Nonvasculitic Autoimmune Inflammatory Meningoencephalitis Imitating Creutzfeldt-Jakob Disease

C. Hoffman Snyder, MSN, NP-BC; K. J. Mishark, MD; J. N. Caviness, MD; J. F. Drązkowski, MD; R. J. Caselli, MD

Background: Nonvasculitic autoimmune inflammatory meningoencephalitis and Creutzfeldt-Jakob disease can present as rapidly progressive encephalopathies with similar clinical features. Slowing of background rhythm is an electroencephalographic characteristic shown by both, but persistent periodic sharp waves are more specific for Creutzfeldt-Jakob disease and have not been reported in nonvasculitic autoimmune inflammatory meningoencephalitis or related autoimmune meningoencephalitides.

Objective: To describe a patient with clinical (rapidly progressive myoclonus, dementia, and Parkinsonism) and electroencephalographic findings (persistent periodic sharp waves) that diagnostically suggest Creutzfeldt-Jakob disease.

Design and Setting: A case report at the Mayo Clinic Arizona, Scottsdale.

Results: The patient made a dramatic recovery with resolution of the periodic sharp wave complexes after treatment with high-dose corticosteroids. Our case is the first reported case of a patient with probable nonvasculitic autoimmune inflammatory meningoencephalitis and electroencephalographic periodic complexes suggestive of Creutzfeldt-Jakob disease.

Conclusion: Rapidly progressive encephalopathy with periodic sharp wave complexes can be associated with a reversible autoimmune syndrome.

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CREUTZFELDT-JAKOB DISEASE (CJD) is a rare, invariably fatal prion disease characteristically presenting with rapidly progressive dementia and myoclonus with more variable extrapyramidal and cerebellar symptoms (Figure 1).1 Sporadic, infectious, and hereditary forms related to mutations of the prion protein (PrP) gene have been described.1 Reliable biomarkers for sporadic CJD are lacking, but several diagnostic features may be helpful in diagnosing CJD including generalized, persistent, periodic sharp wave (PSW) complexes that are an electroencephalographic (EEG) abnormality characteristic of CJD (Figure 2).2-4

Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) is a rare autoimmune cause of encephalopathy that can present in acute or chronic fashion and that is often highly responsive to corticosteroid therapy. Nonvasculitic autoimmune inflammatory meningoencephalitis has multiple, nonspecific autoimmune serologic associations, and Hashimoto encephalopathy may be an acute form of NAIM associated with thyroid autoimmunity.2 Although the relationship of these disorders to one another remains unproven, they all share the clinical features of a steroid-responsive encephalopathy associated with autoimmunity.2 Magnetic resonance images and angiographic images of the brain may show meningeal enhancement but are usually normal. Spinal fluid studies may reveal elevated immunological indices (IgG index and synthesis rate, oligoclonal bands) and occasionally a mild lymphocytic pleocytosis.5,6 Typical EEG findings in patients with NAIM show moderate to severe nonspecific dysrhythmic slowing.5,6 Most patients with NAIM are highly responsive to corticosteroid therapy with significant clinical improvement evident within days of beginning treatment. We describe a patient with NAIM whose clinical features strongly suggested Creutzfeldt-Jakob, including PSWs on EEG.

REPORT OF A CASE

A 67-year-old woman sought care for a 4-month history of rapidly progressive...
confusion with disorientation and fluctuating levels of alertness, aphasic speech, multifocal myoclonic jerks, moderate cogwheel rigidity, a shuffling gait, and mild rest tremor.

Brain magnetic resonance images with gadolinium and cerebral angiographic images were unremarkable. Electroencephalographic images showed slow-wave activity and paroxysmal PSW complexes suspicious for Creutzfeldt-Jakob disease. Comprehensive metabolic study results were normal. Endocrine study results including thyroperoxidase antibody were negative. Creatine kinase levels were normal. Serum protein electrophoresis showed hypoalbuminemia. Paraneoplastic antibody evaluation detected antitriglutamic acid decarboxylase antibodies (anti-GAD) and acetylcholine receptor (AChR) antibodies (there was no clinical sign of stiff-person syndrome), and the remaining panel was negative. Immunologic study findings including extractable nuclear antigen, antineuronal nuclear antibody, antineutrophil cytoplasmic antibody, and C-reactive protein levels were normal.

Cerebrospinal fluid (CSF) levels were abnormal; total protein level was 92 mg/dL; glucose level, 2.61 mmol/L (47 mg/dL); white blood cell count, 30/μL; IgG index of 0.95; and IgG synthesis rate of 26.19 mg per 24 hours; oligoclonal bands, 8; and IgG (CSF) level of 9.94 mg/dL. Microbiological cytologic studies were negative and 14-3-3 protein antigen levels were normal. Additional CSF analysis for the following revealed negative results: cytomegalovirus using rapid polymerase chain reaction (PCR), West Nile virus antibodies, Whipple disease using PCR, varicella-zoster virus using PCR, Epstein-Barr virus using PCR, herpes simplex using PCR, and Lyme disease using PCR. Fungal serologic results were negative for Coccidioides immitis, Cryptococcus neoformans, histoplasma antibodies, and blastocytes antibodies.

During her medical evaluation, the patient’s condition deteriorated rapidly to the point where she became wheelchair bound and had a fluctuating level of consciousness, which necessitated hospitalization. Empirical therapy with intravenous methylprednisolone (1000 mg/d) with rapid improvement in cognition and motor function; periodic sharp waves tend to disappear with sleep. A diagnosis of Creutzfeldt-Jakob disease was made.

Figure 1. Criteria for the diagnosis of sporadic Creutzfeldt-Jakob disease. CSF indicates cerebrospinal fluid; EEG, electroencephalogram.

Figure 2. Electroencephalographic image criteria in Creutzfeldt-Jakob disease. PSW indicates periodic sharp wave.

Figure 3. Electroencephalographic images taken on 3 separate occasions. A, Periodic sharp waves were visible on the electroencephalographic image when the patient was severely encephalopathic. B, Image taken 48 hours after administration of intravenous methylprednisolone (1000 mg/d) with rapid improvement in cognition and motor function; periodic sharp waves were no longer observed. C, Image taken 1 week later at time of discharge showing further improvement with faster frequencies present and continued clinical responsiveness.

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<tr>
<th>Definite:</th>
<th>Diagnosed by standard neuropathologic examination.3</th>
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<td>Probable:</td>
<td>Progressive dementia and at least 2 of the following 4 clinical features:</td>
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<td>Myoclonus</td>
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<td>Visual or cerebellar disturbance</td>
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<td>Pyramidal/extrapyramidal dysfunction</td>
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<td>Akinetic mutism and a typical EEG during an illness of any duration and/or a positive 14-3-3 CSF assay and a clinical duration to death &lt;2 years; routine investigations should not suggest an alternative diagnosis.4</td>
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<tr>
<td>Possible:</td>
<td>Progressive dementia and at least 2 of the following 4 clinical features:</td>
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<td>Myoclonus</td>
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<td>Pyramidal/extrapyramidal dysfunction</td>
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<td></td>
<td>Akinetic mutism and a typical EEG or no EEG available; duration &lt;2 years:</td>
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Biphasic or triphasic morphology of periodic complexes.

0.5- to 2-s frequency (interval 500-2000 ms) otherwise severely slow background.

100 to 300-ms duration.

Rarely lateralizing features or PSW complexes lateralized to 1 hemisphere.

PSW discharges are generalized with maximum over anterior head region (Hendenhain variant with posterior maximal).

PSW tends to disappear with sleep.2-4,7

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mg/d) for 5 days was instituted before the 14-3-3 CSF results were available. Within 48 hours of therapy, she showed remarkable clinical improvement with a normal level of consciousness. She regained her ability to walk and converse. Repeat EEGs at that time showed equally dramatic improvement with resolution of the periodic sharp wave complexes (Figure 3B and C). She was discharged from the hospital within a week after having received oral prednisone and within 1 month after returning to her normal baseline. Currently, she is receiving a slow steroid taper with close clinical monitoring.

Our patient met the criteria for probable CJD (Figure 1); she presented with progressive dementia, 3 clinical features (myoclonus, cerebellar disturbance, and extrapyramidal signs), no alternative diagnosis on routine investigation, and persistent PSW complexes.1-4,7 Although spinal fluid analysis in our patient disclosed an inflammatory process, many patients with periodic complexes on their EEG would not undergo a CSF examination and therefore may elude diagnosis.

Periodic sharp wave complexes are found in approximately 70% of the sporadic cases of CJD but in less than 30% of the familial cases.5,7 With disease progression, periodic discharges may disappear so their absence does not exclude the diagnosis of CJD but their presence adds to the probability. Steinhoff et al7 reported in their study of 150 autopsy-proven cases of CJD that when their criteria for PSWs were used in analysis of the electroencephalogram, it resulted in the sensitivity of 64%, specificity of 91%, and positive and negative predictive values of 95% and 49%, respectively, for the diagnosis of CJD (Figure 2).

Most patients with NAIM show moderate to severe, nonspecific slowing of cerebral rhythms on EEG that improve in parallel with clinical improvement after treatment with corticosteroids. A review by Schauble et al8 of 51 EEGs in 17 patients with steroid-responsive encephalopathy associated with autoimmune thyroiditis showed mild to severe slowing on the EEG, which corresponded to the clinical severity of the underlying encephalopathy. Several cases of Hashimoto encephalopathy (as well as other causes of subacute NAIM) have been reported in the literature that describe clinical features that mimic CJD; however, none of these cases had PSW findings on the EEGs.5,6,8,10

In patients with rapidly progressive encephalopathy with PSWs that are common in CJD, CSF analysis and autoimmune serologic findings may be helpful in identifying an alternative diagnosis to prion disease. The alternative diagnosis in this case was NAIM and steroid responsiveness resulted in complete remission of her symptoms.

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REFERENCES