Herpes Zoster Encephalitis: Successful Therapy with Vidarabine

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A 77-year-old woman was seen who had encephalitis complicating trigeminal herpes zoster. Diagnosis was made by clinical and cerebrospinal fluid findings and electroencephalogram. As a result of parenteral vidarabine therapy, the patient recovered.

Herpes zoster is a common infection in immunocompromised and debilitated elderly patients and is life threatening in its visceral disseminated form. Fortunately, a recent collaborative antiviral study (1) by the National Institute of Allergy and Infectious Diseases has shown that accelerated clearance of virus from the vesicles, cessation of new vesicle formation, and a shorter time to total pustulation results when herpes zoster is treated with intravenous vidarabine (adenine arabinoside, ara-A). However, while this drug shows promise for therapy in immunocompromised patients, its efficacy has not been established in patients with the visceral complications of encephalitis and pneumonitis. Taber, et al reported no apparent benefit of vidarabine therapy in five patients with clinical encephalitis secondary to herpes zoster (2). Contrary to this report, we have recently had good clinical results using intravenous vidarabine to treat a patient with herpes zoster encephalitis complicating trigeminal herpes zoster.

Case Report

A 77-year-old black woman was admitted to Henry Ford Hospital after experiencing four days of pain and burning in the right periorbital region. She had diabetes mellitus with chronic renal failure, quiescent rheumatoid arthritis, congestive heart failure secondary to arteriosclerotic heart disease, mitral regurgitation, and congenital ovalocytosis. Her medications on admission were insulin, furosemide, digoxin, and folic acid. She had no recent or past history of alcohol abuse. One day before admission, she noted blisters near her right eye and began to complain of excruciating pain there. She was nauseated and vomited several times the day before she was admitted.

On admission, the patient was somnolent but arousable. She had no muscle weakness, tonic-clonic movements, or incontinence. Her temperature was 36°C, the blood pressure 140/70 mm Hg, and the respiratory rate was 20/mnt. Hemorrhagic vesicles were noted primarily in the right first trigeminal dermatome and, to a lesser extent, on the right second trigeminal dermatome, and on the hard and soft palate bilaterally. The right upper and lower lids were moderately swollen, and numerous vesicles were present. A mucoid discharge was seen between the lids. The conjunctiva and cornea appeared free of inflammation, and the pupils were round, reactive to light, and pinpoint. The fundi could not be visualized. The patient had several soft anterior cervical nodes and slight nuchal rigidity. Chest auscultation revealed bilateral inspiratory rales. The apical heart rate was 120/mnt and intermittently irregular. There was generalized cardiomegaly; an S3 gallop and III/VI systolic murmur were heard at the apex with radiation to the left axilla. The liver edge was palpable 6 cm below the right costal margin. The patient's hands showed chronic deformities of rheumatoid arthritis without acute synovitis.

The patient followed simple commands well, and was oriented to time, place and person, but could not provide other useful information. Her cranial nerves were normal, and her motor function was intact. Deep tendon reflexes could not be elicited, except for 1+ biceps jerks bilaterally. Babinski sign was negative. No grasp or snout reflexes were noted.

At admission, the results of her laboratory tests were hemoglobin 7.6 gm%, WBC count 4,600 with 78% poly, 1% bands, 18% lymphocytes and 3% monocytes, BUN 68 mg%, creatinine 4.7 mg%, calcium 8.3 mg, phosphate 6.8 mg%. The rest of the tests were within normal limits.
We initially believed that the patient had herpes zoster involving the ophthalmic and maxillary divisions of the right trigeminal nerve with no eye involvement. Herpetic infection was confirmed by positive Tzanck smear. An electroencephalogram performed on the second hospital day revealed a severe diffuse disturbance of cerebral activity over both the hemispheres with prominent cortical and subcortical irritability. Cerebrospinal fluid was clear and colorless on four tests. There were 3-37 cells/mm³ with 99% lymphocytes on differential count by cytocentrifuge. CSF protein ranged from 48-104 mg%, and glucose ranged from 49-125 (with RBS of 147 and 315, respectively). Gram stain and cultures for bacteria, tuberculosis, and fungi were negative. On the basis of the clinical presentation, EEG results, and CSF findings, a diagnosis of herpes zoster encephalitis was made. The patient was started on vidarabine intravenously on the second hospital day. Based on her renal function, she received 5 mg/kg/day intravenously for eight days (recommended dose is 15 mg/kg/day for those with normal renal function). She also received intravenous phenytoin prophylactically. A computerized axial tomograph scan of the brain on the fourth hospital day showed marked widening of the cerebral sulci. The ventricular system was not enlarged or displaced. An area of decreased density was seen in the right posterior frontal region without mass effect, compatible with a localized inflammation.

After two days of intravenous vidarabine, the patient’s mental status slowly began to improve and continued to do so during her stay. On the fourth day, she developed myoclonus of the left upper extremity and a positive Babinski reflex on the left, but these resolved within the next week. A repeat EEG five days after treatment with vidarabine showed improvement over the initial EEG, but a moderate diffuse encephalopathic pattern was still present, affecting cortical and subcortical structures over both hemispheres, with minimal emphasis over the right central parietal region. When discharged, the patient was fully oriented and conversant, able to feed and bathe herself, and to walk with a cane.

Her skin lesions of herpes zoster were treated with Burrow’s solution, and no evidence of secondary infection was seen during hospitalization. Two days after vidarabine had been started, the lesions were becoming dry and crusting. Only crusted erosions and right periorbital edema were present on the fifth day of treatment. There was no evidence of hepatic, hematologic, or gastrointestinal side effects.

Discussion

Dissemination of herpes zoster virus may occur to skin and to viscera and is associated primarily with increased morbidity rather than mortality. The central nervous system can be involved with localized or disseminated infection, including two clinically distinct forms of encephalitis, namely ophthalmic zoster with hemiplegia and diffuse encephalitis (4). As many as 40% of patients with uncomplicated zoster show a mild pleocytosis or slightly elevated protein in the cerebrospinal fluid or both, without any symptoms or signs of meningitis. Spinal nerve root and peripheral nerve involvement, and motor neuropathies with or without muscle paralysis are more commonly seen in zoster than is encephalitis (4). In varicella, on the other hand, encephalitis is 25 to 30 times more common than myelitis. Manifestations of herpes zoster encephalitis may appear within one week before a cutaneous eruption appears. Most cases occur within two weeks after a rash appears. Approximately one third of patients with encephalitis manifest a distinct syndrome characterized by ophthalmic zoster and contralateral hemiplegia.

The average age of reported patients was 43, ranging from four to 74 years, and men outnumbered women approximately two to one. Significant underlying disease was present in about one sixth of the patients. Headache was common in all patients, whereas altered states of consciousness were more common in those with diffuse encephalitis. Convulsions and ataxia are rarely present in patients with ophthalmic zoster and hemiplegia, but are not uncommon in the other group. The reverse is true of fever and hemiplegia. An unusually high frequency of cranial nerve involvement is associated with encephalitis (one out of three), even when the ophthalmic zoster and hemiplegia group is excluded. Cerebrospinal fluid findings include mononuclear pleocytosis ranging from 19 to 440 cells/mm³ with moderate elevations of protein in one half and a normal sugar. Electroencephalograms are usually diffusely abnormal. Brain scan shows focal areas of increased isotope uptake or an abnormal flow pattern. Angiograms may show segmental angiitis and numerous vascular occlusions (on the affected side). Granulomatous angiitis of intracranial vessels has also been noted at autopsy (4).

The diffuse encephalitic syndrome carries a 33% mortality rate (4). However, only one fatal case of ophthalmic zoster with hemiplegia has been reported in a group of 14 patients, although seven patients had significant sequelae. Most of the deaths occurred in patients reported before 1947, and this figure may be reduced by the supportive care available today. Significant sequelae consist of hemiplegia, dementia, ataxia, and aphasia. In most cases, hemiplegia is mild and resolves at the time of discharge. Therefore, in contrast to the high mortality rate associated with untreated herpes simplex encephalitis (3), most patients with herpes zoster encephalitis have a reasonably good prognosis, although significant sequelae do occur.

Taber, et al, in a review of eight cases with clinical encephalitis, found that central nervous system symptoms and signs began soon after dissemination and included obtundation (5 patients), confusion (3), coma (1), hallucinations (1), and meningismus (2). All eight patients had a mononuclear pleocytosis and elevated protein in the cerebrospi-
Vidarabine was synthesized in 1960 for use as a potential cancer agent. Four years later, the drug was shown to have a broad spectrum of anti-viral activity in tissue culture, particularly for classic DNA viruses, including herpes simplex, cytomegalovirus, and varicella-zoster virus. It is an analogue of the purine base adenine. Recent reports of its efficacy in patients such as ours.

The pathogenesis of encephalitis associated with zoster is not clear. Direct viral invasion of spinal cord and brain in two severely immunosuppressed patients with zoster was presumed after intraneural inclusions and herpes-like particles were found in autopsy material. In addition, the virus was isolated from the brain of one patient. The preponderance of zoster involving cranial nerves in cases of encephalitis also supports direct viral spread as a potential mechanism of pathogenesis. However, histopathologic studies suggested "postinfectious changes of hemorrhage and vasculitis." Perivascular demyelination has also been described as the characteristic lesion of diffuse encephalitis.

A controlled trial of vidarabine in localized and disseminated herpes zoster was carried out by a collaborative antiviral study group sponsored by the National Institute of Allergy and Infectious Diseases. All 87 patients received both drug and placebo during the trial: either vidarabine (Group A) or placebo (Group B) during the first five days of the study, then the opposite regimen for a second five days. The drug was administered as a single intravenous infusion of 10 mg/kg/day given intravenously every 12 hours. Progress of the infection was monitored daily, and the healing process was assessed by various parameters. The two study groups had similar characteristics. In spite of rapid natural healing, those receiving vidarabine over the first five days had accelerated clearance of virus from vesicles, cessation of new vesicle formation, and a shorter time to total pustulation. Factors modifying the response to therapy included age (virus clearance was significantly accelerated in patients younger than 30), underlying disease (patients with reticuloendothelial neoplasia cleared the virus from lesions at significantly accelerated rates), and duration of zoster before therapy (most effective when administered during the first six days of disease). However, results of therapy for six patients with visceral complications of encephalitis and pneumonitis were not encouraging. Two patients died of

Herpes simplex encephalitis is a potentially fatal disease when untreated. In a recent double-blind placebo controlled study, Whitley, et al., reported 28 brain biopsy-proved cases. Among 18 who received vidarabine, the mortality was 28%. Seven of the 10 untreated cases died. The level of consciousness at the time of therapy was found to be a significant variable. The dosage recommended at present is 15 mg/kg/day given intravenously in a concentration not to exceed 0.7 mg/ml, due to low drug solubility. The low level of toxicity, coupled with the documented effectiveness of vidarabine when used early in the course of herpes simplex encephalitis, suggests that vidarabine should be started early in patients suspected of having the disease. Therapy can be terminated in five days in patients lacking virologic proof of diagnosis. For patients with proven disease, ten days of therapy is recommended. At these doses, toxic effects of vidarabine are minimal and consist of nausea and vomiting, weight loss, weakness and diarrhea. At higher doses, megaloblastosis of bone marrow, SGOT elevation, tremors, and thrombophlebitis at the intravenous site may occur. However, all of these adverse reactions are reversible.

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unrelated causes after the study was completed. Two others died shortly after they were enrolled in the study. Both had received placebo, and their deaths were attributed to zoster. Although results of this study were discouraging for disseminated visceral zoster, systemic vidarabine therapy appears promising in patients similar to our patient.

The NIAID collaborative study showed that vidarabine is a promising drug for therapy in both localized and disseminated cutaneous herpes zoster in immunocompromised patients and the elderly. The outcome of our case supports its continued use in zoster encephalitis with an ongoing evaluation of its efficacy.

References


