Peripheral nervous system hyperexcitability in VV2 sporadic Creutzfeldt-Jakob disease

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Summary

Creutzfeldt-Jakob disease (CJD) is a fatal, rapidly progressive neurodegenerative disease. Most cases are sporadic (sCJD). The pathogenesis of sCJD is associated with a conformational change in abnormal prion protein causing widespread neuronal degeneration, and clinical manifestations can be quite protean. Peripheral nerve hyperexcitability syndrome (PNHS) is rarely associated with CJD and is more commonly associated with autoimmune/paraneoplastic syndromes associated with antibodies against the voltage-gated potassium channel complex (VGKC-Abs). Reports of PNHS in CJD are rare. We report 2 patients with progressive cognitive decline in the setting of peripheral nerve hyperexcitability on electrodiagnostic testing. In both patients VGKC-Abs were negative, and autopsy confirmed that both had sCJD, VV2 subtype. While uncommon, it is important to consider sCJD in patients presenting with PNHS and rapidly progressive dementia.

Creutzfeldt-Jakob disease (CJD) is a fatal and rapidly progressive neurodegenerative disease. The pathogenesis of sporadic CJD (sCJD) is associated with a conformational change in abnormal prion protein (PrP^{Sc}) causing widespread neuronal degeneration. Most CJD cases are sporadic, with 6 recognized molecular subtypes based on the PRNP codon 129 polymorphism (129M or 129V) and the PrP^{Sc} protein type

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(1 or 2)¹ (MM1, MM2, MV1, MV2, VV1, and VV2). It is well-established that the molecular subtype, in addition to age at onset and disease duration, is an important determinant of the clinical phenotype (including results of standard diagnostic testing).^{1–4} Accordingly, the clinical manifestations of sCJD can be quite protean, and a great deal of the recommended diagnostic workup for these patients focuses on screening for treatable “mimics” of the disease, particularly autoimmune encephalopathies.^{4–6}

Amyotrophy is a well-established peripheral nervous system manifestation of sCJD,⁷ but peripheral nerve hyperexcitability (PNH) is less common. To date there have been 3 patients described, albeit in limited detail.^{8–10} PNH is defined clinically by the presence of spontaneous or continuous muscle activity and manifests as muscle twitching (fasciculations/myokymia), cramps, pseudomyotonia, or any combination of these.¹¹ EMG evidence of PNH includes fasciculations, doublets/multiplets, myokymia, neuromyotonia, cramp discharges, and continuous motor unit activity. The presence of afterdischarges with repetitive stimulation of the tibial or median nerves has also been used to identify PNH.¹²

We report 2 additional cases of sCJD manifesting with PNH. Both had similar disease courses and absence of typical brain MRI features on initial presentation, and both were confirmed as the sCJD VV2 subtype on autopsy.

Case 1

A 68-year-old man was admitted with a 4-month history of unsteady gait and falls. His family reported inattention and abnormal speech. He was hypersomnolent and frequently regarded strangers as family. He had no pertinent family history and a 35 pack-year smoking history.

The patient was inattentive on mental status examination. Additional physical examination findings included axial and appendicular ataxia, occasional myoclonic jerks, and widespread spontaneous continuous muscle activity without muscle wasting or atrophy.

Brain MRI demonstrated mild global atrophy and changes consistent with chronic small vessel disease but was otherwise unremarkable (figure 1, A and B). An EEG showed generalized slowing. Results of CSF analysis are available in the table. Whole body PET/CT (screening for occult malignancy) revealed no abnormalities. An EMG-nerve conduction study (NCS) showed a mild length-dependent sensorimotor axonal polyneuropathy with fasciculations and myokymia in the gastrocnemius (figure 1C).

Given the strong suspicion for an immune-mediated encephalopathy with PNH (i.e., Morvan syndrome), the patient was empirically treated with 2 g/kg of IV immunoglobulin (IVIg, 0.5 g/kg/day for 4 consecutive days) while awaiting the results of voltage-gated potassium channel antibody (VGKC-Ab) testing. An extensive battery of blood tests, including a complete paraneoplastic autoantibody panel (Mayo Clinic), showed no significant abnormalities (table). There was no improvement after IVIg. Over the next 3 weeks the patient's cognitive status continued to decline rapidly, resulting in readmission. CSF biomarkers from the initial admission resulted in a “positive” 14-3-3 and a total tau value of 7,560 pg/mL (decision point 1,200 pg/mL). Repeat brain MRI showed new diffusion restriction in the right caudate nucleus and bilateral frontal cortex. The patient died 133 days after symptom onset, and brain-only autopsy demonstrated findings consistent with sCJD VV2.

Figure 1 EMG manifestations of peripheral nerve hyperexcitability in the absence of brain MRI findings to suggest sporadic Creutzfeldt-Jakob disease

Fluid-attenuated inversion recovery (FLAIR; A, D) and diffusion-weighted imaging (DWI; B, E) sequences from patients 1 (A, B) and 2 (D, E). Images selected include structures demonstrating clear diffusion restriction on follow-up imaging (right caudate and bilateral frontal cortex in patient 1 and bilateral basal ganglia and thalami in patient 2). While images from patient 2 show increased FLAIR signal in the bilateral basal ganglia, subtle diffusion restriction was not appreciated until after the follow-up scan was obtained. Patient 1 had myokymic discharges in the gastrocnemius (C) whereas patient 2 had continuous motor unit activity on EMG of the vastus medialis (F). Both EMG screen shots have a sweep speed of 1 second and a sensitivity of 100 μ V.

Case 2

A 62-year-old man with diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea was admitted with 3 months of rapidly progressive cognitive decline. His wife described increasing postural instability and frequent falls. Within a few months he was dependent on his wife for many activities of daily living. He experienced recurrent hallucinations of burning houses and delusions in which he owned a firearm. At the time of admission he was unable to walk without assistance and started to choke while eating.

On admission he was oriented to name only and could follow one-step midline commands inconsistently. His responses were infrequent and monosyllabic. His attention was severely impaired. Generalized, continuous, and spontaneous muscle activity was present but there was no muscle wasting or atrophy. Examination findings also included hypomimia, slow saccades, areflexia, and severe truncal ataxia.

Initial brain MRI demonstrated increased T2/fluid-attenuated inversion recovery signal in the bilateral basal ganglia without clear diffusion restriction and nonspecific T2 white matter abnormalities most consistent with microvascular disease (figure 1, D and E). EEG showed generalized slowing. CSF analysis and blood tests were unremarkable (table). A full-body CT showed no evidence of an occult malignancy.

EMG-NCS showed evidence of PNH with continuous afterdischarges following 10 Hz repetitive stimulation of the tibial nerve and EMG evidence of fasciculations, doublets, and triplets in most muscles examined, as well as continuous motor unit activity in the vastus medialis (figure 1F). There was no electrodiagnostic evidence of a large fiber polyneuropathy.

Plasmapheresis was initiated given concern for Morvan syndrome/VGKC-Ab-associated encephalopathy. However, he completed only 2 cycles due to persistently low fibrinogen. He was then treated with 2 g/kg of IVIg. A complete paraneoplastic panel, including anti-VGKC-Ab, run at the Mayo Clinic eventually returned negative. Anti-Lgi-1, Ma, and Ta

Table CSF and serum studies

	Patient 1	Patient 2
CSF analysis		
Nucleated cells	9 cells/ μ L (lymphocytic predominance)	0 cells/ μ L
Red blood cells	14 cells/ μ L	0 cells/ μ L
Glucose	70 mg/dL	63 mg/dL
Protein	35 mg/dL	43 mg/dL
Oligoclonal bands	0	0
Bacterial and fungal cultures	Negative	Negative
Viral PCRs	Negative	Negative
Cytology	Negative	Negative
Flow cytometry	Negative	Negative
14-3-3	Positive	Positive
Tau	7,560 pg/mL	2,818 pg/mL
Serum analysis		
TSH (0.35–5.50)	1.34 mIU/mL	2.14 mIU/mL
Free T4 (0.9–1.8)	1.2 ng/dL	1.2 ng/dL
Thyroglobulin	Not collected	6
TPO (0–60)	147 U/mL	<60 U/mL
RPR	Nonreactive	Nonreactive
B₁₂	513 pg/mL	420 pg/mL
CRP	7.7 mg/L	5.8 mg/L
ESR (0–15)	39 mm/h	12 mm/h
RT-QuIC	Not performed	Positive
ANA, ENA, ANCA	Negative	Negative
HIV	Negative	Negative
Paraneoplastic panel^a	Negative	Negative
Anti-Lgi-1	Not performed	Negative
Anti-Ma and Ta	Not performed	Negative

Abbreviations: ANA = antinuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; CRP = C-reactive protein; ENA = extractable nuclear antigen; ESR = erythrocyte sedimentation rate; RPR = rapid plasma reagin; RT-QuIC = real-time quaking-induced conversion; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

^aComplete paraneoplastic panel includes: voltage-gated potassium channel and antineuronal nuclear antibody type 1–3, Anti-glial nuclear antibody type 1, Purkinje cell cytoplasmic antibody type 1 and 2, amphiphysin antibody, CRMP-5-IgG, striational antibody, P/Q-type calcium channel antibody, N-type calcium channel antibody, acetylcholine receptor (muscle) binding antibody, and acetylcholine receptor ganglionic neuronal antibody.

were also negative. CSF 14-3-3 was “positive” and CSF tau was elevated at 2,818 pg/mL (decision point 1,200 pg/mL). The real-time quaking-induced conversion assay was positive. Repeat brain MRI after IVIg demonstrated subtle diffusion restriction in the bilateral basal ganglia and thalami. The patient died 113 days after symptom onset. Brain autopsy showed sCJD, VV2 subtype, and immunohistochemical analysis of a cervical spinal cord sample

This report of PNH in autopsy-confirmed sCJD VV2 patients is notable because this sCJD subtype is less common in the North American population.

showed evidence of PrP deposition in the central gray matter, dorsal root entry zones, and medial posterior columns (figure 2).

DISCUSSION

Commonly reported peripheral nervous system manifestations of sCJD include muscular atrophy, amyotrophy, autonomic dysfunction, polyneuropathy, and absent deep tendon reflexes.^{13–17} PNH, which is more commonly associated with autoimmune diseases like Morvan or Isaac syndrome, is not as well-recognized, with only 3 prior cases reported.^{8–10}

The patient described in one report⁸ had limb ataxia, myoclonus, myokymia, and reduced reflexes followed by cognitive decline, dystonia, and choreoathetosis. However, this patient was found to have serum VGKC-Abs in addition to pathology-confirmed CJD. The codon 129 genotype of this patient and the predominant PrP^{SC} type (i.e., 1 or 2) were not reported. The authors postulated that the atypical finding of myokymia in this patient might have been related to a concurrent autoimmune process given the serum VGKC-Abs. Ultimately they concluded that the lack of clear benefit with treatment made it more likely to be a rare manifestation of CJD. While neither of our patients had serum VGKC-Abs, autoantibodies are fairly common in patients with sCJD.⁸ In fact, 30% of patients diagnosed with definite CJD at our institution in the last 4 years have had low titers of serum autoantibodies (anti-thyroperoxidase or at least one antibody on the Mayo Clinic paraneoplastic panel). We also opted to treat our patients while antibody testing was pending given the differential diagnosis of an immune-mediated channelopathy in both cases.

A second report⁹ described a patient who did not undergo molecular subtyping but presented similarly to the other cases with subacute cerebellar ataxia, dementia, and undulating myokymia. Workup was notable for “abnormal hyperintensity” of the basal ganglia on MRI and negative serum VGKC-Ab. Prion disease was confirmed on autopsy 6 months after the onset of symptoms.

The third report¹⁰ described an MM1 sCJD patient with dementia, parkinsonism, pyramidal signs, myokymia, and lower extremity hyporeflexia. Granular PrP deposits were observed in the dorsal horns of the spinal cord, but no PrP deposits were present in peripheral nerve tissue, a puzzling finding given that the abnormal spontaneous activity in PNH is felt to arise in the axon and distal nerve terminal.¹⁸ However, PrP deposition in peripheral nerve was observed in other patients described in this study.¹⁰ In keeping with these findings, our second patient had evidence of prion disease in the dorsal root entry zone, posterior column, and central gray matter of his cervical spinal cord. Unfortunately, peripheral nerve tissue was not available at autopsy in our patient.

We report 2 cases of autopsy-confirmed sCJD VV2 presenting with PNH. The clinical phenotype of both of these patients fits well with that typically associated with the sCJD VV2 subtype, which is characterized primarily by ataxia and cognitive impairment at presentation.¹⁹ This report of PNH in autopsy-confirmed sCJD VV2 patients is notable because this sCJD subtype is less common in the North American population. While intriguing and certainly deserving of future attention, it would be premature to suggest that PNH is more common in the VV2 subtype of sCJD.

Figure 2 Global involvement by prion disease includes brain and spinal cord

A representative hematoxylin and eosin (H&E) stained section of the thalamus demonstrates prion-related spongiform changes including neuronal loss, microvacuolation, and reactive astrocytosis (A: 200 $\times$, B: 1,000 $\times$ original magnification). By immunohistochemistry (IHC) for the prion antibody 3F4, widespread granular deposits are present throughout the thalamus (C: 200 $\times$, D: 1,000 $\times$ original magnification). The upper cervical spinal cord in this case shows some spongiform changes (E, H&E whole mount section) with granular prion deposition in the dorsal nerve root entry zones, medial dorsal columns, and central gray matter (F, 3F4 IHC whole mount section). The anterior motor neurons are somewhat atrophic with mild surrounding spongiform changes (G, H&E 1,000 $\times$ original magnification), and there are prion granular deposits in the anterior motor horn (H, 1,000 $\times$ original magnification).

VGKC-autoimmune encephalitis is an important differential diagnosis to consider in patients presenting with a rapidly progressive dementia. In addition to PNH, patients can develop amnesia, seizures, insomnia, and psychiatric disturbances, as well as autonomic dysfunction including constipation or diarrhea, urinary incontinence, and cardiac arrhythmia.²⁰ While the presence of VGKC-Abs warrants strong consideration of an autoimmune encephalopathy, these antibodies are by no means 100% specific to this diagnostic entity.

Our experience suggests that sCJD should be considered in patients presenting with PNH in the setting of a rapidly progressive encephalopathy, particularly in patients who are seronegative for VGKC-Abs and/or fail to respond to immunomodulatory therapy. We agree with the approach of empirically treating these patients with immunomodulatory therapy, given the potential for irreversible damage associated with delaying treatment of a potentially reversible disorder and the relatively low risk of potential harm in treating patients who are later diagnosed with CJD.

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AUTHOR CONTRIBUTIONS

Charlene Ong: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Muhammad Al-Lozi: study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Patrick Cimino: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Robert Bucelli: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data.

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