The Role for Intravenous Immunoglobulin in the Treatment of West Nile Virus Encephalitis

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Intravenous immunoglobulin (IVIG) with high titers to West Nile virus was used as an adjuvant therapy for a patient with West Nile virus encephalitis that did not respond to supportive care. We present this case report and review the evidence supporting the use of high-titer IVIG.

A 55-year-old white man with chronic lymphocytic leukemia presented to the outpatient radiology department at the National Institutes of Health Clinical Center for restaging of his leukemia. Three weeks before his presentation, he had completed his third cycle of chemotherapy (fludarabine, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin) in preparation for peripheral blood stem cell transplantation. At the time of radiological evaluation, he was found to be febrile (temperature, 39.3°C). Additional questioning revealed no localizing symptoms. The findings of physical examination were unremarkable except for chronic cachexia secondary to leukemia. The patient was admitted to the hospital for observation, at which time laboratory studies revealed a total leukocyte count of 0.997 x 109 leukocytes/µL, an absolute neutrophil count of 631 neutrophils/µL, a hemoglobin concentration of 9.5 g/dL, and a platelet count of 85,000 x 10³ platelets/mm³. The findings of renal and hepatic panels were unremarkable. Samples of blood, urine, sputum, and stool were obtained for culture, and the patient started receiving empirical antibiotic therapy with vancomycin, ampicillin, and ceftriaxone was started for treatment of apparent clinical sepsis.

The patient’s condition continued to deteriorate. By the third day of the second hospitalization, the weakness had continued to progress and was now associated with intermittent complaints of horizontal diplopia and difficulty speaking. Although the patient was cognitively intact and responded appropriately to questioning, there was impaired memory recall, with only 2 of 3 objects remembered at 2 min. An additional neurological examination revealed intact cranial nerves; severe neck weakness, with inability to lift his head up and off a pillow; and a coarse tremor associated with extremity movement. The patient was transferred to the intensive care unit for further monitoring. Additional brain imaging with gadolinium-enhanced MRI revealed no meningeal or intracranial abnormalities. Lumbar puncture revealed an opening pressure of 35 cm H₂O, a leukocyte count of 125 leukocytes/mm³ (58% neutrophils, 28% lymphocytes, and 14% others), a protein level of 59 mg/dL, and a glucose level of 62 mg/dL. Empirical antibiotic therapy with vancomycin, ampicillin, and ceftriaxone was started for treatment of meningitis while we awaited the results of CSF cultures and assays.

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Additional evaluation of the brain with gadolinium-enhanced MRI revealed no meningeal or intracranial abnormalities. Lumbar puncture revealed an opening pressure of 35 cm H₂O, a leukocyte count of 125 leukocytes/mm³ (58% neutrophils, 28% lymphocytes, and 14% others), a protein level of 59 mg/dL, and a glucose level of 62 mg/dL. Empirical antibiotic therapy with vancomycin, ampicillin, and ceftriaxone was started for treatment of meningitis while we awaited the results of CSF cultures and assays.

The day after discharge, the patient was readmitted to the hospital after being found on the floor of his home complaining of muscle weakness, fatigue, and diplopia. Despite these symptoms, there was no associated headache, loss of consciousness, confusion, neck stiffness, or pain. Physical examination now revealed an alert and oriented man with a temperature of 40.8°C. Full neurological examination revealed intact cranial nerves, new muscle weakness with bilateral 3+/5 strength in the shoulder girdle and hip flexor muscles, chronically diminished reflexes (associated with previous neurotoxic chemotherapy), and normal sensation. Laboratory studies revealed no significant changes, except appropriate filgrastim-mediated increases in leukocyte and absolute neutrophil counts.

Intravenous immunoglobulin (IVIG) with high titers to West Nile virus was used as an adjuvant therapy for a patient with West Nile virus encephalitis that did not respond to supportive care. We present this case report and review the evidence supporting the use of high-titer IVIG.
Because of a worsening of his mental status with associated obtundation, the patient required intubation on day 4 of hospitalization. Later that afternoon, the presence of West Nile virus in the CSF was confirmed by PCR. IgM and IgG were not detected in serum or CSF samples at that time.

Given the progressive nature of the West Nile encephalitis and the patient’s hypogammaglobulinemia, intravenous immunoglobulin (IVIG) therapy was started. A case report from Israel, where West Nile virus is endemic, suggested that IVIG containing high titers of immunoglobulin against the West Nile virus might be useful [1]. Therapy was started with IVIG containing high titers of immunoglobulin to West Nile virus (Omr-IgG-am; Omrix Biopharmaceutical) for a course of 5 doses (0.5 g/kg each) over a 6-day period. (Titters were measured by Omrix Biopharmaceutical [Brussels, Belgium] internally, using an ELISA; the lot was shown to have 1004 arbitrary units, which corresponds roughly to a dilution titer of 1:1600 [N. Mashiach, personal communication]). During the second day of treatment, the patient developed seizure-like activity. MRI of the brain revealed new lesions in the thalamus and midbrain. The patient completed the course of IVIG. CSF PCR for West Nile virus indicated that the virus had cleared (table 1), and IgM remained undetected in serum and CSF specimens. His coma persisted and was accompanied by worsening lesions in the thalamus, substantia nigra, red nucleus, pons, and deep cerebellar nuclei visible on radiographs. He became apneic and ventilator dependent. Ventilatory support was withdrawn, and the patient died of profound neurological damage 32 days into his illness.

Since the first North American outbreak of West Nile virus infection in the New York City area in 1999, the virus has received much medical and public attention. The increased awareness of this pathogen has sparked interest from the medical community with regard to potential treatment options. We report a case of severe encephalitis associated with West Nile virus infection and subsequent treatment with IVIG.

This case represents the atypical severe sequelae of infection with West Nile virus. The degree to which the patient’s underlying chronic lymphocytic leukemia and associated hypogammaglobulinemia played a role in acquisition of this infection is unknown. However, deficiencies of humoral immunity have been linked to an increased risk of viral infection [2–5], and, in patients with hypogammaglobulinemia, some of these infections have responded to treatment with IVIG [6–9]. IVIG has been used successfully against viral infections even in patients who are not hypogammaglobulinemic; examples include treatment of parvovirus in HIV-infected persons [10], treatment of Argentine hemorrhagic fever [11], and treatment of disseminated vacamia after smallpox vaccination [12]. Specific antibody has been reported to be effective for post-exposure prophylaxis for varicella [13] and hepatitis B [14] and for preexposure prophylaxis for respiratory syncytial virus infection [15].

Antibodies of several classes (IgG, IgM, and IgA) have long been recognized to inhibit extracellular viruses from infecting host cells [16, 17]. These neutralizing antibodies can independently prevent viral infection of host cells. The West Nile virus, a single-stranded RNA virus of the Flavaviridae family, has an envelope (E) glycoprotein that mediates virus–host cell binding and membrane fusion [18]. The E glycoprotein contains an array of epitopes that are the target of virus-neutralizing antibodies. Theses antibodies have been found to be protective and to prevent the development of other flaviviral encephalitides in a murine model after viral inoculation [19]. Although this model did not specifically include West Nile virus, augmenting the level of antibodies directed at the West Nile E glycoprotein may prove to be a reasonable treatment strategy, especially in patients with preexisting deficiencies in humoral immunity, such as our patient, who had chronic lymphocytic leukemia.

IVIGs are therapeutic preparations of pooled IgG that contain antibodies directed at a wide variety of microbial pathogens. Because IVIG is a pooled product, the specific antimicrobial activity of a batch of IVIG is directly related to the human pathogens encountered by the population that has contributed to the pool. Not surprisingly, IVIG products in areas where West Nile virus is endemic have shown high titers to West Nile virus [1]. IVIG has broad antimicrobial activity and has been found to be effective in reducing the number of bacterial infections when given prophylactically to patients with chronic lymphocytic leukemia [20]. However, its application as an effective treatment for viral eradication after infection is not well established. Data obtained after West Nile virus infection of mice suggest a possible therapeutic effect [21]. Immunosuppressed mice were challenged with West Nile virus, followed by 1 injection of immune sera after infectious challenge. Immune sera given on day 6 prevented death in 9 (82%) of the 11 mice, whereas 1 (3%) of 31 controls survived [21]. The clinical utility of IVIG in human West Nile infection has not been tested, but the success of IVIG in human enteroviral encephalitis and other viral diseases makes it an appealing treat-

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**Table 1. PCR data for CSF specimens obtained from a patient who received intravenous immunoglobulin (IVIG) for treatment of West Nile virus encephalitis in August 2002.**

<table>
<thead>
<tr>
<th>Date specimen was obtained</th>
<th>PCR result</th>
</tr>
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<tbody>
<tr>
<td>3 August (initial presentation)</td>
<td>Positive</td>
</tr>
<tr>
<td>9 August (before IVIG therapy)</td>
<td>Positive</td>
</tr>
<tr>
<td>12 August (after first dose of IVIG)</td>
<td>Positive</td>
</tr>
<tr>
<td>16 August (after fifth dose of IVIG)</td>
<td>Negative</td>
</tr>
<tr>
<td>21 August</td>
<td>Negative</td>
</tr>
</tbody>
</table>
ment option to consider when dealing with severe West Nile virus infections [10, 22, 23].

The timing and route of administration of IVIG may be particularly important. Although no studies of West Nile virus infection in humans have been published, animal studies involving another flaviviral encephalitis (St. Louis encephalitis) suggest that viral brain invasion may occur as early as 3 days after infection and that the window for successful application of antibody administration to prevent encephalitis closes 4–6 days after infection (concomitant with viral brain invasion) [19].

The titer and route of administration of IVIG in cases of West Nile virus encephalitis may be as important as the timing for achieving a successful therapeutic effect. Meningeal inflammation, which can accompany the developing encephalitis, makes the blood-brain barrier more porous to IVIG. However, the degree of penetration is unpredictable, and the administration of intraventricular or intrathecal immunoglobulins may be necessary for optimal penetration. In our patient, we chose to administer the immunoglobulin intravenously on the basis of the single case report of successful treatment of West Nile encephalitis [1]. However, intraventricular or intrathecal administration would deliver higher levels of immunoglobulins to the CSF. This idea is supported by the examples of enteroviral encephalitis in which some patients did not have a response to IVIG until immunoglobulin was directly infused into the CSF [6–8].

Despite the poor outcome for our patient, IVIG does have some appeal. Although there is no evidence that IVIG will change the natural course of a severe West Nile infection, it represents a treatment strategy for a disease that currently has no specific therapy. Additional studies to determine its clinical efficacy are warranted. These studies will need to address the timing and route of IVIG administration, the clinical efficacy of different West Nile virus titers in IVIG, and whether certain patients will derive more benefit than others from treatment.

References