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Case Report *Medical research*

Isaacs syndrome : A rare clinical entity

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ABSTRACT

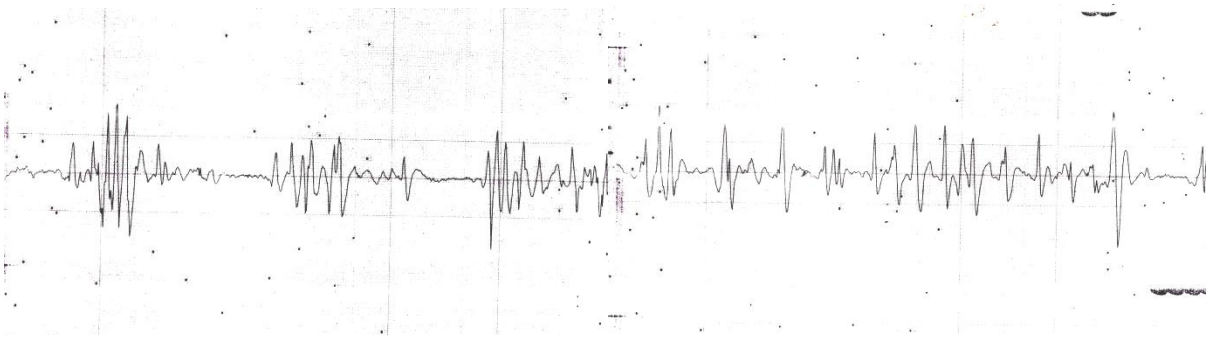
Neuromyotonia is a rare syndrome of continuous motor unit activity of peripheral nerve origin that manifests as various combinations of muscle stiffness, cramps, twitching and weakness. Isaacs syndrome is a form of acquired neuromyotonia due to an underlying autoimmune or paraneoplastic mechanism. We wish to report a case of acquired paraneoplastic neuromyotonia presented in neurology outpatient department with painful twitching of muscles all over the body for the last 6 months. While searching for an underlying cause a mass lesion was found in anterior mediastinum on radio imaging suggestive of tumor. Patient was treated with antiepileptic drugs and intravenous immunoglobulins. Tumor was removed through thoracoscopic surgery, which on histopathological examination was confirmed as thymoma. Patient responded well to treatment and after a month patient was completely asymptomatic with no fresh complaints.

INTRODUCTION

Isaacs syndrome or acquired neuromyotonia is a rare immune mediated neurological disorder characterized by abnormal continuous muscle activity generated by spontaneous activity in peripheral motor nerves resulting in muscle cramps and fasciculations. This is a case of acquired paraneoplastic neuromyotonia/ Isaacs syndrome.

CASE REPORT

A 35 years male presented in Neurology outpatient department with complaints of painful muscle cramps all over the body for last 6 months. There was no history of fever, joint pains, altered sensorium/behavior, seizures, memory loss, muscle weakness, sensory deficit. There was no history of any chronic illness or similar complaints in the past. There was no history of similar complaints in family members. On examination patient was conscious, oriented and anxious. His vitals were stable. Higher mental functions and all cranial nerve were intact. Motor examination showed muscle fasciculations which were seen predominantly over shoulder and leg muscles with normal tone, bulk and power in all four limbs. Deep tendon reflexes were normal (2+) in all four limbs. Gait and coordination was normal. Sensory examination was also normal. Rest of the systemic examination was also within normal limits. Routine laboratory investigations were within normal limits. Thyroid function test was also within normal limits. Nerve conduction studies were within normal limits. Electromyography showed fasciculations and neuromyotonic discharges. A diagnosis of neuromyotonia was made on the bases of clinical and electromyography findings. Patient was started on carbamazepine and phenytoin.

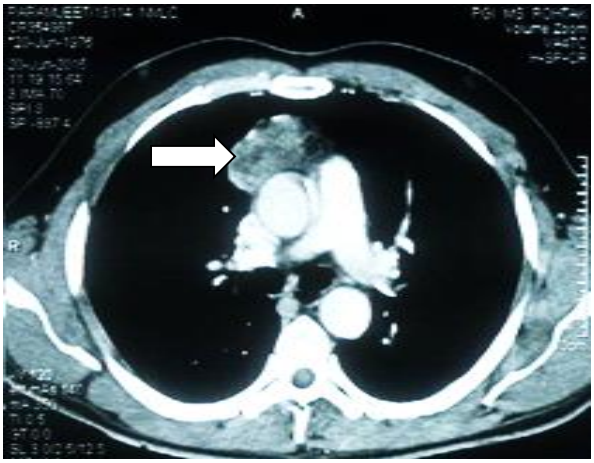


A B

EMG A (right deltoid) & B (left posterior tibialis) showing spontaneous Moto unit action potential discharges (fasciculations)

To rule out an underlying autoimmune etiology, test for autoantibodies like antinuclear antibodies, anti-VGKC antibodies, anti-LG1 antibodies and anti-CASPR-2 antibodies, anti Hu antibodies, antiYo antibodies were negative. A CECT chest and abdomen was done to rule out an underlying tumor, which showed an anterior mediastinal mass (as shown below). A whole body 18F-FDG PET scan also showed an abnormal high uptake in anterior mediastinum suggestive of tumor. Patient started on IVIG given at dose of 400 mg /Kg/day for 5 days and tumor was removed with video assisted thoracoscopic surgery which was on histopathological examination was confirmed as thymoma (Type B2, Stage IIa). Perioperative period was uneventful and patient recovered well. On follow up after discharge patient was completely asymptomatic after one month.

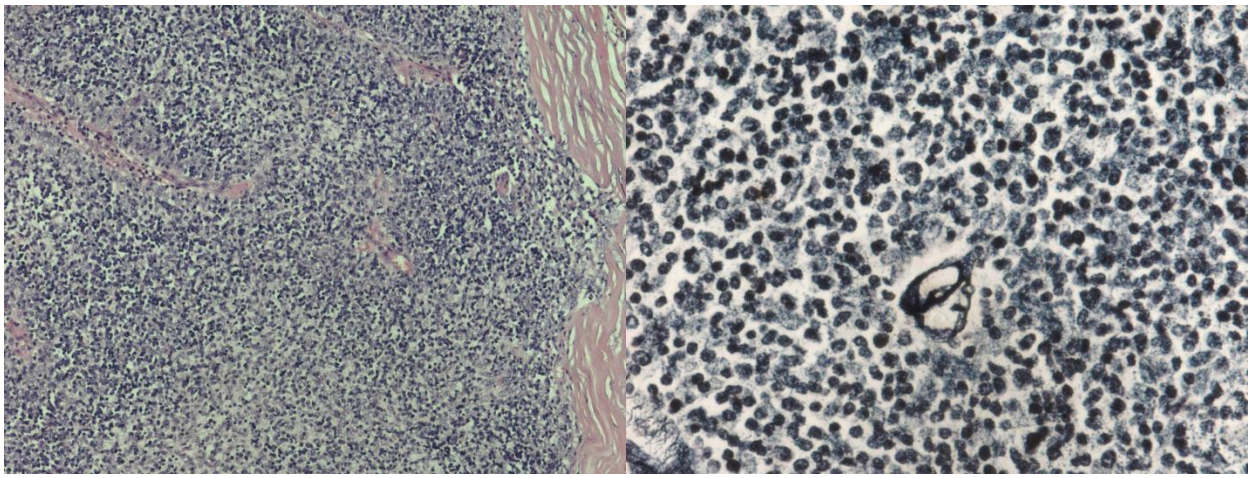
CECT thorax: - showing anterior mediastinal mass



DISCUSSION

Isaacs syndrome (also known as neuromyotonia, Isaacs-Mertens syndrome and continuous muscle fiber activity syndrome) is a rare disorder where hyperexcitability of peripheral motor nerves leads to incapacitating muscle twitching and cramps. This uncommon disorder was first described in 1961 by Hyam Isaacs in his paper 'A syndrome of continuous muscle-fiber activity giving the triad of myokymia, muscular stiffness, and decreased deep tendon reflexes [1]. This abnormal activity persists during sleep. Dyspnea may occur when respiratory muscle is involved. There have been only a few reports of bulbar and laryngeal involvement in Isaacs syndrome. The tongue and jaw become stiff, making swallowing difficult, and the voice turn hoarse. Peripheral nerve hyperexcitability is the chief manifestation of Issacs syndrome. However, in addition to neurological symptoms involving the peripheral nervous system, autonomic symptoms like hyperhidrosis, severe constipation, urinary incontinence, and cardiac arrhythmia and central

nervous system symptoms like severe insomnia, hallucinations, impairment of short-term memory and epilepsy can be associated with neuromyotonia [2]. This syndrome of neuromyotonia with autonomic and central nervous system symptoms is recognized as Morvan syndrome. The underlying etiopathogenesis involves an autoimmune mechanism where autoantibodies are usually detected against the Voltage-Gated Potassium Channel (anti-VGKC antibodies). These antibodies are directed against leucine rich glioma inactivated protein 1 (LGI1), contactin associated protein 2 (Caspr2) and other unknown proteins that form a complex with VGKC [3]. Tumors like thymoma, hodgkin lymphoma, plasmacytoma, bronchogenic carcinoma can be associated with neuromyotonia [4].



A B

Images A & B: - Sections from the tumor revealed cellular nodules consist of small lymphocytes mixed with large polygonal epithelial cells with open chromatin and prominent central nucleoli. Focal extracapsular tumor extension noted.

This has been area of interest to find association between infectious diseases and neuromyotonia [5]. This syndrome may also be associated with other autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy, myasthenia gravis or the presence of antiacetylcholine receptor antibodies [6]. The diagnosis of Isaacs syndrome is based on clinical features and electromyography findings. Classical electromyography studies detect myokymic and neuromyotonic discharges. In addition, fasciculations, doublet, triplet and positive sharp waves are also demonstrated in this syndrome [7].

Treatment of Isaacs syndrome with antiepileptic drugs or immunotherapy often improves the clinical and electrophysiologic findings. Carbamazepine, phenytoin, lamotrigine and sodium valproate can be used alone or if necessary in combination. Paraneoplastic neuromyotonia usually improves after treatment of the underlying tumor [8]. In patients whose symptoms are debilitating or refractory to symptomatic therapy, immunomodulatory therapies should be tried. Plasma exchange often produces useful clinical improvement lasting from 6 weeks up to 6 months. Treatment with intravenous immunoglobulins is recent lines of management with good response. There are no good trials of long-term oral immunosuppression. However, prednisolone, with or without azathioprine or methotrexate, has been useful in selected patients [8] [9].

This case highlights several important aspects of evaluation and management of patients with acquired neuromyotonia/Issacs syndrome. There is well known association between neuromyotonia and thymoma, so screening for thymoma should be a routine part of the diagnostic evaluation in patients with neuromyotonia.

CONCLUSION

Issacs syndrome or acquired neuromyotonia is an autoimmune disorder that should be recognized clinically and diagnosed using specific autoantibody tests. Patients with this disorder should also be screened for tumors.

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