

Olfactory Seizures Related to Herpes Zoster Encephalitis

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Herpes zoster encephalitis is a relatively rare neurologic disease process that must be recognized based on clinical signs and symptoms. This form of encephalitis carries increased risk of morbidity and mortality if treatment is not initiated promptly. Symptoms may range from vague to extreme, and most diagnostic testing is slow to yield concrete results. This report describes a case of herpes zoster encephalitis that was initially thought to be an early sinus infection and thus recognition was delayed. The article discusses etiology, clinical features, diagnosis, and treatment of herpes zoster encephalitis.

CASE PRESENTATION

Initial Presentation

A 46-year-old woman presented to the emergency department (ED) by ambulance with generalized tonic-clonic seizures. The patient had no history of seizures prior to this incident. On the morning of the seizure, she had been somewhat difficult to awaken; however, her husband felt it was secondary to a mild illness she had been experiencing for a few days prior and did not attempt to wake her. At some point in the morning, the patient awoke and called a friend. On the telephone, the patient was incoherent and confused. When the friend went to the patient's house, she found her disoriented and not knowing who or where she was. When the ambulance arrived, the patient suffered a generalized tonic-clonic seizure.

The husband reported that the patient began feeling ill 3 days earlier, with generalized malaise, anorexia, mild headache, and a low-grade fever. The patient also had complained of smelling flowers. The olfactory symptoms were constant, and the patient attempted various measures to stop the smell, including over-the-counter nasal sprays, but the smell persisted. Two days prior to presentation, the patient saw a physician regarding the olfactory symptoms because they were quite disturbing. The smell was resulting in other symptoms, such as nausea and lack of taste and ap-

petite. She was unable to differentiate any smell other than the constant floral scent. Her physician placed her on nasal steroids for sinus difficulties. The patient had no other neurologic complaints until the day of presentation to the ED. On the previous day, her temperature had spiked to 103°F (39.4°C) and the floral smell began to abate. According to the husband, the patient did not complain of any visual difficulties, stiff neck, focal loss of sensation or movement, or memory problems. With the exception of mild fatigue, the patient did not have any overt weakness prior to the morning of presentation.

Medical History

The patient's medical history was significant only for endometriosis, which had been controlled. The patient had no history of seizures or previous neurologic symptoms. There had been no recent travel. The patient had chicken pox as a child but had no history of shingles or cold sores. The husband had shingles approximately 2 to 3 months previously, which had resolved without incident.

The patient had one previous diagnostic laparoscopy, was not allergic to any medications, and was currently on a nonsteroidal anti-inflammatory medication and a nasal steroid. The patient did not use tobacco or alcohol and was a teacher by profession.

Physical Examination

On physical examination, the patient initially appeared postictal. Her temperature was 101.6°F (38.7°C)

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Figure 1. Horizontal magnetic resonance image of the case patient on presentation demonstrating involvement of the right temporal region.

with a blood pressure of 126/41 mm Hg, pulse of 93 bpm, and respiration rate of 16 breaths/min. The neck was supple with full range of motion and no signs of meningismus. No lymphadenopathy was present. The lungs were clear to auscultation with no signs of respiratory distress. The heart rate and rhythm were regular without evidence of murmurs, gallops, or thrills. Pulses were equal at +2 in the upper and lower extremities bilaterally. The abdomen was soft and nontender with positive bowel sounds and no signs of guarding or rebound.

On neurologic evaluation, the patient knew her name and what city she was in, but otherwise she was disoriented and confused. She was lethargic upon initial presentation but responded to voice. When awake, she was agitated and seemed to make eye contact but would not follow commands appropriately. The patient was mostly mute upon initial presentation, but did vocalize rarely and would state her name. In assessing cranial nerve II, the eyes reacted to light directly and indirectly and responded to visual challenge bilaterally. Cranial nerves III, IV, and VI were intact for extraocular motion bilaterally. Cranial nerve V showed good muscles of mastication, but sensation was difficult to assess. Cranial nerve VII demonstrated no facial asymmetry. Cranial nerve VIII was grossly intact. Gag reflex was present, demonstrating function of cranial nerve IX.

Cranial nerves X, XI, and XII were grossly intact; however, the patient would not cooperate fully with the examination. Funduscopic examination revealed no evidence of papilledema or other abnormalities. Sensory function was difficult to assess; however, the patient was able to feel protopathic stimulation with movement of all 4 extremities. She moved the left side of her upper and lower extremities slightly better than the right. Muscle strength was +4 on the right and +5 on the left in the upper and lower extremities. The patient had motor impersistence during much of the examination and was uncooperative. Examination for extrapyramidal tract signs was negative for hypertonicity, hypotonicity, and hypokinesia. No evidence of cogwheeling, gegenhalten, or lifting tremors were found. There were no involuntary movements. Examination for pyramidal tract signs demonstrated no Hoffman's, Oppenheim's, or Chaddock's reflexes. No evidence of clonus was found and the plantar reflexes were flexor. Muscle stretch reflexes were 2/4 bilaterally and symmetric for biceps, triceps, brachial radialis, and ankle. The patellar reflex was 3/4 bilaterally.

Radiographic Studies

A computed tomographic (CT) scan of the head was significant for an abnormality of the right temporal lobe, with involvement of the adjacent right central lobe and right frontal lobe. This finding initially was thought to be consistent with cerebral infarction, which would have been unusual for the patient's age and presentation. Magnetic resonance imaging (MRI) was then performed and was significant for signal abnormality of the right temporal lobe, right hippocampus, and right central lobe, consistent with probable herpes encephalitis (**Figure 1**). A chest radiograph showed no abnormalities. An electroencephalogram (EEG) was not performed at this time.

Laboratory Studies

Results of the initial laboratory studies are presented in **Table 1**. Results of kidney function testing were normal, and a urine drug screen was negative. After CT scan of the head was performed and evidence of elevated intracranial pressure was not seen, lumbar puncture was performed. Upon initial evaluation, the cerebrospinal fluid (CSF) appeared clear and an opening pressure of 210 mm (normal 100–200 mm) was obtained. Laboratory analysis of the spinal fluid demonstrated 50 mg/dL protein (normal, 15–45 mg/dL) and 69 mg/dL glucose (normal 50–75 mg/dL). There were 0 leukocytes/mm³ and 309 erythrocytes/mm³. Gram stain of the CSF was negative and a rapid antigen

screen was negative. Urinalysis demonstrated a small amount of blood but was otherwise negative. An electrocardiogram demonstrated a sinus rhythm.

Initial spinal fluid cultures were negative. Polymerase chain reaction (PCR) analysis of the spinal fluid for herpes simplex virus (HSV) and varicella-zoster virus (VZV) at this time also was negative.

Empiric Therapy

A pan-culture was performed, and the patient was empirically treated with ceftriaxone 2 g intravenously every 12 hours and vancomycin 1 g intravenously every 12 hours for possible meningitis. Once the MRI findings were obtained, the patient was placed on acyclovir 10 mg/kg body weight daily given intravenously every 8 hours, for a total dosage of 30 mg/kg daily. Fosphenytoin sodium was begun empirically to control seizure activity. The patient was given a loading dose of 1 g of fosphenytoin sodium intravenously and then placed on 300 PE (phenytoin equivalents) intravenously daily.

Clinical Course

On hospital day 2, the patient continued to be febrile and the acyclovir dosage was increased to 15 mg/kg intravenously every 8 hours. The patient was found to have hypothyroidism and was started on appropriate replacement (levothyroxine tablets, 0.1 mg orally daily). All cultures were negative and the antibiotics were discontinued on hospital day 3; the acyclovir was continued.

On hospital day 7, the patient experienced another seizure. The serum phenytoin level was low at 4.3 µg/mL (normal, 10–20 µg/mL) and the fosphenytoin sodium dosage was increased to 500 PE daily. Other than the seizure on day 7, the patient's neurologic function was beginning to improve. Her mental status and speech improved and was fluent, although she had to re-learn the proper use of words and phrases. She was able to feed herself minimally and walk with assistance. She had no short-term memory and her long-term memory was slightly impaired. The olfactory hallucinations were not present after hospital day 4, but the patient complained of an inability to taste or smell most foods or fragrances. This problem persisted throughout her hospital stay. Physical therapy, occupational therapy, and speech therapy all were initiated during the first several days of treatment. The patient continued to run low-grade fevers consistent with the clinical course for herpes encephalitis. During the course of the patient's hospital stay, she was

Table 1. Initial Laboratory Results of the Case Patient

Variable	Result	Normal Range
Leukocyte count	15.9 × 10 ³ /mm ³	4.5–11.0 × 10 ³ /mm ³
Monocytes	13.2%	4%–11%
Segmented neutrophils	66.2%	45%–75%
Erythrocyte sedimentation rate	1 mm/h	1–25 mm/h
Potassium	2.8 mEq/L	3.4–4.8 mEq/L
Sodium	133 mEq/L	135–145 mEq/L
Chloride	98 mEq/L	100–108 mEq/L
Carbon dioxide	18 mEq/L	24–30 mEq/L
Blood glucose	113 mg/dL	70–110 mg/dL
Thyroid-stimulating hormone	7.96 µU/mL	0.5–5.0 µU/mL
Thyroxine, free (T ₄)	1.0 ng/dL	0.45–1.09 ng/dL

switched from fosphenytoin sodium to carbamazepine as it was felt this may assist with improving her cognitive skills over the long term. The patient also continued to be febrile, and fosphenytoin sodium has been associated with fever.¹

An MRI was repeated on hospital day 10 and demonstrated increased edema in the right temporal lobe, insula, and right parietal region. Mild edema of the left temporal lobe medially and the posterior right and left frontal lobes also was demonstrated. The right ventricle was slightly effaced. A repeat lumbar puncture was performed on hospital day 14, and CSF PCR was positive for varicella zoster virus. On hospital day 18, MRI of the brain was significant for decreased edema in the right frontal lobe as well as mild microhemorrhages in the layer of cortex covering the right temporal lobe. No associated subdural hemorrhages were seen. An EEG performed on day 19 showed significant asymmetrical slowing bifrontally, with the greatest amplitude on the right. No focal abnormalities or specific seizure discharges were observed. The majority of the tracing consisted of a 7 to 7.5 Hz theta frequency seen in the posterior head region with symmetrical distribution. Attenuation of activity was observed in the right temporal and frontal regions. Throughout this period, the patient was improving in her ability to perform activities of daily living and in long-term memory, although short-term memory did not improve.

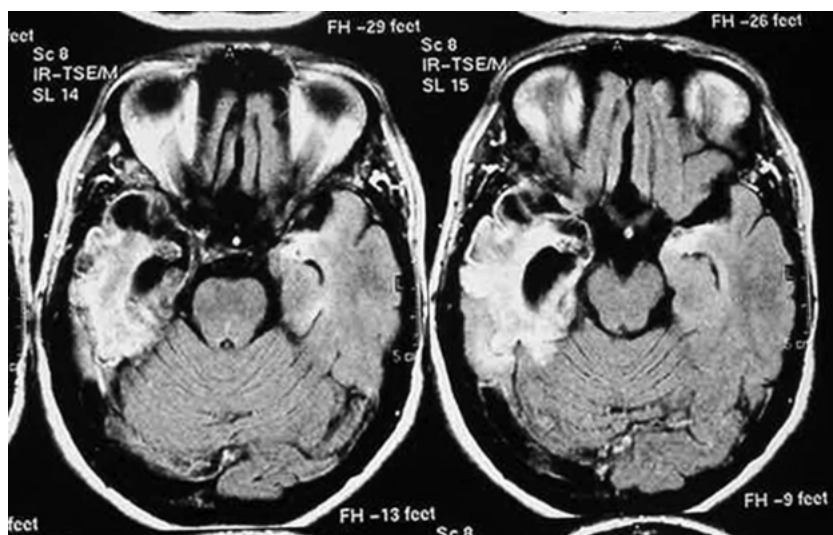


Figure 2. Horizontal magnetic resonance images of the case patient 3 months after discharge from the hospital demonstrates the destruction and continued inflammation of the right temporal lobe region and mild damage to the left temporal lobe.

Outcome

On hospital day 25, the patient was transferred to a rehabilitation facility. She was medically stable and her fevers had resolved. The patient was continued on carbamazepine to prevent seizures and was switched from intravenous acyclovir to oral valacyclovir (1000 mg every 8 hours) for treatment of the encephalitis. The decision was later made to discontinue the valacyclovir because oral anti-herpes agents had not been proven to improve morbidity and/or mortality of herpes encephalitis.²

When seen in follow-up 3 months after discharge from the hospital, the patient had returned home. She was doing well medically and had fully recovered all physical functioning. She had not had any additional seizures. The patient did not recall any of her hospitalization and her short-term memory was still limited. Her organizational skills were improving, her sense of taste and smell had fully recovered, and she had returned to teaching part-time. MRI evaluation at this time demonstrated atrophy at the site of the viral involvement; specifically, the right temporal lobe and hippocampus (**Figure 2**). Mild atrophy was present in the medial left temporal and frontal lobes.

Neuropsychological evaluation was performed approximately 4 months following discharge from the hospital. The patient's mood was characterized as dysthymic with a blunted affect. The patient was easily overwhelmed and suffered from significant anxiety. Difficulties were found with new learning as well as recent and remote memory. Her processing speed was slow compared to normal and she had difficulty with higher processing skills.

DISCUSSION

Etiology

Approximately 20,000 cases of viral encephalitis are reported each year. The most widely encountered viruses responsible in immunocompetent patients are HSV 1 (human herpesvirus 1), VZV (human herpesvirus 3), and enteroviruses. Epidemics of encephalitis are generally caused by arboviruses.^{2,3}

Clinical Manifestations

Patients with herpes encephalitis generally present with an acute febrile illness. An altered level of consciousness, abnormal mental state, and focal neurologic deficits follow. Patients are generally confused and disoriented, and may be in a coma. Focal or generalized seizures occur in more than half of patients with viral encephalitis. Motor weakness and hyperactive deep tendon reflexes may occur.² The hypothalamic-pituitary axis can be involved, causing hyperthermia, diabetes insipidus, or inappropriate antidiuretic hormone secretion. In herpes encephalitis (both simplex and zoster), signs also may include personality changes, hallucinations and aphasia.⁴ Anecdotally, patients also may present with olfactory hallucinations, as in the case described. These are caused by temporal lobe localization of the infection and represent temporal lobes seizures.⁵

Herpes simplex encephalitis usually presents as a sudden, life-threatening illness, but may present subacutely. The infection displays an affinity for the medial temporal and inferior frontal lobes. Because of this, focal disease is usually present, resulting in symptoms such as bizarre behavior, speech disorders, and olfactory

hallucinations. Consciousness quickly becomes altered, and coma and death ensue if treatment is not initiated quickly.⁶

Herpes zoster encephalitis, in contrast, has a subacute presentation. Symptoms are similar but present with less severity. Delirium generally occurs within several days following a vesicular eruption but may precede the eruption by up to a week.⁷ Rarely, herpes zoster encephalitis occurs in the absence of cutaneous dissemination, as in the patient presented here.⁴ Most patients who contract herpes zoster encephalitis are immunosuppressed, whereas herpes simplex encephalitis occurs more often in immunocompetent hosts.⁷

Two forms of herpes zoster encephalitis predominate. Small vessel herpes zoster encephalitis is the most common form. It develops predominately in people who are immunosuppressed and is often fatal.^{4,8} Brain MRI reveals large or small ischemic or hemorrhagic infarcts in the cortex and subcortical gray matter.⁴ CSF findings include elevated monocytes, normal or mildly elevated protein levels, and a normal glucose content.⁹ The case patient ultimately was diagnosed with this type of herpes zoster encephalitis, which is unusual because most cases develop in immunosuppressed or elderly patients.¹⁰

The second form is large vessel herpes zoster granulomatous arteritis. The distinguishing feature of this entity is an acute focal deficit that develops within weeks to months following a herpes zoster eruption on the contralateral trigeminal nerve distribution. Most patients that present with this form are 60 years of age or older.⁴ CSF findings include elevated monocytes, oligoclonal bands, and increased IgG.⁹ Other symptoms include transient ischemic attacks, mental disturbances, hemiplegia, and central retinal artery occlusion on the same side as the zoster outbreak. Examination of vessels in the brain have revealed involvement of the middle cerebral, internal carotid, and anterior cerebral arteries. No proven treatment exists for this form of herpes zoster encephalitis; however, acyclovir and steroids are currently under investigation as a treatment modality.⁴ The disease is often fatal, and survivors frequently have severe neurologic sequelae.

Patients diagnosed with herpes encephalitis frequently suffer from retrograde and anterograde amnesia caused by destruction of the diencephalon, temporal lobe, and/or frontal lobes. The damage can either be localized to one side or occur bilaterally, although most cases of herpes encephalitis tend to cause bilateral destruction. The extent of damage correlates to the

severity and duration of amnesia. In most cases, recall of autobiographical incidents and famous news events as well as that of personal experiences is affected.^{11,12} In early observations, involvement of the left temporal and frontal lobes was associated with the greatest impairment of cognition; recent evaluation of patients with herpes encephalitis, however, have demonstrated that right temporal and frontal lobe involvement lead to similar impairment. The right temporal and frontal lobe regions make a greater contribution to retrieval of past episodic memories, whereas the left temporal region is more involved with lexical-semantic labeling of remote memories.^{12,13}

DIFFERENTIAL DIAGNOSIS

The diagnosis of viral encephalitis in this case was made relatively quickly owing to the availability of emergent MRI. The difficulty came in determining which virus was causing the disease. Due to the predominance of changes in the temporal lobe, affecting specifically the white matter, a preliminary diagnosis of herpes simplex encephalitis was made and the patient was empirically started on intravenous acyclovir. Diagnosis of herpes zoster encephalitis was subsequently confirmed by CSF PCR analysis; however, the treatment is the same for both viruses. The symptoms were consistent with small vessel herpes zoster encephalitis.

The most common illnesses that mimic viral encephalitis include vascular diseases, empyema, abscess, fungal, parasitic, and tuberculous infections. Once nonviral causes of encephalitis are excluded, determining which virus is causing the symptoms is imperative in order to begin proper treatment.^{2,14} Tests that distinguish viruses are time intensive, and treatment is usually initiated based on symptoms. Herpes simplex or herpes zoster encephalitis should be considered whenever clinical features suggest involvement of the frontotemporal region of the brain.

Epidemiologic factors, such as time of year, age of the patient, geographic location, travel history, and exposure to animal bites or rodents also can provide clues to diagnosis. The Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report* provides weekly reports on the prevalence of specific viruses throughout the country (www.cdc.gov/mmwr).

DIAGNOSIS

CSF examination is essential in all patients with suspected viral encephalitis. The usual findings include elevated lymphocytes, a mildly elevated protein level, and a normal glucose level. Approximately 20% of patients have a significant quantity of erythrocytes in the

CSF, suggesting possible hemorrhagic encephalitis. This complication may occur with herpes simplex encephalitis, Colorado tick fever virus infection, and California encephalitis. If the CSF glucose level is decreased, viral encephalitis is unlikely, except in rare causes of advanced herpes simplex encephalitis.²⁴

CSF PCR amplifies the viral nucleic acid and can distinguish most types of viral encephalitis. This test has become the diagnostic procedure of choice. HSV has been widely studied, and PCR has a 98% sensitivity and 94% specificity rate for detection of the virus.¹⁵ The rate of positive CSF PCR results declines after the second week of illness and after 1 week of antiviral therapy.^{16–18}

Patients suspected of having herpes simplex or herpes zoster encephalitis should be empirically started on acyclovir and undergo a CSF PCR assay for HSV and VZV DNA. If results of PCR are negative, brain biopsy may be considered. Viral cultures from the CSF have a very low yield and are not recommended.²

MRI is the most sensitive noninvasive test for both herpes simplex and herpes zoster encephalitis. Findings include areas of increased signal intensity in the frontotemporal, cingulate, and insular regions of the brain.⁴ Lesions found on MRI tend to be spherical white matter lesions that mimic infection. Gray matter is not initially affected but can become involved late in the disease process. The lesions lack surrounding edema and are scattered, distinguishing these lesions from those associated with tumor. The lesions typical of herpes encephalitis tend not to follow an arterial distribution and are discrete in nature, distinguishing them from those associated with an infarction.⁸ CT may show evidence of acute stroke, with areas of low absorption or mass effect seen in the temporoparietal region.¹⁹

EEG can be used to aid in the diagnosis of herpes encephalitis. Findings may include uni- or bilateral periodic sharp waves, attenuation of amplitude, focal or generalized slow waves, or periodic lateralized epileptiform discharges (PLEDs), which are surface-negative bi-, tri- and polyphasic spikes and sharp waves that are usually maximal on the side of injury.^{10,19} The presence of slow waves (theta and delta) is always an abnormal finding in an awake patient and usually points to a focal brain lesion.²⁰ The case patient's EEG demonstrated theta waves in the posterior head region, with some lateralization to the right temporal and frontal lobes.

Brain biopsy was the gold standard for diagnosis prior to the advent of PCR but now is used only when CSF PCR fails to lead to a specific diagnosis and empiric treatment is not improving symptoms.²¹

TREATMENT

Acyclovir is the treatment of choice for herpes simplex and herpes zoster encephalitis, and should be started empirically in any patient with symptoms suggestive of disease. The initial starting dose is 10 mg/kg intravenously every 8 hours (30 mg/kg daily) for a minimum of 14 days.^{2,8} Dosages can be increased if response to the initial dosage is inadequate. Inadequate response can be characterized by increased fever, worsening mental status, or increased seizure activity. Although it is not the standard of care, it is suggested that CSF PCR be repeated after 14 days of therapy.¹⁶ If the results of PCR are negative, the acyclovir can be discontinued; if results are positive, treatment should be continued for an additional 7 days and PCR repeated. The acyclovir should be diluted to a concentration less than 7 mg/mL and given slowly (over a period of at least 1 hour) to avoid renal dysfunction. Penetration into the CSF is excellent. Complications of acyclovir therapy can include renal failure, thrombocytopenia, nausea, vomiting, diarrhea, and neurotoxicity (manifested as lethargy, confusion, agitation, tremors, hallucinations and/or seizures).² Acyclovir resistance has not been seen, except in immunocompromised patients. Oral antiviral therapy for the treatment of herpes encephalitis is not recommended either for primary or secondary therapy following intravenous administration, although studies are currently under way to clarify whether secondary oral therapy may improve long-term neurologic outcomes.²

In addition to acyclovir, supportive therapy is recommended. This includes monitoring in the intensive care unit during the initial stages of treatment. Seizures are treated with standard therapy and prophylactic regimens should be considered as incidence of seizures are high with encephalitis.² A consensus on duration of anticonvulsant therapy is not found in the literature, but duration consistently correlates with severity of symptoms.

PATIENT OUTCOMES

The incidence of sequelae from herpes simplex or herpes zoster encephalitis varies widely. Patients may recover completely without evidence of neurologic dysfunction, or they may have severe neurologic problems including seizures, hemiparesis, or memory loss.^{7,8} McGrath and colleagues²² evaluated long-term neurologic outcomes and mortality following acyclovir treatment in patients with herpes simplex encephalitis. Herpes simplex and herpes zoster encephalitis are similar, so findings of this study can be used as a guide for sequelae in herpes zoster encephalitis patients. Forty two

patients were involved in the study, of whom 34 survived. Only 1 of the 34 who survived was free from neurologic impairment at 11 years post-encephalitis. Approximately 48% had mild impairment. Twenty one percent were living independently but had significant neurologic impairment. Twelve percent had severe neurologic impairment. The most common sequelae included short-term memory impairment, personality and behavioral changes, epilepsy, anosmia, and dysphagia.²² Recent studies also have demonstrated that outcomes are correlated to the amount of viral DNA present in the CSF at the time of presentation.^{14,15}

CONCLUSION

Herpes zoster encephalitis is relatively rare but is important to recognize because expedient diagnosis and treatment are key to patient survival and subsequent recovery of neurologic function. Initial symptoms can be subtle, such as the constant flowery smell experienced by the patient in this case. This symptom represented a simple partial seizure and, in retrospect, reflected the temporal lobe involvement of the VZV infection. Empiric therapy with acyclovir can limit the morbidity and mortality associated with this disease, but therapy must be started based on clinical judgment. It is, therefore, important for clinicians to be able to recognize the symptoms that suggest herpes zoster encephalitis.

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