Barw Medical Journal | 2024;2(2):7-12
Journal home page: https://barw.krd/index.php/BMJ

Original Article

# Viral Meningitis (Enterovirus) Outbreak in The Pediatric Population of Sulaymaniyah Governorate, Iraq: A Multi-Center Experience

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**Keywords:**
Aseptic meningitis
Children
Pediatric
Empirical antibiotics

Received: April 5, 2024
Revised: April 20, 2024
Accepted: April 29, 2024
Published: May 10, 2024



Citation: Najmadden ZB, Salih KH, Khurshid BQ, Ahmed SM, Mahmood SO, Faraj AH, et al. Viral meningitis (enterovirus) outbreak in the pediatric population of Sulaymaniyah Governorate, Iraq; a multi-center experience. Barw Medical Journal. 2024 May 10;2(2):7-12. https://doi.org/10.58742/bmj.v2i2.88

## Abstract

### Introduction

Viral meningitis, often caused by enteroviruses in children, is prevalent globally but is difficult to distinguish from bacterial forms. Molecular testing like PCR is vital; however. This study investigates the characteristics of viral meningitis in pediatric patients during an outbreak in Sulaymaniyah Governorate, Iraq.

### Methods

This is a multicentered prospective study that included children with a confirmed diagnosis of viral meningitis who have visited pediatric clinics throughout Sulaimani, Halabja, Kalar, and Ranya cities during the period from May 2023 to June 2023.

### Results

In total, 116 cases were included, of whom 75 (64.7%) were male and had a mean age of 6.5 ± 3.2. Most were between the ages of 4-6 (38, 32.8%) and 7-12 years (55, 47.4%). Only 53.4% had contact with another patient. Common symptoms included fever (63.8%) and headache (62.1%). Lymphocyte predominance was observed in 46.6% of CSF samples. Upon molecular diagnosis, the inflammation in all of the cases was due to enterovirus infection. Most of the patients (75%) received empirical antibiotics. The average hospital stay was 10 days. While 95.7% of patients had no complications during recovery, a few experienced issues like weakness and malaise. All had good clinical outcomes.

### Conclusion

The viral meningitis outbreak in Sulaymaniyah Governorate is caused by enterovirus, with epidemiological, clinical, and laboratory findings similar to that of the literature. The condition has resulted in a high prescription rate of empirical antibiotics due to late diagnosis.

## 1. Introduction

Meningitis is an inflammation of the membranes covering the brain and spinal cord, which is a serious condition with potential long-term complications, especially when it affects pediatric populations [1]. Generally, the yearly occurrence remains unclear due to insufficient reporting of the situation. It affects individuals of all age groups but is more prevalent in children compared to adults. It is estimated that the overall occurrence is 11 cases per 100,000 individuals annually in the US, with males being three times more susceptible than females. This condition leads to 26,000 to 42,000 hospitalizations annually in the US. European research indicates an incidence of 70 per 100,000 infants under one year old, 5.2 per 100,000 children aged one to fourteen, and 7.6 per 100,000 adults [2]. According to the cause, meningitis can be categorized into bacterial and aseptic types, with the latter being either associated with viral infection or not [3]. Viral meningitis, although less severe than its bacterial counterpart, remains a significant health concern that affects people of all age groups, but children contract it more frequently [4]. Viral meningitis primarily affects young children, with its occurrence declining as individuals age. In regions with high immunization rates, viral meningitis is more prevalent than bacterial meningitis, constituting approximately 3 to 18% of childhood cases [5]. The estimated incidence of viral meningitis ranges from 0.26 to 17 cases per 100,000 individuals. In the United States, enteroviral meningitis accounts for up to 75,000 cases annually [6]. it occurs throughout the year. Enteroviruses stand out as the primary cause of viral meningitis in numerous regions globally, with reported incidences ranging from 12 to 19 cases per 100,000 individuals annually in certain affluent nations [7]. Among the numerous pathogens responsible for viral or aseptic meningitis, enteroviruses have consistently been identified as a leading infectious cause in children, accounting for 90% of aseptic meningitis cases [3]. Specific enteroviruses, such as coxsackievirus B5, echovirus 6, 9, and 30, are prone to triggering outbreaks of meningitis, whereas others, like coxsackievirus A9, B3, and B4, are predominantly endemic [7].

Viral meningitis is a worldwide condition that occurs in both epidemic and sporadic forms. Overall, the annual incidence of viral meningitis is higher than the other forms of the disease [8]. Globally, the patterns and impacts of enterovirus meningitis (EVM) vary widely. Factors like regional healthcare infrastructure, public health initiatives, climate, population density, and cultural practices can influence the incidence, clinical manifestations, and outcomes of this disease [9]. Despite the global scale of the issue, a comprehensive understanding of EVM remains fragmented. Regional studies often lack the scale or comparative data to provide broader insights, while global overviews can sometimes miss the unique nuances of specific areas or communities, especially as there is limited data from developing countries, such as Iraq. Moreover, to date, there is no surveillance system for the condition [1,10]. Transmission of enteroviruses can occur through respiratory secretions or via the fecal-oral route. Additionally, vertical transmission from an infected mother to her infant can occur through crossing the placenta or breastfeeding. Typically, the virus enters through the oral-fecal route until it reaches the lower gastrointestinal (GI) tract, where it binds to a specific receptor on the enterocytes' surface and crosses the intestinal lining, reaching the Peyer's patches to continue replication [11].

Several risk factors have been identified that elevate the possibility of acquiring viral meningitis, such as a weakened immune system, age, travel background, and HIV infection [12]. The clinical presentations can differ based on the viral serotype; however, most often, the clinical findings are not enough to allow a specific etiologic diagnosis. It has been reported that most cases with aseptic meningitis are hospitalized and given empirical antibiotics until the confirmed diagnosis is reached [13]. It is important to mention that the early symptoms of viral and bacterial meningitis often appear alike. Thus, quickly identifying the cause is highly beneficial, preventing the unnecessary administration of medications [2,14]. The diagnosis of meningitis typically begins with a physical examination and a thorough review of the patient's medical history, focusing on symptoms indicative of the condition. A newer and less widely recognized physical examination method used to evaluate meningeal irritation is referred to as "jolt accentuation of headache". The polymerase chain reaction (PCR) is considered the definitive diagnostic method for identifying viral meningitis. It works by detecting and measuring viral DNA or RNA in the cerebrospinal fluid (CSF) of the patient [8]. Polymerase chain reaction (PCR) testing is highly accurate and can distinguish between viral and bacterial meningitis. However, it might not be feasible in developing and low-resource countries [10].

Saif Al-Badr, the representative of the Iraqi Ministry of Health, has stated that instances of meningitis in children persistently arise nearly every day. As of April 30, approximately 190 cases have been documented in the Kurdistan Region, with around 150 occurrences in Sulaymaniyah province and 40 cases reported in Halabja city. Additionally, a significant proportion of these meningitis cases have been observed in school-aged children. In May 2023, the World Health Organization (WHO) announced an outbreak of meningitis in Iraq, with particular impact noted in Sulaymaniyah governorate and Halabja city since mid-April 2023[15]. This multicentered study aims to investigate the epidemiological and clinical characteristics and laboratory findings of viral meningitis in pediatric patients during an outbreak in Sulaimanyiah Governorate, Iraq.

## 2. Methods

### 2.1 Study design and setting

This is a multicentered prospective study that included children who were diagnosed with viral meningitis and visited pediatric clinics throughout Sulaimani, Halabja, Kalar, and Ranya cities during the period from May 2023 to June 2023. The ethics committee of the College of Medicine at the University of Sulaimani granted ethical approval (Decree No. 45).

### 2.2 Inclusion and exclusion criteria

Suspected pediatric patients of having viral meningitis were initially recognized using these indicators: a fever exceeding 38.3°C when measured axillary, at least one vomiting incident within a 24-hour period, symptoms of a headache, photophobia, signs of meningeal irritation such as Kernig sign, Brudzinski sign, neck stiffness, and impaired consciousness. Only those with confirmed PCR results of viral meningitis who had entirely negative results from Gram stain evaluations and cultures were included in the study. The microbiological methods utilized to rule out bacterial etiology included culture techniques such as VITEK 2 system (BioMérieux), and occasionally manual culture methods in accordance with WHO guidelines. The types of culture media employed encompassed blood, MacConkey, and chocolate agars. Patients with meningitis due to other etiologies such as Streptococcus pneumoniae, Haemophilus influenzae, and Human herpesvirus 6, were excluded from the study, these causative agents were diagnosed through culture.

BioFire® FilmArray® Meningitis/Encephalitis Panel was used for the simultaneous detection and identification of various bacterial, viral, and fungal nucleic acids directly from cerebrospinal fluid samples obtained from individuals exhibiting signs or symptoms of meningitis. The Panel menu comprises the following microorganisms: Bacteria: Escherichia coli K1, Haemophilus influenza, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae; Viruses: Cytomegalovirus (CMV), Enterovirus, Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human par echovirus, Varicella zoster virus (VZV); Fungus: Cryptococcus neoformans/gattii.

### 2.3 Cerebrospinal fluid (CSF) analysis

CSF samples from all the participants were collected through lumbar puncture and analyzed by laboratory personnel of a local hospital. The analysis included appearance evaluation, protein and glucose level determination, total and differential cell counts, culturing, and direct microscopy of CSF to detect bacterial or fungal pathogens. Additionally, BioFire® FilmArray® Meningitis/Encephalitis Panel was used for the simultaneous detection and identification of various bacterial, viral, and fungal nucleic acids directly from cerebrospinal fluid samples obtained from individuals exhibiting signs or symptoms of meningitis and/or encephalitis.

### 2.4 Data collection and analysis

Demographic, medical, and epidemiological background, as well as clinical and laboratory data, were entered into the electronic systems used by the clinics during patient visits or at admission, and required data were retrospectively collected from there. Microsoft Excel (Microsoft Corporation) was used to collect and organize the data. Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp.) was used for encoding and descriptive analysis of the data

## 3. Results

In total, 116 viral meningitis cases were included in the study, of whom 75 (64.7%) were male, and 41 (35.3%) were female. They had a mean age of 6.5 ± 3.2 (ranging from 5 months to 14 years). Most of these affected children were between the ages of 4-6 (38, 32.8%) and 7-12 years (55, 47.4%). Among the cases, 42 (36.2%) had a family member with the same disease, and 62

**Table 1: Characteristics of the enrolled participants.**

| Characteristics | N. (%) / Mean ± SD |
|---|---|
| Age, years, mean (SD) | 6.5 ± 3.2 |
| <1 | 5 (4.3%) |
| 1 – 3 | 15 (12.9%) |
| 4 – 6 | 38 (32.8%) |
| 7 – 7 | 55 (47.4%) |
| 13-14 | 3 (2.6%) |
| Sex | |
| Male | 75 (64.7%) |
| Female | 41 (35.3%) |
| Level of education | |
| Pre-Kindergarten | 40 (34.5%) |
| Kindergarten | 15 (12.9%) |
| Elementary school | 59 (50.9%) |
| Secondary school | 2 (1.7%) |
| Race | |
| Kurd | 113 (97.4%) |
| Arab | 3 (2.6%) |
| Past Medical History | |
| Epilepsy | 1 (0.8%) |
| Thalassemia minor | 1 (0.8%) |
| Convulsion | 3 (2.6%) |
| Favism | 2 (1.7%) |
| Admission for Upper respiratory tract infections | 2 (1.7%) |
| Tonsilitis | 3 (2.6%) |
| Hodgkin lymphoma | 1 (0.8%) |
| Coronary heart disease | 1 (0.8%) |
| Past Surgical History | |
| Tonsillectomy | 7 (6%) |
| Herniorrhaphy | 1 (0.8%) |
| Open Heart surgery | 1 (0.8%) |
| Drug allergy | |
| Vancomycin | 2 (1.7%) |
| Cow -milk allergy | 1 (0.8%) |
| Travel History | 16 (13.8%) |
| Vaccination History | |
| Complete | 96 (82.7%) |
| incomplete | 6 (5.2%) |
| Up to date | 14 (12%) |
| Family member with the same disease | 42 (36.2%) |
| History of contact with patients with the disease | 62 (53.4%) |

(53.4%) had a history of contact with patients with meningitis. Further demographic and history details have been provided in (Table 1).

The main chief complaints by these patients were fever (74, 63.8%) and headache (39, 33.5%). However, overall, the proportion of associated symptoms reported by these patients are as follows; back pain (53, 45.7%), decreased activity (69, 59.5%), excessive crying (58, 50%), fever (74, 63.8%), headache (72, 62.1%), irritability (68, 58.6%), malaise (84, 72.4%), neck stiffness (71, 61.2%), phonophobia (56, 48.3%), photophobia (73, 62.9%), poor feeding (56, 48.3%), sleep disturbance (69, 59.5%), and vomiting (95, 81.9%), lasting 4.1 ± 2.5 days until the day of their visit. Kernig's and Brudzinski's signs were observed in 80 (69.0%) and 66 (56.9%) patients, respectively. Laboratory findings showed positive CRP (levels above 5 mg/L) in 50 (43.1%) cases, mean WBC of 2665.3 ± 5625.7. Moreover, CSF analysis revealed no microbial growth in any of the cases (0%), a clear appearance in 49 (42.2%) cases and turbid in 67 (57.8%), CSF WBC mean of 826.0 ± 1272.5 with lymphocytes being the predominant cell in the CSF in 54 (46.6%), while neutrophils and monocytes were predominant in only 6 (5.2%) and 1 (0.8%) of the patients, respectively. The mean CSF protein and glucose levels were found to be 43.4 ± 19.4 and 62.3 ± 20.5, respectively. See (Table 2) for more details. In all the cases, PCR results confirmed the inflammation to be caused by enterovirus infection.

After achieving a definitive diagnosis, the patients were not given anti-viral drugs, as it was not deemed necessary. The mean hospitalization duration for these patients was 10.0 ± 2.2. During recovery, 111 (95.7%) lacked any complications; however, a single instance was documented for each of the following complications: weakness, abdominal pain, agitation, backache, malaise, and feeling drowsy. All the patients were associated with good clinical outcomes (Table 3).

**Table 3: Management and clinical outcome.**

| Characteristics | N. (%) / Mean ± SD |
|---|---|
| Empirical antibiotic | |
| Vancomycin and Ceftriaxone | 54 (46.6%) |
| Ceftriaxone | 3 (2.6%) |
| Azithromycin | 9 (7.8%) |
| Amoxicillin and Ceftriaxone | 1 (0.8%) |
| Amoxicillin | 6 (5.2%) |
| Cefixime | 9 (7.8%) |
| Cefixime and Azithromycin | 4 (3.5%) |
| Amoxicillin and Azithromycin | 1 (0.8%) |
| None | 29 (25%) |
| Duration of Hospitalization, mean (SD) | 10.0 ± 2.2 |
| Complications | |
| None | 111 (95.7%) |
| Weakness | 1 (0.8%) |
| Abdominal pain | 1 (0.8%) |
| Agitation | 1 (0.8%) |
| Backache | 1 (0.8%) |
| Malaise and feeling drowsy avism | 1 (0.8%) |
| Complete resolution | 116 (100%) |

## 4. Discussion

**Table 2: Clinical characteristics and laboratory findings of the participants.**

| Characteristics | N. (%) / Mean ± SD |
|---|---|
| Chief Complaint | |
| Backpain | 1 (0.8%) |
| Fever | 74 (63.8%) |
| Headache | 39 (33.5%) |
| Malaise | 1 (0.8%) |
| Vomiting | 1 (0.8%) |
| Associated symptoms | |
| Back pain | 53 (45.7%) |
| Decreased activity | 69 (59.5%) |
| Excessive crying | 58 (50%) |
| Fever | 74 (63.8%) |
| Headache | 72 (62.1%) |
| Irritability | 68 (58.6%) |
| Malaise | 84 (72.4%) |
| Neck Stiffness | 71 (61.2%) |
| Phonophobia | 56 (48.3%) |
| Photophobia | 73 (62.9%) |
| Poor feeding | 56 (48.3%) |
| Sleep disturbance | 69 (59.5%) |
| Vomiting | 95 (81.9%) |
| Duration, days, mean (SD) | 4.1 ± 2.5 |
| Fever | |
| < 37.4 | 1 (0.8%) |
| 37.4-38 | 23 (19.8%) |
| > 38 | 92 (79.4%) |
| Kernig's sign | 80 (69.0%) |
| Brudzinski's sign | 66 (56.9%) |
| CRP | |
| Negative | 66 (56.9%) |
| Posiyive | 50 (43.1%) |
| WBC, cells/μL, mean (SD) | 2665.3 ± 5625.7 |
| CSF Appearance | |
| Clear | 49 (42.2%) |
| Turbid | 67 (57.8%) |
| CSF WBC, mean (SD) | 826.0 ± 1272.5 |
| Predominant cell in CSF | |
| Lymphocyte | 54 (46.6%) |
| Monocyte | 1 (0.8%) |
| Neutrophil | 6 (5.2%) |
| CSF Protein, mean (SD) | 43.4 ± 19.4 |
| CSF Glucose, mean (SD) | 62.3 ± 20.5 |
| CSF Culture (Microbial Growth) | 0 (0%) |

Meningitis, with its diverse etiological strains, remains a significant and recurrent global health challenge, with viral meningitis capturing a sizable share of this burden [1]. Our in-depth exploration into the recent viral meningitis outbreak encompassing 116 pediatric cases from the Sulaimanyiah Governorate in Iraq provides a timely addition to the current understanding of this disease's behavior in diverse geographical settings.

In our multi-centered study, the gender-based prevalence of the disease skews noticeably towards males at 64.7%. Previous research from different geographic cohorts have occasionally highlighted such a gender disparity [9,16-19]. While hormonal, biological, and immunological variances between genders could potentially factor in, the role of socio-cultural elements cannot be marginalized. This biological differences in how males and females respond to viral infections might be attributed to

variations in the expression of genes found on the X and Y chromosomes. Biological processes related to the X chromosome and its associated genes seem to provide females with an immunological upper hand [20]. Additionally, gender-based access to healthcare, coupled with disparate patterns of outdoor activities between adult boys and girls, might be influential undercurrents dictating these statistics [21].

The mean age of affected children in the current cohort was 6.5 years. Such data points underscore the existing literature's claims that children, particularly those in younger age brackets, are at heightened risk for viral meningitis [9,16-19]. This heightened vulnerability amongst younger children could be attributed to their still-maturing immune defenses, as well as their frequent exposure to high-contact environments like schools and playgrounds [21].

In our study, 36.2% of the affected children had a family member with the illness, and 53.4% had been in contact with patients before diagnosis, strongly indicating a community-driven transmission model. Enteroviruses are known for their facile person-to-person spread, especially within family units, reinforcing the importance of early detection and quarantine measures [14].

A deeper dive into the clinical manifestations of our cohort revealed symptomatology that largely aligns with global trends. The infections might show no symptoms or have general symptoms like myalgia, headache, fever, sore throat, malaise, chills, vomiting, abdominal pain, nausea, drowsiness, photophobia, and neck stiffness [2,22]. Similar findings were observed in our study, with fever (63.8%) and headache (62.1%) being most commonly reported. Additionally, the spectrum of symptoms like back pain, neck stiffness, and vomiting observed in our study, exemplifies the multifaceted nature of the disease, sometimes making its differentiation from bacterial meningitis, especially in the early stages, quite challenging [2]. The primary method for diagnosing enteroviruses in laboratories relies on molecular techniques, with classical virus-isolation methods still employed in reference laboratories. Antigen detection and serology, once common, are now seldom utilized in diagnosis and are becoming outdated. An integral aspect of diagnosing and monitoring enterovirus infections involves viral typing through VP1 gene sequencing, traditionally using the Sanger technique, and more recently, full-genome next-generation sequencing. The latter method enables typing of all enteroviruses, enhanced investigation of outbreaks, detection of coinfections, and identification of severity markers within the enterovirus genome [23].

The presence of clear CSF in 42.2% and turbidity in 57.8% of our cases somewhat reflects observations from the literature, as the turbid CSF cannot guarantee the presence or absence of viral meningitis [24]. Furthermore, the dominance of lymphocytes in CSF samples, a hallmark of viral infections, was evident in 46.6% of our study group. Such CSF trends can serve as vital diagnostic cues, especially in settings where advanced molecular tests might be scarce or unfeasible [25]. The causative agent for viral meningitis was found to be enterovirus infection in all of our cases. This is not surprising as enteroviruses are the leading cause of viral meningitis in children, accounting for 90% of aseptic meningitis cases. Meanwhile, neutrophils and monocytes where predominant in only 5.2% and 0.8% of the patients, respectively. This is in agreement with the study by Alves et al. that highlighted CSF lymphocyte predominance as a hallmark of viral meningitis [2]. However, some past researches have indicated that 25% of patients with viral meningitis might have neutrophilic pleocytosis [26].

Jaijakul and colleagues reported that 47% of individuals with enteroviral meningitis exhibited neutrophilic pleocytosis [27]. Additionally, Masri et al. showed a 20.6% neutrophil predominance [9].

A worrisome observation was the high prescription rate of empirical antibiotics given by the clinicians observed in our study (75%). This is not an uncommon practice and was reported in the literature in around one-third of pediatric patients [26]. While this widespread use of antibiotics is precautionary, driven by the overlapping clinical presentations of viral and bacterial meningitis, it might lead to antibiotic resistance and unnecessary healthcare expenditure [9]. Reducing such trends requires rapid and precise diagnostic tools, combined with heightened physician awareness.

On a more positive note, our study shed light on the generally favorable prognosis of EVM. With a staggering 95.7% of patients exhibiting a complication-free recovery and all patients being associated with a good clinical outcome. As highlighted by the existing literature, it is reassuring to know that while the disease might be distressing, its long-term implications are typically benign [8,28].

While the current study offers a nuanced and regional perspective, inherent limitations, typical of retrospective designs, cannot be overlooked. The relatively condensed study duration might not capture the full epidemic curve. Future research endeavors, harnessing larger datasets and employing longitudinal designs, could render a more comprehensive understanding.

## 5. Conclusion

The viral meningitis outbreak in Sulaimanyiah Governorate is caused by enterovirus infection, with epidemiological, clinical, and laboratory findings similar to that of the literature. The condition has resulted in a high prescription rate of empirical antibiotics due to the lack of rapid diagnostic modalities resulting in late diagnosis. Our exploration underscores the undeniable importance of early diagnostics, informed therapeutic strategies, and proactive public health initiatives in combating such outbreaks. Bridging regional insights to craft a cohesive global strategy remains a challenge, broader studies encompassing diverse populations and extended durations might further elucidate the intricacies of this disease.

## Declarations

**Conflicts of interest:** The author(s) have no conflicts of interest to disclose.

**Ethical approval:** Not applicable.

**Patient consent** (participation and publication)**:** Not applicable.

**Source of Funding:** Smart Health Tower.

**Role of Funder:** The funder remained independent, refraining from involvement in data collection, analysis, or result formulation, ensuring unbiased research free from external influence.

**Acknowledgments:** None to be declared.

**Authors' contributions:** ZBN was a major contributor to the conception of the study, as well as in the literature search for related studies. MNH, KHS, BQHK, and SMA were Involved in the literature review, the writing of the manuscript, and data analysis and interpretation. SOM and AHF Literature review, final approval of the manuscript, and processing of the tables. GSA, AMQ, MSM, and JIH were involved in the literature review, the design of the study, and the critical revision of the manuscript. ZBN and MNH Confirmation of the authenticity of all the raw data All authors approved the final version of the manuscript.

**Use of AI:** AI was not used in the drafting of the manuscript, the production of graphical elements, or the collection and analysis of data.

**Data availability statement:** Not applicable.

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