An adolescent with herpes simplex encephalitis, presenting with mild symptoms and rapid deterioration: A case report

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Abstract
Headaches in children are a common, but unspecific symptom that can have many underlying causes, ranging from unspecific tension headache through migraine and up to encephalitis and intracranial hypertension. We present the case of a 14-year-old boy who presented to our emergency department with headache, nausea as well as vomiting and developed seizures later on. The initial diagnosis was complicated by a magnetic resonance imaging which did not show any signs of inflammation, but was of limited informative value due to orthodontic appliances. Despite the unremarkable imaging, prophylactic antiviral and antibiotic treatment was started after lumbar puncture. Herpes simplex virus as well as human herpes virus 7 were confirmed in the cerebrospinal fluid. Although both viruses are ubiquitous, severe infections are a rare complication. Immunodeficiency syndromes are predisposing factors for serious complications and genetic analysis of UNC93B and TLR-3 might be helpful for decision-making. No genetic or immunologic predisposition was found in our patient. The patient’s condition deteriorated rapidly, so he had to be admitted to the pediatric intensive care unit, where he was intubated and his antiviral treatment with acyclovir was extended by foscarin. After prolonged mechanical ventilation, he slowly improved. With intensive neurorehabilitation, he could finally return to his daily life activities 3 months after diagnosis. Despite headaches being an unspecific symptom, the possibility of a herpes simplex virus encephalitis should always kept in mind, especially in patients presenting with additional symptoms such as vomiting, altered mental status and/or focal neurological deficits. An initial magnetic resonance imaging might be misleading if orthodontic appliances are in place. Initiation of treatment without delay is crucial for neurologic outcome of herpes simplex virus encephalitis.

Keywords
Neurology, infectious diseases

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Introduction
Typical clinical manifestations of herpes simplex encephalitis (HSE) include an altered mental status (disorientation, confusion, behavioral changes) for over 24 h, fever, seizures, headaches and focal neurological deficits. The clinical presentation is often accompanied by prodromal symptoms, such as upper respiratory tract infections or other systemic infections.¹

Diagnosis and therapy of a patient who presents with apparently harmless symptoms, but whose condition deteriorates rapidly can be a challenging task. Here, we describe the diagnostic process and therapy of a patient with HSE, presenting with mild symptoms but rapid deterioration.
Case report

A 14-year-old boy presented at our pediatric emergency department with a 3-day history of unilateral frontal pulsatile headache, nausea, vomiting, poor appetite, but without fever at admission. The pain had not responded to oral pain medication. A magnetic resonance imaging (MRI) was performed and showed no sign of intracranial tumor or ischemia. However, the patient was wearing fixed orthodontic appliances which caused artifacts in the area of the temporal lobes. The patient was admitted for observation. On the next day, the headache had improved, yet, on neurological examination, just before discharge was planned, the patient suddenly showed oral automatisms and started fiddling with his clothes.

The electroencephalogram (EEG) showed a focal cerebral dysfunction over the right hemisphere with a maximum over the temporal lobe. No signs of meningism were present, but the patient became more sensitive to light.

After lumbar puncture, which revealed clear, non-hemorrhagic cerebrospinal fluid (CSF) with 282 cells/µL (70% lymphocytes), treatment with intravenous acyclovir (60 mg/kg/day) and ceftriaxone (85 mg/kg/day) for suspected encephalitis was started immediately, and antiepileptic treatment with oxcarbazepine was initiated.

Over the next few hours, the patient became somnolent and was transferred to the pediatric intensive care unit (PICU) where he had to be intubated. Despite antiviral medication, mechanical ventilation and deep analgesic sedation, the cranial computed tomography (CT) scan showed a progressive brain edema of the right temporal lobe as well as multiple foci of hemorrhage. The polymerase chain reaction (PCR) was positive for herpes simplex virus type 1 (HSV-1, virus concentration: 7 × 10^3 copies/mL, altona Diagnostics, Hamburg, Germany) and human herpes virus 7 (HHV-7, virus concentration: ct: 35.5, in-house PCR). Therapy was extended by foscarnet (120 mg/kg/day) and dexamethasone. Because of persistent CSF abnormalities, lacosamide was added to the antiepileptic therapy. Finally, the patient could be weaned from mechanical ventilation after 2 weeks.

One month after admission, repeated lumbar puncture showed 28 cells/µL, proved negative for HSV-1 and showed a very low HHV-7 concentration (ct: 37.1). Acute treatment of acyclovir and foscarnet was discontinued, and oral prophylactic acyclovir (16 mg/kg/day) was started. MRI showed bilateral asymmetric signal alterations in both temporal lobes and the frontobasal region (Figure 1), in the insular cortex and cingulate gyrus on the right side and mild brain atrophy. During the following weeks, the EEG and the patient’s clinical condition improved gradually.

Neurologically, the patient showed a reduced vigilance but was fully orientated. His speech was slow, he suffered from amnestic aphasia, showed tongue fasciculations, as well as dysdiadochokinesia of the left side. After intensive neurorehabilitation of 7 weeks, the patient could continue his daily life activities. An EEG 5 months after the acute infection under antiepileptic treatment only showed a diffuse slowing.

Immunological and genetic testing excluded an underlying immunodeficiency of UNC93B, TLR-3, the innate immunity and T-cells. Oral prophylactic acyclovir was continued until these results proved negative 9 months after diagnosis. One year after the diagnosis, the patient was attending regular school again, but achieved less well results compared to the time before the encephalitis, he was seizure-free, and the EEG was normal, while the patient was still under antiepileptic treatment.

Discussion

HSV-1 and HHV-7 are neurotropic human DNA virus and belong to the family of Herpesviridae. The HSV-1 seroprevalence varies widely among European countries, with the lowest age-adjusted prevalence in Finland (52.4%) and the highest in Bulgaria (83.9%).

Despite the ubiquitous seroprevalence, a periodic reaction occurs only in 25% of the infected population. Herpes encephalitis is a rare complication with an incidence of two to four per million per year. Immunocompromised people are at increased risk. However, it is still not clear why some apparently healthy individuals are more susceptible than others.

In some previously healthy patients, a genetic etiology with a mutation in the UNC93B gene could be detected. The UNC93B protein is a transmembrane protein, crucial for the transportation of endosomal toll-like receptors (TLRs), which play a key role in the immune response to viruses. The location and expression of TLRs is highly regulated with TLR-3 typically expressed in central nervous system (CNS)-resident cells. A disruption of the signaling induced by TLR-3, when in contact with HSV, leads to a decreased antiviral response especially in the brain, therefore to a predisposition for HSV encephalitis (HSE). The antiviral response is not only affected with a TLR-3 mutation but also if downstream proteins such as UNC93B, TRIF, TRAF, TBK1 and IRF3 are dysregulated. Our patient did not take any immunosuppressive medication neither did he report any atypical or recurrent infections. Nevertheless, a genetic analysis for UNC93B and TLR-3 was performed but proved negative. Prophylactic antiviral medication was stopped after the genetic results arrived.

Typical clinical manifestations of HSE include an altered mental status (disorientation, confusion, behavioral changes) for over 24 h, fever, seizures, headaches and focal neurological deficits. The clinical presentation is often accompanied by prodromal symptoms, such as upper respiratory tract or other systemic infections.

Our patient presented with the typical symptoms of headache, nausea and vomiting. These symptoms increased the likelihood for migraine as an alternative diagnosis, especially after the initial MRI did not reveal pathologic findings.
He was in a good general condition until he suddenly presented with a seizure, followed by rapid deterioration and the necessity of admission to the PICU. This sudden decline highlights the importance of rapid diagnosis and treatment of HSE. Antiviral treatment with acyclovir is the most important factor for favorable outcome and initiation of therapy should not be delayed by diagnostic procedures. Cranial MRI should be performed if possible, since it is more sensitive than the CT, especially in the early course of the disease. Typical signs of HSE are bilateral asymmetric hyperintense lesions in the limbic system on T2-weighted sequences, especially in the temporal lobes. Restricted diffusion of the affected cortex, contrast enhancement and hemorrhagic components may be seen. In the initial MRI, these signs were missing, but the sensitivity of the imaging was further reduced by orthodontic appliances. Since a substantial number of adolescents are treated with fixed orthodontic appliances, such artifacts visible in MRI might be a growing diagnostic problem.

Our patient’s CSF was not only positive for HSV-1, but also for HHV-7, a ubiquitous virus that can be found in almost everybody’s saliva and shows a tropism for lymphocytes and neurons. Data derived from autopsies have also shown that a significant proportion of asymptomatic adult brain tissue is

**Figure 1.** Magnetic resonance tomography. Coronal (a) and sagittal (b) FLAIR images showing bilateral yet asymmetrical T2-hyperintensities and mild swelling in the temporal lobes and the frontobasal region (thin white arrows). Axial T1 MPRAGE image (c) demonstrating cortical T1-hyperintensities in the right temporal lobe (block arrow) consistent with cortical laminar necrosis. Note the hemorrhagic components (*) visible in the axial SWI sequence (d). FLAIR: fluid-attenuated inversion recovery; SWI: susceptibility weighted imaging.
PCR positive for HHV-7.10 Most primary HHV-7 infections are asymptomatic; some patients present with exanthema subitum, but there have been reports about more severe cases in immunocompromised patients.11 However, there are also reports about neurological manifestations in previously healthy children, such as febrile seizures12 or acute encephalitis, especially when the primary infection is delayed into adolescence.13,14

Foscarnet is considered to be the first-line treatment for HHV-7 infections and has been added to acyclovir in our case of concomitant infection.15 With acyclovir and foscarnet therapy, the patient improved gradually, he could be transferred to a rehabilitation unit and finally returned to his normal daily life activities.

Conclusion

Our case highlights the fact that HSE might mimic migraine and the importance to consider the possibility of HSE in patients with headache and increased sensitivity to light and/or seizures. An initial MRI showing no typical signs of HSE might be misleading if orthodontic appliances are in place. Despite a severe disease progression and extended lesions visible on MRI, the outcome of the patient can be good after rapid initiation of treatment and extensive neurorehabilitation.

Author contributions

N.S. provided direct patient care to the patient, drafted the initial manuscript, and reviewed and revised the manuscript. R.S., J.Ge., J.Go. and A.P. provided direct patient care to the patient, and reviewed and revised the manuscript. M.-T.S. performed the interpretation of radiology, providing figure legends, and reviewed and revised the manuscript. L.W. performed the interpretation of virological results, and reviewed and revised the manuscript.

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Ethical approval

Ethical approval to report this case was obtained from the Ethics committee of the Medical University of Vienna.

Informed consent

Written informed consent was obtained from the patient and his legally authorized representative for their anonymized information to be published in this article.

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References

1. Brashaw MJ and Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics 2016; 13(3): 493–508.
2. Whitley RJ and Roizman B. Herpes simplex virus infections. Lancet 2001; 357: 1513–1518.
3. Pebody RG, Andrews N, Brown D, et al. The seroepidemiology of herpes simplex virus type 1 and 2 in Europe. Sex Transm Infect 2004; 80(3): 185–191.
4. Mielcarska MB, Bossowska-Nowicka M and Toka FN. Functional failure of TLR3 and its signaling components contribute to herpes simplex encephalitis. J Neuroimmunol 2018; 316: 65–73.
5. Casrouge A, Zhang SY, Eidenschken C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 2006; 314: 308–312.
6. Jouanguy E, Béziat V, Mogensen TH, et al. Human inborn errors of immunity to herpes viruses. Curr Opin Immunol 2020; 62: 106–122.
7. Hsieh WB, Chiu NC, Hu KC, et al. Outcome of herpes simplex encephalitis in children. J Microbiol Immunol Infect 2007; 40(1): 34–38.
8. Granered J, Davies NWS, Mukonoweshuro W, et al. Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement. Clin Radiol 2016; 71(10): 1050–1058.
9. Emery VE and Clark CA. HHV-6A, 6B, and 7: persistence in the population, epidemiology and transmission (chapter 49). In: Arvin A, Campadelli-Fiume G, Mocarski E, et al. (eds) Human herpesviruses: biology, therapy, and immunoprophylaxis. Cambridge: Cambridge University Press, 2007, https://www.ncbi.nlm.nih.gov/books/NBK47441/ (accessed 1 June 2020).
10. Chan PK, Ng HK, Cheung JL, et al. Prevalence and distribution of human herpesvirus 7 in normal brain. J Med Virol 2000; 62(3): 345–348.
11. Riva N, Franconi I, Meschiari M, et al. Acute human herpes virus 7 (HHV-7) encephalitis in an immunocompetent adult patient: a case report and review of literature. Infection 2017; 45(3): 385–388.
12. Epstein LG, Shinar M, Hesdorffer DC, et al. Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. Epilepsia 2012; 53(9): 1481–1488.
13. Schwartz KL, Richardson SE, Ward KN, et al. Delayed primary HHV-7 infection and neurologic disease. Pediatrics 2014; 133(6): e1541–e1547.
14. Fay AJ, Noetziel MJ and Mar SS. Pediatric hemorrhagic brainstem encephalitis associated With HHV-7 infection. Pediatr Neurol 2015; 53(6): 523–526.
15. Corral I, Sainz de la Maza S, Rodríguez M, et al. Molecular detection of human herpesvirus 7 DNA in cerebrospinal fluid from adult patients with neurological disorders. J Neurovirol 2018; 24(3): 333–338.