

LGI1 and CASPR2-related Morvan syndrome - diagnostic challenges in a pediatric case

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ABSTRACT

Morvan syndrome is a rare immune-mediated pathology involving the central, peripheral and autonomic nervous systems. Although it was described in adults, mostly as a paraneoplastic syndrome, it is rarely seen in pediatric patients. In this report, we present the case of a 15-year-old male patient who experienced insomnia, peripheral nerve hyperexcitability and autonomic signs, highly suggestive for Morvan syndrome, but prone to diagnostic dilemmas as well. The diagnosis was confirmed by the presence of antibodies against voltage-gated potassium channels (VGKC). This article aims to highlight the unique clinical picture of a rare syndrome, diagnostic pitfalls and treatment options in pediatric patients.

Keywords: Morvan syndrome, children, autoimmune

INTRODUCTION

Morvan syndrome is a disorder characterized by nerve hyperexcitability, central nervous system signs and autonomic symptoms. It is an uncommon pathology that mainly affects men, with less than 100 cases reported worldwide [1]. It occurs less frequently than 1/1000000, generally in adulthood, with an average age of 50. Data concerning the children population is limited [2,3].

Subsequent studies performed after Augustin Morvan first described the syndrome in 1890 concluded that it is probably an autoimmune disorder, hypothesis supported by the fact that it is associated with the presence of voltage-gated potassium channel (VGKC) serum or cerebrospinal antibodies in many patients – mainly leucine-rich glioma inactivated protein 1 (LGI1) or contactin-associated protein 2 (CASPR2), and, occasionally, anti-contactin 2 antibodies [3,4,6].

It has also been frequently described as a paraneoplastic syndrome associated with thymoma, pulmonary adenocarcinoma, sigmoid colon cancer and prostate adenocarcinoma, especially in double-positive CASPR2 and LGI1 cases [1-3]. Most reports on CASPR2 autoimmunity relate, in addition to Morvan

syndrome, to patients with epilepsy or chronic pain syndromes [4,8]. A connection with myasthenia gravis was also identified [9]. A case of neuromyotonia was reported in association with the presence of *Staphylococcus aureus* [1,7]. Contactin 2 is expressed in cardiac conduction tissue and, as a result, the presence of anticontactin antibodies 2 may be correlated to cardiovascular instability [3].

Central nervous system symptoms include significant insomnia, hallucinations, delirium, confusion, temporal and spatial disorientation, amnesia and agitation, which overlap with the clinical features of limbic encephalitis. The autonomic signs may consist of hyperhidrosis, hypersalivation, palmo-plantar erythema, pruritus, excessive lacrimation, weight loss, digestive dysfunction, erectile dysfunction, fever, arrhythmias and hypertension. Some cases associate hyponatremia [5]. Peripheral nervous system signs involve continuous muscle activity: myokymia, fasciculations, loss of deep tendon reflexes, distal sensory loss and neuropathic pain. Clinical features may depend on the type of identified antibodies [11,13].

Neurophysiology plays an important role in the diagnostic workup of a suspected Morvan case, as

electromyographic (EMG) studies may reveal myokymia and neuromyotonia [11,12].

Differential diagnoses include Isaacs' syndrome (acquired neuromyotonia, characterized by nerve hyperexcitability without central nervous system or autonomic dysfunctions), limbic encephalitis (amnesia, seizures, abnormal MRI findings of the temporal lobe, lack of autonomic manifestations or neuromyotonias and the presence of LGI1 antibodies), Guillain-Barré syndrome (immune-mediated ascending neuropathy both motor and sensory) and fatal familial insomnia (prion disease which involves abnormal brain MRI findings, psychiatric and autonomic signs).

Treatment options consist of oral immunosuppressors such as prednisone, cyclophosphamide, azathioprine, rituximab, plasmapheresis and intravenous immunoglobulins [14].

The evolution of Morvan syndrome without treatment is remarkably variable, from spontaneous remission to exitus, strongly influenced by the associated pathologies (e.g., malignancies).

CASE PRESENTATION

A 15-year-old male patient with a history of asthma and psoriasis was admitted to the "Dr Victor Gomoiu" Children's Hospital's Pediatric Neurology Department for lumbar pain with onset three weeks prior to his presentation, arthralgias lacking any sign of inflammation, muscle weakness, especially during the morning, fatigue, hyperhidrosis and weight loss of 8 kg, over 10% of his total weight, within three weeks. He also experienced insomnia, nausea, compulsive impulse to defecate 4-5 times a day, erectile dysfunction and behavioral changes (e.g., he had been more emotionally attached to his mother than usual).

The physical examination revealed pale skin, palmar erythema, a dry plate covered with scales localized paravertebrally in the lumbar region and dorsal pain. The neurological examination was normal, except the mild motor deficit in the lower limbs, with a score of 4 on Medical Research Council (MRC) Muscle Power Scale, and the fasciculations predominantly located on the limbs.

EMG

0.1mV/D 50ms/D

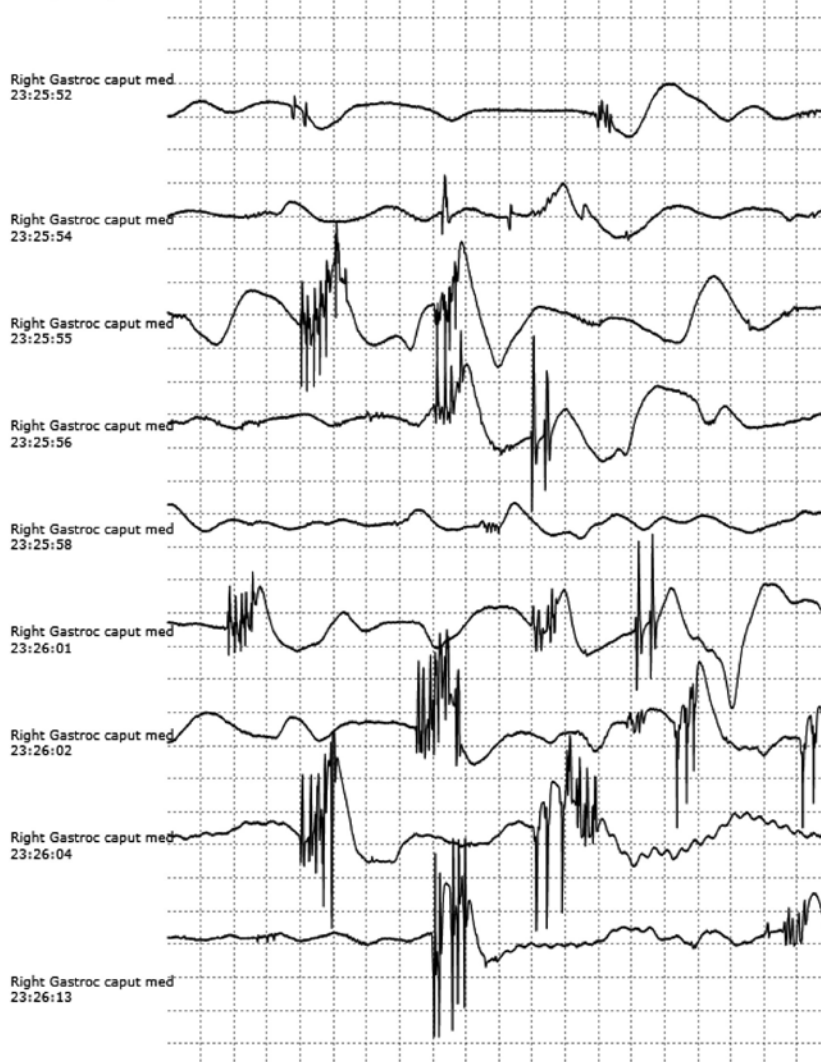


FIGURE 1. Electromyography showing potentials of fasciculations synchronous with the clinical involuntary contraction (from "Dr. Victor Gomoiu" Children's Hospital's Archive)

Laboratory workup showed no hematological or metabolic changes, normal levels of anti-DNA antibodies, antinuclear antibodies, complement component 4, rheumatoid factor, low amount of complement component 3 and normal levels of carcinoembryonic antigen and alpha-fetoprotein.

VGKC antibodies panel found both LG1 and CASPR2 antibodies.

Laboratory tests for pathogens, including HIV, hepatic viruses and *T. pallidum*, detected only MRSA nasal colonization with no arguments for an active infection.

Except for small circumferential cervical and thoracic bulging discs, 1,5 T spinal and cerebral MRI showed no abnormalities. No pathological findings were present on contrast-enhanced mediastinum MRI. Abdominal ultrasonography discovered no abnormalities.

Nerve conduction studies (NCS) were normal, but EMG studies revealed multiple suggestive elements for peripheral nerve hyperexcitability (fasciculation potentials synchronous with clinical involuntary contraction) (Figure 1).

Diagnostic workup further consisted of cardiological, endocrinological, gastroenterological, orthopedic and psychiatric evaluations addressing the symptoms suggesting multisystemic involvement, which did not reveal any abnormalities except for an emotional disorder.

The patient was diagnosed with Morvan Syndrome given the association of central (insomnia, behaviour changes), peripheral (muscle weakness,

fasciculations) and autonomic (hyperhidrosis, nausea, digestive and erectile dysfunction) nervous system signs and symptoms, supported by positive VGKC serum antibodies and EMG findings (Table 1).

The patient received a five-day intravenous high-dose methylprednisolone immunotherapy as well as symptomatic treatment with carbamazepine and melatonin.

Following treatment, the patient had a decrease in lumbar pain and fasciculations, gained weight and had no longer experienced insomnia. The neurological examination revealed no motor deficits – 5 on the MRC scale.

DISCUSSION

The patient had a complex clinical picture, with multisystemic involvement that has proven to be very challenging from a diagnostic point of view.

Given the lumbar and polyarticular pain, orthopedic evaluation and imaging studies were performed in order to exclude a possible autoimmune disorder, which showed no significant abnormalities.

Serum tumor markers were measured and serological tests for pathogens were performed for the detection of a neoplastic or infectious etiology of the significant weight loss and fatigue.

NCS and EMG studies were used to confirm the presence of nerve hyperexcitability and to rule out a lower motor neuron lesion. Another entity that involves muscle twitching, with the distinctive aspect of EMG as well, is Isaacs' syndrome, however, it does not include central and autonomic nervous systems involvement [11].

Searching for VGKC antibodies is of considerable value when facing a possible diagnosis of Morvan Syndrome. VGKC are transmembrane channels that form complexes with proteins such as LGI1 and CASPR2 and repolarize the active neurons to their resting state. They have an imperative role in modulating excitability in the central and peripheral nervous systems. LGI1 and VGKC are expressed in many brain structures (e.g. thalamic, hypothalamic neurons, raphe nuclei, locus coeruleus neurons) and the autoantibodies target these proteins. Brain MRI is useful for correlating insomnia, behavioral changes and the presence of LGI1 antibodies with a potential limbic encephalitis - in our case, the investigation did not show any abnormalities. Also, a psychiatric evaluation determined that the condition did not have psychiatric causes, despite the fact that the patient experienced an associated emotional disorder [3,10,12].

Given the association with tumors, especially thymoma, chest radiography, mediastinum MRI and abdominal ultrasonography were carried out. These investigations did not show any signs of malignancy or other abnormal growths.

TABLE 1. Signs and symptoms of Morvan Syndrome in our case

Sign/Symptom found in Morvan Syndrome patients	Presence in our case
Central Nervous System	
Insomnia	Yes
Agitation	No
Confusion	No
Hallucinations	No
Delirium	No
Temporal/Spatial disorientation	No
Amnesia	No
Peripheral Nervous System	
Continuous muscle activity	Yes
Fasciculations	Yes
Loss of deep tendon reflexes	No
Distal sensory loss	No
Neuropathic pain	Yes
Autonomic Nervous System	
Hyperhidrosis	Yes
Hypersalivation	No
Excessive lacrimation	No
Palmoplantar erythema	Yes
Pruritus	No
Weight loss	Yes
Digestive dysfunction	Yes
Erectile dysfunction	Yes

The autonomic signs and symptoms required multidisciplinary evaluation, therefore cardiologic, ophthalmological, gastroenterological and endocrinological examinations were performed, in order to rule out other pathologies and also in the interest of determining the safety of corticotherapy.

The patient had a complete remission under methylprednisolone therapy and symptomatic treatment. The possibility of starting treatment with intravenous immunoglobulins remained under review in the event of a relapse.

CONCLUSION

We highlight the importance of early recognition and treatment, given that Morvan Syndrome is

highly responsive to immunomodulatory treatment and has an increased probability for an unfavorable outcome in the absence of therapy. Morvan syndrome is a rare disease, especially in children, but it should always be considered in the presence of an association between central, peripheral and autonomic signs and symptoms. The particularity of our case also consisted of the absence of malignancies, even in the presence of double-positive CASPR2 and LG1 antibodies. Lastly, we emphasize the importance of multidisciplinary management in such complex cases with multisystemic involvement, in order to reach a fast and correct diagnosis and start early treatment for the best possible outcome.

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