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Olgu Sunumu / Case Report

A Case of Meningitis İnvolving Both Enterovirus and Human Herpes Virus 6; Which is the Real Causative Agent?

Enterovirüs ve Human Herpes Virüs 6'nın Birlikte Saptandığı Menenjit Olgusu; Hangisi Gerçek Etken?

[1]Merve Iseri Nepesov, [2]Murat Yagci, [1]Omer Kilic, [2]Ener Cagri Dinleyici

[1]Department of Child Health and Diseases, Faculty of Medicine, Osmangazi University, Department of Pediatric Infection, Eskisehir, Turkey
[2]Department of Pediatrics, Osmangazi University Faculty of Medicine, Eskisehir, Turkey

Abstract: Being mostly a self-limiting central nervous system infection, viral meningitis can now be diagnosed more easily with the increasing use of polymerase chain reaction method in routine clinical practice. Viruses are being reported in the etiology of meningitis at increasingly higher rates, non-polio enteroviruses being the most common causative agent of viral meningitis. The ability of human herpes virus 6, which is known to be another causative agent for meningitis/encephalitis, to integrate into the chromosomal structure and lead to a genetic transition makes it debatable whether it is a real cause of central nervous system infections. This article discusses, also referring to the literature, a case of viral meningitis associated with enterovirus and human herpes virus-6 detected in a 42-day old patient who had fever and poor feeding.

Keywords: Enterovirus; human herpesvirus-6; viral meningitis

Özet: Viral menenjitler çoğunlukla kendi kendini sınırlayan merkezi sinir sistemi enfeksiyonları olup polimeraz zincir reaksiyonu (PZR) yönteminin rutin klinik uygulamada giderek artan oranda kullanılmaya başlanmasıyla tanı şansı artmıştır. Virüsler, menenjit etiyolojisinde giderek artan oranda bildirilmekte, non polio enterovirüsler en sık viral menenjit etkeni olarak tanımlanmaktadır. Bir diğer menenjit/ensefalit etkeni olarak bilinen HHV-6'ın (human herpes virüs 6) ise kromozom yapısına entegre olup genetik geçişe yol açabilmesi gerçek merkezi sinir sistemi enfeksiyonu etkeni olup olmamasını tartışmalı hale getirmiştir. Aşağıda ateş ve beslenememe yakınmaları ile getirilen 42 günlük hastada Enterovirüs ve Human Herpesvirüs-6 (HHV-6) ilişkili viral menenjit literatür verileri ışığında tartışılmıştır.

Anahtar Kelimeler: Enterovirüs; Human herpesvirüs-6; Viral menenjit

ORCID ID of the authors: M.İ.N 0000-0003-4584-1818, M.Y 0000-0002-2981-5137, Ö.K0000-0003-0168-4080, E.Ç.D 0000-0002-0339-0134

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Correspondence: Merve İŞERİ NEPESOV, Department of Child Health and Diseases, Faculty of Medicine, Osmangazi University, Department of Pediatric Infection, Eskisehir, Turkey e-mail: iserimerve@yahoo.com

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1. Introduction

Since conjugate vaccines introduced in National Childhood Immunisation Schedule across the world, viruses have become a frequent and major cause of meningitis (1). The incidence of viral meningitis has been shown to range between 0.26 and 17 in 100,000 depending on patient age and vaccination status (1). Non-polio enteroviruses (Coxsackieviruses B2, B3, B4, B5 and A5, Echoviruses 4, 6, 9 and 11, and Enteroviruses 31 and 71) have been reported most commonly as a causative agent of viral meningitis, typically in the early stages of life. Meningitis associated with a non-polio enterovirus has a good short-term prognosis, but its long-term data is limited (2). The primary infections of human herpes virus 6 (HHV-6) appear mostly as roseola infantum with symptoms of fever and rashes during the first years of life. However, HHV-6 is also known to cause meningitis or encephalitis (3). HHV-6 can integrate into the chromosomal structure and lead to a genetic transition. Since HHV-6 can also be isolated in the cerebrospinal fluid (CSF) in persons without any symptoms of meningitis or encephalitis, it becomes controversial whether it is a real causative agent for central nervous system infections (4). This report discusses in the light of literature data a 42-day-old patient who was presented with fever and poor feeding, and was found by way of multiplex polymerase chain reaction (PCR) method to have enterovirus and HHV-6 in her CSF.

2. Case Report

A 42-day-old girl presented with signs of fever and poor feeding continuing for a day. During the examination at the time of admission, she appeared irritable and had generalized cutis marmorata, a bulge 2x2 cm in size fontanel, hypoactive neonatal reflexes, axillary body temperature of 38.2oC, a peak heart rate of 168/min, a respiratory rate of 52/min, and an arterial blood pressure of 91/43 mmHg. In her laboratory tests, leukocyte count was 7,200/mm3 (neutrophil 65%, lymphocyte 35%), procalcitonin 1.13 ng/mL, and C reactive protein 30 mg/L. Her transfontanel ultrasonography examination was assessed normal. Since the lumber puncture procedure performed due to the initial diagnosis of meningitis was traumatized, a sample of the cerebrospinal fluid was sent to the laboratory for only culture and multiplex PCR examination. An empirical ampicillin and cefotaxime therapy was started due to the initial diagnosis of meningitis. The CSF multiplex PCR method used revealed that the central nervous system panel was enterovirus and HHV-6 positive (BioFire; FilmArray® Meningitis/Encephalitis PCR Panel; USA). In the second day of her treatment, a generalized maculopapular rash developed on the whole body of the patient with continuing fever and feeding insufficiency. Her fever diminished on the third day of her hospitalization and the other system examination findings were normal. Her immunoglobulin and lymphocyte lower-group test results were within normal limits for her age. No microorganism growth was found in her CSF, blood or urine cultures. Her antibiotic therapy was completed in ten days before she was discharged and no complication was seen in her 1-year follow-up.

3. Discussion

Patients under three months of age who are examined for fever without focus comprise a privileged group in paediatric practice because they show fewer signs of localized infection and the causes of their infection differ from those of other age groups. Patients who appear infected or do not meet the low-risk criteria (healthy prenatal life and full-term delivery, absence of any clinical and laboratory findings of bacterial infection) require a lumbar puncture (5). Viral meningitis is a generally self-limiting central nervous system infection characterized by fever, headache, nausea, and vomiting with lymphocyte-dominant pleocytosis in the cerebrospinal fluid. In the neonatal period or in infancy, either irritability, lethargy, or a bulging fontanel, as in our patient, may appear as the only symptom (2).

Eichinger et al. demonstrated using PCR that the causative agent was viruses in 15 of the 44 patients aged 8-84 days who underwent a lumbar puncture due to fever without focus. The most frequently isolated virus was enterovirus and the second most frequent were HHV-6 and parechovirus, but no relationship between the causative agents and the clinical findings at the time of admission could be shown. The investigators also could not find a difference between the clinical findings of the babies whose CSF contained virus and those whose CSF did not contain any virus as shown with PCR. The impossibility to clinically identify the causative agent of meningitis through physical examination or laboratory findings highlights the importance of laboratory tests (6). The PCR method is a laboratory technique that started being used increasingly more in routine clinical practice, replacing viral cultures. The introduction of PCR in routine clinical practice prevents unnecessary antibiotic use and resulting complications, and helps clinicians detect the possible causative pathogen faster, enabling them to decide on a cause-specific therapy.

Non-polio enteroviruses are the most common cause of viral meningitis across the world (2). In the UK where routine PCR is used to diagnose meningitis in the national healthcare system, enteroviruses were observed to be responsible for half of all viral meningitis cases and 92% of those occurring in patients aged under 3 months (7). A combination of enterovirus-related meningitis and bacterial meningitis has also been reported in the literature in rare cases. In those cases, the CSF findings were compatible primarily with bacterial meningitis (8). In this respect, although viral meningitis was considered first, continuation of antibiotherapy was decided in our patient because the CSF sample was traumatized during the lumber puncture, a CSF cell count and biochemical assessment could not be performed and her family did not consent to taking a second CSF sample.

HHV-6 is rarely encountered as a causative agent of meningitis or encephalitis (3, 9). In the study made by Messacar et al. (3) with babies aged under 6 months who had the initial diagnosis of meningitis, HHV-6 was found only in 2.1% of the patients during their CSF examinations. Most of the HHV-6 positive patients were over the age of one month and 60% of them had rashes at the same time (3). Our patient also had a maculopapular rash. The importance of HHV-6 positivity in a CSF examination for clinical assessments is debatable. HHV-6 is able to integrate into the chromosomal structure leading to a genetic transition and such genetic transfer is thought to occur at a rate of 1% in a society (4). It should also be noted that since HHV-6 can remain latent in lymphocytes, it can make transit from blood to CSF in a traumatic CSF sample and cause a false positivity (3). HHV-6 can reactivate especially in persons whose immune system is suppressed and there are reports arguing that detection of the replicated active virus through real time PCR would be necessary to be able to define it as a central nervous system infection (9). Since our patient did not have a known immune deficiency and her CSF sample was haemorrhagic, we did not think that HHV-6 was the primary cause of meningitis, but we could not make a final judgement.

With this case report, attention was drawn to the importance of detecting the causative agent in CSF using PCR in children aged under 3 months who are being treated for fever without focus. There is a need for broader studies on this subject due to the debatable place of HHV-6 in the etiology of central nervous system infections.

REFERENCES

1. McGill F, Griffiths MJ, Solomon T. Viral meningitis: current issues in diagnosis and treatment. *Curr Opin Infect Dis* 2017;30:248-56.
2. Rudolph H, Schroten H, Tenenbaum T. Enterovirus infections of the central nervous system in children: an update. *Pediatr Infect Dis J* 2016;35:567-9.
3. Messacar K, Breazeale G, Wei Q, Robinson CC, Dominguez SR, et al. Epidemiology and clinical characteristics of infants with human parechovirus or human herpes virus-6 detected in cerebrospinal fluid tested for enterovirus or herpes simplex virus. *J Med Virol* 2015;87:829-35.
4. Zhang E, Bell AJ, Wilkie GS, Suárez NM, Batini C, Veal CD, et al. Inherited chromosomally integrated human herpesvirus 6 genomes are ancient, intact, and potentially able to reactivate from telomeres. *J Virol* 2017;91:e01137-17.
5. Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann* 2008;37:673-9.
6. Eichinger A, Hagen A, Meyer-Bühn M, Huebner J, et al. Clinical benefits of introducing real-time multiplex PCR for cerebrospinal fluid as routine diagnostic at a tertiary care pediatric center. *Infection* 2019;47:51-8.
7. Kadambari S, Okike I, Ribeiro S, Ramsay ME, Heath PT, Sharland M, et al. Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004-2013. *J Infect* 2014;69:326-32.
8. Basmaci R, Mariani P, Delacroix G, Azib S, Faye A, Taha MK, et al. Enteroviral meningitis does not exclude concurrent bacterial meningitis. *J Clin Microbiol* 2011;49:3442-3.
9. Whitley RJ, Lakeman FD. Human herpesvirus 6 infection of the central nervous system: is it just a case of mistaken association? *Clin Infect Dis* 2005;40:894-5.