Altered mental status in a 66-year-old woman during the late summer months

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In the summer of 2003, a 66-year-old woman presented to the emergency department with fever, chills, and decreased oral intake. She was discharged home after intravenous hydration. Routine laboratory evaluation showed all relevant values to be within normal limits. After returning home, the patient's clinical status progressively worsened. She returned to the emergency department with continued fever and the onset of ataxia. A chest x-ray revealed a probable right lower lobe pneumonia.

The patient was admitted, blood cultures were drawn, and broad-spectrum antibiotics, including a third-generation cephalosporin and a macrolide, were administered. After 2 days of antibiotics, the patient's clinical status continued to decline and her mental status worsened. An unenhanced computed tomography scan of the brain was unremarkable. A lumbar puncture revealed an elevated white blood cell count with a predominance of lymphocytes as well as elevated protein levels with a normal glucose. Additional cerebrospinal fluid laboratory studies were ordered.

As the patient's clinical status continued to decline, she also began to develop bilateral, lower greater than upper, extremity weakness as well as multiple cranial nerve deficits. Enhanced magnetic resonance (MR) images of the brain were obtained *(Figures 1–4)*.

What is the most likely diagnosis based on the MR images and clinical presentation? What test will help confirm the diagnosis?

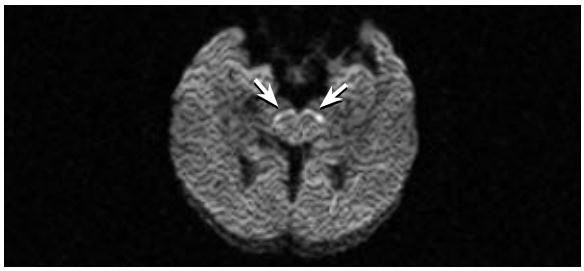

Figure 1. Axial diffusion-weighted MR image demonstrates linear hyperintense signal involving the substantia nigra compatible with restricted diffusion.

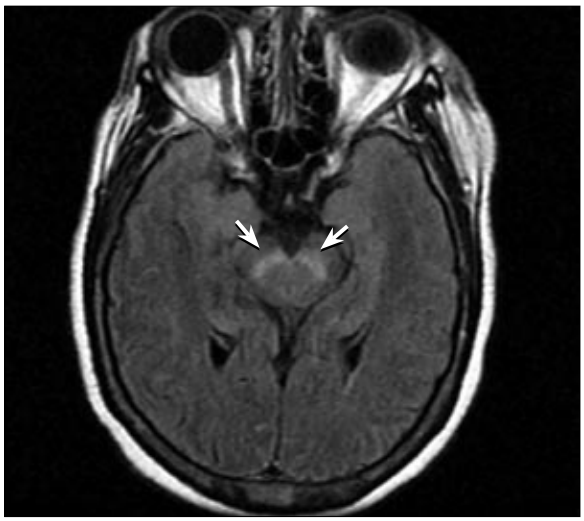

Figure 2. Axial FLAIR MR image shows hyperintense signal in the location of the previously visualized restricted diffusion on day 6.

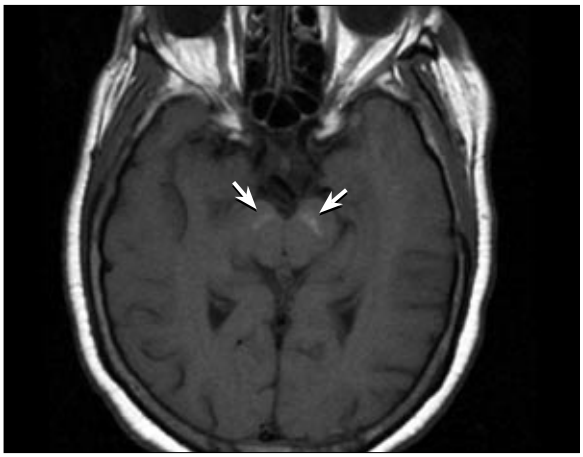

Figure 3. Axial spin-echo T1-weighted MR image demonstrates hyperintense signal in a location analogous with the substantia nigra on day 6.

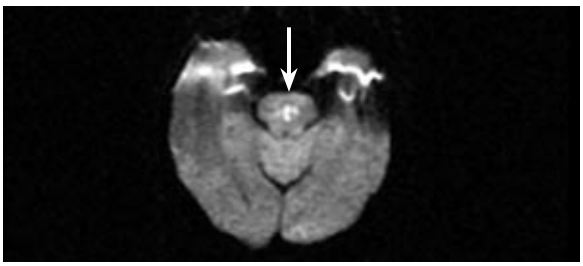

Figure 4. Axial diffusion-weighted MR image shows hyperintense signal within the central and bilateral paramedian pons.

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DIAGNOSIS: West Nile encephalitis.

The West Nile antibody screen demonstrated arbovirus antibody, indicating exposure to West Nile virus or other viruses in the Flavivirus group. Enzyme-linked immunoassay testing of the patient's cerebrospinal fluid showed the presence of West Nile immunoglobulin M.

DISCUSSION

The West Nile virus is an arthropod-borne virus (an "arbovirus") in the *Flaviviridae* family. Other well-known viruses in this family include St. Louis encephalitis and Japanese encephalitis. The transmission cycle of the West Nile virus begins with immunocompetent bird reservoirs that develop life-long immunity. Mosquitoes feed on the birds and transmit the virus to other birds, completing the life cycle. People, horses, and other mammals, as well as several species of birds, serve as incidental hosts that do not transmit the virus to humans. Humans can transmit the virus to other humans through blood transfusions, organ transplantation, and even lactation. In the USA, West Nile virus is primarily transmitted by the *Culex* species of mosquito (1).

Since its initial report in the USA in 1999, the number of West Nile virus cases has risen to epidemic proportions. The virus has emerged in recent years during the warm and rainy seasons and has presented predominantly as a threat to human and equine populations. The presentation can vary from mild flulike symptoms to its most serious presentation, West Nile meningoencephalitis. Severe neuroinvasive manifestations are reported by the Centers for Disease Control and Prevention to occur in <1% of infected persons; however, approximately 30% of the cases reported in 2003 had the neuroinvasive form of West Nile (1).

The virus was initially described in a febrile woman from Uganda in 1937. It was further reported in Egypt in the 1950s but gained infamy in 1957 during a large outbreak in Israel, where it was first identified as causing neurologic sequelae and resulting in severe morbidity and even mortality in 14% of the infected patients (2). Multiple outbreaks of West Nile encephalitis have been identified in Africa, Europe, the Middle East, and west and central Asia during the early and mid 1990s. Until 1999, West Nile virus was never reported in the Western Hemisphere. The first report of the virus in the West was during the outbreak of West Nile meningoencephalitis in the New York City area during August and September of 1999 (3). The virus quickly spread to all of the states in the eastern seaboard. Each year since, the virus has geographically progressed westward. In 2002, cases were already reported in 41 states; by 2003, all of the continental 48 states with the exception of Washington and Oregon reported cases of West Nile virus in humans. From 1999 to 2001, only 149 cases of West Nile virus resulting in 18 deaths were reported in the USA (4). In 2002 and 2003, the numbers rose to 4156 and 8567, respectively, as this mosquito-transmitted disease became widespread (1). In the 2004 West Nile virus season, the number of cases is predicted to double or even triple from 2003.

Currently, there is no reported cure for the West Nile virus. The infected individual requires hospitalization and intensive supportive care. Intravenous fluids, occasional respiratory support, and the prevention of opportunistic infections are the mainstay of treatment. Most patients require extended rehabilitation for recovery from their neurologic deficits. Some sources have described prompt initiation of treatment with high-dose interferon alfa-2b as a means of preventing long-term neurologic sequelae (5).

REVIEW OF BAYLOR CASES OF WEST NILE VIRUS

We retrospectively analyzed MR imaging studies of 9 patients with serologically proven West Nile virus treated at Baylor University Medical Center (BUMC). The 4 men and 5 women were 49 to 85 years of age, with an average age of 66 years.

Several articles have described MR image findings associated with West Nile virus: hyperintense basal ganglia or thalami on T2-weighted images, enhancement of the leptomeninges or periventricular white matter, and abnormalities of the pons, dentate nuclei, substantia nigra, and red nuclei (5–7). In addition to these findings, our observations included abnormal diffusion-weighted images with bilaterally symmetric substantia nigra, bilateral medial temporal lobe, central pons, and thalamic signal abnormalities as early indications of West Nile meningoencephalitis. Images obtained later in the disease process also showed fluid-attenuated inversion recovery (FLAIR) and occasionally even T1 hyperintense signal abnormalities in many of these same anatomic locations.

Figures 1 through 4 were obtained from sequential MR studies on the same patient. Figure 1 demonstrates hyperintensity on linear diffusion-weighted signal abnormality in the bilateral substantia nigra, indicating restricted diffusion and suspected cytotoxic edema. In MR imaging, restricted diffusion may serve as an indicator of cytotoxic edema that is the likely result of a shift of extracellular water into the intracellular compartment and is seen with ischemic states and other conditions in which cell membrane damage has occurred (7). This patient also demonstrated a similar diffusion signal abnormality involving the left superior cerebellar peduncle (not pictured). Figures 2 to 4 are images of the same patient obtained 6 days later. In this time interval, the previously visualized linear diffusion abnormality in the substantia nigra had progressed to a hyperintense signal on FLAIR (Figure 2), most likely representing edema, and on T1 images (Figure 3), as a likely consequence of the development of bilateral substantia nigra hemorrhages. Similar MR diffusion signal abnormalities that eventually become hemorrhagic have been described with other Flavivirus infections, in particular Japanese and St. Louis encephalitis (8, 9). These events have been postulated as an etiology for the transient Parkinsonism seen in Japanese encephalitis and may explain a similar symptom complex seen in neuroinvasive West Nile virus (10). The diffusion images in Figure 4 document the resolution of the abnormal signal in the substantia nigra with development of restricted diffusion in the central and bilateral paramedian pons. This patient also showed FLAIR signal abnormality in bilateral dentate nuclei (not pictured).

MR images in another patient demonstrated bilateral, left greater than right, FLAIR signal abnormality in the dentate nuclei of the cerebellum *(Figure 5)*. This patient also had subtle hyperintensity on T1-weighted images in the substantia nigra.

In the third patient, *Figure* 6 documents restricted diffusion of the bilateral medial temporal lobes. These findings have previously been described as manifestations of other viral infections such as herpes simplex.

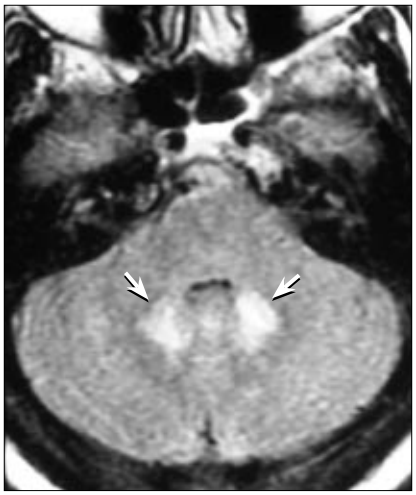

Figure 5. Axial FLAIR MR image demonstrates hyperintense signal in the dentate nuclei of the cerebellum.

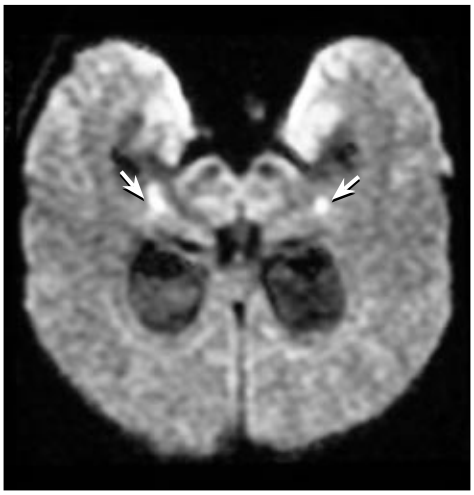

Figure 6. Axial diffusion-weighted MR images shows hyperintense signal in bilateral medial temporal lobes.

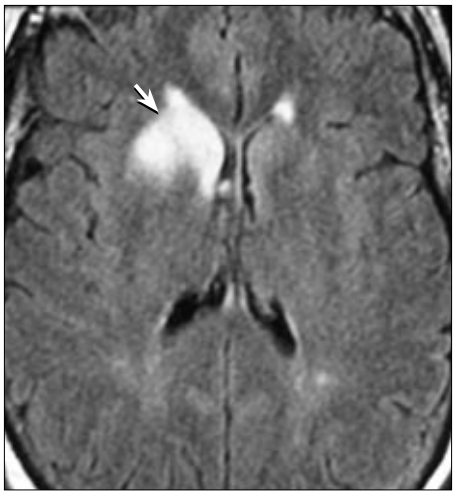

Figure 7. Axial FLAIR MR images demonstrates hyperintense signal of the right putamen and caudate head.

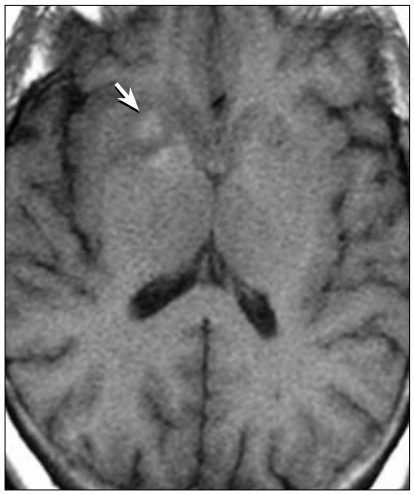

Figure 8. Axial spin-echo T1-weighted MR image demonstrates hyperintense signal of the right caudate indicating hemorrhage.

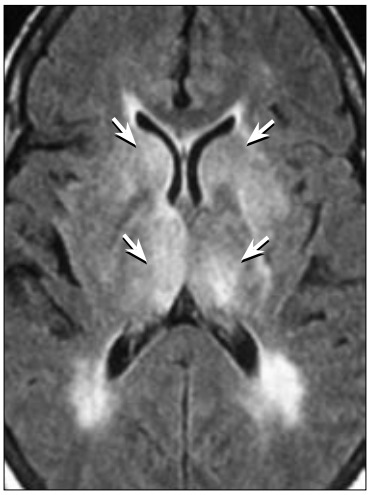

Figure 9. Axial FLAIR MR image shows bilateral hyperintense signal throughout the bilateral basal ganglia.

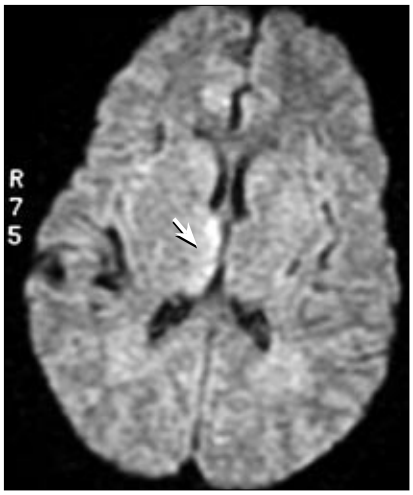

Figure 10. Axial diffusion-weighted MR image demonstrates subtle hyperintense signal of the medial right thalamus.

As described in several recent articles (5, 6), *Figure 7* also demonstrates hyperintense signal abnormalities involving the deep gray nuclei on FLAIR and T2-weighted images. In this case, there is also mild T1-signal hyperintensity *(Figure 8)*, which may represent basal ganglia hemorrhage. Similar signal abnormalities have previously been described in cases of the closely related Japanese encephalitis.

In the last patient, similar intense signal abnormalities of the deep gray nuclei are once again identified on FLAIR sequences *(Figure 9)*. In addition, *Figure 10* shows evidence of mild restricted diffusion with asymmetric hyperintensity of the medial right thalamus. In light of the diffuse FLAIR abnormality, the small, asymmetric hyperintensity is felt to represent restricted diffusion that is normalizing.

In the above cases, the discordance among diffusion, FLAIR, and T1-signal abnormalities may reflect an underlying temporal sequence of events in which restricted diffusion progresses to FLAIR signal abnormality and eventually T1-signal hyperintensity indicating hemorrhage. Our case series demonstrates MR images that depict multiple findings previously reported as well as several new findings not previously described. Patients in all phases of signal evolution are illustrated.

CLINICAL OUTCOMES

Our limited follow-up of these patients has suggested slow, progressive improvement in weakness. Several of these patients also developed transient swallowing abnormalities, with at least one patient requiring a gastrostomy tube. None of the patients died during the acute phase of the disease while at BUMC or Baylor rehabilitation centers. All of the patients required extended care in rehabilitation or nursing home facilities until they were able to regain enough strength to return to their predisease baseline.

CONCLUSION

Particularly in the summer, clinicians should be aware of the presenting signs and symptoms of West Nile virus and indicators of progression to the neuroinvasive form of the disease. The typical West Nile virus patient complains of malaise and fever after a 3- to 14-day incubation period. Patients also develop nonspecific

influenza-type symptoms, including myalgias, abdominal pain, nausea, emesis, arthralgias, headache, and possibly even a recently resolved rash. With the neuroinvasive form, the patient usually develops progressive disorientation, confusion, dysphagia, dysarthria, proximal extremity weakness evolving into flaccid paralysis, and other cranial nerve abnormalities including disconjugate gaze and diplopia. Coma and the necessity for ventilatory support are well-known complications (1–3, 5, 6, 10). Cerebrospinal fluid studies may reveal elevated lymphocyte counts and protein levels with near-normal glucose levels. While awaiting final serological results and providing supportive care, MR imaging may be useful in excluding other disease processes and in identifying more typical manifestations of West Nile encephalitis.

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