



A Rare Case of Aseptic Herpes Simplex Virus-1 Meningitis in a Patient with Recent COVID-19

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Received: 15 Oct 2020 ♦ **Accepted:** 19 Feb 2021 ♦ **Published:** 28 Feb 2022

Citation: Dimitrova M, Yotova V, Dimitrova K. A rare case of aseptic herpes simplex virus-1 meningitis in a patient with recent COVID-19. *Folia Med (Plovdiv)* 2022;64(1):148-51. doi: 10.3897/folmed.64.e59677.

Abstract

The aim of presenting this case was to show the difficulties in making the differential diagnosis of viral meningitis during the COVID pandemic situation.

We report a case of a young man with clinical features of viral meningitis and with epidemiological history of COVID-19 in his family. The patient complained of fever, headache, photophobia, nausea, myalgia, and fatigue. He gave a history of diarrhea and vomiting two weeks before admission and close relatives with COVID-19. The neurological examination revealed a meningeal irritation syndrome. The diagnostic tests we performed were as follows: nasopharyngeal swab and PCR of cerebrospinal fluid (CSF) for SARS CoV-2, computed tomography scan of the head, general CSF examination, viral tests, and microbiology of CSF, enzyme-linked immunosorbent assay (ELISA) IgM and IgG.

The results were consistent with viral meningitis due to HSV-1 in simultaneously found high titres of plasma SARS CoV-2 specific IgA and SARS CoV-2 specific IgG and active viral serum infection for CMV and EBV.

Keywords

COVID-19, HSV-1, meningitis

INTRODUCTION

Aseptic meningitis is an illness characterized by serous inflammation of the linings of the brain (i.e., meninges), usually with an accompanying mononuclear pleocytosis. Clinical manifestations vary, with headache and fever predominating, stiff neck, photophobia, drowsiness, myalgias, chills, sore throat, abdominal pain, nausea, and vomiting. The illness is usually mild and runs its course without treatment; however, some cases can be severe and life-threatening. Immunosuppressed patients are largely at a high risk for developing the condition. Aseptic meningitis syndrome is not caused by pyogenic bacteria. Although it is usually caused by certain viruses, it has a number of other etiologies as well, both infectious and non-infectious. Hence,

the term aseptic meningitis is no longer synonymous with viral meningitis, although the two are still often used interchangeably. Viral causes include the following: enteroviruses (coxsackievirus, echovirus, poliovirus), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus, arboviruses, the Epstein-Barr virus, HIV, influenza virus types A and B, the mumps virus, lymphocytic choriomeningitis virus (LCMV), and rabies. Mollaret meningitis is a recurrent disorder whose causative agent remains unknown. However, recent data suggest that herpes simplex virus (HSV-2 and, less frequently, HSV-1) may cause some if not most cases.¹ It is characterized by repeated episodes of meningitis, typically lasting two to five days, occurring weeks to years apart.²

Viral meningitis is a relatively common disorder. The

incidence of aseptic meningitis has been reported as 11 per 100,000 person-years, compared with a rate of 8.6 per 100,000 for bacterial meningitis.¹

No specific treatment exists for most of the viruses that cause meningitis; therefore, management, for the most part, is supportive and includes analgesics, antiemetic medications, intravenous fluids, and prevention and treatment of complications. Given the potential for serious neurological morbidity and the persistently high mortality rates of bacterial meningitis, a rapid institution of antibiotic coverage is essential when the diagnosis of bacterial meningitis is suspected. A third-generation intravenous cephalosporin is a customary choice. Effective antiviral therapy is available against HSV-1, varicella, and cytomegalovirus. In immunosuppressed patients, long-term therapy may be necessary. Acyclovir is recommended for immunocompetent hosts with HSV-2 meningitis and a primary genital herpes infection. In patients with Mollaret meningitis, acyclovir (intravenous or oral) or valacyclovir (oral only) are worthy of consideration for both therapy and prophylaxis. In general, corticosteroids are avoided in aseptic meningitis because of their inhibitory effects on host immune responses. Occasionally, glucocorticoids, such as dexamethasone, are useful when meningitis is associated with signs of increased intracranial pressure.¹

Of the three herpesviruses that can remain latent in the host for a lifetime, herpes simplex virus 1 (HSV-1) is more associated with encephalitis, whereas HSV-2 and varicella-zoster virus (VZV) cause meningitis. These viruses cause primary infection of mucocutaneous surfaces, establish latency in the peripheral sensory ganglia through retrograde transportation, and reactivate periodically with anterograde transmission to the nerve endings and mucocutaneous surfaces. HSVs (HSV-1, HSV-2, VZV) enter the brain mainly via the peripheral and cranial nerves. Once inside the brain, the virus spreads through the subarachnoid space in cerebrospinal fluid (CSF), and its rapid replication can overcome the host defences. Inflammatory WBCs such as lymphocytes accumulate and target the virus. Consequently, inflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α are released. Inflammatory responses can increase the permeability of the blood-brain barrier, allowing the entrance of circulating immunoglobulins.³

Novel coronavirus (SARS-Coronavirus-2; SARS-CoV-2) emerged in December 2019 in Wuhan, China, and has become a global health crisis. The SARS-CoV-2 virus affects mainly the respiratory system, although other organs are involved.⁴ Symptoms are associated with lower respiratory tract infection, including fever, dry cough, and shortness of breath. Also, headache, dizziness, generalized weakness, vomiting, and diarrhea may occur.⁵ The neurological complications described in SARS-CoV-2 are encephalitis and meningitis, acute necrotizing encephalopathy, acute transverse myelitis, cerebrovascular pathology, myopathy, and Guillain Barre syndrome.⁶

Infection with SARS-CoV-2 is mediated by binding be-

tween the receptor-binding domain of viral thorns and the cellular angiotensin-converting enzyme-2 (ACE2) receptor. ACE2 is expressed in many tissues (lungs, heart, kidneys, CNS, intestines, testicles), which suggests the emergence of multiorgan complications.⁷

The T-cell response is initiated by antigen presentation by dendritic cells and macrophages. CD4+ and CD8+ T cells play a key role. CD4+ T cells activate B cells to stimulate the production of a virus-specific antibody, while CD8+ T cells can kill virus-infected cells.^{8,9}

CASE REPORT

A 23-year-old man without any concomitant diseases presented to the emergency room with a 3-day history of headache, photophobia, nausea, myalgia, fever, and fatigue. Painkillers had no effect on the symptoms. A CT scan was performed 3 days before admission was without any pathological findings. The patient had complained of diarrhea and vomiting two weeks before admission, physical examination was performed by a general practitioner, without additional examinations.

Additional epidemiological history was obtained. The patient's father died with acute respiratory distress syndrome due to COVID-19 2 months prior to the event and his grandmother was hospitalized in ICU with COVID-19 acute respiratory syndrome. The patient presented a negative result of the ambulatory nasopharyngeal swab PCR – SARS-COV-2 test.

The physical examination was normal except for the high temperature of 37.7°C. The neurological examination revealed a meningeal irritation syndrome with neck stiffness, positive Brudzinski's and Kernig's signs as well as signs of altered consciousness – the patient was oriented but drowsy.

Diagnostic and therapeutic management

On admission, a chest X-ray was performed with a normal result. Nasopharyngeal swab for PCR-SARS-COV-2 was performed with a negative result. Blood counts also remained within the normal range, with only a slight increase in the percentage of leukocytes relative to lymphocytes, with a normal total number of white blood cells (WBC 8.3 G/l; Lym 0.5 G/l; Lym% 6.8%; GRAN 7.6 G/l; GRAN% 90%). CRP, D-dimer, and ferritin values were also within the reference ranges. Brain CT angiography and brain magnetic resonance tomography were also performed without any abnormalities.

The cerebrospinal fluid leaked under normal pressure, clear, colourless. The general CSF examination was normal and the microbiological culture remained sterile. The CSF SARS-CoV-2 PCR was negative. Positive antibody titres were detected for EBV IgG (+) and IgM (+), CMV IgM (+) IgG (+), VZV IgM (+), HSV-1 IgM (+) IgG (+) in serum and CSF. Immunoglobulins are glycoproteins that act as antibodies in the body. IgM antibodies appear in the serum between 7-12 days after infection, and IgG antibodies appear in the serum

after 14 days of meeting with the infectious agent. The presence of both IgM and IgG in the serum may mean that the patient is in the active phase of the infection or the recovery period. The presence of antibodies in the CSF indicates a neuroinfection.

Because of the epidemiological history and recent gastrointestinal complaints we suspected COVID-19. Therefore we performed an ELISA SARS-CoV-2 IgM/IgG in serum and cerebrospinal fluid. The results were as follows: serum SARS CoV-2 specific IgA 2.03 (reference values <1.1), serum SARS CoV-2 specific IgG 1.7 (reference values <1.1), normal results for CSF ELISA tests. This proved that the patient had undergone an intestinal form of SARS-Cov-2 infection. Additionally, the patient was tested for tuberculosis and HIV and the samples were negative. Based on these data the final diagnosis was viral HSV-1 meningitis in an immunocompromised patient due to COVID-19.

The patient was treated with antibiotic therapy (intravenous ceftriaxone 2x2 g), antiviral therapy (acyclovir 400 mg 5 times daily), antiedema therapy (mannitol 4x125 ml intravenously, and dexamethasone 2x8 mg intravenously), symptomatic therapy with antipyretic and analgesic medications. The patient was discharged fully recovered after 10 days of hospital treatment. Therapy with acyclovir was prescribed for 10 days.

DISCUSSION

The first reported case of SARS CoV-2 meningitis and encephalitis was described by Moriguchi et al.¹⁰ in May 2020. They described a 24-year-old man with typical symptoms of meningoencephalitis with negative nasopharyngeal SARS CoV-2 PCR and positive CSF PCR, abnormalities consistent with encephalitis on brain MRI.¹⁰

The first differential diagnosis we suspected was SARS-CoV-2 associated meningitis. Moreover, both epidemiological history and gastrointestinal complaints supported this theory. The results of nasopharyngeal and CSF SARS-CoV-2 PCR were not consistent with this suggestion. But serum ELISA SARS CoV-2 confirmed that our patient was “immune” and had undergone COVID-19 recently. As a result of severe inflammation, it is possible to reach an “exhausted immune system”. T-cell exhaustion is term characterizing the progressive loss of T-cell functions and can culminate in the physical deletion of the responding cells. Exhaustion is well-defined during chronic lymphocytic choriomeningitis virus infection, severe viral infections, and commonly develops under conditions of antigen-persistence, which occur following many chronic infections that are of significant public health concern including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus infections, as well as during tumor outgrowth.¹¹ This makes the body susceptible to many other infectious agents.

We tend to assume that this is exactly what happened in the clinical case presented above. To date, numerous data

have been reviewed and presented on how a decline in the immune system can lead to more serious manifestations of SARS-CoV-2 infection. But let's assume the opposite - is it possible that this viral infection contributes to the clinical manifestation of other infectious diseases? To date, no report has denied or confirmed this two-way link. The question remains open for further research.

We performed a wide viral assessment in the patient's serum and CSF. Despite its high cost, polymerase chain reaction (PCR) can rapidly and accurately detect EV, HSV, VZV, EBV, and SARS-CoV-2. The results proved the presence of HSV-1 in CSF and positive serum IgM CMV and EBV.

HSV-1 meningitis is extremely rare. Encephalitis is the most frequent clinical central nervous system (CNS) manifestation of HSV-1. HSV-2 typically causes meningitis.

There are two main types of HSV CNS infection, primary and recurrent. In more than 70% of cases, HSV meningoencephalitis is caused by the reactivation of a latent virus in individuals who have previously been infected. Once reactivation has occurred, viral particles are transported via the anterograde axonal transport via the olfactory and trigeminal pathways to the CNS. In 30% of cases, HSV meningoencephalitis is caused by a primary infection, and the virus also reaches the CNS by the olfactory and trigeminal nerves. In immunocompetent hosts, HSV meningoencephalitis affects brain regions such as the limbic system, mesial temporal, and frontal regions (amygdala, hippocampus, parahippocampal gyrus, temporal uncus, insula, and cingulate gyrus) earlier and most severely. The putamen and basal ganglia are usually unaffected.¹²

Poesy Payal et al. report a clinical case of a 47-year-old male, an alcoholic with a previous history of tuberculous lymphadenitis, who presented with headache, fever, and altered speech. CSF analysis proved positive PCR HSV-1 and *Cryptococcus neoformans*.¹³

Somayeh Azadfar et al. evaluated HSV meningitis in 45 children in Gorgan province, Iran. Forty-five cerebrospinal fluid samples taken from children with negative bacterial culture results were tested for viral, biochemical, and cytological assays. DNA extraction and PCR were performed. HSV-1 was detected in 4 (8.8%) samples without any HSV-2 infections. Their conclusion was that the distribution of HSV types in children with meningitis in Gorgan province was predominantly type 1 compared with type 2, which was reported more in other areas.¹⁴

HSV-1 meningitis is extremely rare. In most reported cases, meningitis is due to coinfection with HSV-1 and other agent or it is found in patients with immunodeficiency. The treatment obligatory includes antiviral medications. In our case, both key findings are the COVID-19 “terrain” and rare HSV-1 cause for meningitis.

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Редкий случай асептического менингита, вызванного вирусом простого герпеса-1, у пациента с недавним COVID-19

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Дата получения: 15 октября 2020 ♦ **Дата приемки:** 19 февраля 2021 ♦ **Дата публикации:** 28 февраля 2022

Образец цитирования: Dimitrova M, Yotova V, Dimitrova K. A rare case of aseptic herpes simplex virus-1 meningitis in a patient with recent COVID-19. Folia Med (Plovdiv) 2022;64(1):148-51. doi: 10.3897/folmed.64.e59677.

Резюме

Цель представления этого случая состояла в том, чтобы показать трудности дифференциальной диагностики вирусного менингита во время пандемии COVID-19.

Мы сообщаем о случае молодого человека с клиническими характеристиками вирусного менингита и эпидемиологическим анамнезом COVID-19 в семье. Больной предъявлял жалобы на лихорадку, головную боль, светобоязнь, тошноту, миалгию и быструю утомляемость. Он сообщил о диарее и рвоте за две недели до госпитализации и близких родственниках с COVID-19. При неврологическом осмотре выявлен синдром раздражения мозговых оболочек. Были проведены следующие диагностические тесты: назофарингеальный секрет и ПЦР спинномозговой жидкости (СМЖ) на SARS CoV-2, компьютерная томография головы, общее исследование СМЖ, вирусные тесты и микробиология СМЖ, иммуноферментный анализ (ELISA), IgM и IgG.

Результаты соответствовали вирусному менингиту, вызванному ВПГ-1, при одновременно обнаруженных высоких титрах плазмы специфических IgA к SARS CoV-2 и специфических IgG к SARS CoV-2 и активной вирусной инфекции вирусом Эпштейна-Барр и цитомегаловирусной инфекции.

Ключевые слова

COVID-19, ВПГ-1, менингит