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A Case of Pediatric Enteroviral Meningitis with a Travel History

Seyahat Öyküsü Olan Pediatrik Enteroviral Menenjit Olgusu

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Abstract

Enterovirus meningitis represents a common cause of meningitis worldwide. In this case study, a 5-year-old male with a travel history presenting with persistent nausea, vomiting, fever and headache for 3 days is reported. The patient described a fever of 39.5°C on the first day of symptom onset as well as decreased appetite and pain in the front right side of head. In physical examination, initially there was no sign of stiff neck, however he had neck stiffness the following day, Kernig's sign and Brudzinski's signs were positive. On admission, blood tests showed a slightly increased C-reactive protein and a normal white cell count. He was admitted to the pediatrics service and a lumbar puncture was performed. Intravenous ceftriaxone and acyclovir were empirically administered. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis, with normal protein and glucose concentration. CSF molecular analysis was positive for enterovirus RNA. Cranial magnetic resonance imaging with contrast was normal. Following confirmed diagnosis, ceftriaxone and acyclovir treatments were discontinued and he was given supportive care. He successfully recovered and was discharged without any complication. This case report highlights that rapid molecular testing favorably impacts patient management by improving antimicrobial stewardship through the reduction of intravenous therapy, side effects and inpatient bed-days.

Keywords Enterovirus, meningitis, molecular testing, patient management, RT-PCR, rapid diagnosis

Özet

Enteroviral menenjit dünya çapında yaygın görülen bir viral menenjit türüdür. Bu çalışmada, 3 gün boyunca devam eden mide bulantısı, kusma, ateş ve baş ağrısı şikayetleri ile başvuran ve seyahat öyküsü olan 5 yaşında erkek olgu sunulmaktadır. Hasta, semptomların başladığı ilk gün 39,5°C ateş, iştah kaybı ve başın sağ ön kısmında ağrı ile acil servise başvurdu. Fiziki muayenede, başlangıçta ense sertliği görülmese de ertesi gün ense sertliği belirlendi. Kernig ve Brudzinski bulguları pozitif idi. Başvuru sırasında yapılan testlerde C-reaktif proteinde hafif artış ve beyaz hücre sayısının normal olduğu görüldü. Pediatri servisine yatırılan hastaya lomber ponksiyon yapıldı. Ampirik olarak intravenöz seftriakson ve asiklovir uygulandı. Beyin omurilik sıvısı (BOS) analizinde normal protein ve glikoz konsantrasyonu ile birlikte lenfositik pleositoz saptandı. BOS moleküler analizi enterovirüs RNA açısından pozitif bulundu. Kontrastlı kraniyal manyetik rezonans görüntüleme normal idi. Tanının doğrulanmasının ardından seftriakson ve asiklovir tedavileri durdurularak destek tedavisi başlandı. Hasta başarılı bir şekilde iyileşti ve herhangi bir komplikasyon yaşanmadan taburcu edildi. Bu olgu sunumu, hızlı moleküler testlerin, intravenöz tedaviyi, yan etkilerini ve yatılı tedavi süresini azaltarak antimikrobiyal yönetimi iyileştirdiğini ve hasta yönetimini olumlu yönde etkilediğini vurgulamaktadır.

Anahtar Kelimeler *Enterovirüs, menenjit, moleküler test, hasta yönetimi, RT-PCR, hızlı tanı*

INTRODUCTION

The human enteroviruses (HEVs) are small, non-enveloped, single-stranded RNA viruses belonging to the Picornaviridae family. They are among the most common viruses that infect humans. HEVs are associated with a range of diseases, some of which involve the central nervous system (CNS). The prototypical HEV poliovirus, is the causative agent of paralytic poliomyelitis, while other HEVs are responsible for most cases of aseptic meningitis.[1]

There are currently more than 100 serotypes of HEVs described. On the basis of the phylogenetic clustering, these viruses have been assigned to four species; HEV-A, HEV-B, HEV-C and HEV-D which include coxsackieviruses, echovirures, polioviruses and other enteroviruses based on serotypes other viruses, such as human rhinoviruses (HRVs) A, B and C, the most frequent cause of the common cold, have recently been added to this genus based on their genetic properties.[2]

HEVs replicate in the human oropharynx and gastrointestinal tract and are primarily spread by fecal-oral route. Enteroviruses primarily infect individuals during the warm months of summer and autumn, particularly when hygiene measures are not adequately applied. Although most HEV infections can be asymptomatic, they are associated with a wide spectrum of clinical presentations such as hand, foot, and mouth disease, conjunctivitis, acute myalgia, upper and lower respiratory disease and severe syndromes of the CNS including aseptic meningitis, encephalitis, paralytic myelitis, acute flaccid paralysis, and cerebellar ataxia.[3] HEVs are known to be the major causative agents of aseptic meningitis in many countries particularly during the first year of life. The prevalence of enteroviral meningitis is globally high, with an estimated 75.000 cases in the United States every year, making this type of meningitis highly relevant to both patients and caregivers.

Meningitis is the inflammation of the meningeal membranes that surround the brain and spinal cord.[4] It is a serious condition with symptoms such as fever, headache, vomiting, neck stiffness, and excessive drowsiness, which requires urgent medical attention. Coxsackievirus (CV) A9, A10, B3, and B5; echovirus (E) 4, 5, 9, 11, 19, and 30; and EV-A71, 75, 76, and 89 have often been reported in sporadic meningitis cases and epidemics.[5] The long-term consequences of EV infection upon the CNS are mostly unknown. However, these viruses are known to persist, and the presence of viral RNA by itself has been shown to be potentially pathogenic in certain cases. In addition, EVs have been linked to autoimmune-like diseases such as diabetes and chronic myocarditis, possibly due to the long-term presence of viral material. Therefore, EVs may be able to persist within the CNS and potentially cause lasting neuropathology.

In this report, an aseptic meningitis case confirmed by cerebrospinal fluid (CSF) RT-PCR for enterovirus in a 5-year-old child with travel history was presented.

CASE PRESENTATION

A 5-year-old male presented to the emergency service of a private hospital with persistent nausea, vomiting, fever and headache for 3 days. The patient had a travel history to Kazakhstan two weeks prior to symptom onset. Patient described a fever of 39.5°C on the first day which gradually improved as well as decreased appetite, nasal congestion and pain in the front right side of his head. On physical examination, the patient was conscious and was able to cooperate with blood pressure 100/60mmHg, frontal sensitivity and no sign of neck stiffness. Upon admission, blood, oro-nasopharyngeal and throat samples were collected. Patient's COVID-19 (SARS-CoV-2), Group A streptococcus and influenza A/B antigen test results were negative. The patient was admitted to the pediatrics service. The following day, upon physical examination, the patient had neck stiffness and Kernig's sign was positive. Laboratory test results indicated a slight increase in C-reactive protein (CRP) level (0.63 mg/dL, normal range 0.00-0.50), while the white blood cell count ($4.8x10^3/\mu l$), neutrophil

count (3,40x10^3/µl) and lymphocyte count (0.70x10^3/µl) were within in the normal range. Furthermore, patient's serum alanine aminotransferase (ALT) (17 U/L), aspartate aminotransferase (AST) (33 U/L), urea (20 mg/dL), and creatinine (0.52 mg/dL) were at normal levels.

Following admission of the patient, empirical intravenous ceftriaxone and acyclovir treatment was initiated. A lumbar puncture was performed. CSF pressure was normal at 11.5 cm/H2O. CSF biochemical analysis indicated normal levels of total protein and glucose levels (Table 1).

Table 1. Laboratory parameters and biochemical analysis of patient's cerebrospinal fluid (CSF) sample

Test	Result	Reference
Appearance	Clear	N/A
Pressure (cm/H2O)	11.5	5-18
Glucose (mg/dL)	62.0	40-70
Total Protein (mg/dL)	32.2	15-45
Leukocyte cell count (/mm^3)	53.0	<5

No bacterial growth was detected in CSF culture on blood agar and eosin-methylene blue (EMB) agar. Blood culture was not performed. The CSF analysis showed an elevated leukocyte cell count of 53/mm^3. Gram staining of the CSF indicated 1-3 polymorphonuclear leukocytes (PNLs). The patient's CSF sample was simultaneously analyzed using RT-qPCR analysis with QIAstat-Dx Meningitis/Encephalitis Panel (Qiagen, Hilden, Germany) and was positive for enterovirus (Figure 1). No pathological findings were detected in MRI with contrast.

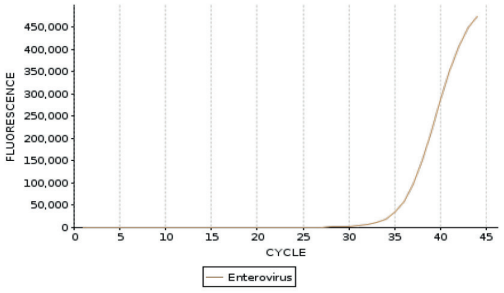

Figure 1. RT-qPCR amplification of enterovirus RNA in the patient CSF sample

The ceftriaxone and acyclovir treatments were discontinued following the PCR result. The patient was managed supportively with intravenous fluids and antipyretics. He symptomatically improved during 7 days of admission with no complication and was followed up to ensure no neurological sequelae.

DISCUSSION

The current study represents a case of enteroviral meningitis in a 5-year-old male patient with travel history presenting with non-remitting headache, fever and loss of appetite. Analysis of CSF revealed a positive enterovirus RT-qPCR test, CSF pleocytosis with normal total protein and glucose levels. The patient was diagnosed with enteroviral meningitis using molecular testing.

Aseptic meningitis which occur during the summer or fall is known to be commonly caused by non-polio EVs such as coxsackievirus and echovirus. It is self-limiting and only requires supportive treatment. However, clinically enteroviral meningitis cannot be differentiated from other CNS infections and has been associated with significant morbidity, including hospitalization and impairment of daily activities. Therefore, molecular testing represents an important step towards making a confirmed diagnosis and starting immediate appropriate therapy. While the clinical course of enterovirus meningitis is benign and there is no need for antibiotic administration in the case of diagnosis, empirical therapy is usually preferred by the clinicians in the case of a prognosis, until the test results are obtained. In particular, syndromic testing platforms have been proven to be valuable tools for the detection of a large number of pathogens in clinical laboratories, with short turnaround time and reduced hands-on-time. They have also been reported to shorten the median time to optimal therapy from 14.68 h to 4.65 h.[6] In the current study, although ceftriaxone and acyclovir prophylaxes were used on patient admission, the antibacterial and antiviral treatments were discontinued once the enteroviral meningitis diagnosis was made. Therefore, rapid molecular testing

platforms can be indicated to reduce the unnecessary use of antibiotics as well as antivirals, which may also have important implications for antimicrobial resistance in a given community.

The incidence of enteroviral meningitis has been described to decrease with age, with the highest incidence observed in infants and toddlers. The prevalence of enteroviral meningitis is also reported to be higher in males.[7] Literature indicates that up to two-thirds of patients with the disease may have a CSF polymorphonuclear predominance when examined early during the course of the illness. Repeat lumbar puncture after 12-24 hours, if performed, usually shows evolution to a lymphocytic predominance.[8] In the current study, CSF microscopy showed a predominance of PMNs. In a previous report by Dawood et al., the authors have reported an 18-year-old patient diagnosed with enteroviral meningitis via the detection of enterovirus RNA by reverse transcriptase PCR in CSF, who had normal CSF microscopy as well as CSF protein and glucose levels within the normal range.[9] This correlates well with the results obtained in the patient described here, in which normal CSF total protein and glucose levels were obtained. In a cohort study of 72 cases of echovirus meningitis in Germany, routine CSF analysis (pleocytosis, protein level) was indicated to be an impractical tool for the discrimination between enterovirus-positive and negative cases, but CSF protein level was described to correlate with length of stay in hospital.[10]

Despite the generally good outcome of aseptic meningitis presenting with milder clinical illness, there are rare instances of complicated courses that can lead to persistent neurological disability or even death, particularly in infections due to EV71 serotype. Strategies for the containment of endemic diseases are focused on ensuring hygiene measures to prevent the spread of viruses, as infectious pathogens are known to be still be excreted via the feces for few weeks after illness.

CONCLUSION

In conclusion, this study reports a case of pediatric enteroviral meningitis with a travel history, and highlights the importance of early diagnosis of the infection via rapid molecular testing to prevent the administration of unnecessary empirical therapy.

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Concept: B.B., Design: B.B., B.S., Data collection or Processing: T.A., Y.D., Analysis or interpretation: T.A., Y.D., B.B, Literature Search: T.A., Y.D., B.B., Writing: B.B., B.S., T.A., Y.D.

Conflict of Interest

The authors declare that they have no conflict of interest.

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