Stiff-Person Syndrome Following West Nile Fever

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Background: Stiff-person syndrome is a rare autoimmune disorder associated with antibodies against glutamic acid decarboxylase (GAD), the key enzyme in γ-aminobutyric acid synthesis. In most cases, a trigger cannot be identified.

Objective: To describe a 41-year-old man who developed stiff-person syndrome and antibodies to GAD following acute West Nile virus infection.

Design: A case report and a search in GenBank for common epitopes.

Result: The search revealed a stretch of 12 amino acids in the NS1 protein of West Nile virus with a high degree of homology to the GAD65 region (an isoform of GAD) containing the PEVKEK motif.

Conclusion: Cross-reactivity between antibodies directed against West Nile virus and GAD may have contributed to the development of stiff-person syndrome in this patient.

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STIFF-PERSON SYNDROME (SPS) is a rare disorder that is characterized by progressive muscle stiffness, rigidity, and spasms predominantly affecting axial musculature.1 Stiff-person syndrome is thought to be an autoimmune disorder caused by autoantibodies to glutamic acid decarboxylase (GAD), interfering with central γ-aminobutyric acid (GABAergic) synaptic transmission.2-4 In most cases of SPS, no specific triggers can be identified.

West Nile fever (WNF) is a febrile illness caused by West Nile virus (WNV), a flavivirus maintained in nature through a bird-mosquito cycle. Various neurological complications can be associated with acute WNV infection, including meningitis and encephalitis.5-8 Israel is endemic for WNV, and a serious epidemic broke out in the late summer of 2000, causing several deaths and significant morbidity secondary to encephalitis.

We describe a patient who developed anti–GAD-positive SPS following serologically proved acute WNF. Because molecular mimicry has been suggested as a mechanism for the evolution of autoimmune diseases, we searched for a possible amino acid homology between WNV and GAD65 (an isoform of GAD).

OBSERVATION

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REPORT OF A CASE

A 41-year-old man presented in September 2000, during a WNF epidemic in Israel,9,10 with fever, headache, and malaise; the serological findings suggested WNF. In the past, he was treated for hypothyroidism. He had seasonal bronchial asthma and was allergic to several nonsteroidal anti-inflammatory agents. A few weeks later, while improving, he developed blurring of vision, a feeling of neck and upper back heaviness, and muscle stiffness at the base of the neck and upper extremities. This was followed by motor dysfunction of his left arm and right leg. There were no spontaneous muscle spasms, but in certain postures of his arms, the stiffness increased. He had no sensory symptoms or changes in bowel or bladder function.

A neurological examination showed decreased facial expression and well-developed muscle bulk, especially in the shoulder girdle region and arms. There was stiffness and limitation in the range of active and passive movements of the neck and left arm. There was also slowing of finger, hand, and arm movements, more on the left than on the right side. Hyperreflexia was noted in the arms, more on the
left than on the right side, and in the legs, more on the right than on the left side. Tone was increased in the left arm and both legs. Plantar responses were extensor bilaterally. The patient seemed stiff when walking, and his arm swing was decreased with posturing of both arms.

The results of routine blood work, including the determination of antinuclear antibody levels, were normal, except for the levels of creatine kinase (242 IU/L; upper limit, 190 IU/L) and thyroidotropin (6.39 mIU/mL). The patient also displayed mild eosinophilia (14.6%).

The results of cervical and cranial magnetic resonance imaging were normal. The opening pressure of his first lumbar puncture was normal, as were cerebrospinal fluid (CSF) chemistry, cytology, and culture results.

IgM and IgG antibodies to WNV in serum and CSF were noted (Figure 1), as were trace oligoclonal IgG antibodies in the CSF. Test results were also positive for serum antithyroglobulin antibodies.

The results of nerve conduction studies, repetitive nerve stimulation, and electromyography were normal, with the exception that it took longer for the patient to relax and discontinue voluntary recruitment of motor unit potentials.

A month later, the results of a neurological examination were unchanged except for blurring of the borders of the optic discs. The results of a computerized visual field examination were normal. The results of a computed tomographic scan of the head were normal as well. A second lumbar puncture demonstrated an elevated opening pressure of 290 mm H2O, with normal CSF glucose and protein levels and 6 polymorphonuclear cells.

The result of a polymerase chain reaction for WNV was negative, but test results were still positive for IgM and IgG antibodies to WNV in the serum and CSF (Figure 1). Retrospectively, serum anti–GAD antibody levels (CIS bio international, France [subsidiary of SCHERING SA]) were elevated during the initial short-term phase of his infection (level, 71 U/mL) and increased (to 105 U/mL in serum and 84 U/mL in CSF) when he first complained of stiffness (Figure 2).

Given a tentative diagnosis of SPS, the patient was treated with clonazepam. After a couple of weeks, action-induced muscle spasms developed involving the shoulder girdle muscles, and clonazepam was replaced by diazepam, 15 mg/d, and baclofen, 75 mg/d, with partial improvement. The increased intracranial pressure was treated with acetazolamide, 250 mg, 3 times a day for 3 weeks, with resolution of the blurring of the optic disc margins. He received 5 courses of plasma exchange 4 months after the onset of his symptoms, with some improvement of his stiffness.

When examined 3 months after the onset of his symptoms, his pyramidal signs were no longer present and the stiffness in his right leg was nearly resolved.

A third lumbar puncture performed 7 months after the onset of his symptoms showed a normal opening pressure and normal cytologic and chemistry results. At this time, the WNV IgM level was low in the serum, but still relatively high in the CSF. Serum and CSF IgG titers for WNV remained high. The anti–GAD antibody level in the serum and CSF decreased following plasma exchange.

Because of insufficient improvement 7 months after the onset of his symptoms, he was treated with intravenous immunoglobulins (Omr-IgG-am; Omrix Biopharmaceutical Ltd, Tel Hashomer). He received preparations from donors in Israel, containing high titers (1:1600) of antibodies against WNV.11 The initial dosage was 0.4 g/kg of body weight once daily for 5 days. He received additional treatment with intravenous immunoglobulins, 0.4 g/kg of body weight, once a month for 3 more months.12-15 Following treatment with intravenous immunoglobulins, there was marked improvement of his symptoms.

Three years following WNF, the patient is much improved, although still minimally symptomatic. He still has mild stiffness of his left upper limb and rare spasms
in his shoulders and neck. He has been able to resume his professional and leisure activities. He still takes baclofen, 75 mg/d. His serum anti-GAD titers remain elevated (last value, 146 U/mL).

A search of GenBank for an amino acid homology between WNV and GAD65 revealed a possible common epitope to GAD65 and the viral NS1 protein, which surrounds and partially overlaps the GAD65-PEVKEK epitope (Figure 3).

**Comment**

In this report, we describe a patient with SPS following WNF. The diagnosis of WNV infection was based on the development of a febrile illness during a known local epidemic of WNV; the patient had negative serological results. Although the patient’s clinical course of WNF lasted only a few weeks, the serological data (Figure 1) indicated a long-lasting immunological response to the virus, including IgM and IgG in the serum and CSF. Infection with flaviviruses can induce a long-term virus-specific IgM response in the serum and CSF. Long-term sequelae following acute WNV CNS infection were recently reported, as increased mortality (M. Green, MD, PhD, MPH, unpublished data, 2002). The reason for these phenomena is not known, but virus persistence is a possible mechanism. Indeed, flavivirus persistence in cell cultures, animals, and humans has been described. Thus, we raise the possibility of long-term subclinical infection with WNV in the patient with SPS; although the results of the polymerase chain reaction studies for WNV in the serum and CSF in this patient were negative, the sensitivity of polymerase chain reaction testing for WNV has not been defined, so this possibility is not ruled out.

The neurological symptoms of SPS began a few weeks following incomplete recovery from acute WNV infection. While WNV is known to cause meningitis and encephalitis, there was no conclusive evidence that this patient had meningitis or encephalitis because a lumbar puncture was not performed during the short-term phase of his illness.

The development of neurological abnormalities within weeks after acute WNF is suggestive of a postinfectious process, although we have no evidence that anti-GAD65 antibodies were absent before the viral infection. The development of mild papilledema, increased CSF pressure, and 6 cells in the CSF with elevated antibodies is suggestive of ongoing central nervous system infection or an inflammatory process. The development of acute idiopathic polyneuritis following WNF has been reported, and serves as a model for the development of postinfectious immune-mediated disorders after infection with WNV.

Recent evidence suggests that SPS is caused by an autoimmune process. Genetic and environmental factors are involved in the cause of autoimmune diseases, and viral infections have been implicated as nongenetic triggers of autoimmune reactions to self antigens. Type 1 diabetes mellitus is an immune-mediated disease that results from selective loss of the insulin-producing pancreatic β cell. Numerous epidemiological and clinical studies have linked enteroviral infections, particularly infections with coxsackievirus B4, with a progression to type 1 diabetes mellitus.

Except for the rare case of SPS as a paraneoplastic syndrome, no specific triggers for the onset of clinical symptoms are usually present. Rarely have infectious processes been associated with SPS. Two atypical cases of SPS were reported to occur after Lyme borreliosis. Two cases of fulminating progressive encephalomyelitis with rigidity have been reported, one in a patient coinfected with human immunodeficiency virus type 1 and Epstein-Barr virus and the other in a patient after hepatitis C virus infection.

The natural history of SPS is usually a slowly progressive course without rapid declines or spontaneous remissions. Most patients respond to a combination of therapy with diazepam and baclofen. There have been several reports of improvement with immunomodulatory therapies, such as corticosteroids, plasma exchange, and intravenous immunoglobulins. In this patient, although plasma exchange was followed by decreased serum levels of anti-GAD antibodies, the clinical response was suboptimal. Only after treatments with intravenous immunoglobulins, enriched with anti-WNV antibodies, was a significant clinical improvement noted, lasting a couple of years. There has not been a clinical worsening since then, but serum anti-GAD antibody levels remain elevated.

We suggest that following acute WNV infection, this patient developed a postinfectious immune-mediated process affecting mainly GABAergic neurons in the brain and spinal cord. In this case, the patient had a propensity for autoimmune diseases based on his history of immune-mediated thyroid disease with the presence of serum antithyroglobulin antibodies. The presence of the putative autoimmune homologous epitope between WNV and GAD65 is supportive of this hypothesis.

Human type 1 diabetes mellitus is also associated with anti-GAD65 antibodies and with infection with enteroviruses. A mechanism of molecular mimicry has been suggested because the PEVKEK motif, which was recently recognized as a dominant B-cell epitope for type 1 diabetes mellitus, was also found in coxsackievirus B4 protein 2C.

Further investigation of the cross-reactivity between anti-WNV and anti-GAD65, identification of the oligoclonal bands in the patient’s CSF, and functional analysis of the common epitope are required to establish a causative link.

**Figure 3**. Amino acid similarity of a motif of the NS1 protein of West Nile virus (WNV) with the PEVKEK epitope region of human glutamic acid decarboxylase (GAD) isoforms 65 and 67 using a computer program (BESTFIT program of the GCG Software Package using blosum62). The asterisk indicates a gap.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amino Acid Sequence</th>
<th>% Similarity</th>
<th>% Identity</th>
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<td>40</td>
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<tr>
<td>WNV</td>
<td>RKYYPETGQLAKL</td>
<td>—</td>
<td>—</td>
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<tr>
<td>GAD67</td>
<td>RKYKPEVKAGNMV</td>
<td>73.3</td>
<td>53</td>
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</table>

**Table**

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REFERENCES