Potassium Channel Antibody–Associated Encephalopathy Presenting With a Frontotemporal Dementia–like Syndrome

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Objective: To describe a patient who presented with features suggestive of frontotemporal dementia (FTD) but with some atypical findings and antibodies to neuronal voltage-gated potassium channels (VGKC-Abs).

Design: Case report.

Setting: Mater Misericordiae University Hospital, Dublin, Ireland.

Results: An 82-year-old man presented with progressive changes in personality, social conduct, and executive function with preservation of memory, deteriorating from baseline to requiring acute hospitalization within 6 months. Transient deterioration (episodic speech arrest) with spontaneous recovery, atypical for frontotemporal dementia, was observed. The patient had an elevated VGKC-Ab titer (2624 pM [normal range, <100 pM]), elevated protein levels in cerebrospinal fluid, and a negative evaluation for malignancy. Magnetic resonance imaging of brain was normal but [18F]-fluorodeoxyglucose positron emission tomographic imaging revealed bifrontal hypometabolism. A marked and sustained improvement with steroid therapy was observed.

Conclusion: Workup for a potentially reversible autoimmune-mediated encephalopathy, including a VGKC-Ab titer, should be considered in patients presenting with rapidly progressive behavioral and cognitive decline.

Antibodies reactive with neuronal voltage-gated potassium channels (VGKC-Abs) were initially described in acquired neuromyotonia and other disorders characterized by peripheral nerve hyperexcitability.1,2 The VGKC-Abs have also emerged as a serologic marker of potentially reversible autoimmune encephalopathies.3-5 To date, they have usually been reported as a nonparaneoplastic disorder indistinguishable from paraneoplastic limbic encephalitis, characterized by amnesia, delirium, and seizures, termed VGKC-Ab–associated encephalopathy.3 These patients usually have hyponatremia due to syndrome of inappropriate secretion antidiuretic hormone (SIADH) and mesial temporal signal changes on magnetic resonance imaging (MRI). The VGKC-Abs have also been associated with Morvan syndrome6 and rapid eye movement sleep behavior disorder7 and, in some patients, with epilepsy.8 However, progressive loss of social comportment, language, and executive function has not been described in association with autoimmune encephalopathies but is usually attributed to frontotemporal dementia (FTD), a neurodegenerative disease primarily affecting the frontal and anterior temporal lobes.9 Herein we describe a patient who presented with rapidly progressing behavioral changes and loss of executive function, but with a fluctuating course, who was found to have high serum VGKC-Ab titters and improvement of the syndrome with immunotherapy.

An 82-year-old man presented to the emergency department of our hospital with a 6-month history of progressive personality change characterized by increasing irritability, aggressive outbursts, poor self-care, repetitive facial grimacing, and diminished insight. Because of his rapid decline from a normal cognitive baseline to loss of functional independence, acute hospitalization of the patient was arranged. Examination revealed disinhibition, intermittent speech arrest, and stereotyped facial movements. The Mini-Mental State Examination (MMSE) score was 27 of 30 (with mild deficits in orientation and calculation only and 3/3 on testing recall). His Frontal Assessment Bat-
tery score (FAB) was 11 of 18 with deficits in mental flexibility, motor programming, and inhibitory control. The FAB is a bedside cognitive and behavioral battery (maximum possible score, 18) consisting of 6 subtests assessing conceptualization, mental flexibility, motor programming, resistance to interference, inhibitory control, and environmental autonomy; subjects without frontal lobe dysfunction typically score 17 or 18. A neurodegenerative process causing frontal lobe dysfunction was initially suspected. Magnetic resonance imaging showed age-appropriate generalized atrophy only. Electroencephalography demonstrated continuous frontal slow-wave activity but no epileptiform changes despite ongoing facial movements. A facial electromyogram demonstrated no evidence of peripheral nerve hyperexcitability. Cerebrospinal fluid (CSF) was acellular but with an elevated protein level of 1316 mg/L. Serum VGKC-Ab titer was markedly elevated at 2624 pM (normal range, <100 pM). Blood work revealed SIADH with a serum sodium level of 123 mEq/L (the conversion to millimoles per liter is 1-to-1), and subsequent testing did not reveal any alternative cause for this. Test results for paraneoplastic and thyroid autoantibodies and vasculitic markers were negative. An $[18F]$-fluorodeoxyglucose positron emission tomographic (FDG-PET) image of the brain (Figure) demonstrated bilateral frontal hypometabolism. Whole-body FDG-PET was negative for malignancy. A diagnosis of VGKC-Ab–associated encephalopathy with a disinhibited, dysexecutive presentation was made. Treatment consisted of prednisolone 70 mg (1 mg/kg) daily and subsequent taper. A treatment benefit was noted after 3 weeks, and within 6 weeks the behavioral syndrome, aphasia, and facial grimacing had improved to the extent that the patient was discharged to his own home, where further improvements took place. After 6 months of treatment, the MMSE score was 29 of 30, FAB score was 17 of 18, SIADH had resolved, and VGKC-Ab titer had fallen into the normal range. At this point, the patient was taking 20-mg prednisolone by mouth daily and had resumed all his premorbid self-care, household activities, and outdoors activities, including going to the grocery store and to church.

Our findings broaden the phenotypic spectrum of central nervous system disease associated with VGKC-Abs to include patients with deterioration in social conduct and personality change (cardinal features of FTD) along with other features commonly seen in FTD, such as executive dysfunction, decline in self-care, stereotypical behavior, and altered speech output but with relative preservation of memory. The therapeutic implications of our findings are important because the patient in this report showed reversibility with immunosuppression.

The patient described had a disinhibited and dysexecutive state and repetitive stereotyped facial movements. Personality change was an important presenting feature, and unlike in limbic encephalitis, memory was preserved. The rapid progression from a normal baseline over months, rather than an insidious course over years, and the fluctuating speech disorder were key clinical features atypical for FTD that supported testing for an autoimmune etiology, which included VGKC-Abs. The repetitive facial grimacing seen in our patient likely represented a stereotypy. Such patterned repetitive, purposeless movements are often seen in disorders of frontal function such as FTD. Peripheral nerve hyperexcitability and seizures were also considered, but a facial electromyogram did not demonstrate any neuromyotonic discharges, and the electroencephalograph, captured during these movements, was normal. Although neuropsychometric testing pretreatment and posttreatment is not readily available at our institution, the MMSE and FAB scores assisted in demonstrating the domains of cognition affected and monitoring response to therapy, although we do acknowledge that test-retest reliability has not been established for the FAB. Eighty percent of patients with VGKC-Ab–associated encephalopathy have been reported to have SIADH, and it typically resolves in tandem with falling VGKC-Ab titers when immunotherapy is undertaken.

Magnetic resonance imaging is typically abnormal in VGKC-Ab–associated limbic encephalitis with high signal seen in mesial temporal cortices on T2 or fluid-attenuated inversion recovery sequences. Our patient had a normal MRI scan but had abnormalities on functional neuroimaging, demonstrating bifrontal abnormalities, in keeping with a disinhibited, dysexecutive state. A previous report described a patient with a VGKC-Ab–associated limbic encephalitis and bitemporal hypermetabolic changes on FDG-PET occurring in tandem with ongoing electrographic seizure activity. Simi-
lar to that of our patient, FDG-PET also demonstrated bilateral frontal and neocortical temporal hypometabolism, adding further weight to the idea that the effects of VGKC-Ab–associated disorders are not just confined to the mesial temporal cortex.

Protein level in CSF was elevated in this patient, although other features of central nervous system autoimmunity (elevated white cell count and supernumerary oligoclonal bands) were absent. Our patient had a negative evaluation for malignancy in keeping with previous reports of VGKC-Ab–associated encephalopathy being usually a nonparaneoplastic disorder. However, lung cancers and other solid tumors have been associated with elevated VGKC-Ab titers, and vigilance for an occult malignancy should be maintained. It also should be borne in mind that only a limited number of paraneoplastic antibodies were ordered in this case, and more extensive autoimmune profiling (for collapsin response-mediated protein 5 [CRMP-5] IgG and other markers of paraneoplastic autoimmunity) is important where the remote effect of a cancer is suspected as the cause. Testing for VGKC-Ab in CSF (not undertaken in our patient) is of limited utility, tending only to be positive in those with high serum titers.

Consistent with previous literature regarding treatment of VGKC-Ab–associated limbic encephalitis, this patient had a beneficial response from steroids after a few weeks, but further improvements occurred with several months of therapy in tandem with a reduction in VGKC-Ab titer. The benefit from plasma exchange and intravenous immunoglobulin is less certain but may play a role in the initial stages of therapy. The duration of illness is likely important in predicting the treatment response, and in 1 report, patients with symptoms for more than 9 months responded poorly.

This case expands the spectrum of central nervous system disorders associated with VGKC-Abs. In the evaluation of patients presenting with rapidly progressive changes in personality, social conduct, and executive function, testing should be considered for inflammatory CSF and serological markers of autoimmune disease, including VGKC-Ab.

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REFERENCES