Morvan’s syndrome is a constellation of clinical presentations including encephalitis, peripheral nerve hyperexcitability and dysautonomia manifesting with fluctuating delirium, insomnia, muscle twiching, and autonomic symptoms. The syndrome was first described by the name of “la chorée fibrillare” in the late 19th century by Augustin Marie Morvan. Various European and subsequently, Asian authors have reported individual case reports or case series of Morvan’s syndrome. The pathogenesis of Morvan’s syndrome was earlier speculated to be due to exposure to toxins, particularly heavy metals and/or presence of autoantibodies. The association of the syndrome with malignancies mostly thymoma as a paraneoplastic manifestation was subsequently recognized. The observation of autoimmune disorders such as myasthenia gravis and thyroiditis, detection of autoantibodies to voltage-gated potassium channels (VGKCs), and improvement on treatment with immunosuppressive/immunomodulatory therapies established Morvan’s syndrome as an autoimmune disorder affecting both the central and the peripheral nervous system. Antibodies to VGKC have been identified in several other neurological disorders including neuropsychiatric syndromes, epilepsies, Creutzfeldt–Jakob disease mimickers, and frontotemporal dementia. VGKC complex antibodies have been reported in hitherto unsuspected situations such as patients with neoplastic pain syndromes, children with status epilepticus, and chronic epilepsies. This has greatly expanded the clinical spectrum of anti-VGKC complex protein antibody associated autoimmune neurological disorders.

VGKC protein complex is a group of proteins that are intensely associated in situ and even after extraction in mild detergent. The antibodies to VGKC were initially thought to be against the epitopes of VGKC. Subsequent research revealed that the most of these antibodies are directed against leucine-rich glioma inactivated protein-1 (LGI1) and contactin-associated protein-like 2 (CASPR2). Recently, patients with VGKC antibodies negative for both the LGI1 and CASPR2 have been recognized. VGKC antibodies are detected with radioimmunoassay that labels Kv1.1 and Kv1.2 subunits. Immunofluorescence tests and cell-based assay are used to further characterize VGKCs. Anti-LGI1 antibodies are associated with limbic encephalitis, and anti-CASPR2 antibodies are observed in neurological syndromes presenting with encephalitis, peripheral nerve hyperexcitability, or a combination of both known as Morvan’s syndrome. The alteration in the two proteins, LGI1 and CASPR2, provides basis for the pathophysiological mechanisms for the clinical symptoms of each type of autoimmune response. Associated hyponatremia has been found in up to 60% of patients with LGI1 antibodies. The target proteins and sites for these LGI1 and CASPR2 negative VGKC antibodies are continuously being further characterized with each passing year. In this issue, the authors describe a case with VGKC antibodies positive for CASPR2 presenting with Morvan’s syndrome and syndrome of inappropriate antidiuretic hormone (SIADH). The authors report that SIADH is known to be associated with LGI1 antibodies and this observed association with CASPR2 antibodies has not been reported. LGI1 is a neuronal protein secreted at the synapses and interacts with presynaptic ADAM 23 and postsynaptic ADAM 22 to organize a trans-synaptic protein complex. This has been linked to epilepsy in humans. Presynaptic Kv1.1 and Kv1.2 subunits of potassium channels and postsynaptic alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor form the other components of this protein complex. LGI1 gene mutations have been associated with autosomal dominant lateral temporal lobe epilepsy and autosomal dominant partial epilepsy with auditory features. In animal models, the mutation has been linked with increased neuronal excitability possibly resulting from decreased AMPA receptor activity in inhibitory neurons and increased glutamate release.

CASPR2 belongs to neurexin superfamily that binds to contactin 2. This is axonal transmembrane protein...
that is involved in clustering of Kv1 potassium channels in the juxtaparanodal region. The protein is present in the hippocampus and cerebellum as well. The mutated gene that codes for CASPR2 (CNTNAP2) has been detected in patients with psychiatric illness, drug-resistant epilepsy, and peripheral nerve hyperexcitability.

In the case report presented, the authors mention that LGI 1 antibodies bind to neuronal cell bodies including antidiuretic hormone secreting hypothalamic neurons explaining the presence of SIADH in more than half of LGI 1 positive patients. Whether the CASPR2 antibodies also affect these areas is an open question. In view of the importance of stringent, rigorous methods for detecting and quantitating the antibodies levels and lack of resources for such testing at most of the centers, there is need to develop cooperation and coordination between researcher of the basic sciences and the clinical researchers.

Bhupender Kumar Bajaj
Department of Neurology, PGIMER, Dr. RML Hospital, New Delhi, India

Address for correspondence:
Dr. Bhupender Kumar Bajaj, Department of Neurology, PGIMER and Dr. RML Hospital, New Delhi - 110 001, India.
E-mail: docbajaj@yahoo.co.in

References


This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.