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Issacs' syndrome in pediatric patient and voltage-gated potassium channels antibodies

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Pratical implications

Consider Isaacs' syndrome in children with disabling myalgia and undulating skin surface movements, called myokymia, even with negative VGKC antibodies.

Introduction

Isaacs' syndrome (IS), also known as acquired neuromyotonia, is a rare neuromuscular disease, manifested by involuntary continuous motor activity.[1] Although there are reports in children,[2,3] IS is more frequent in adults.[1] The clinical presentation can include muscle cramps, fasciculations, myokymia, and pseudomyotonia. Electromyography (EMG) remains the gold standard for diagnosis.[1,4] Dysfunction of peripheral nerve voltage-gated potassium channels (VGKC) appears to be related to the development of the disease.[1,3,4,5] Paraneoplastic factors also play an important role in IS.[5] Anticonvulsants are the first therapeutic option.[1,4,5]

Case report

A 10-year-old male child, with fever and rhinorrhea, presented suddenly with myalgia and disabling generalized myokymia of distal predominance. On physical observation (Video 1, http://links.lww.com/CPJ/A194), there were limbs fasciculations, abdomen and limbs myokymia, and hands pseudomyotonia, with hyperhidrosis. On neurological examination he presented a grade 4+ in global stregth evaluation and osteotendinous reflexes difficult to elicit. Blood tests revealed an increased creatine kinase (2484U/L), and positive IgM and IgG antibodies for parainfluenza type 1 and parvovirus B19. On

electrophysiologic studies, nerve conduction (on popliteal sciatic and saphenous nerves) was normal and needle electromyography, tested on right vastus lateralis muscle and left internal gastrocnemius muscle, showed a pattern of spontaneous irregular discharges in activity and at rest, with myokymic and neuromyotonic discharges (Figure 1), suggestive of IS. The patient was submitted to brain MRI, thorax, abdomen and pelvis CT-scan, and testicular ultrasonography to exclude malignancies. Screening for paraneoplastic antibodies, including anti-neuronal antibodies, and VGKC antibodies, anti-CASPR2 and anti-LG1, in the serum were negative. Treatment was initiated with carbamazepine showing an overall improvement of symptoms. After three weeks of treatment, his mother self-discontinued carbamazepine with a sudden worsening of myokymia, wich had improved after reintroduction of the therapy. The patient is currently on follow-up maintining treatment with residual distal myokymia.

Discussion

IS belongs to generalized peripheral nerve hyperexcitability disorders, and was first described in 1961 in two patients, one of them within pediatric age.[2] However it is more frequent in adults with the average age of onset in the mid-40s.[1]

Clinical manifestations include muscle cramps, fasciculations, myokymia and pseudomyotonia. Myokymia is present in about 90% of patients, being the main clinical finding of IS.[3] In contrast pseudomyotonia is present in only 1/3 of patients.[4] Patients may also experience hyperhidrosis, paraesthesias, mild muscle weakness, or even CNS symptoms, such as hallucinations or insomnia. They often have muscle hypertrophy and osteotendinous reflexes can be weak or difficult to elicit, due to difficulty in muscle relaxation,[4] as described in our patient.

IS may occur alone or in association with other diseases, including autoimmune and paraneoplastic diseases.[1,4] Its pathophysiology is still unknown but may be due to acquired autoimmunity or genetic changes in VGKC.[1,3,4] VGKC antibodies have been identified in 40% of patients, which supports their autoimmune mechanism.[1,4] There are two types of VGKC antibodies, one directed against leucine-rich glioma-inactivated protein 1 (LGI1) and other directed against contractin-associated protein 2 (CASPR2).[1] LGI1 has less peripheral nerve expression than CASPR2, so it has not been identified in patients with IS.[1,6] However, most patients are VGKC antibodies negative, as in our patient, probably because anti-CASPR2 antibodies are rare in children,[7] showing that

other mechanisms or receptors may be involved. Neoplasic diseases appear to be closely related to IS, suggesting that tumor antigens can trigger an autoimmune response against VGKC.[1,5] Vaccination and infections may also be triggers for IS.[1,4] In our report, parainfluenza virus type 1 and parvovirus B19 may have been the trigger for the disease.

Electrophysiologic studies remain the gold standard for diagnosis. Nerve conduction studies are usually normal but electromyographic recordings present spontaneous irregular and continuous discharges, even at rest.[1,3,4,5] Typical discharges make the diagnosis and can be divided into neuromyotonic and myokymic discharges. Neuromyotonic discharges are irregular high frequency discharges, while myokymic discharges consist of irregular spontaneous low frequency discharges, both present during sleep.[1,3,4] Muscle or nerve biopsy is not recommended given its lack of specificity.[1]

By interacting with VGKC, anticonvulsants reduce repetitive discharges leading to symptomatic control.[1,4] Carbamazepine and phenytoin are the most widely used anticonvulsants in IS. In refractory situations it may be necessary to use immunosuppressants, such as prednisolone and azithioprine.[4,6] In patients with high titers of anti-VGKC antibodies response to anticonvulsants is poor and plasma exchange may be required.[1,6]

There is a strong association between IS and cancer[5] and anti-CASPR2 antibodies are known to be associated with a higher risk of paraneoplastic disease.[1,6] Thus it is essential to perform screening exams and long-term follow-up in patients with IS.[1,5]

Appendix 1: Authors

Name	Location	Contribution
Andreia Forno, MD	Department of Pediatrics, Hospital Central do Funchal, Portugal	Collected and synthesized the data; participated in literature review; drafted the manuscript for intellectual content
Alexandra Rodrigues, MD	Department of Pediatrics, Hospital Central do Funchal, Portugal	Participated in literature review; revised the manuscript for intellectual content
Rui Vasconcellos, MD	Department of Pediatrics, Pediatric Neurology Unit, Hospital Central do Funchal, Portugal	Revised the manuscript for intellectual content
Paulo Rego Sousa, MD	Department of Pediatrics, Pediatric Neurology Unit, Hospital Central do Funchal, Portugal	Revised the manuscript for intellectual content

Video 1 - http://links.lww.com/CPJ/A194

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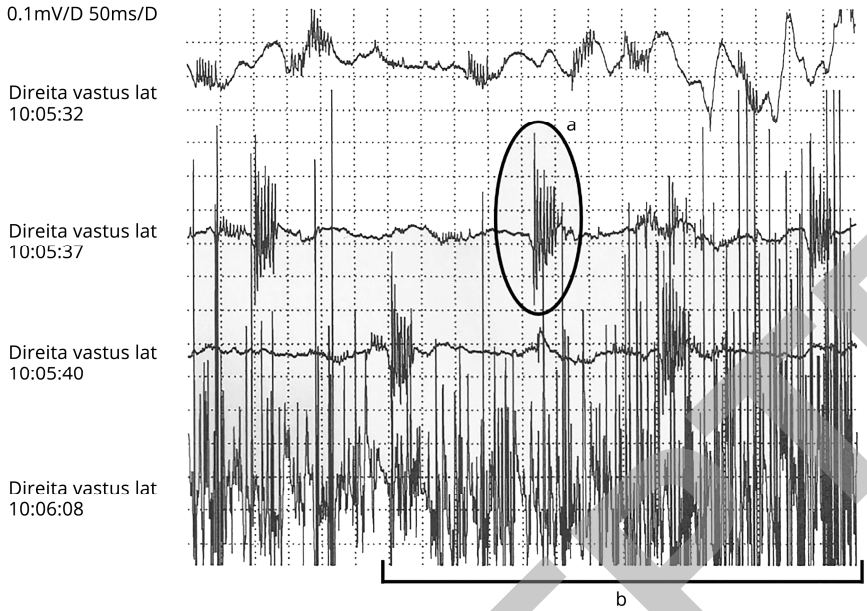
Figure 1. Electromyography at diagnosis

EMG showed a pattern of spontaneous irregular discharges with myokymic (a) and neuromyotonic (b) discharges, and normal motor unit action potencials (on right vastus lateralis muscle).



Video 1. Clinical findings before treatment

Physical examination showing limbs fasciculations, abdomen and limbs myokymia, and hands pseudomyotonia.

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