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Case Study
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HSV-2 Encephalitis in Immunocompetent Adult

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Case Study

Encephalitis caused by Herpes Simplex Virus (HSV) is a rare diagnosis that requires swift recognition and treatment. This infection has a potentially fatal disease course, from which only a minority of affected patients return to normal function, and for which outcomes are highly related to how early therapy is initiated [1]. Patients with this disease present with either acute or subacute symptoms including altered mentation lasting more than 24 h, fevers, headaches, seizures, and focal neurological defects, sometimes accompanied by cognitive, behavioral, and personality changes. There is often a prodrome of fever, malaise, headache, and nausea [2].

HSV-2 encephalitis constitutes less than 10% of all cases of HSV encephalitis. Almost all of these cases occur in the neonatal period, with the exception of HSV-2 encephalitis infections recorded in immunocompromised adults [2]. Furthermore, a case series conducted at the Mayo Clinic in Rochester suggests that the prognosis of cases of HSV-2 encephalitis in adults may be unfavorable despite antiviral therapy initiation [3]. Our case represents an extremely rare case of HSV-2 encephalitis in an otherwise healthy patient. In this case study we aim to describe a rare presentation of an uncommon infectious disease, and to hypothesize at the potential causes and factors that contribute to its etiology.

Our patient is a 38-year-old male truck driver with a past medical history of traumatic brain injury secondary to a motorcycle accident (years prior, without deficits) who presented with progressive altered mental status. The patient had a mild afebrile respiratory illness approximately 10 days prior with sore throat, malaise and congestion which was followed by a tooth extraction with use of prophylactic amoxicillin 6 days prior to presentation. Thereafter he clinically declined. He was briefly evaluated and later discharged at a local hospital, however his partner noted that he was progressively weaker, started 'staring into space' and was less responsive. His affect was blunted and had significant poverty of speech. The morning of his admission to Waterbury Hospital, he was found by the roadside by police and was sent to the hospital *via* EMS.

The patient does not take any medications, apart from the short course of amoxicillin he took for his dental procedure. He denied alcohol, smoking, or illicit drug use and had no recent tick bites or rashes. He was found to be febrile and tachypneic on presentation. His EKG and chest X-ray were within normal limits while his labs were only significant for monocytosis. His physical exam was notable for poverty of speech without signs of nuchal rigidity, Kernig or Brudzinski signs. An MRI without contrast confirmed encephalitis in the right temporal lobe with a 3 mm midline shift to the left without acute infarct changes.

We started empiric treatment for meningoencephalitis with vancomycin, ceftriaxone and acyclovir, and we proceeded with a lumbar puncture. Cerebrospinal fluid analysis revealed monocytosis with an elevated protein content. Further testing of the fluid resulted with positive HSV-2. All other relevant cultures and serologies returned negative. We continued management with IV acyclovir and consulted an Infectious Disease specialist.

Neurology recommended initiation of levetiracetam for seizure prophylaxis; however, an EEG was obtained which demonstrated cerebral irritability, but no focal seizures. Despite appropriate therapy, his mental status did not improve days after initiation of therapy, becoming less responsive and no longer oriented. Dexamethasone was subsequently initiated with remarkable improvement in clinical picture. Within 24 h he became verbally responsive, following commands, and asking insightful questions about his treatment plan.

This patient's excellent response to steroids raised the concern for an autoimmune component to his condition. HSV has been documented in case reports as a potential trigger for NMDA receptor encephalitis [4,5]. Therefore, he was screened for anti-NMDA receptor antibodies, along with an associated teratoma [6] or malignancy, where all work-ups were ultimately negative. Due to

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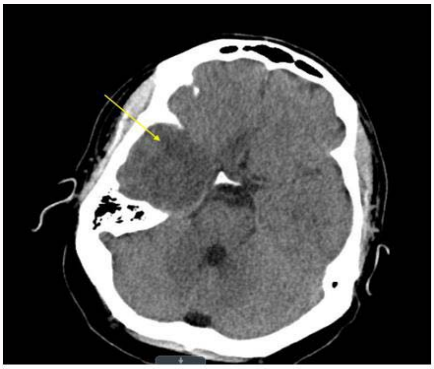

Figure 1: CT head without contrast revealing diffuse edema throughout the right temporal lobe, suspicious for right MCA distribution infarction versus temporal lobe encephalitis. Slight right midline shift of 3 mm.

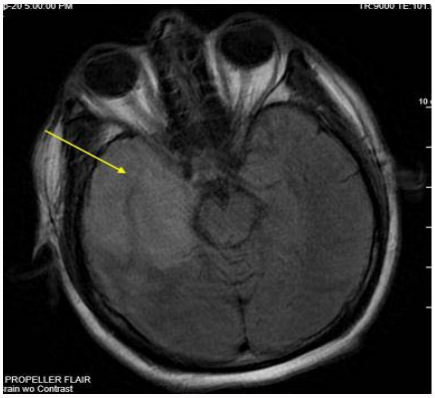

Figure 2: MRI brain without contrast revealing gyral edema and diffusion restriction in the temporal lobe, insular cortex and inferior frontal lobe. The pattern and distribution are suspicious for encephalitis.

this new information, the care team concluded that his mental status improvement with dexamethasone was likely related to improvement of the cerebral edema initially seen on imaging.

He was discharged on oral dexamethasone with a taper, three weeks of IV acyclovir infusions, and a plan for close follow up with his newly established primary care, neurology, and infectious diseases team.

There are approximately 20,000 yearly cases of encephalitis in the USA. The majority are secondary to viral causes, although many are an unknown identity [7]. The most commonly associated virus known to cause encephalitis in immunocompetent adults is herpesviruses, including Herpes Simplex Virus 1 (HSV-1), Varicella-Zoster Virus (VZV), and Epstein-Barr virus (EBV). In an immunocompromised host, Cytomegalovirus (CMV) is the most common cause of encephalitis. HSV-2 encephalitis is an even rarer form, afflicting less than 2% of the adult population and it typically occurs in elderly, immunocompromised patients with poor prognosis, despite treatment with antiviral therapy [3]. This is a stark comparison to our young and otherwise healthy patient.

Of note, only 6% to 10% of patients with HSV-2 encephalitis have a history of genital herpes [8] and even fewer have associated oral lesions, suggesting that traditional presentations of genital or oral herpes in adults do not necessarily correlate with developing encephalitis. Although it is worthy to mention that while HSV typically lies dormant in peripheral nerve ganglia and thereby can reactivate and travel to the CNS, patients may also contract HSE from an acute episode of viremia.

The clinical presentation of Herpes Simplex Encephalitis (HSE), including types 1 & 2, typically starts with a prodrome of general malaise, headache, nausea and fevers. It later develops into an altered level of consciousness and several non-specific focal neurological deficits, including "aphasia, altered olfactory perception, seizures, clouding of consciousness and behavioral changes suggest[ing] a diagnosis of encephalitis" [9]. The pathological lesions best associated with HSV-1 & 2 Encephalitis (HSE) are focally located in the temporal lobe [9]. Untreated HSE patients can rapidly progress to having brain edema and eventual destruction of the brain. In the most severe cases, death can occur as early as 7 to 14 days from onset and mortality rate persists at 20% to 30% despite appropriate and timely treatment [2,9].

Treatment consists of IV acyclovir 10 mg/kg every 8 h for a total of 14 to 21 days. Even with appropriate and timely treatment, patients still have a high chance of mortality (up to 30%) and also have a high chance of relapse [10]. Adjunctive therapy with corticosteroids is not officially proven effective; however, there have been case reports with positive outcomes [10].

As described previously, HSV-2 is a highly unusual cause of encephalitis. However, it is more commonly the culprit in cases of recurrent aseptic meningitis. This condition is referred to as Mollaret's Meningitis and it is almost always caused by HSV-2. It is characterized by fevers, severe headaches and meningeal signs that are most often self-limited [1] but have a chronic trajectory.

Another important recognized complication of HSE is autoimmune encephalitis caused by the anti-NMDA receptor antibodies. Up to 30% of patients with recovering HSE develop anti-NMDA receptor encephalitis which is why long term follow up is crucial [4]. As stated previously, we sent this test approximately 1 week after our patient's presentation to Waterbury Hospital due to no improvement in his mental status despite appropriate treatment. The test was non-reactive, but it is possible that the disease will develop later in the disease course. It typically presents at most 2 months after onset of HSE but can develop as late as several months [5,11].

Our case represents an exceedingly rare cause of encephalitis in a previously healthy young adult male, with no previous genital or oral lesions, presenting with an acute onset of encephalitis days after a mild flu-like illness and a dental procedure. While HSV-2 encephalitis is almost exclusively seen in neonates and immunocompromised patients, this interesting case goes to show that atypical presentations are always possible, and that the differential must always be kept broad. Close follow up is crucial in HSE patients and, in this case, will allow us to further explore the course of disease and possible sequela of HSV-2 encephalitis.

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