Double Positive Anti-CASPR2 and LGI1 Antibodies Associated with Two Episodes of Clinically Distinct Disorders

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Contactin associated protein-like 2 (CASPR2) and leucine-rich glioma-inactivated protein 1 (LGI1) voltage gated potassium channel (VGKC) proteins are found in both the central and peripheral nervous systems [1]. Antibodies against these proteins are associated with encephalopathy, seizures, peripheral nerve hyper-excitability, autonomic dysfunction, hyponatremia, pain, and insomnia in varying severity and combination [1].

Morvan syndrome, first described in 1890, combines symptoms of peripheral nervous system (PNS), central nervous system (CNS), and autonomic nervous system dysfunction. It was later found to be associated with VGKC-complex antibodies, mainly against CASPR2 or LGI1 or both.

Our patient had a history of anti-LGI1 positive limbic encephalitis, which presented years later with anti-CASPR2 positive Morvan syndrome.

PATIENT DESCRIPTION

A 74-year-old man presented to the neurology department following 4 days of fluctuating confusional state accompanied by acoustic hallucinations. His past medical history included endovascular abdominal aorta repair and acute myeloid leukemia treated with allogenic stem cell transplantation 5 years earlier. He also experienced an episode of LGI1-positive autoimmune encephalitis 2 years prior to his current illness. At that time, he presented with acute fluctuating confusion, recurrent falls, and disinhibited behavior, but no seizures. Laboratory evaluation showed hyponatremia (125 meq/l) but otherwise toxic metabolic (TSH, Vitamin B12). Infectious disease workup was normal. Non-contrast head computed tomography (CT) showed non-specific findings, and brain magnetic resonance imaging (MRI) showed a bilateral mesial temporal enhancing lesion with mild mass effect, which was suspected to be due to limbic encephalitis. Serum was therefore tested for paraneoplastic and autoimmune encephalitis panels. These tests identified the presence of anti-LGI1 antibodies and were negative for antibodies against glutamate receptor type NMDA, Ma1, Ma2, CASPR2, glutamate receptor type AMPA1, amphiphysin, LGI1, CV2, Ri, GABA B Receptor, YO, HuD, anti SOX1, anti-Tr (DNER), anti-Zic4, and GAD65. Slow correction of hyponatremia did not resolve the patient's symptoms. Accordingly, he was treated with high-dose methylprednisolone, which was followed by clinical and radiological resolution. Interestingly, a repeated anti LGI1 test after 6 months showed a change in detection intensity, from positive to weakly positive. He was subsequently followed in the outpatient clinic and was doing well until the admission discussed in this case communication.

His neurological examination showed complete disorientation to place and time, partial orientation to situation, and severe retro- and anterograde memory disturbance. The Montreal Cognitive Assessment score was 19/30. His speech was normal. Mild dysmetria was present on left finger-nose-test and knee-heal-shin tests. Mild tremor and bradykinesia were evident as well. Laboratory investigation showed mildly elevated C-reactive protein (15 mg/L, normal range is 0–5) and thrombocytopenia (67 K/microL, normal is 130–440). The remainder of the blood count, kidney, liver function, and coagulation tests were within normal limits. The electroencephalogram was normal and the non-contrast brain CT showed mild chronic white matter changes. Brain MRI showed chronic ischemic changes in the bilateral white matter and a small acute left parieto-occipital infarct, but no sign of inflammation. Lumbar puncture was avoided at that point due to thrombocytopenia. At that time, determination of the etiology for his confusion was deferred, considering evolution of stroke, intermittent seizures, or possibly recurrent autoimmune encephalitis. Accordingly, a repeated autoimmune encephalitis panel was sent for analysis.

One week following admission, hyperhidrosis was noted, as was pruritus with repeated active scratching and muscle twitches in all limbs and neck flexor muscles. Morvan syndrome was suspected and therefore electrodiagnostic studies were performed. Motor conduction studies of the median, ulnar, tibial, and peroneal nerves, as well as sensory conduction of the median, ulnar, radial, sural, and superficial-peroneal nerves were all

normal. The tibial F response study, however, showed after-discharges following M waves [2], which obscured the F waves [Figure 1]. Needle electromyography showed myokymic discharges in multiple muscles (biceps brachii, triceps, tibialis anterior, gastrocnemius, gluteus medius) [Figure 1]. Together, these findings suggested a peripheral nerve hyperexcitability disorder. Autoimmune panels subsequently were positive for anti-CASPR2 and weakly positive for anti-LGI1 antibodies. These electrophysiological and serologic findings confirmed the clinical diagnosis of Morvan syndrome. The patient was treated with high dose intravenous methylprednisolone without improvement. We planned for treatment with IVIG or plasma exchange. Unfortunately, his situation was followed by *Escherichia coli* sepsis. ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography suggested endovascular aneurysmal repair infection with no evidence of an underlying malignancy, including thymoma. Even with aggressive antibiotic treatment, the patient died due to septic shock 6 weeks after admission.

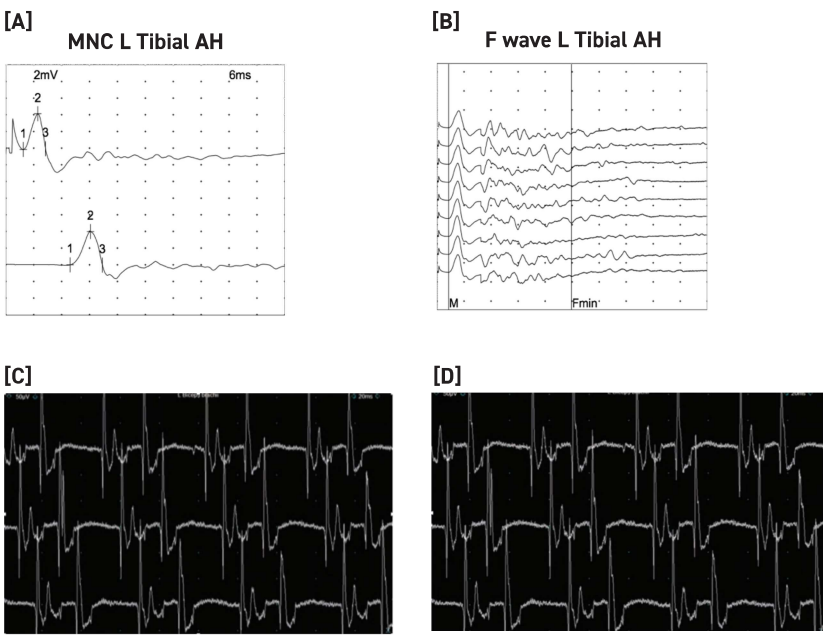
Figure 1. Multiple waves following compound muscle action potentials

[A] M response

[B] Obscuring the F waves (expected position marked by vertical line), consistent with after discharges, which indicate peripheral nerve hyperexcitability

[C,D] Needle electromyography showing semi-rhythmic myokymic discharge at a frequencies of approximately 20 Hz, composed of triplets, followed by a few doublets and silence motor nerve conduction

AH = abductor hallucis, L = left, MNC = motor nerve conduction



COMMENT

VGKC-complex antibodies, particularly CASPR2 and LGI1, are associated with a spectrum of clinical syndromes, according to involvement of CNS, PNS, and/or autonomic nervous system dysfunction. Our case showed two separate clinical presentations, the first was consistent with LG1-positive limbic encephalitis and the second, 2 years later, with CASPR2-positive Morvan syndrome.

While both LGI-1 and CASPR2 are expressed in the central nervous system, CASPR2 is more prominently expressed in the peripheral nervous system, and more commonly associated with peripheral nerve hyperexcitability, expressed as myokymia and neuromyotonia [1]. Autoantibodies against CASPR2 are also more commonly associated with autonomic dysfunction and pruritus, as in our case. Accordingly, when both antibodies were identified in Morvan cases, anti-CASPR2 antibodies showed a higher titer than LGI1 antibodies.

The coexistence of these two antibodies has been described to be more common than expected for their independent prevalence. The double positive phenotype was previously described, commonly including pain, dysautonomia, and neuromyotonia, and less frequent seizures, faciobrachial dystonic seizures, and movement disorders [1].

Jia et al. [3] described three patients with dual seropositive anti CASRP2 and LGI1 antibodies and reviewed the literature on cases published with positive LGI1 and CASPR2 antibodies. The most prevalent clinical syndrome associated with dual positivity for LGI1 and CASPR2 was Morvan syndrome, and in general, the presence of both antibodies was associated with a wider range of symptoms. Tumor prevalence was highest for patients who were double seropositive, followed by patients with anti CASPR2 antibodies, and was lowest in patients with LGI1 antibodies. Gadoth and colleagues [4] conducted a study on patients positive for LGI1, CASPR2, or both. Nine of 256 patients were dual positive, cancer was found more frequently in CASPR2 seropositive patients and most frequently (44%) in patients positive for both LGI1 and CASPR2. The most frequent tumor found was thymoma. This study also showed age to be a strong predictor for CNS involvement (in IG1, CASPR2, or both) and showed serum to be more sensitive than CSF [4]. Both LGI1 and CASPR2 seropositive patients displayed PNS symptoms, mainly pain and dysautonomia. Paroxysmal dizziness

spells were experienced by 14% of seropositive patients, which were thought to be partial seizures or epileptic aura phenomena, all of which were LGI1 positive patients [4]. Response rate to immunotherapy was high, but relapse rate was also high, reported to be 59% [4].

An interesting case report described a female patient, who presented with both peripheral and CNS symptoms, including pain, myokymia, hyperhidrosis, confusion, and seizures. Brain MRI showed bilateral medial lobe hyperintensity consistent with limbic encephalitis and serum antibody panels tested positive for both LG1 and CASPR2. Somewhat reminiscent to our case, her CNS symptoms improved after LGI1 antibodies became negative, while peripheral symptoms resolved only later when CASPR2 antibodies became negative [5].

We presented the occurrences of two separate VGKC-antibody associated clinical syndromes. These correspond to LG1 followed by CASPR2 antibodies associated syndromes; that is, limbic encephalitis and Morvan syndrome.

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If the doors of perception were cleansed everything would appear to man as it is, infinite.
William Blake (1757–1827), English poet, engraver, and painter

There are two kinds of light – the glow that illuminates, and the glare that obscures.
James Thurber (1894–1961), American cartoonist, writer, humorist, journalist, and playwright

Capsule

The hormonal X fact

Postmenopausal women comprise the majority of Alzheimer's disease patients (70%). This population has been shown to have increased toxic neuronal tau protein deposition compared with age-matched men. However, how sex, age, and hormone replacement therapy (HRT) affect tau deposition in cognitively unimpaired individuals remains unclear. Using tau imaging in cognitively normal postmenopausal women and age-matched men, **Coughlan** and co-authors showed that women had higher tau deposition in several brain areas. Early menopause and late initiation of HRT were associated with increased neuronal tau compared with late menopause and early HRT.

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Capsule

Not all fiber is the same

A healthy diet must include a high fiber intake to sustain a healthy microbiota. However, fiber is a heterogenous substance, and its composition is likely to influence the range of microorganisms that ferment it. Using fecal batch cultures, **Solvang** and associates tested microbial growth on a variety of edible plant extracts. At 72 hours, fermentation products, bacterial abundance, and community composition were measured. More complex substrates supported a more variable community, which also varied by fiber source. For example, high arabinan from beetroot and high galactan from carrots predicted specific microbial enrichment. Thus, knowledge of dietary fiber composition is valuable in designing diets that optimize desirable composition and function in a patient's microbiota.

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