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Case Report

Isaacs' syndrome-possible etiopathogenesis and clinical aspects: a case report

L. R. Sathisha Deshan Liyanage[1]*, Grishma Rajendrakumar Patel[2], Malevskaya Alexandra Sergeevna[1]

[1]Department of Neurology, Grodno State Medical University, Grodno, Belarus
[2]Department of Endocrinology, Grodno State Medical University, Grodno, Belarus

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***Correspondence:**
Dr. L. R. Sathisha Deshan Liyanage,
E-mail: sathishadeshan666@gmail.com

ABSTRACT

Isaacs' syndrome (IS) is a rare condition which is characterized by peripheral nerve hyperexcitability which is due to continuous motor activity. The exact etiology for this condition is unknown yet there are several etiopathologies like autoimmune, genetic, or hereditary which can be an etiology for the IS. In our case report the likely etiology is autoimmune. Its clinical feature includes fasciculation, myokymia, and hyperhidrosis. To confirm the diagnosis mostly imaging methods of examination are performed like MRI, ultrasound, and EMG. In our patient MRI and EMG examination was performed. There are no particular therapeutic treatments that can help in this condition only symptomatic treatment can be delivered. Plasma exchange has a promising outcome for a momentary. In our case report, we propose the possible etiology of the condition.

Keywords: IS, MRI, Plasmapheresis, Anti-TPO

INTRODUCTION

Isaacs' syndrome (IS), also referred to as neuromyotonia, is a disease of the immunological system.[1] One of the more severe variations of peripheral nerve hyperexcitability syndromes is IS; milder presentations of this spectrum include benign fasciculation syndrome, which is known to have a reciprocal relationship with anxiety, and cramp fasciculation syndrome.[2]

Only 100-200 cases of IS have been reported overall among the 41 countries in Orphanet's network of the afflicted population.[1] Of those affected, men make up the majority (67%), with a median age of 55. Nevertheless, patients as young as 15 years have been reported to have had the disease.[3] The interplay of genetic, autoimmune, and paraneoplastic variables in etiopathogenesis necessitates a thorough examination of underlying causes.[4] Genetic factor includes mutations in the histidine triad nucleotide-binding protein 1 (HINT1) gene on chromosome 5q31.1 have been identified in patients with autosomal recessive axonal neuropathy associated with neuromyotonia (ARAN-NM).[5] ARAN-NM is characterized by delayed muscle relaxation and spontaneous neuromyotonic discharges on EMG (electromyography).[6] The etiopathogenesis appeared to be a loss of function, possibly resulting in the accumulation of toxic metabolites.[5,7] Antibody-mediated autoimmune mechanisms directed against peripheral nerve voltage-gated potassium channels (anti-VGKC antibody), which regulate nerve excitability, are implicated[8] and leucine-rich glioma-inactivated protein (LGI1), and contactin 2.[3,9] CASPR2 and LGI are widely spread in the central nervous system and it has involvement on the pathophysiology as well as the CNS effects which were seen in some cases of IS; the proteins are frequently found in the neurons of the thalamus, hypothalamic, raphe nuclei and the locus coeruleus.[10] Neuromyotonia can also be seen in association with non-

immune-mediated conditions. There are case reports of associations with toxins such as lead and silver.[11]

However, there are 60% of patients with IS have no defined target.[12] IS is found to be associated with other autoimmune diseases including myasthenia gravis and Crohn's disease. It is also associated with certain neoplasms, of which thymoma is the major risk factor.[13] Due to the Peripheral nerve hyperexcitability, IS is characterized by spontaneous and or continuous muscle fiber activity together with generalized muscle twitching, muscle hypertrophy, and stiffness. As well as weight loss, hyperhidrosis, cramps, and continuous muscle-fiber activity.[4,14]

The widespread fasciculations and myokymia are noted. These are overlapping but distinct findings. Fasciculations are random, spontaneous twitches of a group of muscle fibers that produce movement of the overlying skin or mucous membrane. In contrast, myokymia is an undulating wavelike movement visible on the muscle surface.[15] Strength generally is normal, as are deep tendon reflexes. Distal sensory loss can be noted in a minority of patients.[2] Most often, the hypertrophy is in the calf muscles, but it can also be seen in the forearm and hand muscles.[16] The degree of hypertrophy corresponds to the severity of over activity in individual muscle groups and is usually bilateral.[16,17]

Two other clinical entities that should be considered when evaluating a patient with possible IS are cramp-fasciculation syndrome and rippling muscle syndrome.[11] Brain magnetic resonance imaging (MRI) scan can show exaggerated periventricular white matter hypodensity, and high signal intensity lesions in the bilateral hippocampus and hypothalamus on T2 weighted images with normal CT scan of the chest, abdomen, and neck.[18,19]

Patients usually respond to immune-active treatments, including steroids, intravenous immunoglobulins, plasma exchanges, and rituximab, and immunomodulatory treatments including high-dose intravenous immunoglobulins.[20] Rituximab can improve myokymia in the extremities and resolve severe pain.[21] Other drugs have been used less commonly for symptomatic relief, with variable success. These include valproic acid, acetazolamide, lamotrigine, and clonazepam.[22,23] Treatment with these agents may not be sufficient to effectively control symptoms of IS.[4] Oral agents alone can be used but are usually combined with intravenous therapy because of the more rapid onset of action.[19,24] Intravenous immunoglobulin (IVIg) has been reported to be less effective.[24] If there is no response or a poor response to plasma exchange, then IVIg is an alternative therapy. It is reasonable to begin oral steroids or immunosuppression concurrently, generally with prednisone and azathioprine.[25] If there are no contraindications, it is recommended to begin prednisone at 10 mg/day initially, increasing up to 60 mg/day as tolerated, in combination with azathioprine 2-3 mg/kg/day. The goal should be to taper and discontinue plasma exchange (or IVIg) and steroids after 4-6 months to allow the patient to be on a single oral immunosuppressive agent. While on azathioprine, regular monitoring of liver function and complete blood count is essential. Inactivation of azathioprine is catalyzed by thiopurine S-methyltransferase (TPMT). If the activity of this enzyme is low, then patients treated with azathioprine are at increased risk for myelosuppression, resulting in leukopenia.[26,27] The efficacy of therapy is assessed by monitoring the clinical response. Electrodiagnosis can be used as a secondary outcome measure. In most instances, after-discharges and abnormal needle examination findings improve after symptomatic or immunomodulating therapy.[28,29] Serial quantitative measurements of neuronal ion channel antibodies may help monitor disease progression and response to immune therapy.[30] The plasma exchange can be effective for a short period. So, there is a need for repetitive plasma exchange.[21]

CASE REPORT

In May 2023, 51 years old female was presented to the regional hospital of Grodno, Belarus with complaints of weakness of the hands more on the right hand, muscle twitching, and general weakness. According to her, since the summer of 2022, the above complaints have appeared. Gradually there was an increase in weakness in both hands and legs. At the time of 2022, she didn’t seek any medical help for these symptoms.

In February 2023, her symptoms worsened. Therefore, she decided to seek medical help. The patient presented with weakness in her hands, hypotrophy of the muscles, decreased sensitivity in her fingers, tremors in her hands, generalized fasciculation of the arm muscles, shoulder blades, and right thigh, mild paresis of the distal parts of both hands, pyramidal insufficiency of legs and decreased vision in both eyes. Therefore, she was referred to an ophthalmologist and it was revealed patient had retinal angiopathy. Patient also complained of mood fluctuations such as excitement, tearfulness, and insomnia. Based on medical history, patient’s complaints, objective data, and neurological status the provisional diagnosis was made as ALS (Amyotrophic lateral sclerosis). The patient was treated with amitriptyline 25 mg in the morning, 50 mg sulpiride in the morning, and zopiclone 7.5 mg at night as a sleeping pill. Medication did not give a positive result. Plasmapheresis was performed using ASTEC 204 (Fresenius, Germany), which increased slight muscle strength in her right hand for a short time. Therefore, repetitive plasmapheresis was carried out.

A radiological examination was done. MRI of the brain showed that there was thickening of the mucous membrane of the right maxillary sinus, up to 7x6 mm in size. MRI of the cervical spine revealed, degenerative changes in the cervical spine, disc protrusions at C3-C4, C5-C8 levels and disc extrusion at C4-C5 level,

subchondral edema on the left area of C5-C6 vertebral bodies and Modic type-1. Schmorl's bodies were also determined at the lower end plate of C5 and upper end plate of C6 vertebrae, the height and hydration of the discs at the level of C2-C7 was slightly reduced as shown in Figure 1.

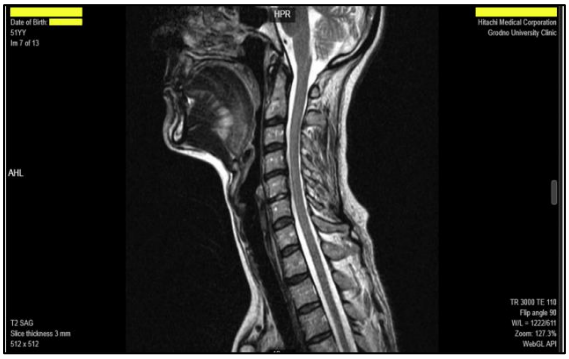

Figure 1: MRI of cervical spine showing degenerative changes.

EMG results determined that when stimulating ulnar and median nerves by f-waves the tremors lead to a lot of artifacts. When the f-wave was stimulated on the left side, the C8-Th1 conduction level along the proximal segment of the motor radicular system revealed blocks of 32% and repeated waves revealed blocks of 25%. Laboratory analysis was done on the patient. In complete blood count, WBC- 3.89×10^2/l, lymphocytes-46%, activated partial thromboplastin time (according to Sysmex time)- 32.6 sec, monocytes- 10.8%, neutrophils-42.9%, eosinophils- 0.50%, Hb-17 g/l. In hormonal analysis-there was an elevated level of anti-thyroid peroxidase (anti-TPO) of about 178.7 mIU/ml in biochemical analysis-creatine kinase-687 U/l, lactate dehydrogenase-324 U/l.

DISCUSSION

IS is a clinical and electrophysiological syndrome of spontaneous muscle fiber activity owing to hyperexcitability of peripheral nerve origin.[12] IS presents with muscle twitching, cramps, hyperhidrosis, and slow relaxation of a muscle after muscle contraction.[4] Our patient had symptoms of weakness, twitching, fasciculation of hand muscles, and decreased vision in both eyes. There can be several causes such as hereditary, genetic, immune-mediated, and other miscellaneous factors.[12] The etiology in our patient could be due to autoimmune, she had an elevated level of anti-TPO. Another method of establishing a diagnosis is performing an EMG with a high intra-burst of irregular frequency. The abnormal EMG is characterized by doublet, triplet, and multiplet single-unit discharges that were also present in our patient.[4,31] These changes are also known as myokymic and neuromyotonic discharges.[31] The EMG results of the patients showed f-waves and tremors with a lot of artifacts. Patients who had Morvan's syndrome have findings that are similar to those seen in IS, but they also have encephalopathy, headaches, drowsiness, and hallucinations.[4] The patient has not complained of hallucinations, headaches, or drowsiness nor has she had encephalopathy. Brain MRI scans can show exaggerated periventricular white matter hypodensity.[18] The patient's MRI revealed a thickening of the mucous membrane in the maxillary sinus. MRI of the spine revealed subchondral edema on the left area of C5-C6 vertebral bodies and Modic type-1. Schmorl's bodies at the lower-end plate of C5 and an upper-end plate of C6 vertebrae were observed, and the height and hydration of the discs at the level of C2-C7 were slightly reduced.

In a patient with IS, plasmapheresis resulted in a notable improvement in clinical status, which was accompanied by a reduction in both spontaneous motor unit activity and F-wave after discharge.[14] The patient showed improvement in muscle strength after the course of plasmapheresis for a short time and again the course was repeated.

CONCLUSION

A 51-year-old female was presented in the regional hospital of Grodno, Belarus. The patient presented with general weakness in muscles, muscle twitching, generalized fasciculation, decreased sensitivity in fingers, tremors, decreased vision in both eyes, and mood fluctuation. The exact etiology of her condition was unknown but the possible cause of her condition was an autoimmune; her anti-TPO level was greatly elevated. Hence, the anti-TPO could bind at the neuromuscular junction blocking the release of a trophic factor near the neuromuscular junction. Therefore, there can be elevated levels of LDH and creatine kinase levels as the result of muscle wasting. Her EMG revealed frequent artifacts and her MRI revealed thickening of mucous in the maxillary sinus, schmorl's bodies, and height and hydration of the discs at the level of C2-C7 were reduced. The patient showed improvement with the repetitive course of plasmapheresis treatment.

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