever and vomiting. Our findings were consistent with those of previous studies, which reported fever, vomiting, and headache as the most common symptoms associated with aseptic meningitis (6, 17). A total of 90.6% (29/32) of the children infected with the virus had received the full vaccination schedule. Among the vaccinated cohort, it was observed that the only group that had received a complete vaccination were those with mumps meningitis. The occurrence of aseptic meningitis in children following MMR vaccination has been documented in various countries (18). Mumps represents a significant cause of aseptic meningitis in children who have received the MMR vaccination (17, 20). In Iran, the implementation of a mumps vaccination program commenced in 2003. Subsequently, numerous cases of aseptic meningitis in Iranian children following MMR vaccination have been documented (21). One potential explanation is the adverse effects of the Leningrad-Zagreb and Leningrad-3 strains, which are utilized in certain mumps vaccines, in contrast to the Jeryl-Lynn and RIT 4358 strains (22). Another potential explanation is that the vaccine fails to induce a protective immune response in some children (13). Postoperative meningitis is a rare occurrence following spinal lumbar surgery. To facilitate an expedient diagnosis and the formulation of an efficacious treatment plan for patients, it is imperative that medical follow-up, including the measurement of fever and the examination for other potential indications of aseptic meningitis, be conducted. Some studies have indicated that postoperative bacterial meningitis is a significant contributor to prolonged hospitalization, antibiotic consumption, and high mortality rates among affected patients (23). In the present study, an examination of the children's previous surgical histories was conducted to investigate the potential relationship between postoperative meningitis and different viruses. Among the 32 patients with virus-related meningitis, four out of 15 (26.7%) of those with enterovirus meningitis had a history of surgery. No statistically significant

correlation was identified between a history of surgery and viral meningitis (p-value = 0.075). Nevertheless, additional research may provide further insight into the phenomenon of postoperative viral meningitis. Congenital immunodeficiency disorders, otherwise referred to as primary immunodeficiency, are medical conditions characterized by an increased susceptibility to various infections. Previous studies have indicated that meningitis may be a presenting manifestation of immune deficiency in children. It is therefore recommended that children with meningitis be screened for primary immunodeficiency, such as congenital immunoglobulin or complement deficiencies (24). Neither patient with viral meningitis had a history of primary immunodeficiency. Maternal viral infections, including those that are transmitted from mother to child, are a significant cause of maternal and infant morbidity and mortality. These infections have the potential to transmit to the fetus in one of three ways: transplacentally, prenatally (from vaginal secretions or blood), or postnatally through breast milk or other sources. The transmission of viral infections to the fetus can be influenced by various risk factors, which depend on the timing of the infection in pregnancy, the mode of infection, the type of infection (primary, chronic, or re-infection), the duration of membrane rupture, the type of birth delivery, socio-economic conditions, and infant feeding (breastfeeding occurrence). The severity of the complications that maternal viral infections can have on the fetus depends on the viral agents involved and the gestational age at which the infection occurs. Some of these complications include spontaneous abortion, fetal death, intrauterine growth retardation, and the infants' congenital anomalies and organ diseases with sequelae of varying severity. Among these, aseptic meningitis represents one of the abnormalities that can be induced by different viruses, including mumps, herpes simplex virus type 1 (HSV-1), and enterovirus, during pregnancy (25). In this study, 56.25% (n=18) of patients infected with the virus were born via cesarean section. Additionally, children with herpes simplex virus (HSV)-induced meningitis were born at an earlier gestational age than patients infected with mumps. Furthermore, a notable statistical correlation was observed between birth term week and the incidence of viral meningitis among patients infected with HSV and mumps (p-value = 0.04). One potential explanation for this discrepancy is the diminished immunity of infants born prematurely, which may render them more susceptible to viral infections such as HSV-1. Additionally, HSV-1 may influence the mother's hormonal profile during pregnancy, potentially leading to premature birth. Furthermore, previous studies have indicated that the timing of infection is a significant factor in the transmission of viral infections. The risk of transmission of HSV infection to infants is estimated to be high (30–50%) if mothers have acquired genital HSV in the proximity of delivery and low (<1%) if there is a history of recurrent HSV infections or if genital HSV infection has occurred during the initial half of pregnancy. The findings revealed that mumps infection during the initial trimester of pregnancy was a significant risk factor for potential severe complications (49, 51). It must be acknowledged that this study was not without limitations. Firstly, had the sample size been larger, it would have been possible to obtain further information regarding the etiological role of the aforementioned meningitis viruses. Secondly, all samples were obtained from a single hospital in Tehran. A more comprehensive indicator of the prevalence of viral meningitis in Iran would be a sampling strategy that encompasses a greater number of hospitals distributed across the country's diverse geographical regions. Third, the research project did not include a follow-up period, which may have resulted in an underestimation of long-term outcomes, such as the case fatality rate. It is therefore recommended that further studies be conducted with larger sample sizes, sampling from different regions within the country, and with patient follow-up. The authors of the present study posited that enteroviruses were the primary etiological agent of aseptic meningitis among young children. Mumps and herpes simplex virus (HSV) were identified as the second and third most prevalent viruses in cerebrospinal fluid (CSF) samples, respectively. A statistically significant correlation was identified between birth term week and the occurrence of viral meningitis, particularly in cases caused by HSV and mumps. Furthermore, a borderline relationship was observed between a history of surgery and the acquisition of viral meningitis. To develop effective public health strategies, it is essential to further assess the potential role of viruses in postoperative meningitis. Accordingly, further studies with a larger sample size on individuals with a history of surgery are recommended. An accurate diagnosis of viruses in patients with aseptic meningitis would assist physicians in prescribing appropriate antiviral therapy, reducing the overuse of antibiotics, and improving the prognosis of patients with critical conditions.

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Authors' Contribution

Study concept and design: SJK, ZY
Acquisition of data: A.A, M.R, B.S, A.N.
Analysis and interpretation of data: S.J.K, Z.S, T.D

Drafting of the manuscript: S.J.K, Z.S
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Statistical analysis: S.J.K, Z.S
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Ethics
The present study was conducted in accordance with the ethical standards of the Ethics Committee of Iran University of Medical Sciences (code: IR.IUMS.FMD.REC.1399).

Conflict of Interest
The authors have no conflict of interests.

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Data Availability
All data used and analyzed are available from the corresponding author.

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