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Voltage-Gated Potassium Channel Autoimmunity Mimicking Creutzfeldt-Jakob Disease

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Abstract

Background—Rapidly progressive dementia has a variety of causes, including Creutzfeldt-Jakob disease (CJD) and neuronal voltage-gated potassium channel (VGKC) autoantibody-associated encephalopathy.

Objective—To describe patients thought initially to have CJD but found subsequently to have immunotherapy-responsive VGKC autoimmunity.

Design—Observational, prospective case series.

Setting—Department of Neurology, Mayo Clinic, and the Memory and Aging Center, University of California, San Francisco.

Patients—A clinical serologic cohort of 15 patients referred for paraneoplastic autoantibody evaluation. Seven patients were evaluated clinically by at least one of us. Clinical information for the remaining patients was obtained by physician interview or medical record review.

Main Outcome Measures—Clinical features, magnetic resonance imaging abnormalities, electroencephalographic patterns, cerebrospinal fluid analyses, and responses to immunomodulatory therapy.

Results—All the patients presented subacutely with neurologic manifestations, including rapidly progressive dementia, myoclonus, extrapyramidal dysfunction, visual hallucinations, psychiatric disturbance, and seizures; most (60%) satisfied World Health Organization diagnostic criteria for CJD. Magnetic resonance imaging abnormalities included cerebral cortical diffusion-weighted imaging hyperintensities. Electroencephalographic abnormalities included diffuse slowing, frontal

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intermittent rhythmic delta activity, and focal epileptogenic activity but not periodic sharp wave complexes. Cerebrospinal fluid 14-3-3 protein or neuron-specific enolase levels were elevated in 5 of 8 patients. Hyponatremia was common (60%). Neoplasia was confirmed histologically in 5 patients (33%) and was suspected in another 5. Most patients' conditions (92%) improved after immunomodulatory therapy.

Conclusions—Clinical, radiologic, electrophysiologic, and laboratory findings in VGKC autoantibody-associated encephalopathy may be confused with those of CJD. Serologic evaluation for markers of neurologic autoimmunity, including VGKC autoantibodies, may be warranted in suspected CJD cases.

Creutzfeldt-Jakob Disease (CJD), a prion disease with no established disease-modifying treatment,¹ is an important consideration in rapidly progressive dementia accompanied by myoclonus, parkinsonism, or ataxia.² The diagnosis is supported by characteristic abnormalities on electroencephalography (EEG)³ or brain magnetic resonance imaging (MRI)^{4,5} and possibly by elevation of neuronal injury markers in cerebrospinal fluid (CSF).^{6–8} Creutzfeldt-Jakob disease is mimicked clinically by several other conditions, particularly rapid presentations of other neurodegenerative diseases and autoimmune neurologic conditions.^{8,9}

Voltage-gated potassium channel (VGKC) autoantibodies were reported initially in acquired neuromyotonia¹⁰ and subsequently in Morvan syndrome,¹¹ limbic encephalitis,¹² other subacute encephalopathies,¹³ and limited manifestations of autoimmune dysautonomia.¹⁴ Conditions of most patients improve after early initiation of antibody-depleting immunomodulatory therapies.¹⁵ The observations described in this article, made independently at 2 separate institutions, involve 15 patients given an initial diagnosis of CJD but subsequently confirmed to have VGKC autoantibody-associated encephalopathy.

METHODS

Between January 1, 2001, and December 31, 2007, the Mayo Clinic Neuroimmunology Laboratory's serologic evaluation and clinical interpretive service detected serum VGKC autoantibodies in 15 patients in whom CJD was suspected on initial clinical evaluation by a consultant neurologist from approximately 150 000 samples tested on a clinical service basis for autoantibody markers of autoimmune (possibly paraneoplastic) neurologic disease. These autoantibodies were detected incidentally during immunofluorescence screening¹⁶ and were confirmed by means of radioimmunoprecipitation assay using antigen solubilized cerebral cortical membranes complexed with ¹²⁵I-labeled α -dendrotoxin.¹⁷

Four patients were referred for evaluation to the Department of Neurology, Mayo Clinic, and 3 to the Rapidly Progressive Dementia Program, Memory and Aging Center, University of California, San Francisco (UCSF). Eight patients were evaluated at other institutions. Clinical information was obtained by means of structured patient and family interviews, medical record review, or physician telephone interview. The Mayo Clinic and UCSF institutional review boards approved the study.

RESULTS

Seven of the 15 patients were women; the median patient age was 69 years. The median serum VGKC autoantibody level was 1.24 nmol/L (range, 0.16–51.9 nmol/L; reference range, ≤ 0.02 nmol/L). The clinical presentations, EEG and MRI findings, VGKC autoantibody titers, and treatment responses of the 7 patients evaluated directly by us are summarized in the Table.

CLINICAL PRESENTATIONS

In all cases, neurologic symptoms were subacute in onset. The median time from neurologic symptom onset to serologic diagnosis was 5 months (range, 0–13 months); median follow-up from onset was 9 months (range, 1–88 months). All of the patients had short-term memory impairment, 12 had myoclonus, 12 had seizures, 10 had behavioral or affective disturbance, 8 had dyssomnia, 6 had extrapyramidal dysfunction, 5 had autonomic dysfunction, 5 had gait ataxia, and 5 had visual hallucinations. Nine patients (60%) satisfied the World Health Organization diagnostic criteria for sporadic CJD¹⁸: 3 probable and 6 possible. Nine patients had hyponatremia (presumed to reflect hypothalamic involvement), including 2 with hyperphagia.

Five patients had documented coexisting organ-specific autoimmune disease: 3 with thyroiditis (1 with vitiligo) and 2 with diabetes mellitus. Two patients had a remote history of neoplasia in remission. Active neoplasia was confirmed histologically in 3 patients (2 had colonic adenocarcinoma and 1 had renal oncocytoma) and was suspected in 5 others (1 had a prostatic nodule and a serum prostate-specific antigen level elevation and 4 had mass lesions on thoracic or abdominal computed tomography).

Comprehensive serologic evaluation¹⁹ documented coexisting organ-specific autoantibodies in 8 patients. Six patients had autoantibody markers of thyrogastric autoimmunity: 4 had striated muscle autoantibodies, 3 had glutamic acid decarboxylase (65-kDa isoform) autoantibodies, and 2 had thyroid peroxidase autoantibodies. Three patients had autoantibodies that frequently accompany cancer: Purkinje cell cytoplasmic autoantibody type 2,²⁰ neuronal ganglionic acetylcholine receptor autoantibody,²¹ and N-type voltage-gated calcium channel autoantibody.²²

INVESTIGATIONS

Brain MRI abnormalities, noted in 9 of 13 patients in whom images or reports were available, included cerebral cortical diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) abnormalities in 2 (Figure 1A–C and Figure 2), T2-weighted or FLAIR hyperintensities in 5 (all involving hippocampi and 2 involving additional cerebral foci), and generalized atrophy in 2. Both patients with apparent DWI abnormalities had normal attenuation diffusion coefficient maps.

The CSF analysis in 10 patients revealed elevated protein levels in 3 (0.057–0.112 g/dL; range, 0.014–0.045 g/dL [to convert to grams per liter, multiply by 10.0]), lymphocytosis in 2 (white blood cell counts, 6 and 28/ μ L [to convert to $\times 10^9$ per liter, multiply by 0.001]), and supernumerary (4) oligoclonal bands in 1. The CSF markers of neuronal injury were elevated in 5 of 8 patients tested: 14-3-3 protein (National Prion Disease Pathology Surveillance Unit, Cleveland, Ohio) was positive in 4 and neuron-specific enolase (Mayo Medical Laboratories, Rochester) was positive in 2.

The EEG findings were abnormal in 9 of 13 patients with available data. All 9 patients had diffuse slowing, 1 had frontal intermittent rhythmic delta activity, and 3 had focal epileptogenic activity (1 temporal, 1 frontal, and 1 frontotemporal). None had periodic sharp wave complexes.

TREATMENT

Information about initial treatment and outcome was available for 13 patients: 9 received corticosteroids, 2 received intravenous immunoglobulin, and 2 received plasmapheresis and corticosteroids combined. Clinical improvement was reported by the treating physician in 12 patients (92%; 5 dramatic, 6 moderate, and 1 mild). Of those 12 patients, 8 experienced relapses

that required continued or repeated immunomodulatory therapy: corticosteroids (7 patients), immunoglobulin (2 patients), plasmapheresis (1 patient), mycophenolate mofetil (2 patients), rituximab (1 patient), or azathioprine (1 patient).

ILLUSTRATIVE PATIENT 1

A 73-year-old woman (patient 1 in the Table) presented to the UCSF Memory and Aging Center with an 8-month history of involuntary movements of the right upper extremity and face and a 4-month history of rapidly progressive cognitive decline, abulia, insomnia, and frequent falls. Examination revealed fluctuating alertness, a Folstein Mini-Mental State Examination score of 18 (maximum possible score is 30) (impairment across multiple domains), myoclonus and spasms of the right upper extremity and face, mild generalized bradykinesia, right upper extremity rigidity, and gait ataxia.

Laboratory evaluation revealed hyponatremia (sodium, 127 mEq/L [to convert to millimoles per liter, multiply by 1.0]) and 4 CSF-unique oligoclonal bands. The CSF 14-3-3 protein level was mildly elevated initially (considered “ambiguous” for CJD) but was normal on 2 subsequent spinal taps. Brain MRIs were considered suggestive of CJD, showing increased DWI and FLAIR signal in the left anterior cingulate gyrus and insula (Figure 1A–C); however, the attenuation diffusion coefficient map was normal. Biopsy of the left frontal lobe revealed microgliomatosis and neuronophagia without inflammation and astrocytic gliosis without vacuolation or prion deposition. During serologic evaluation for paraneoplastic autoantibodies, indirect immunofluorescence screening suggested the presence of VGKC specific IgG (Figure 1D). Reflex radioimmunoprecipitation assay confirmed the presence of VGKC autoantibodies (51.9 nmol/L; reference range, ≤ 0.02 nmol/L). N-type voltage-gated calcium channel autoantibody was also detected (0.17 nmol/L; reference range, ≤ 0.03 nmol/L). Computed tomography revealed a renal mass suggestive of adenoma.

After 3 days of intravenous methylprednisolone therapy, alertness, verbal output, and cognitive performance (a Mini-Mental State Examination score of 30) improved remarkably. Subsequent brain MRI showed reduced DWI and FLAIR hyperintensity in the left insula and cingulate gyri but new T2 hyperintensity involving the left caudate and putamen (data not shown). Repeated pulsed corticosteroid therapy was required in the ensuing 18 months for recurrent generalized tonic-clonic seizures and cognitive impairment; intravenous immunoglobulin therapy, plasmapheresis, mycophenolate therapy, and partial nephrectomy (confirming a renal oncocytoma) did not seem to provide additional benefit. Rituximab therapy commenced 23 months after onset was followed by considerable clinical improvement, comparable with that seen previously with pulsed corticosteroid therapy.

ILLUSTRATIVE PATIENT 2

A 75-year-old man (patient 4 in the Table) with a 50-pack-year history of smoking and a past diagnosis of colonic adenoma presented to Mayo Clinic with a 5-month history of cognitive impairment and a 3-month history of startle myoclonus, hypnagogic jerks, urinary and fecal incontinence, shuffling gait, and a presumed rapid eye movement sleep behavior disorder characterized by episodic screaming and thrashing. He scored 30 (maximum possible score is 38) on the Kokmen short test of mental status; short-term recall and abstract thinking were most impaired. Myoclonic jerks of both upper extremities and the face were observed, with hypomimia, hypophonia, and parkinsonian gait.

Brain MRI showed mild global atrophy. The CSF protein level was mildly elevated (0.057 g/dL; reference range, 0.014–0.045 g/dL), without lymphocytosis or oligoclonal bands. The EEG documented diffuse slowing during wakefulness and focal rhythmic theta activity (consistent with a frontal lobe seizure) during a typical sleep episode of abrupt yelling, right arm jerking,

and stiffening. Movement laboratory evaluation documented spontaneous multifocal cortical myoclonus, and serologic evaluation revealed VGKC autoantibody (0.16 nmol/L) and striated muscle autoantibody (1:30 720; reference range, $\leq 1:60$). Chest computed tomography revealed mediastinal lymphadenopathy; subsequent biopsy revealed hyalinized granulomata but no neoplasm.

Treatment with intravenous methylprednisolone led to complete resolution of all deficits (including a Kokmen score of 38), but pulsed corticosteroid treatment was required intermittently for 12 months because of neurologic relapse. In the following 18 months, he remained in remission without further treatment.

COMMENT

This article illustrates clinical presentations of VGKC autoimmunity that mimic CJD and demonstrates the potential for misdiagnosis of a reversible condition for a terminal one. This cohort's age and sex distribution²³ and observed clinical manifestations¹⁸ (except for dysautonomia and hyponatremia) are compatible with CJD. Most patients fulfilled the World Health Organization diagnostic criteria, presenting with rapidly progressive dementia with myoclonus, extrapyramidal or cerebellar signs, visual disturbances, or psychiatric dysfunction.

Hyponatremia (60%) provides an important diagnostic clue favoring an autoimmune basis for neurologic disease.²⁴ The frequency of neoplasia observed in these patients is consistent with our recent report of neoplasia in 33% of serologically ascertained cases of VGKC autoimmunity.¹⁶ The generally favorable response to immunomodulatory therapies accords with previous studies^{24,25} of treatment-responsive limbic encephalitis.

The VGKC autoimmunity is frequently associated with epileptic seizures¹⁶ and was a common finding in this cohort (80%). Although less commonly encountered, seizures are also a recognized and sometimes presenting feature of CJD.^{26–28} Therefore, in an individual patient, the presence of seizures should prompt consideration of alternative diagnoses but should not exclude the possibility of CJD.

Two patients had DWI hyperintensities of the cerebral cortex on MRI, with both neuroradiologists reporting the appearance to be consistent with CJD.⁴ However, the absence of restricted diffusion on attenuation diffusion coefficient mapping in both patients is atypical for CJD. Because attenuation diffusion coefficient mapping is not performed at many imaging centers, these findings caution against overinterpreting the DWI series in isolation. The T2-weighted and FLAIR hyperintensities of the mesial temporal regions in 5 patients match recognized MRI appearances of autoimmune limbic encephalitis^{24,25} but are also compatible with CJD. For example, of 49 patients with sporadic CJD whose MRIs were performed at the UCSF, 94% had FLAIR or DWI hyperintensities of the limbic cortex, including the medial temporal lobes.²⁹

Elevation of CSF neuronal injury markers, especially 14-3-3 protein (part of the World Health Organization diagnostic criteria)¹⁸ casts further doubt on the utility of these tests in the diagnosis of CJD.⁷ Diffuse slowing and other observed EEG abnormalities are recognized accompaniments of sporadic and variant CJD, although no patient had the periodic sharp wave complexes considered characteristic of sporadic CJD.³⁰

The high VGKC autoantibody levels (≥ 1.0 nmol/L in most patients), the reported improvement after immunomodulatory therapy, and the absence of VGKC autoantibodies in 10 UCSF patients with histologically confirmed CJD (9 sporadic and 1 familial) (M.D.G., unpublished data, 2008) suggest that these autoantibodies are true markers of neurologic autoimmunity and not an epiphenomenon of nonimmune-mediated neuronal degeneration.

The prevalence of VGKC autoimmunity in patients with suspected CJD requires further study. The experiences presented in this article, and the starkly divergent long-term outcomes for CJD and VGKC autoimmunity, justify comprehensive serologic evaluation for markers of autoimmune encephalopathy in patients with suspected CJD. Seropositivity for VGKC autoantibodies justifies early consideration of immunomodulatory therapy and thorough investigation for a neoplasm.

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Figure 1.

Brain magnetic resonance images of a patient with immunotherapy-responsive voltage-gated potassium channel (VGKC) autoimmunity and renal oncocytoma illustrate increased signal in the left anterior cingulate gyrus and insular cortex on diffusion-weighted imaging (A, arrows) and fluid-attenuated inversion recovery sequences (B and C, arrows). Indirect immunofluorescence testing of the patient's serum revealed IgG binding to VGKC-rich synapses in mouse cerebellar cortex (D). ML indicates molecular layer; GL, granular layer; and PC, Purkinje cells (unstained).

Figure 2.

Diffusion-weighted magnetic resonance images in a patient with immunotherapy-responsive voltage-gated potassium channel autoimmunity illustrate increased signal in the left temporo-occipital cortex (A and C, arrows) and the bilateral mesial frontal cortex (B, arrows).

Clinical Characteristics of 7 VGKC Ab–Positive Patients With Suspected CJD, Evaluated Directly by the Authors

Table 1

Patient No./Sex/ Age, y	Initial Symptoms	STM Impairment	Myoclonus	Seizures	Behavior/ Affect	Hallucinations	Dysomnia	Extrapyramidal Dysfunction	Gait Ataxia	Hyponatremia	EEG Findings	Brain MRI Findings	Response to Intravenous Corticosteroid Therapy	VGKC Ab Titer, Initial → Final, nM
1 ^a /F/73	Myoclonus, facial spasm	+	+	+	+	–	+	+	+	+	Diffuse slowing	L anterior cingulate and insular cortex T2/FLAIR/DWI hyperintensities	MMSE score of 18 → 30	51.9→3.62
2/F/55	Seizures, myoclonus, spasms	+	+	+	+	+	+	+	–	+	Normal	Bilateral hippocampal, anterior cingulate, and insular cortex T2/FLAIR hyperintensities	Seizures ceased, returned to living independently	0.35→0.00
3/F/66	STM impairment, prolixity, personality change	+	+	+	+	+	–	+	–	+	Normal	Bilateral hippocampal, and L amygdala T2/FLAIR hyperintensities	Seizure frequency reduced dramatically	1.08→NA
4 ^a /M/75	Myoclonus, seizures	+	+	+	+	+	–	+	–	–	Diffuse slowing, R frontal seizures	Generalized atrophy, maximal midbrain	All deficits resolved completely	0.16→0.36
5 ^a /M/60	STM impairment, personality change, hallucinations	+	–	+	+	+	–	–	–	+	Diffuse slowing, L TIRDA and temporal seizures	L hippocampal, L inferior frontal, and R caudate T2/FLAIR hyperintensities	Kokmen score of 20 → 33, MRI hyperintensities resolved, but L hippocampal atrophy and normal EEG findings	2.68→NA
6/M/65	STM impairment, myoclonus, ataxia	+	+	+	–	–	+	+	–	–	Diffuse slowing	Bilateral hippocampal T2/FLAIR hyperintensities, maximal R	Kokmen score of 21 → 33 and normal MRI findings	0.96→0.06
7/M/70	STM impairment	+	+	+	+	+	+	–	–	+	Diffuse slowing, L frontotemporal seizures	Bilateral mesial frontal, and L temporo-occipital DWI hyperintensities	Seizures ceased, normal EEG findings, MMSE score of 1 → Kokmen score of 26	4.34→1.87

Abbreviations: Ab, autoantibody; behavior/affect, behavioral and affective disturbances; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted imaging; EEG, electroencephalographic; FLAIR, fluid-attenuated inversion recovery; Kokmen, Kokmen short test of mental status (maximum possible score is 38); L, left; MMSE, Folstein Mini-Mental State Examination (maximum possible score is 30); MRI, magnetic resonance imaging; NA, not available; R, right; STM, short-term memory; TIRDA, temporal intermittent rhythmic delta activity; VGKC, voltage-gated potassium channel; +, present; –, absent.

^aDenotes 3 patients included in a previous case series of 72 patients with VGKC autoimmunity.¹⁶