CASE REPORT

Presence of voltage-gated potassium channel complex antibody in a case of genetic prion disease

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SUMMARY

Voltage-gated potassium channel (VGKC) complex antibody-mediated encephalitis is a recently recognised entity which has been reported to mimic the clinical presentation of Creutzfeldt-Jakob disease (CJD). Testing for the presence of this neuronal surface autoantibody in patients presenting with subacute encephalopathy is therefore crucial as it may both revoke the bleak diagnosis of prion disease and allow institution of potentially life-saving immunotherapy. Tempering this optimistic view is the rare instance when a positive VGKC complex antibody titre occurs in a definite case of prion disease. We present a pathologically and genetically confirmed case of CJD with elevated serum VGKC complex antibody titres. This case highlights the importance of interpreting the result of a positive VGKC complex antibody with caution and in the context of the overall clinical manifestation.

BACKGROUND

The differential diagnosis for rapidly progressive dementia includes, but is not limited to, autoimmune, infectious, neoplastic or rare neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD). Among these, distinguishing between autoimmune encephalopathy and CJD can be challenging. Pathological examination of brain tissue, considered the 'holy grail' of diagnosing CJD, is all too often performed postmortem. Analysis of clinicoradiological and laboratory features is therefore crucial for diagnosing CJD and ruling out its mimics. As there is a lack of established disease modifying treatment for CJD, it is of utmost importance to rule out autoimmune-mediated encephalitis (AME) for which treatment can often halt or reverse the disease process. It is unforgivable on ethical as well as medicolegal grounds to overlook a treatable condition such as AME by prematurely committing to a false diagnosis of an untreatable illness such as CJD. However, overreliance on positive autoantibody titres is not without its pitfalls, as it may lead to delays in accurate diagnosis and a false sense of hope for the patient and his/her family on rare circumstances. This report describes the third case in the literature to document positive voltage-gated potassium channel (VGKC) complex autoantibody in a case of definite CJD.

CASE PRESENTATION

A 67-year-old woman was admitted after a 2-week history of gradually worsening speech difficulty and impaired use of her right arm and leg. She had a

history of hypertension, peptic ulcer disease and lumbar spinal stenosis. Her father died of a progressive neurological illness with a presumed diagnosis of amyotrophic lateral sclerosis. At presentation, her examination was notable for the presence of expressive aphasia, ideomotor apraxia and alien limb phenomenon involving her right arm and leg. No significant cognitive impairment was detected on admission.

INVESTIGATIONS

Routine haematological and biochemical studies were normal. Serological screening for systemic vasculitides and rheumatological disorders was negative. Microsomal and thyroglobulin antibody titres were normal.

Cerebrospinal fluid (CSF) analysis revealed a mildly elevated protein and a normal cell count. MRI of the brain showed gyriform hyperintensity on diffusion-weighted imaging (DWI) confined to the cerebral cortex of the left insula, posterior temporal, anterior parietal, lateral frontal and paracentral frontal gyri with sparing of the full cortical thickness and subcortical white matter (figure 1). Brain positron emission tomography (PET) scan revealed global diffuse hypometabolism, more significant in the left hemisphere (not shown). A whole body PET scan did not disclose any hypermetabolic lesions.

Prolonged bedside electroencephalographic monitoring for 16 consecutive days revealed slow activity more pronounced on the left side intermixed with intermittent periodic sharply contoured triphasic-like discharges arising from the left frontocentral region. A total of six very brief subclinical seizures, all arising from the left hemisphere were recorded, which were ultimately controlled with lacosamide and phenytoin.

Serum paraneoplastic antibody evaluation was positive for VGKC complex antibody by radioimmunoprecipitation assay with a titre of 460 pM (normal <20 pM).

CSF VGKC complex antibody was not tested. CSF τ -protein was elevated at 3886 pg/mL (reference range <1150 pg/mL) while the 14-3-3-protein level was mildly elevated.

TREATMENT

A 3-day course of 1000 mg/day of intravenous methylprednisolone followed by a 5-day treatment with intravenous immunoglobulin were given, with no noticeable clinical improvement.

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Figure 1 Diffusion-weighted imaging of the brain revealed hyperintensity restricted to the left cerebral cortex in the areas of the insula (arrow), posterior temporal (arrowhead; A), anterior parietal (arrow head; B), and paracentral frontal gyri (arrows; C) with sparing of the full cortical thickness and subcortical white matter.

OUTCOME AND FOLLOW-UP

The patient gradually developed significant confusion and agitation, in addition to progressive lethargy and worsening aphasia. Prior to her discharge home for palliative management, a percutaneous endoscopic gastrostomy was placed. The patient ultimately died 4 months after symptom onset.

A brain autopsy was performed which revealed evidence of cortical neuronal loss, intracytoplasmic vacuolation (spongiform changes) and severe astrogliosis (supplementary figure). No inflammatory responses were detected. Immunohistochemistry using the monoclonal antibody 3F4 demonstrated diffuse prion protein (PrP) immunostaining, confirming the diagnosis of CJD.¹ Genetic analysis revealed a E200K-129M mutation in the PrP-encoding gene, the most common mutation in genetic CJD in North America.²

DISCUSSION

The differential diagnosis for a rapidly progressive cerebral dysfunction includes autoimmune, infectious, neoplastic or rare neurodegenerative diseases such as CJD. Among these, distinguishing between autoimmune encephalopathy and CJD can be challenging. While clinical and laboratory features generally are sufficient for a 'probable' diagnosis of CJD, pathological examination of brain tissue remains the gold standard. As there is a lack of established disease modifying treatment for CJD, it is

particularly important to rule out autoimmune conditions for which treatment can often halt or reverse the disease process.

The clinical spectrum of VGKC complex antibody autoimmunity includes acquired neuromyotonia, dysautonomia, limbic encephalitis and subacute encephalopathy.³ In a subset of patients with VGKC autoimmunity, rapidly progressive cognitive impairment, seizure and myoclonus are often encountered, reminiscent of the clinical presentation of CJD. Geschwind *et al* reported that in a cohort of 15 patients with VGKC complex antibody autoimmunity, most patients presented with acute memory loss, myoclonus, seizure and psychiatric dysfunction. Nine of 15 (60%) cases satisfied WHO diagnostic criteria for CJD (3 probable and 6 possible). Twelve of 13 (92%) patients improved after immunomodulatory therapy. Given the absence of VGKC complex antibody in 10 patients with pathologically proven CJD, the authors concluded that VGKC complex antibody is a specific marker of autoimmunity rather than an epiphenomenon of non-immune-mediated neuronal degeneration such as CJD.⁴ In another report, 6 of 346 (1.7%) patients suspected to have CJD had in reality autoimmune encephalitis as evidenced by the presence of CSF antibodies against neuronal surface antigens and the clinical improvement with appropriate treatment in 5 of them. Two of these six cases had antibodies against the VGKC complex (one with anti-leucine-rich glioma-inactivated 1 protein (anti-LGI-1) and the other with anticontactin-associated protein-like 2 (CASPR2) antibodies).⁵

Table 1 Cases of CJD with positive VGKC complex antibody

Reference	Sex/age, years	Diagnosis (PrP gene mutation)	Clinical presentation	VGKC-Ab titre (pM)	Brain MRI findings	CSF findings	Immune therapy and response (yes/no)
Current study	F/67	gCJD (E200K)	Ideomotor apraxia and speech disturbance	460	Left hemispheric cortical ribboning	Elevated τ , ambiguous 14-3-3	Intravenous immunoglobulin and intravenous methylprednisolone (no)
Fujita <i>et al</i> ⁶	M/60	gCJD (M232R)	Ideomotor apraxia, visual object agnosia, hemineglect, Gerstmann syndrome and memory disturbance	603.5	Bilateral occipital and parietal cortical ribboning	Elevated S-100b, positive 14-3-3	No immune therapy given
Angus-Leppan <i>et al</i> ⁷	M/68	sCJD (none)	Insomnia, confusion, myoclonus stimulus sensitive dystonia or choreoathetosis	210	Not performed	Elevated τ , positive 14-3-3	Intravenous immunoglobulin, cyclophosphamide, plasmapheresis and prednisolone (no)

CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; gCJD, genetic CJD; PrP, prion protein; sCJD, sporadic CJD; VGKC-Ab, voltage-gated potassium channel complex antibody.

The results of both reports suggested that in cases suspected to be CJD, whether or not they are compatible with the WHO CJD diagnostic criteria, the presence of VGKC complex antibody in the serum or CSF may point to an alternative diagnosis and aggressive immunotherapy should be considered to alter the disease course. Most standard neuronal autoantibody evaluations do not include the most recently characterised neuronal surface antibodies such as those targeting the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and γ -aminobutyric acid type B (GABA-B) receptors. Therefore, even if such standard panel-based autoantibody evaluations come back unrevealing, an immunotherapy responsive encephalopathy cannot be definitively ruled out. It could therefore be argued that all patients with clinically suspected CJD who have undergone a very thorough and unrevealing workup excluding all other aetiologies of rapidly progressive dementia may still have an autoimmune encephalopathy and that a trial of immune therapy should be contemplated.

Recent reports described elevated serum VGKC complex antibody levels in two isolated CJD cases (table 1). A 60-year-old seaman presented with visual object agnosia, hemineglect, apraxia and instant memory disturbance. The patient's MRI of the brain showed hyperintensity in the bilateral occipital and parietal cortices. EEG revealed the presence of periodic sharp wave complex. CSF 14-3-3 protein and total τ -protein were both elevated. The serum VGKC complex antibody titre was significantly elevated at 603.5 pM which became undetectable 8 months later while receiving no immunotherapy. His neuropathological examination revealed spongiform changes and synaptic deposition of PrP in the cerebral cortex, confirming the diagnosis of definite CJD. A known pathogenic M232R mutation in the PRNP gene was detected further confirming the diagnosis of genetic CJD.⁶ Angus-Leppan *et al* reported a 68-year-old man presenting with rapidly progressive insomnia, confusion, myoclonus and stimulus-sensitive dystonia or choreoathetosis. EEG revealed diffuse slowing. MRI of the brain was not performed. CSF S-100b and 14-3-3 protein were both elevated. VGKC complex antibody was positive at 210 pM which turned negative 1 month later. Cerebrospinal VGKC complex antibody was negative. A brain biopsy revealed severe spongiform changes and prion staining of the synaptic type. PrP gene sequencing revealed no mutations. The patient was treated with steroid, intravenous immunoglobulin, plasma exchange and cyclophosphamide without definite improvement.⁷

Many differences exist among the three cases of CJD with positive VGKC complex antibody (ours and those of refs. ⁶ and ⁷) and the 15 cases of CJD-mimicking VGKC complex antibody-mediated autoimmunity reported by Geschwind *et al*.⁴

Hyponatraemia was not seen in the three CJD cases but was present in 60% patients of the VGKC autoimmunity group. Neoplasm was undetected in the patients with CJD but seen in a total of five cases of the VGKC-autoimmunity group. No organ-specific antibodies such as striated muscle or thyroid autoantibodies were observed in the CJD cases while being present in 8/15 cases of the latter group. Two of the three CJD cases revealed the cortical ribbon sign on MRI while only two cases in the VGKC-autoimmunity group had similar DWI signal abnormalities, both of which developed intractable focal seizures that could explain the image findings. On EEG periodic sharp wave complex were detected in two of three patients in the CJD group, whereas the predominant finding was generalised slowing in the VGKC-autoimmunity group. Finally, CSF 14-3-3 protein was positive in all three CJD cases but only in four of eight tested patients (50%) in the CJD-mimicking

cohort. CSF τ -protein was elevated in two CJD cases that received the testing. While none of these differences are decisive factors in making a confirmatory diagnosis, the combination of individual findings could be helpful in providing clues to an accurate final diagnosis.

The role of VGKC complex antibody in the pathogenesis of CJD is unclear.

Paterson *et al*⁸ have recently evaluated the clinical relevance of positive VGKC complex antibody titres in the low-positive (100–400 pM) as well as high-positive (>400 pM) ranges.

A total of 55 patients with positive titres were identified. Interestingly, only 4 of the 32 patients with low-positive titres and 11 of the 23 patients in the higher titre range had definite evidence of autoimmunity, suggesting that this antibody may be positive beyond the realm of neurological autoimmunity.

Whether the presence of this antibody in select CJD cases is reflective of neurological autoimmunity or merely an epiphenomenon following acute neuronal injury remains to be determined. It is worth noting that autoantibody production directed against neuronal epitopes in prion diseases has long been recognised. For example, Sotelo *et al*⁹ reported 59% of patients with CJD (13/22) had serum antibodies that were bound to axonal neurofilaments. The presence of anti-N-methyl D-aspartate (NMDA) receptor antibody was reported in the serum of patients with sporadic CJD.^{10 11} It is therefore conceivable that rapid destruction of cerebral tissue by prion disease may release neuronal antigens such as the NMDA receptor or constituents of the VGKC complex, leading to the development of antibodies as a secondary event.

Our case here, along with two previously reported similar cases suggest that the presence of serum VGKC complex antibody does not exclude an underlying diagnosis of prion disease. The differential diagnosis of CJD and VGKC complex antibody-mediated encephalitis may rely on multiple clinical manifestations rather than a simple antibody testing.

Learning points

- ▶ Voltage-gated potassium channel (VGKC) complex antibody-mediated encephalitis is a recently recognised cause of autoimmune-mediated limbic encephalitis, typically presenting with encephalopathy, seizures and psychiatric disturbances.
- ▶ VGKC complex antibody-mediated encephalitis, which can mimic the clinical presentation of Creutzfeldt-Jakob disease (CJD), often responds to immunomodulatory drugs in contrast to CJD. At times, the only way to differentiate these two diseases would be a trial of immune therapy.
- ▶ In the workup of subacute encephalopathy, a positive serum VGKC complex antibody should not be regarded as unequivocal evidence of autoimmune-mediated limbic encephalitis, as it can also be present in CJD.

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