A Rare Case of Peripheral Nerve Hyperexcitability in Childhood: Isaacs Syndrome

Seda Kanmaz, Muhittin Özcan¹, Erdem Şimşek, Hepsen M. Serin, İbrahim Aydogdu², Sarenur Gökben, Hasan Tekgül

Isaacs syndrome is a rare disorder with peripheral nerve hyperexcitability syndromes with acquired neuromyotonia in childhood. We present a 13-year-old girl with muscle stiffness and neuromyotonia diagnosed Isaacs syndrome with spontaneous discharge potentials on motor unit in electromyography and the diagnosis supported by the presence of antinuclear antibodies. A successful treatment was obtained using low-dose carbamazepine. Cause of Isaacs syndrome is unknown, generally thought to be an autoimmune etiology with voltage-gated potassium channelopathy; it sometimes occurs as a paraneoplastic syndrome. Early use of electromyography has critical role in the differential diagnosis with certain muscle disorders and peripheral nerve hyperexcitability syndromes.

Keywords: Isaacs syndrome, neuromyotonia, peripheral nerve hyperexcitability, pseudomyotonia

INTRODUCTION

Neuromyotonia is a clinical and electrophysiological syndrome of spontaneous muscle fiber activity due to hyperexcitability of peripheral nerve and characterized by muscle stiffness, cramps, fasciculations, myokymia, and pseudomyotonia. Isaacs syndrome (acquired neuromyotonia or idiopathic generalized myokymia) is a rare neurologic disease, which is one of the peripheral nerve hyperexcitability (PNH) syndromes.[1,2] The syndrome is an autoimmune disorder and PNH develops due to autoantibodies against voltage-gated potassium channels (VGKC). Although various autoantibodies have been identified with PNH in adults, few cases have been reported in childhood.[2] Here we report a 13-year-old girl with Isaacs syndrome diagnosed with clinical characteristics and electromyography (EMG) findings and successfully treated with sodium channel blocker.

CASE

A previously healthy 13-year-old girl presented with stiffness in hands and legs and unable to relaxation for 2 months [Figure 1]. These symptoms occurred suddenly and progressively worsened limiting daily routine activities. There was no history of drug use or infection.

On examination, the stiffness of palmar and gastrocnemius muscles was observed. No significant changes were observed in resting, activity, sleeping, and cold. She also had thenar muscle atrophy and hypoactive deep tendon reflexes. Her mental status was normal. Complete blood count, renal and liver function tests, thyroid function tests, electrolytes, plasma copper level, ceruloplasmin, and vitamin B12 levels were normal. Serum creatine kinase was 356 IU/L (normal: 0–145 IU/L). Cranial and spinal magnetic resonance imaging were also normal. EMG findings, both nerve conduction studies and motor-unit action potential (MUAP) morphology, were normal. Without denervation, especially upper and lower extremity flexor muscles had a continuous burst of MUAP and high-frequency bizarre wave activities, complex repetitive and myokymic discharges [Figure 2]. On the basis of...
the clinical and EMG findings, she was diagnosed with Isaacs syndrome.

The underlying etiologies of Isaacs syndrome (autoimmune disorders or paraneoplastic syndromes) were examined. Thoracic computed tomography, abdominal ultrasonography, and paraneoplastic panel were normal. Antinuclear antibody (ANA) was 1/2560 centromere positive, ANA centromere B was ++++, and ANA dense fine speckled (DFS) 70 was +++. VGKC, N-methyl-D-aspartate receptor (NMDAR), selective glutamate receptor 1 (AMPA1), AMPA2, anti-contactin-associated protein-like 2 (ANTI-CASPR2), anti-leucine-rich glioma inactivated-1 (ANTI-LG1), anti-γ-aminobutyric acid-B receptor (GABA B), anti-glutamic acid decarboxylase (GAD), acetylcholine (ACh) receptor, muscle-specific kinase (MUSK), anti-ds-DNA, anti-Ro, anti-La, direct Coombs test, and anticardiolipin antibodies were negative. Systemic lupus erythematosus and scleroderma could not be diagnosed with these tests, but the patient has to be followed up for rheumatologic diseases.

The patient was treated with carbamazepine 400mg twice daily. Clinical findings and stiffness regressed on the third day; she became asymptomatic on the second week. The patient was followed up for 6 months with a good neurologic condition and asymptomatic.

**Discussion**

Isaacs syndrome in childhood is a rare acquired immune-mediated disorder associated with VGKC and frequently needs intravenous immunoglobulin (IVIG) and/or immunomodulatory treatment modalities.[1,2] Here we report a pediatric case of the syndrome associated with elevated ANA levels successfully treated with a sodium channel blocker.

Clinical manifestations of Isaacs syndrome include generalized muscle stiffness, which persists during sleep and slow relaxation following muscle contraction called neuromyotonia.[1] The muscular stiffness can be so strong that it can almost stabilize hands and feet in certain postures and make them almost unusable in daily activities as in our patient.[3] Muscle hypertrophy, continuous muscle twitching, and myokymia were seen in the clinical presentation of syndrome. Myokymia characterized with continuous muscle twitching described as bag-of-worms movements. The limbs are mostly affected. Other symptoms include fasciculations, carpopedal spasms, intermittent cramps, increased sweating, and pseudomyotonia (impaired relaxation after a strong muscle contraction but without the typical waxing-and-waning EMG abnormality of true myotonia.[1]

The diagnosis of Isaacs syndrome is based on the above clinical findings, and results of nerve conduction and EMG studies, which show characteristic abnormalities; these abnormalities include after-discharges on nerve
conductions studies and, on needle EMG studies, fasciculation potentials, myokymic discharges, neuromyotonic discharges, fibrillation potentials, and cramp discharges, most prominent in distal limb muscles. In the differential diagnosis of neuromyotonia and muscle stiffness, EMG has a critical role. In the presence of myotonic discharges in EMG, congenital myotonia, congenital paramyotonia, congenital myopathy and Pompe disease should be considered at the initial stage of differential diagnosis. Of these patients, there are some changes in MUAP morphology without spontaneous motor unit activities. However, spontaneous motor unit activities as well as fasciculation potentials, myokymic discharges, and neuromyotonic discharges are major signs in needle EMG at PNH as presented in our case.[1] EMG examination performed by an experienced electromyographer in the early stage of the initial differential diagnosis of muscle stiffness may prevent some case from harmful investigation such muscle biopsy and/or from expensive genetic analysis of mentioned muscle disorders.

Isaacs syndrome is an acquired immune-mediated disorder and approximately 40% of patients have elevated antibody levels. Recently, VGKC antibodies, especially against CASPR2 and, less often, LGI1 proteins, which regulates excitation of muscle in the neuromuscular junction, were identified in many patients diagnosed with Isaacs syndrome.[3] These antibodies are considered to cause hyperexcitability due to damage to the peripheral nerves. An inherited form has been described with the gene abnormality on KCNA1, KCNA2, KCNA6, KCNQ2, and CAV.[4]

Isaacs syndrome is also associated with certain autoimmune diseases (myasthenia gravis, thyrotoxicosis, systemic sclerosis, systemic lupus erythematosus, and demyelinating polyneuropathy).[2] Thyroid function tests, autoimmune encephalitis panels, anti-acetylcholine receptor antibody, anti-MUSK, ANA, and ANA profiles should be examined in these patients. Malignancy should also be screened with Isaacs syndrome because tumors such as small cell pulmonary tumors and Hodgkin lymphoma may be appeared as a paraneoplastic syndrome as Isaacs syndrome. Idiopathic patients with negative autoimmune antibodies and malignancy should be screened for malignancy periodically for a few years.[9] Our patient was evaluated as sporadic Isaacs syndrome because of a specific rheumatologic disease was not diagnosed despite antibodies positivity of ANA, anticentromere B, and DFS 70. However, a follow-up scheduled because of Isaacs syndrome may be a sign of rheumatologic diseases.

Symptoms of the PNH are relieved by administration of Na channel blockers and immunotherapy. All patients with severe symptoms and complaints affecting their daily activities should be given symptomatic treatment includes carbamazepine, phenytoin, valproate, lamotrigine, acetazolamide, gabapentine, or mexiletine. Due to evidence on the autoimmune etiology of the PNH, immunomodulatory treatments should be considered. Plasma exchange, corticosteroids, IVIG, cyclophosphamide, azathioprine, cyclosporine, and rituximab treatment can be used in patients who have not been treated adequately by symptomatic treatment and have a rapid course and severe symptoms.[1,6]. Gonzalez et al.[7] did not detect antibody positivity, treated their patients with oxcarbamazepine, and received a dramatic response to treatment in 1 week like our case. Oskarsson et al.[7] were able to treat with IVIG in patient with antACh receptor antibody positive, who was unable to obtain adequate response to benzodiazepine and phenytoin treatment. However, their patient continued to undergo IVIG treatment every 3 weeks because of recurrence. It has been reported in the literature that immunomodulatory therapy is more effective in patients with autoantibody positivity and likewise our patient rapid response to symptomatic treatment within 3–7 days.[8] Although our patient had ANA, VKGC Ab was not detected and symptomatic treatment was sufficient.

Isaacs syndrome, which is a rare acquired subtype of PNH, should be in the initial stage of differential diagnosis of neuromyotonia in children for the early appropriate treatment of the syndrome.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Sawlani K, Katirji B. Peripheral nerve hyperexcitability syndromes. Continuum (Minneap Minn) 2017;23:1437-50.
2. Gonzalez G, Barros G, Russi ME, Nuñez A, Scavone C. Acquired neuromyotonia in childhood: case report and review. Pediatr Neurol 2008;38:61-3.
3. Küçükali CI, Kurtüncü M, Akcay HI, Tüzün E, Öge AE. Peripheral nerve hyperexcitability syndromes. Rev Neurosci 2015;26:239-51.
4. Falace A, Striano P, Manganelli F, Coppola A, Striano S, Minetti C, et al. Inherited neuromyotonia: a clinical and genetic study of a family. Neuromuscul Disord 2007;17:23-7.
5. Rana SS, Ramanathan RS, Small G, Adamovich B. Paraneoplastic Isaacs’ syndrome: a case series and review of the literature. J Clin Neuromuscul Dis 2012;13:228-33.
6. van den Berg JS, van Engelen BG, Boerman RH, de Baets MH. Acquired neuromyotonia: superiority of plasma exchange over high-dose intravenous human immunoglobulin. J Neurol 1999;246:623-5.
7. Oskarsson B, Zawadzki L, Benke T, Quan D. Neuromuscular hyperexcitability associated with acetylcholine receptor antibodies in a child. J Child Neurol 2009;24:90-2.