West Nile Virus–Associated Encephalitis in Recipients of Renal and Pancreas Transplants: Case Series and Literature Review

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Although West Nile fever is mild in the vast majority of infected persons, there is growing evidence that the disease may be more severe in the immunocompromised population. We describe 3 recipients of kidney or pancreas transplants who developed West Nile fever, 2 of whom had meningoencephalitis. As is the norm when treating serious infections in transplant recipients, a reduction of immunosuppression was pursued for these patients. Despite the severe nature of the disease in 2 patients, all recovered from the disease. The time course of neurologic recovery in the 2 patients with meningoencephalitis is highlighted. We also review the literature on West Nile fever in organ transplant recipients. In areas where West Nile virus is endemic, one must have a high index of suspicion for the illness when dealing with fever in transplant recipients.

West Nile fever is caused by a single-stranded RNA flavivirus. The disease is mosquito borne and is endemic in Africa, the Middle East, and southwestern Asia. It has recently spread to Europe and North America [1, 2]. Since it was first recognized in New York in 1999 [2], the West Nile virus has rapidly spread across the United States, and human disease has been reported from 45 states [3].

The virus is maintained in a bird-mosquito-bird cycle, and human infection results from mosquito bites. Other rare modalities of transmission that have been reported include transplacental transmission [4], breast-feeding [5], blood transfusion [6], organ transplantation [6], and percutaneous inoculation [7].

Most West Nile virus infections are mild, and only 20% of infected persons develop West Nile fever [8]. Severe infection resulting in neurological manifestations occurs rarely; only 1 in 150 patients develop serious illness [9]. Neurological presentation may include meningitis, encephalitis, and acute flaccid paralysis [10]. Advanced age (>70 years) is a widely recognized risk factor for serious illness [11]. Immunosuppressed patients have also been noted to have poor outcomes [12].

Solid-organ transplant recipients, by virtue of receiving life-long immunosuppressive medication, are potentially at risk of serious disease when exposed to West Nile virus. As a result of the rising menace of West Nile fever in the United States, transplant physicians are likely to see an increasing number of their patients contracting this disease. Unfortunately, there is scant literature available on the risks of acquisition or disease profile of West Nile virus in this patient population. There are also no guidelines available on management of West Nile fever in these patients.

We describe 3 recipients of kidney and/or pancreas grafts who developed clinical West Nile virus infections and who were seen at the University of Nebraska Medical Center (Omaha), a large solid-organ transplantation center where >100 renal and pancreas transplantations are performed each year. In each of the 3
reported patients, the transplantation procedure had been performed much earlier (11, 17, and 48 months, respectively) and was not directly linked to the viral illness.

In addition, none of the patients had received blood products since their transplantations. Presumably, the source of infection was mosquito bites received in the community. All the patients were seen in the summer of 2003 during a large outbreak of West Nile fever in the state of Nebraska.

**CASE STUDIES**

**Patient 1.** A 44-year-old white man who had undergone simultaneous kidney-pancreas transplantation 17 months earlier presented in September 2003 with fever, confusion, and tremors. His immunosuppressive therapy included tacrolimus (serum levels, 11–15 ng/mL), mycophenolate mofetil (500 mg b.i.d.), and prednisone (5 mg q.d.). There was no history of blood product transfusion since his transplantation. A week before admission, he developed malaise, muscle pain in back and limbs, and nausea. Three days later, he had diarrhea and high-grade fever with chills. This was soon followed by onset of mental status changes, tremors, and weakness of all limbs. At admission, he was confused and had a right VIth nerve palsy. He had reduced power in all limbs (3/5), but the sensations were intact. In addition, myoclonic movements were noted. Over the next 24 h, he became encephalopathic, and his deteriorating level of consciousness necessitated ventilator support.

The pancreas and kidney grafts continued to function satisfactorily. CSF analysis revealed 73 WBCs (53 polymorphs, 32 lymphocytes, and 16 monocytes) and 13 RBCs, a protein level of 52 mg/dL, and a glucose level of 32 mg/dL. IgM antibody for West Nile virus (determined using IgM ELISA; Focus Technologies) was positive in both serum (ratio, 5.5) and CSF (ratio, 7.1) specimens. The results of other virus studies of CSF specimens, including tests for herpes simplex virus 1 and 2, were negative. An electroencephalogram showed diffuse slowing consistent with mild-to-moderate encephalopathy. MRI did not reveal any significant abnormality, except for a tiny cluster of deep white matter signal abnormality in the left frontal lobe. Serum biochemistry values were within normal limits, with the exception of a low sodium level (125 mmol/L).

The cornerstone of management was supportive care. Immunosuppression was reduced, mycophenolate mofetil therapy was stopped, and the tacrolimus dose was scaled down to a serum level of 5 ng/mL. However, because the patient had a low serum cortisol level for a stress situation (cortisol level, 10.3 μg/dL), the dosage of prednisone was increased from 5 mg to 20 mg per day. The patient became afebrile after a week, and extubation was performed. His level of consciousness gradually improved over the next 2 weeks. An additional MRI showed thoracic spinal cord involvement. The patient developed secondary parkinsonism and initiated therapy with carbidopa-levodopa (Sinemet; Merck), with significant improvement in symptoms. Over the next 10 weeks, progressive improvement in motor strength was seen during physical therapy in the rehabilitation unit.

**Patient 2.** A 37-year-old white woman presented in September 2003 with history of high-grade fever, nausea, vomiting, and diarrhea of 3 days’ duration. She had history of type 1 diabetes since childhood and had undergone an isolated pancreas transplant 4 years earlier. Her immunosuppressive therapy consisted of cyclosporine (serum levels, 100–150 ng/mL), mycophenolate mofetil (500 mg b.i.d.), and prednisone (2.5 mg q.i.d). She had not received blood product transfusion since her transplantation. Clinical examination and the routine laboratory tests were unremarkable. Blood, fungus, urine, and stool cultures were negative. The results of virus serological tests for cytomegalovirus and Epstein-Barr virus were negative. Chest radiography and imaging of the abdomen revealed no abnormalities. However, the results of IgM serological tests for West Nile virus (IgM ELISA; Focus Technologies) returned positive, with a titer of 1.75. This level increased 4 days later to 2.9. Treatment included lowering the dose of cyclosporine and mycophenolate mofetil. The fever subsided in 6 days, and the patient made a gradual and complete recovery.

**Patient 3.** A 2.5-year-old boy was admitted in October 2003, a total of 11 months after a successful living donor kidney transplant for end-stage renal disease caused by vesicoureteral reflux secondary to posterior urethral valves. His medication consisted of cyclosporine (serum level, 10–15 ng/mL) and mycophenolate mofetil. He had excellent graft function and was in good health before hospital admission. He, too, had not received any blood products since the time of his transplantation.

The boy had acute onset of high-grade fever and an episode of generalized convulsions before hospital admission. The findings of a clinical examination at admission were unremarkable. Over the next 48 h, the child became increasingly encephalopathic. As his level of consciousness declined, elective ventilation was instituted. CT scan of the head revealed nothing abnormal, but CSF analysis revealed leukocytosis (WBC count, 538 cells/mm³, with 41% polymorphs and 50% lymphocytes) and an elevated protein level of 0.127 g/dL. MRI of the brain showed mild diffuse arachnoid enhancement consistent with meningitis. The results of bacterial and fungal cultures of blood, CSF, and urine specimens were negative. PCR of the CSF was negative for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpesvirus 6, and adenovirus. IgM antibody for West Nile virus (IgM ELISA; Focus Technologies) was positive in both the serum (ratio, 5.3) and CSF (ratio, 3.1) samples.

Immunosuppression was reduced after admission. Mycophenolate therapy was stopped, and the trough level of tacrolimus decreased to <5 ng/mL. The child became afebrile in...
8 days. During the next 2 weeks, as his encephalitis resolved, so did his acute flaccid paralysis. At the time of discharge, he was eating and ambulatory, having made a complete neurological recovery.

DISCUSSION

Although the West Nile virus was first isolated in 1937 [13], it remained relatively obscure until 4 years ago. In 1999, the first outbreak of West Nile encephalitis in North America occurred [2]. Since then, the disease has spread to all parts of United States. In 2003 alone, >7000 cases have been reported across the United States, with a case-fatality rate of >2% [3]. Much attention is thus currently focused on this illness. In the general population, only 1 in 150 patients develop severe neurological manifestations [9]. However, recent reports in the medical literature suggest that in immunosuppressed individuals, the West Nile virus may cause serious illness more frequently. To date, there have been very few reports describing the course and outcome of West Nile fever in solid-organ transplant recipients.

Three of 4 recipients of organs transplanted from a West Nile virus–infected donor developed meningoencephalitis [3]. The outcomes for these 3 patients was poor. One died, 1 was discharged to a rehabilitation center, and only 1 was discharged home after a hospital stay of 45 days. A recent report of 23 patients who contracted West Nile fever through blood transfusion included 2 solid-organ transplant recipients [14]; one of them died.

Other differences may exist between the course of disease in transplant recipients and that in normal individuals. The incubation period among recipients of solid-organ, stem cell, or bone marrow transplants in this transfusion-related cohort tended to be longer than the incubation period of those without immunocompromising conditions (median duration, 13.5 days vs. 8 days; P = .08) [14]. In addition, immunocompromised patients may have prolonged viremia, delayed development of antibody, and an increased likelihood of severe disease [14]. The aggressive nature of the illness in immunocompromised patients is further illustrated by the recent report of mortality in 2 stem cell transplant recipients due to West Nile encephalitis [15].

All the reports detailing the occurrence of West Nile fever in solid-organ recipients are shown in table 1. Summarizing the data so far, there have been 7 cases in kidney and/or pancreas recipients, 2 in liver transplant recipients, and 1 each in heart and lung recipients, respectively [12, 14, 16, 17]. Four of these patients were aged >60 years, and only 3 were women. All but 2 developed features consistent with encephalitis. The immunosuppressive therapies are listed in table 1. These cases demonstrate the serious nature of West Nile virus infection in transplant recipients, reflected by a mortality rate of ~17% among reported cases. This is much higher than the reported mortality rate of 2% for patients with West Nile virus infection in the general population [3] but approximates the 12%–14% mortality rate among hospitalized patients with West Nile virus disease [9].

Three categories of serious neurological manifestations are now described for West Nile fever: meningitis, encephalitis, and acute flaccid paralysis. Movement disorders, including myoclonus, tremor, and parkinsonism, were reported to be a prominent manifestation in West Nile fever [10]. In a recent report on neurological manifestations of West Nile virus infection, 1 of 9 patients with encephalitis died of the illness [10]. So far, among the solid-organ transplant recipients reported with West Nile fever, 8 of 9 had encephalitis, and 2 died of the

Table 1. West Nile virus infections in recipients of solid-organ transplants.

<table>
<thead>
<tr>
<th>Reference (year of infection)</th>
<th>Age, years/sex</th>
<th>Type of organ transplanted</th>
<th>Immunosuppressive therapy</th>
<th>Clinical course</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12] (2002)</td>
<td>31/F</td>
<td>Heart</td>
<td>ATG, FK, Rapa, prednisone</td>
<td>Encephalitis</td>
<td>Alive</td>
</tr>
<tr>
<td>[14] (2002)</td>
<td>47/M</td>
<td>Liver</td>
<td>...</td>
<td>Encephalitis</td>
<td>Alive</td>
</tr>
</tbody>
</table>

NOTE. ATG, antithymocyte globulin (rabbit); AZA, azathioprine; CSA, cyclosporine; FK, tacrolimus; MMF, mycophenolate mofetil; PR, present report; Rapa, sirolimus.

* Not mentioned in article.
disease (table 1). Two of 3 patients in our report had encephalitis, but both survived with no specific intervention, other than reduction of immunosuppression and supportive care.

Both patients with West Nile meningoencephalitis developed this infection long after their transplantations. Both were receiving immunosuppressive therapy with tacrolimus (serum levels, 10–15 ng/mL) and mycophenolate mofetil at the time of presentation. As soon as the diagnosis was made, mycophenolate mofetil therapy was stopped, and the tacrolimus dose was decreased, with resulting serum levels of <5 ng/mL. The older patient made a partial neurological recovery, has continued speech tremors, and continues to undergo rehabilitation at time of reporting. In contrast, the child made a faster and complete recovery, despite an equally severe neurological presentation.

The important message that emerges from the recent literature and our report is that one should have a high index of suspicion of West Nile virus infection in all transplant recipients presenting with unexplained fever and/or neurological symptoms, particularly in areas where West Nile fever is endemic. As is commonly done in treating severe infections in transplant recipients who are immunosuppressed, we think that prompt reduction in immunosuppressive therapy may hasten recovery in these patients. However, the recovery noted in the 3 patients reported may have been the natural course of the illness and unrelated to the reduction of immunosuppression.

There is a definite need to prospectively evaluate the seroprevalence of this disease in the transplant population in order to determine what proportion of transplant recipients has developed immunity to West Nile virus without having severe clinical manifestations. In addition, the spontaneous recovery from West Nile encephalitis noted in this report underscores the need for rigorous evaluation of the role of newer medications, such as IFN and intravenous immunoglobulin, in this illness.

References