Insomnia and Dysautonomia with Contactin-Associated Protein 2 and Leucine-Rich Glioma Inactivated Protein 1 Antibodies: A “Forme Fruste” of Morvan Syndrome?

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Abstract
Morvan syndrome (MoS) is typically characterized by neuromyotonia, sleep dysfunction, dysautonomia, and cognitive dysfunction. However, MoS patients with mild peripheral nerve hyperexcitability (PNH) or encephalopathy features have been described. A 46-year-old woman presented with a 2-month history of constipation, hyperhidrosis, and insomnia. Neurologic examination revealed muscle twitching and needle electromyography showed myokymic discharges in all limbs. No clinical or electrophysiological features of neuromyotonia were present. Although the patient denied any cognitive symptoms, neuropsychological assessment revealed executive dysfunction, while other cognitive domains were preserved. Cranial and spinal MRIs were unrevealing and tumor investigation proved negative. Polysomnography examination revealed total insomnia, which was partially reversed upon immune-
modulatory therapy. Investigation of a broad panel of antibodies revealed serum leucine-rich glioma inactivated protein 1 and contactin-associated protein 2 antibodies. The features of this case indicate that the presentation of PNH syndromes may show significant variability and that MoS patients may not necessarily exhibit full-scale PNH and encephalopathy symptoms.

Introduction

Morvan syndrome (MoS) patients present with a combination of peripheral nerve hyperexcitability (PNH), dysautonomia, insomnia, and encephalopathy. PNH is usually characterized by cramps, fasciculations, as well as myokymic and neuromyotonic discharges on needle electromyography [1]. MoS patients may present with various aspects of diencephalon involvement such as sleep dysfunction, hyperhidrosis, and the syndrome of inappropriate antidiuretic hormone secretion. Although cognitive dysfunction in MoS typically manifests as hallucinations and confusion, amnesia and epileptic seizures may also be encountered. Antibodies directed against components of the voltage-gated potassium channel complex, leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein 2 (CASPR2), are found in the majority of patients [1, 2].

We here present a case of MoS admitted with the predominant complaints of insomnia and autonomic dysfunction and who was in due course found out to display LGI1 and CASPR2 antibodies and mild cognitive impairment by neuropsychological testing. To our knowledge, our case is one of the few reported MoS patients presenting with sleep dysfunction as the predominant finding.

Case Presentation

A 46-year-old woman presented with a 2-month history of constipation, excessive sweating, and inability to sleep, which started on the second day of menstruation. She complained of <15 min of sleep duration a day and had been treated with alprazolam without any benefit. Her medical history included chronic migraine and acute rheumatic fever at the age of 3 years.

Neurologic examination revealed persistent twitching of arm and leg muscles and lost ankle and knee reflexes. Cranial nerve functions, muscle strength, pinprick, touch and vibration senses, and cerebellar functions were unaffected; upper limb deep tendon reflexes were normoactive, and plantar responses were flexor bilaterally. She denied cramps, fasciculations, involuntary muscle contractions, or any psychiatric or cognitive symptoms including amnesia, confusion, and psychosis.

Sensory and motor nerve conduction values were normal, while needle electromyography examination revealed myokymic discharges in all limbs. Contrast-enhanced cranial and spinal MRIs and electroencephalography were all normal. Complete blood count and blood biochemistry tests were normal with the exception of mildly reduced potassium levels (3.3 mEq/L). Whole-body computed tomography imaging, positron emission tomography, and serum/urine immunofixation electrophoresis examinations done to exclude a potential underlying tumor were all unrevealing. Likewise, serum paraneoplastic antineuronal antibodies (against Hu, Yo, CV2, Ri, Ma2, and amphiphysin) were found to be negative. A vasculitic process was screened with antinuclear antibody, anti-DNA antibody, and antineutrophil cytoplasmic antibodies, which were all found to be negative. Serum free T4 was mildly elevated.
(1.78 ng/dL) and thyroid peroxidase antibody was positive (256.4 IU/mL). Serum free T3, thyroid-stimulating hormone, and parathormone levels were normal. Among autoimmune encephalitis antibodies, LGI1 (1/100 titer) and CASPR2 (1/320 titer) were positive in serum only, whereas NMDA receptor, AMPA receptor, GABA\(_B\) receptor, and glutamic acid decarboxylase antibodies were negative. Antibodies could not be investigated in the cerebrospinal fluid due to lack of the patient’s consent for lumbar puncture.

A full-night video-polysomnography was performed at the sleep laboratory following a 1-week drug-free period and scored by an expert in sleep medicine. A total of 266.9 min of recording could be made as the patient asked to quit the recordings at 03:45 a.m. During this period, only 12 min of sleep consisting of superficial non-REM sleep periods (N1 and N2 sleep) were observed. Sleep efficiency was calculated as 4.5% (Fig. 1). The patient was diagnosed as having total insomnia, probably secondary to an underlying neurologic condition on the basis of the International Classification of Sleep Disorders [3].

Since LGI1 and CASPR2 antibodies are associated with limbic encephalitis, cognitive functions were assessed despite the absence of relevant complaints. The Mini-Mental State Examination score was 28. However, a detailed neuropsychological assessment showed deficits in sustained attention, information processing speed, set-shifting, and the ability to suppress inappropriate responses, all indicating executive dysfunction. By contrast, time, place, and person orientation, verbal and visual memory, language functions, abstract thinking, as well as lexical and semantic fluency were all intact.

These findings altogether suggested an acquired PNH syndrome prompting immunotherapy. Her complaints did not regress under carbamazepine, phenytoin, and gabapentin treatment. Pulse methylprednisolone (1 g/day for 5 days) and intravenous immunoglobulin (0.4 mg/kg) treatment promptly resolved autonomic symptoms and myokymia within 1 month.

After immune-modulatory treatment, the patient and her husband mentioned that she had started to sleep to some extent. Clinical evaluation revealed about 50% relief in insomnia-related symptomatology. Repeat video-polysomnography was performed at the same sleep laboratory and scored by the same sleep expert. A whole-night investigation consisting of 473.5 min of recording could be performed. During this period, the patient slept for 236.5 min, composed of 20.5% N1 sleep, 58.6% N2 sleep, 7.2% N3 sleep, and 13.7% REM sleep. Sleep efficiency had increased from 4.5 to 49.9% (Fig. 2). In addition, the patient was also diagnosed as having obstructive sleep apnea syndrome being prominent in REM sleep, and treatment with positive airway pressure was planned.

**Discussion**

MoS cases with both LGI1 and CASPR2 antibodies have been described in 12 and 16% of two recently published MoS cohorts, and patients with both antibodies have been found to be inclined to display a more severe disease course typified by cramps, fasciculations, neurogenic pain, insomnia, autonomic dysfunction, cognitive impairment, and an underlying tumor [1, 2]. By contrast, in our case, the clinical presentation of PNH was rather mild, the cognitive dysfunction was unrecognizable at first examination, and no underlying tumor could be identified. Similarly, a few MoS cases with both LGI1 and CASPR2 antibodies and an incomplete clinical picture have been previously reported. However, these patients have displayed either severe PNH features (e.g., cramps, fasciculations, neuromyotonic discharges) without encephalopathy or prominent encephalopathy features (e.g., hallucination, confusion, amnesia, or...
seizures) with mild (e.g., myokymia only) or no PNH findings [4–6], while our patient showed minimal features of both PNH and encephalopathy findings.

Myokymia, which was recognized during neurologic examination, was the only PNH finding, and clinical and electrophysiological findings of neuromyotonia could never be demonstrated. Moreover, Mini-Mental State Examination and brain imaging were both normal, and neuropsychological examination, which was done upon suspicion due to LG1 antibody positivity, only showed executive dysfunction. This finding might have been induced by pathogenic antibodies as well as other medical factors. Alprazolam has not been associated with cognitive dysfunction [7]. However, chronic insomnia is known to induce executive dysfunction and thus may have fortified the poor performance in cognitive tests [8]. Although both peripheral nerves and higher cortical functions were mildly affected and the cognitive dysfunction may not be undeniably attributed to pathogenic antibodies, we considered our patient as a "forme fruste" of MoS due to the presence of several cardinal symptoms such as insomnia, constipation, hyperhidrosis, and some degree of PNH and central nervous system involvement.

The most common type of sleep disorder associated with limbic encephalitis due to autoantibodies is actually reported to be hypersomnolence of central origin. By contrast, in MoS, insomnia is the predominant clinical phenotype and has been reported mainly to be associated with CASPR2 antibody [9]. On the other hand, one recent case report suggested an association with LG1 antibody and insomnia as well [10]. The mechanism(s) by which CASPR2 and LG1 antibody cause insomnia remain(s) unclear, though it was suggested that these proteins, located mainly in the neocortex and limbic areas, may be involved in the regulation of sleep need or efficiency via modulation of potassium channels. Only few reports have highlighted the reversal of insomnia in autoimmune encephalitis upon immune-modulatory therapy [4, 9, 10], as in the present case. Our patient demonstrated a major benefit from immune-modulatory therapy in terms of insomnia, as demonstrated by both clinical and polysomnographic evaluations.

Clinical studies conducted with double-positive MoS patients provide a good opportunity to study the discrepant effects of different voltage-gated potassium channel complex antibodies. LG1 antibody has been associated with cognitive dysfunction, while CASPR2 antibody has been suggested to be related with PNH findings, dysautonomia, and diencephalon involvement [1, 4]. Presence of mild PNH and cognitive symptoms in some MoS cases with LG1 and CASPR2 antibodies might putatively be due to a lack of antibodies reactive with pathogenic epitopes or inability of LG1 antibodies to cross the blood-brain barrier.

In conclusion, our case is merely another example of the clinical diversity of MoS and emphasizes once again that MoS may present with the core findings of autonomic dysfunction and sleep problems and very mild symptoms of PNH and encephalopathy. Investigation results of the patient indicate that in patients with LG1 or CASPR2 antibodies, PNH and cognitive dysfunction should be meticulously investigated despite the absence of obvious clinical findings.

Statement of Ethics

The patient provided written informed consent for the publication of this report.
Disclosure Statement

The authors declare that they have no conflicts of interest. No funds were received for this work.

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Fig. 1. Summary of the sleep study at first polysomnographic investigation. The hypnogram shows a dramatic reduction in total sleep time and complete loss of deep non-REM and REM sleep stages.
Fig. 2. The hypnogram obtained at the second polysomnographic investigation reveals major recovery in sleep organization, with an increased total sleep time and re-acquisition of sleep stages.