Gerstmann-Straüssler-Scheinker disease

Novel *PRNP* mutation and VGKC-complex antibodies

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ABSTRACT

Objective: To describe a unique case of Gerstmann-Straüssler-Scheinker (GSS) disease caused by a novel prion protein (*PRNP*) gene mutation and associated with strongly positive voltage-gated potassium channel (VGKC)-complex antibodies (Abs).

Methods: Clinical data were gathered from retrospective review of the case notes. Postmortem neuropathologic examination was performed, and DNA was extracted from frozen brain tissue for full sequence analysis of the *PRNP* gene.

Results: The patient was diagnosed in life with VGKC-complex Ab-associated encephalitis based on strongly positive VGKC-complex Ab titers but no detectable LGI1 or CASPR2 Abs. He died despite 1 year of aggressive immunosuppressive treatment. The neuropathologic diagnosis was GSS disease, and a novel mutation, P84S, in the *PRNP* gene was found.

Conclusion: VGKC-complex Abs are described in an increasingly broad range of clinical syndromes, including progressive encephalopathies, and may be amenable to treatment with immunosuppression. However, the failure to respond to aggressive immunotherapy warns against VGKC-complex Abs being pathogenic, and their presence does not preclude the possibility of prion disease. *Neurology*® 2014;82:2107-2111

GLOSSARY

Ab = antibody; **CASPR2** = contactin associated protein-like 2; **CJD** = Creutzfeldt-Jakob disease; **GSS** = Gerstmann-Straüssler-Scheinker; **IgG** = immunoglobulin G; **LGI1** = leucine-rich, glioma inactivated protein 1; **OPRI** = octapeptide repeat insertion; **PRNP** = prion protein; **VGKC** = voltage-gated potassium channel.

Voltage-gated potassium channel (VGKC)-complex antibodies (Abs) are associated with classic limbic encephalitis,^{1,2} but there are reports of VGKC-complex Ab-associated syndromes presenting with dementia^{3,4} and a series of patients described who were clinically thought to have Creutzfeldt-Jakob disease (CJD) in whom VGKC-complex Abs were identified and who responded to immunomodulatory therapy.⁵ The spectrum of clinical disorders associated with strongly positive VGKC-complex Abs appears to be expanding. We describe a case of progressive dementia in a patient with high titers of VGKC-complex Abs in whom the postmortem diagnosis was Gerstmann-Straüssler-Scheinker (GSS) disease with a novel mutation in the prion protein (*PRNP*) gene.

METHODS Case history. A 61-year-old Caucasian man with hemochromatosis presented with a 1-year history of memory disturbance, fatigue, apathy, and agitation. The only family history included maternal Parkinson disease. He received no regular medication. Neurologic examination revealed only scant fasciculations in the legs. Routine blood tests, MRI of the brain, and nerve conduction studies were normal. EMG confirmed fasciculations without active denervation changes. Neuropsychological assessment revealed deficits in memory, language, and visual perception. Early-onset Alzheimer disease was diagnosed.

The patient deteriorated rapidly with development of aggression and paranoia. VGKC-complex Abs were strongly positive (4,159 pM, normal range <100 pM) and although the serum immunoglobulin G (IgG) was negative for binding to the VGKC-complex proteins leucine-rich, glioma inactivated protein 1 (LGI1), contactin associated protein-like 2 (CASPR2), and contactin2, the IgG Abs did bind to the surface of hippocampal neurons in culture (see reference 2 for methods). He was admitted to the neurologic unit and on examination had mild limb ataxia. Serum sodium was normal. Paraneoplastic neuronal Abs (Hu, Ri, Yo) were negative, and CT

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scanning of the body revealed no malignancy. An EEG showed nonspecific encephalopathic change. Repeat MRI was normal with no medial temporal lobe change.

Immune-mediated encephalitis was the presumed diagnosis. Prednisolone 60 mg daily was commenced. He received IV immunoglobulin at a dose of 2.0 g/kg. Attempted plasma exchange was not tolerated. He failed to respond despite 2 further courses of IV immunoglobulin at months 2 and 3 of admission. Mycophenolate mofetil was started after 4 months, but 5 months into his admission, he had minimal spontaneous activity, flat affect, and poor comprehension. He was immobile and experienced focal seizures, although not faciobrachial dystonic seizures,⁶ which responded to anticonvulsant therapy. He had limb and trunk dystonia (antipsychotic agents had been used for behavioral management). Repeat paraneoplastic Abs and CT of the body were negative. Rituximab (1,000 mg) was administered in the fifth month of his admission, but there was no clinical improvement and persistently elevated VGKC-complex Abs (>2,000 pM). The patient continued to deteriorate and died 14 months after initial presentation.

RESULTS Postmortem investigations. General postmortem examination revealed no evidence of systemic malignancy. The immediate cause of death was necrotizing bronchopneumonia. Macroscopic examination of the brain revealed no evidence of cerebral or cerebellar atrophy, and no focal abnormalities were identified. Histologic examination showed numerous multicentric amyloid plaques in the cerebral cortex, basal ganglia, thalamus, and cerebellum (figure 1A). Occasional plaques were also identified in the subcortical white matter of the cerebral hemispheres and cerebellum. Spongiform change was absent in the cerebral cortex and subcortical gray matter, and only patchy spongiform change was identified in the cerebellar molecular layer. Immunohistochemistry for prion protein (see Head et al.⁷ for methodology) showed intense labeling of the amyloid plaques, and revealed occasional smaller deposits that were not

apparent on routinely stained sections (figure 1B). Occasional small prion protein deposits (but no plaques) were present in the brainstem and in the substantia gelatinosa of the spinal cord, but not in spinal nerve roots and dorsal root ganglia. No prion protein deposition was observed in the heart, kidney, liver, lungs, pancreas, pituitary gland, prostate, and thyroid gland. Immunohistochemistry for the β -amyloid protein and α -synuclein was negative, while tau immunohistochemistry labeled only a few fine neuritic processes around the plaques in the cerebral cortex. No neurofibrillary tangles were identified, and there was no evidence of inflammation, immunoglobulin, or complement deposition in the brain.⁸

Samples of fresh-frozen gray matter-enriched frontal and temporal cortex were homogenized, proteinase K digested, and analyzed by Western blotting, using the anti-PrP monoclonal Ab 3F4 as described previously.⁷ The 2 brain regions gave qualitatively and quantitatively similar results. Those from frontal cortex are shown (figure 2). PrP was readily detectable before proteinase K digestion, including bands in the 20- to 40-kDa molecular mass range and a fainter low-molecular-mass band (figure 2A, lane 2). After proteinase K digestion, PrP^{res} was seen in the form of 2 very faint low-molecular-mass bands (figure 2A, lane 4), better seen after prolonged exposure of the Western blot to x-ray film (figure 2B, lane 4). The low-molecular-mass PrP^{res} bands were clearly visible after sample concentration (figure 2A, lane 8). No PrP^{res} with the pattern seen in cases of sporadic or variant CJD was detected (compare lane 8 with lanes 3, 5, 7, 9, and 10).

DNA was extracted from the frozen brain tissue, and full sequence analysis of the *PRNP* gene was performed as previously described.⁷ The patient was

Figure 1 Postmortem histopathology

(A) Multicentric amyloid plaques (center) were present in the cerebral cortex in the absence of spongiform change. Hematoxylin & eosin stain, $\times 400$. (B) Immunohistochemistry for prion protein shows extensive deposition in the cerebellum in the form of multicentric plaques, smaller plaque-like deposits, and diffuse deposits (brown). Occasional plaques are also present in the subcortical white matter (upper left). KG9 anti-prion protein antibody with hematoxylin counterstain, $\times 50$.

Figure 2 Western blot analysis

Western blot analysis of a 10% weight-to-volume frontal cortex brain homogenate from this case (lanes 2, 4, 6, and 8). Individual lanes were loaded with 5 μ L without prior digestion with proteinase K (lane 2), 5 μ L after digestion with proteinase K (lane 4), 0.5 μ L after digestion with proteinase K (lane 6), and 50 μ L after digestion with proteinase K and collection of PrP^{res} by centrifugation (lane 8). These were compared with reference standards of 10% weight-to-volume frontal cortex brain homogenates from cases of sporadic Creutzfeldt-Jakob disease (CJD) MM1 subtype (lanes 3 and 7), variant CJD (lanes 5 and 9), and sporadic CJD VV2 subtype (lane 10). Molecular mass standards of 40, 30, and 20 kDa can be seen in lane 1. Panel A is a short (30-second) exposure, whereas panel B is a maximal exposure (30 minutes).

heterozygous (MV) at codon 129 in the prion protein gene and had a silent A117A polymorphism that is not pathogenic.⁹ The novel finding was a mutation at codon 84, P84S, a hitherto undescribed mutation in the *PRNP* gene.

DISCUSSION This patient had high-titer VGKC-complex Abs and was treated for presumed Ab-mediated encephalitis. A number of atypical features should have raised doubts about this diagnosis; he had a relatively long prodrome with mild amnesia, word-finding difficulties, visuospatial deficits, and a behavioral syndrome. The patient then progressed relentlessly with cognitive and neurologic decline, with seizures only as a late feature. MRI scanning revealed no medial temporal lobe changes. There was no

treatment response to prolonged immunotherapies. No specific Ab to LGI1, CASPR2, or contactin2 could be detected, although the serum IgG bound to live neurons in culture, suggesting unidentified Ab(s) to cell surface antigen(s). Over the course of his illness, and regarding his rapid decline, there were clinical features consistent with prion disease; however, his MRI did not reveal signal change on diffusion-weighted or fluid-attenuated inversion recovery sequences. CSF analysis was not performed because CSF findings in VGKC-complex Ab syndromes are usually either normal or nonspecific.^{10,11}

Most patients with nonparaneoplastic VGKC-complex Ab-associated encephalitis have a subacute or acute onset of symptoms characterized by disorientation, amnesia, temporal lobe seizures, and agitation; more than half have MRI changes of medial temporal lobe high signal on T2 or fluid-attenuated inversion recovery, an equal number have plasma hyponatremia at onset, and the majority respond to immunosuppression. Approximately 80% of patients are positive for LGI1 Abs and fewer for CASPR2.² Therefore, our patient differed in many respects from the classic description of VGKC-complex Ab-associated encephalitis.

The postmortem diagnosis of GSS disease was surprising. Our patient had no strong family history to indicate a genetic prion disease; the details of his mother's parkinsonism are unknown. GSS is a rare autosomal dominant inherited prion disease that classically presents with a slowly progressive spinocerebellar syndrome, lower limb areflexia, and late cognitive impairment. Classic ataxic onset GSS disease is associated with a P102L mutation in the prion protein gene, but some patients present with cognitive deficits reminiscent of Alzheimer disease and others with a CJD-like illness.¹² Patients with 6 octapeptide repeat insertion (OPRI) mutations are also clinically heterogeneous, but most present with a multifocal cortical dementia, often slowly progressive, with combinations of ataxia, parkinsonism, and pyramidal signs.¹³ Patients with 5 OPRI mutations may present with CJD-like or Alzheimer-like syndromes.⁹ Thus, while our patient did not clinically conform to a typical GSS disease presentation, the combination of cognitive and behavioral prodrome followed by more rapidly progressive dementia and neurologic decline is recognized within genetic prion disease, and the pathologic and biochemical findings in this case are characteristic of GSS disease.

The P84S mutation in the *PRNP* gene has not been reported previously in association with GSS disease, any other disease, or in normal populations, suggesting that it is highly likely to be a novel pathogenic mutation.^{14–16} Furthermore, the functional effect of the P84S mutation is predicted to be

“probably damaging.”¹⁷ In contrast, the A117A polymorphism is “silent” and not considered pathogenic.⁹ The P84S mutation is located inside the N-terminal domain of the human prion protein, which is unstructured, nonessential for prion propagation, but is one of 2 high-affinity binding sites for divalent transition metals.¹⁸ Altered metal-ion occupancy of prion protein has been found in sporadic CJD and may contribute to the diversity of the disease phenotype, but no comparable information is available for GSS disease.¹⁹

There are no reported cases of strongly positive VGKC-complex Abs in patients with pathologically confirmed prion disease. However, 2 cases of autopsy-confirmed sporadic CJD have been reported with NMDA receptor Abs at relatively low titers.²⁰ Another patient with postmortem-confirmed CJD had both VGKC Abs at low titers (<400 pM) and glycine receptor Abs.²¹ In 49 confirmed CJD cases, no LGI1 or CASPR2 Abs were detected in CSF although lack of serum testing limits the comparison with this study.²² High titers of VGKC-complex Abs are regarded as specific for immune-mediated disease with only one of 150 neurologic control patients positive for VGKC-complex Abs.²³ However, a recent study suggests they may be more frequent.²⁴ The VGKC-complex Abs in our patient may have reflected a coincidental autoimmune process, but the lack of a treatment effect despite high-dose multimodal immunotherapy would argue against this. These Abs may be induced by degenerating neurons but further studies are needed to determine the frequency of VGKC-complex Abs in neurodegenerative disease.

Thus, this case sounds a note of caution. Although some VGKC-complex Ab-positive patients without LGI1 or CASPR2 Abs do have the hallmarks of limbic encephalitis,²⁵ a failure to respond to aggressive immunotherapy should question an immune-mediated illness. As more patients are tested for these Abs, there are likely to be further cases of this kind. The presence of a strongly positive VGKC-complex Ab does not preclude the diagnosis of prion disease.

AUTHOR CONTRIBUTIONS

Matthew Jones: study conception and design, drafting/revising the manuscript. Sola Odunsi: drafting/revising the manuscript. Daniel du Plessis: drafting/revising the manuscript, interpretation of neuropathologic data. Angela Vincent: drafting/revising the manuscript, interpretation of neuroimmunology data. Matthew Bishop: drafting/revising the manuscript, interpretation of genetic and neuropathologic data. Mark Head: drafting/revising the manuscript, interpretation of genetic and neuropathologic data. James Ironside: drafting/revising the manuscript, interpretation of genetic and neuropathologic data. David Gow: study conception and design, drafting and revising the manuscript, acquisition of clinical data, study supervision and coordination.

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