Autoantibodies in Sporadic Creutzfeldt-Jakob Disease

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Rapidly progressive neurological and cognitive syndromes are a complex diagnostic problem. The differential diagnosis includes inflammatory encephalopathies due to infective agents and immune-mediated disorders (both with and without remote neoplasia), central nervous system tumors, cerebral vasculitis, and rare neurodegenerative diseases such as the prion disease Creutzfeldt-Jakob disease (CJD). Imaging, neurophysiological, blood, and cerebrospinal fluid investigations usually confirm the clinical diagnosis rapidly, but there remains a small subgroup of patients in whom the diagnosis is unclear. This applies particularly to autoimmune and neurodegenerative conditions. It is of utmost importance to diagnose autoimmune conditions as treatments such as removing the associated tumor, if present, and immunosuppression can halt or often reverse the progression of autoimmune conditions, but there is no curative treatment for neurodegenerative conditions. The presence of autoantibodies can sometimes be misleading. This report illustrates potential difficulties in differentiating autoimmune encephalopathies from sporadic Creutzfeldt-Jakob disease.

Report of a Case

A 68-year-old retired male taxi driver was admitted to the hospital in June 2011 with a 2-year history of progressive insomnia. Three months before admission, he developed personal-
Investigations
Findings on routine hematological and biochemical investigations were normal. A vasculitis screen was negative. Computed tomography of the head (in July and November 2011) showed mild frontal atrophy. Magnetic resonance imaging of the brain could not be done because of the pacemaker. Electroencephalographic findings were normal from June to August 2011; thereafter, electroencephalography showed progressive slowing, ultimately displaying only delta rhythm in January 2012. Electromyographic findings in July 2011 showed myokymia, without neuropathy or denervation. The myokymia was no longer present clinically or on electromyography 3 months later. The following were found on cerebrospinal fluid examination: acellular; protein level of 0.61 g/L; normal glucose level; oligoclonal bands negative; S-100b protein level of 4.5 ng/mL (reference range, <0.4 ng/mL); and 14-3-3 protein positive. Prion protein gene (PRNP) sequencing revealed no mutations, with valine homozygosity at codon 129.

Antibody Testing
At 2 months, serum antibodies to the voltage-gated potassium channel complex (VGKC complex) were positive (210pM; reference range <100pM) and glycine receptor antibodies (GlyR Ab) were also detectable; N-methyl-D-aspartate, glutamic acid decarboxylase, and paraneoplastic antibodies were all negative. The VGKC-complex antibodies were absent by the following month, but the GlyR antibodies had increased moderately (Figure). Cerebrospinal fluid was negative for both antibodies.

Right Frontal Brain Biopsy
Biopsy of the right frontal brain was performed on January 20, 2012. There was severe transcortical spongiform change with severe neuronal depletion and extensive gliosis. Immunocytochemistry using ICSM35 antibody demonstrated dense prion staining predominantly of synaptic type. There were foci of AT8 immunoreactivity (β-amyloid) without neurofibrillary tangles.

Figure. Antibody Findings and Histopathological Analysis

A. Serum voltage-gated potassium channel complex antibodies (VGKC Ab) and glycine receptor antibodies (GlyR Ab) during the course of the illness. The cutoff values for healthy subjects are indicated by a dashed line. *Negative cerebrospinal fluid titers of each antibody. Treatment modality durations and a summary of symptom development are shown. IVIg indicates intravenous immunoglobulin.

B. Typical spongiform change in frontal biopsy (hematoxylin-eosin, scale bar = 100 μm).

C. Abnormal prion protein immunoreactivity in the biopsy specimen of the frontal brain showing synaptic distribution with ICSM35 monoclonal antibody (scale bar = 100 μm).
and a few short tau-positive threads. No lymphocytic infiltrates were found, and the appearances were of definite sCJD.

**Treatment**

Sepsis was successfully treated with fluid resuscitation and antibiotics. Symptomatic treatment with clonazepam, co-careldopa, and baclofen did not help the rigidity; botulinum toxin injections reduced lower limb spasticity.

In the presence of positive VGKC-complex and GlyR antibodies, immunosuppressant treatment with steroids, intravenous immunoglobulin, plasma exchange, and cyclophosphamide was commenced (Figure). There was no sustained improvement, although eye contact improved for 10 days following plasma exchange.

The major clinical features together with antibody levels are illustrated in the Figure.

**Discussion**

The presenting picture of rapid-onset personality change, insomnia, associated myokymia and myotonia, ataxia, apraxia, and initially relatively preserved cognitive function was more in keeping with Morvan syndrome than sCJD. This presumptive diagnosis was supported by the presence of VGKC-complex antibodies in the serum at levels that, although relatively low (210 pM), are consistent with this diagnosis. Positive GlyR antibodies further suggested an immune basis for the patient's symptoms. There are previous reports of limbic encephalitis with VGKC-complex antibodies misdiagnosed as sCJD, so it was important to seriously consider an immune basis for his condition. Many of the recently described immune-mediated encephalopathies are potentially treatable, particularly those with neuronal surface-directed antibodies; thus, rapid diagnosis and treatment are essential if viable neurons are to be salvaged. However, intensive treatments to remove the antibodies were performed without clear benefit. After considerable delay due to episodes of sepsis, a cerebral biopsy was performed. It showed conclusive evidence of sCJD, with the PRNP sequencing showing no mutations.

What could account for the finding of the antibodies in a case of sCJD? Apart from the remote possibility of extremely rare conditions occurring simultaneously, there was no evidence of an inflammatory encephalopathy at biopsy, although it is possible that the inflammatory process was focused on other brain regions or had resolved by this time. Are the antibodies false-positive? Antibodies to the VGKC complex in the range of 1000 pM to 4000 pM are detected in up to 5% of community controls older than 65 years. Antibodies to LGI1 and CASPR2, the principal known components of the VGKC complex, were negative in our patient. This does not exclude the presence of cell surface–binding antibodies to as yet undefined components of the VGKC complex (A.V., unpublished data, 2012). Insomnia, burning pain, myokymia, and myotonia are features of Morvan syndrome and, apart from insomnia, are infrequent in sCJD. Equally, although also at low to moderate levels in this patient, GlyR antibodies (<2% in controls) are associated with myoclonus and rigidity, which were striking features in our patient. It seems likely that the rapid destruction of cerebral tissue by prion disease released neuronal antigens, leading to development of the antibodies as secondary events. The temporal relationship of the antibodies to the clinical features suggests that they may have contributed to the pathophysiology.

Several other factors complicated the diagnosis in this case. Magnetic resonance imaging is valuable in sCJD, where signal return from the basal ganglia and cortical ribbon on diffusion-weighted imaging sequences has a high sensitivity and specificity, but our patient's pacemaker precluded this investigation and the results can occasionally be found in other conditions. The positive cerebrospinal fluid markers present in our case occur in SCD but are also not disease specific. The patient did not have the typical periodic complexes on electroencephalography described in about two-thirds of patients with sCJD.

This case illustrates the difficulty in determining the etiology of rapidly progressive encephalopathies and that laboratory tests can be misleading and do not exclude a neurodegenerative disease. There are also 2 recent reports of N-methyl-D-aspartate receptor antibodies in sCJD. A prospective study is required to ascertain the frequency of neuronal antibodies in sCJD and other rapidly progressive neurodegenerative diseases. When titers of neuronal antibodies are increased in a patient with a progressive encephalopathy, it is reasonable to treat with immunosuppression because of the potential benefit. At the same time, an open mind to the differential diagnosis should be maintained throughout the course of rapidly progressive encephalopathies, as the classic cerebrospinal fluid markers, imaging, and antibody tests are not pathognomonic.

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**REFERENCES**


**ARTICLE INFORMATION**

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