Voltage-gated potassium channel complex antibody (VGKCc-Ab) encephalitis is an immunotherapy-responsive syndrome usually associated with causative antibodies that target the leucine-rich, glioma inactivated 1 (LGII) protein. Although it is expressed throughout the brain, LGII is not known to be expressed in cardiac tissue. We describe a novel neurocardiac prodrome of VGKCc-Ab/LGII-encephalitis.

Methods

We identified 14 patients with VGKCc-Ab encephalitis evaluated between January 1, 2006, and August 1, 2013, in the University of California, San Francisco Autoimmune Encephalitis Clinic and Rapid Dementia Research Program, 3 patients (2 men and 1 woman; aged 53, 55, and 64 years) exhibited episodic bradycardia that preceded the onset of encephalopathy by approximately 2 months and was severe enough to lead to pacemaker implantation. Serum LGII-Ab results were positive when tested at the time of the subsequent encephalopathy. All 3 patients developed hyponatremia; none had faciobrachial dystonic seizures or malignancy. Brain magnetic resonance imaging was abnormal in 2 cases. None of the patients experienced further symptomatic bradyarrhythmias after 1.7 to 7 years of follow-up.

Report of Cases

Of these 14 patients with VGKCc-Ab encephalitis, 3 had prodromal bradycardia and pacemaker implantation (21%; 2 men and 1 woman; ages 53, 55, and 64 years). None of the patients had a prior cardiac history. All 3 cases had serum VGKCc-Ab and LGII-Abs at the time of encephalitis, which was characterized by amnesia, seizures, and serum hyponatremia. None...
of the cases had faciobrachial dystonic seizures, tumors, or contactin-associated protein-like 2 Abs (Table) and none had antibody testing at the time of the neurocardiac prodrome. Cases 2 and 3 were included in our analysis of neuropsychological testing in LGI1 encephalitis and case 2 was included in our analysis on the use of rituximab in this disorder.

### Case 1

A 53-year-old man developed 3 unheralded syncopal episodes during 2 months, all lasting seconds to less than 1 minute; 1 episode developed while he was driving. Evaluation revealed intermittent sinus arrest with slow junctional escape. He was diagnosed with sick sinus syndrome. No other accompanying symptoms at that time were reported or noted. A pacemaker was implanted. He subsequently experienced episodic unpleasant olfactory hallucinations lasting 10 to 20 seconds. He also felt fatigued and developed intermittent lightheadedness yet pacemaker interrogation at that time revealed no significant abnormalities or pacing episodes. Two months following the pacemaker implantation, he had trouble remembering a recent family trip and was described as speaking glibbishly. He was reported diagnosed clinically and electrographically with nonconvulsive status epilepticus and his cognition partially improved with levetiracetam. He continued to have mild memory problems and was intermittently anxious and uncharacteristically tearful. Serum VGKCc-Ab and LGI1-Ab levels were elevated (Table).

Five months following his pacemaker implantation, he was treated with intravenous methylprednisolone (1 g/d × 5 d) and an oral prednisone taper. Seven months after the pacemaker implantation, neuropsychological testing revealed mild impairment in verbal memory and processing speed. He subsequently received treatment with intravenous immunoglobulin and azathioprine and had steady cognitive improvement, allowing him to return to full-time work in a cognitively demanding profession. Two years after his pacemaker implantation, he had no detectable VGKCc-Ab or LGI1-Abs.

### Case 2

A 64-year-old man developed lightheadedness with associated bradycardia lasting seconds and was diagnosed with sick sinus syndrome. No other accompanying symptoms at that time were reported or noted. A pacemaker was implanted. The next day, he developed episodic anxiety lasting hours and occurring daily. Two months following his pacemaker implantation, he became forgetful, compulsive, and delusional (daily thoughts of people stealing from him and intruders present in the neighborhood). He had a seizure with head version and tonic arm extension (laterality not recalled) and then bilateral clonic limb movements, followed 2 weeks later by a generalized tonic-clonic seizure. Investigations revealed persistent serum hyponatremia (Table). Brain magnetic resonance imaging showed T2/FLUID-ATTENUATED INVERSION RECOVERY HYPERINTENSITIES (Figure). Neuropsychological testing demonstrated verbal memory impairment and slowed processing speed. He was treated with intravenous methylprednisolone (1 g/d × 5 d) with improvement. About 3 weeks later, his cognition worsened, leading to retreatment with intravenous methylprednisolone, intravenous immunoglobulin, and a prednisone taper over several months. Ten months after his pacemaker implantation, he had no cardiac symptoms (pacemaker interrogation revealed 10%-12% pacing with a baseline setting of 55 bpm). At 12 months, he was retreated with intravenous immunoglobulin and continued oral prednisone, with partial improvement of
cognitive deficits but persistent difficulty with verbal recall on cognitive testing. Levels of VGKCc-Abs and LGI1-Abs remained elevated. At 15 months, he was treated with 2 doses of intravenous rituximab, 1000 mg, and continued taking prednisone, 20 mg/d. At 18 months, LGI1-Abs and VGKC-Abs were not detectable. He exhibited additional improvement in episodic memory and emotional lability but continued to have moderate deficits on verbal learning and memory testing.

**Case 3**
A 55-year-old woman developed discrete episodes of fear lasting several minutes that occurred 1 to 2 times daily for 1 to 2 months. Lorazepam was prescribed for panic attacks. One episode culminated in a 10-second loss of consciousness without postictal confusion. Two weeks later, panic episodes with loss of consciousness recurred with documented bradycardia and a sinus pause of 12 seconds. She was diagnosed with cardiogenic syncope secondary to bradyarrhythmias and underwent pacemaker implantation (Table). During the next 3 months, she appeared uncharacteristically apathetic, her short-term memory declined, and she experienced hallucinations. This was followed by a seizure with head deviation and subsequent generalized tonic-clonic activity. Her husband described episodes during which she lost awareness and reached for objects with her right hand, occurring about 6 times a day, each lasting a few seconds. Magnetic resonance imaging results showed T2/fluid-attenuated inversion recovery hyperintensities (Figure). Five months after her pacemaker implantation, she was treated with intravenous methylprednisolone (1 g/d × 5 d), followed by maintenance prednisone with a marked improvement in memory and panic episodes. After tapering off prednisone 2 years following the pacemaker implantation, her panic attacks insidiously recurred and she developed emotional lability. These symptoms resolved following another course of intravenous methylprednisolone and oral prednisone maintenance. Two years after the pacemaker implantation, no significant abnormalities were noted on her cardiac electrophysiology follow-up. Contacted by telephone 7 years after onset, her...
husband reported that she still had mild short-term memory difficulties such as forgetting details of conversations and had no further syncopal episodes or cardiac problems.

Discussion

Episodic bradycardia is a distinctive prodrome of VGKC/LGI1-Ab encephalitis that led to pacemaker implantation in all of our cases and preceded the onset of encephalopathy by about 2 months.

The neuroanatomical localization of this neurocardiac prodrome most likely relates to temporal lobe and insular involvement. In patients undergoing epilepsy surgery, stimulation of the left insular cortex can provoke bradycarrhythmias.8 Temporal lobe seizures involving either hemisphere can trigger ictal bradycardia.9 The episodic course of the neurocardiac prodrome in our patients favors an epileptic cause secondary to focal encephalitis of these brain regions. Further supporting this proposed cause and localization, our patients also exhibited episodes of anxiety, emotional lability, and/or olfactory hallucinations prior to the encephalopathy, focal motor, and generalized tonic-clonic seizures in the context of evolving encephalitis. It is also possible that the bradycardia was accompanied by other symptoms that were not reported because they were overshadowed by syncopal symptoms. As LGI1 is found throughout the neocortex and emerging evidence suggests direct pathogenicity of LGI1-Abs,12,13 it is likely that LGI1-Abs were involved in triggering the autonomic dysfunction that caused bradycardia in our patients.

This finding adds to the spectrum of autonomic symptoms associated with VGKCc encephalitis. Early case reports of VGKCc encephalitis noted some patients with hypersalivation.1,2,14 Episodic hypothermia was also described in a subset of patients with VGKCc-Ab-associated limbic encephalitis.15 Autonomic symptoms are also a prominent feature of the Morvan syndrome, which in addition to neuromyotonia can include hyperhidrosis, lacrimation, constipation, diarrhea, impotence, tachycardia, and alterations in blood pressure. Morvan syndrome is a phenotype more commonly associated with contactin-associated protein-like 2 Abs than LGI1-Abs, although both antibodies may be present in patients with Morvan syndrome.16,17 Furthermore, seizures with prominent autonomic features have been described in patients with VGKCc-Abs and LGI1-Abs.11,18 Interestingly, ictal asystole has been rarely reported in another cell-surface antibody-associated neurological disorder, N-methyl-D-aspartate receptor antibody encephalitis.19,20

Conclusions

Recognition of episodic bradycardia in combination with other limbic features, particularly amnesia or seizures, might prompt early consideration of VGKCc/LGI1-Ab testing. Furthermore, similar to the observation that early immunosuppressive treatment of prodromal faciobrachial dystonic seizures21 may prevent progression to encephalopathy,21 we hypothesize that the same might be true for treatment of this neurocardiac prodrome. Further research is needed to address these possibilities.

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REFERENCES


