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Short Communication

Detection of Human Herpesvirus-6 in Cerebrospinal Fluid of Patients with Meningococcal Meningitis—Report of Two Cases from Gaziantep, Turkey

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ABSTRACT

Meningitis is a very severe and life-threatening clinical table. For rapid diagnosis of meningitis, DNAs or RNAs of the possible pathogens are investigated using syndromic panel-based testing, and it is very commonly used for early guidance to therapy in recent years. Depending on the specificity and sensitivity of the tests, it is possible to detect more than one pathogen. In this research, cerebrospinal fluid of two patients with early diagnosis of meningitis based on their clinical findings were tested using BioFire FilmArray Multiplex PCR (Biomerieux, France). *Neisseria meningitidis* and human herpesvirus-6 were codetected. For further evaluation of clinical meaning of this codetections, this case report is presented.

Keywords: Meningitis, cerebrospinal fluid, meningococcemia

INTRODUCTION

Molecular syndromic panel-based tests provide opportunity to use only one test for the detection of most common pathogens of infectious diseases. The advantages of these multiplex PCR tests are rapidness and being able detect viral, bacterial, and fungal pathogens at the same time.[1] The BioFire FilmArray Meningitis/Encephalitis (ME) panel is used for the detection of bacteria, viruses, and yeast in cerebrospinal fluid (CSF) specimens: 14 pathogens composed of six bacterial, seven viral, and one fungal pathogens in 1 hour time. The FilmArray ME panel test is a rapid and trustworthy diagnostic tool for the management of meningitis and can simply be applied in routine diagnostic workflows. Coordinated evaluation of test results and expected clinical findings requires qualified users and the awareness of probable false-negative or false-positive results.[2] Leber et al.[3] found overall sensitivity and specificity of Biofire FilmArray as 95% and 99.2%, respectively. Human herpesvirus-6 (*HHV-6*) is included in the FilmArray ME panel; however, the overall sensitivity and specificity of the panel is high; HHV-6 exhibits latency and probable chromosomal integration. Hence, cautious analysis of *HHV-6* detection in FilmArray ME panel is required. The clinical diagnosis should usually not be made by molecular detection of *HHV-6* in CSF alone.[4,5]

Neisseria meningitidis is a Gram-negative diplococcus, which is a causative agent for meningoccal meningitis and meningococcemia.[6] HHV-6 has become progressively acknowledged as an emergent central nervous system pathogen. HHV-6 has been confirmed to be neurotropic and is a causative agent for a number of neurologic conditions like multiple sclerosis, post-transplant limbic encephalitis, mesial temporal sclerosis, and encephalitis/meningitis in immunocompetent patients.[7] CSF samples of two patients who had meningitis symptoms, admitted to our clinical microbiology laboratory between December 2019 and January 2020 from Gaziantep University Faculty of Medicine Pediatrics Clinic for bacterial investigation and meningitis/encephalitis multiplex PCR search panel. This panel gives results in 90 minutes duration and used especially in emergency cases.

First case (LC): A 1-year-old female patient attended our hospital with fever, malaise, sleepiness, and refusing to eat complaints. At the first examination by a pediatrician, neck stiffness was seen. Blood tests, lumbar puncture, and computerized tomography (CT) were done for differential diagnosis. In blood tests, hemoglobin was 9.1 g/dL (11.1-14.7 g/dL) and CRP (C-reactive protein) was 90.6 mg/L (0-5 mg/L). CT imaging results showed normal findings. CSF samples taken by lumbar puncture were sent to biochemistry and microbiology laboratories. CSF biochemistry results revealed the micrototal protein in CSF was 84 mg/dL (15-45 mg/dL) and the glucose level in CSF was 61 mg/dL (45-80 mg/dL). In our microbiology laboratory, tuberculosis PCR, brucella agglutination, meningitis/encephalitis multiplex PCR search panel, CSF Gram stain, and bacterial culture investigations of CSF sample were done. Tuberculosis PCR and CSF brucella agglutinations test results were negative. There was no bacteria seen, and 10 white blood cells per high-power field (WBCs/HPF) were seen in CSF Gram stain. Three

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different agar plates, blood agar, chocolate agar, and eosin–methylene blue agar (EMB), inoculated with CSF sample. After a 24-hour incubation, there was a bacterial growth, and the Gram stain from the colonies showed Gram negative diplococci and identified using Vitek 2 automated system (Biomerieux, France) as *N. meningitidis.* Meningitis/encephalitis multiplex PCR search panel (BiofireFilmarray, Biomerieux, France) results showed the sample was HHV-6 and *N. meningitides* positive.

Second case (NS): A 16-year-old female patient attended our hospital with a fever, stomach pain, vomiting, dizziness, and skin rash complaints. At the first examination by a pediatrician, there was no neck stiffness, and Kernig and Brudinzski signs, but skin findings were relatable to meningococcemia. Blood tests, lumbar puncture, and CT were done for differential diagnosis. In blood tests, platelets were 12 $\times$ 10^3/μL (158-374 10^3/μL), prothrombin time (PT) was >200 seconds (12-16 seconds), activated partial thromboplastin time (aPTT) was >500 seconds (26-37.2 seconds), and CRP was 160.4 mg/L (0-5 mg/L). CT imaging results showed normal findings. CSF samples taken by lumbar puncture were sent to biochemistry and microbiology laboratories. CSF biochemistry results revealed the micrototal protein in CSF was 72 mg/dL (15-45 mg/dL) and the glucose level in CSF was 54 mg/dL (45-80 mg/dL). In our microbiology laboratory, tuberculosis PCR, brucella agglutination, meningitis/encephalitis multiplex PCR search panel, CSF Gram stain, and bacterial culture investigations were done with CSF. Tuberculosis PCR and CSF brucella agglutination test results were negative. There was no bacteria seen, and 25 WBCs/HPF were seen at CSF Gram stain. Three different agar plates, blood agar, chocolate agar, and EMB, inoculated with CSF sample. After a 24-hour incubation, there was a bacterial growth, and the Gram stain from the colonies showed Gram negative diplococci and identified using Vitek 2 automated system (Biomerieux, France) as *N. meningitidis.* Meningitis/encephalitis multiplex PCR search panel (BiofireFilmarray) results showed the sample was HHV-6 and *N. meningitidis* positive.

CSF samples from both patients were investigated with in-house PCR method, and both samples were HHV-6 negative.

CONCLUSION

Larger studies may be required to comprehend disadvantages and advantages of multiplex PCR methods for investigating meningoencephalitis. Also, our cases create a question: Is there a need to confirm all codetections by other methods? In previous studies, Du et al.[8] found five codetections among 25 positive specimens in their research using BioFire FilmArray ME panel, and also Leber et al.[3] found five codetections among 136 positive specimens in their research using BioFire FilmArray ME panel. Detection of HHV-6 and *N. meningitides* together by multiplex PCR method needs to be evaluated by larger studies to understand possible relationship in meningitis cases between these infectious agents. Also, there is a need to understand if HHV-6 has an effect on clinical prognosis of meningococcal meningitis patients.

Ethics Committee Approval: This study was approved by the Ethichs Committee and Review Board of Gaziantep University (2021/161, date: 30.04.2021).

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