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ISAAC syndrome

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SUMMARY

ISSAC Syndrome is a form of peripheral nerve hyperexcitability caused by continuous muscle fiber activity. The patient usually presents with the complaints of twitching and stiffness. Symptoms such as myokymia and muscle spasm, may persist during sleep. The patients are reported to be CASPR2 antibody positive which is ought to be the pathogenic antibody in ISSAC Syndrome. The patients are commonly treated with immunomodulatory therapies which includes steroids, plasma exchange therapy and rituximab for nonresponsive cases. Treatment also includes symptomatic management which has no effect on disease progression.

Keywords: ISSAC syndrome; Steroids; Pseudomyotonia.

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INTRODUCTION

ISSAC Syndrome is a rare acquired autoimmune disorder characterized by peripheral nerve hyperexcitability in form of spontaneous continuous skeletal muscle over activity presenting as twitching and painful cramps it is often associated with stiffness, pseudomyotonia, pseudotetany and weakness [1,2]. Patients are commonly treated with symptomatic therapies such as carbamazepine, valproate, phenytoin with no clinical improvement [3,4]. While immunomodulatory approaches are still the mainstay for the treatment, no clinical trial is available to date and specific management is unknown. A pathology of antibody mediated autoimmune mechanisms directed against peripheral nerve voltage gated potassium channels (anti-VGKC antibody), which regulate nerve excitability, is implicated [5]. There are 60 percent of patients with Isaac syndrome having no defined antibody target [4].

Here we are reporting a case of a CASPR 2 and LGI 1 antibody positive patient who presented with continuous muscle twitch on his lower limb and diffuse muscle pain. He was treated and showed good clinical response to immunomodulatory therapy.

CASE PRESENTATION

Our patient is a 34-year-old man who is admitted with complaints of severe backache and paresthesia. However, he had no decline in cognitive function or impairment of higher mental functions. Examination showed fasciculations on her bilateral lower limbs. Power was 5/5 and symmetrical in all four limbs. Radiological investigations such as MRI Brain and MRI Sacroiliac Joint showed no significant abnormality and PET SCAN did not show any uptake. Nerve Conduction Velocity revealed a normal study. Serological studies including ANA vasculitis Pannel was negative. Serum negative HLA B27 was Negative, while Autoimmune Encephalitis panel showed LGI-1 antibody (VGKC type) as well as CASPR2 antibody positivity. Electromyography was done which showed continuous and spontaneous irregular duplets and triplets from a single motor unit in bilateral FDI, Vastus Lateralis, and right Gastrocnemius Muscle. Electrophysiological study showed neurogenic pattern with evidence of active denervation and reinnervation, suggestive of anterior horn cell disease (**Fig. 1**).

After a few days of conservative management, methylprednisolone therapy was initiated with a dose of

Fig. 1. EMG findings.

EMG FINDINGS:-

Electromyography :- Concentric needle electromyography evaluation was done in below mentioned Muscles. Spontaneous muscle activity, motor unit potentials and recruitment pattern was recorded in the sampled muscles.

Muscle	Spontaneous activity			MUAP			Interference
	Fib	PSWs	Fasciculation	Amplitude (mV)	Duration (ms)	Polyphasia	
Rt FDI	-	Couplets	+	0.8-1.0	8-10	-	Complete
Lt FDI	-	Triplet	+	1.0-1.2	10-12	-	Complete
Rt Biceps	-	-	-	0.8-1.0	8-10	-	Complete
Lt Biceps	-	-	-	0.8-1.0	810	-	Complete
Rt TA	-	Couplet	-	0.8-1.0	8-10	-	Complete
Lt TA	-	-	-	2.0-2.5	20-25	+	Moderate
Rt VL	-	-	+	1.2-1.5	12-15	+	Moderate
Lt VL	-	-	+	0.8-1.0	8-10	-	Moderate
Rt Gastoc MH	-	Myotonia	+	0.8-1.0	8-10	-	Complete

EMG FINDINGS:- Spontaneous activity were seen in the form of fasciculation in bilateral FDI,VL & right gastrocnemius Medial head with couplet and triplet MUAP. Large amplitude, long duration with polyphasic MUPs with moderate interference pattern was seen in bilateral VL muscles,Myotonia were seen in right gastrocnemius medial head with normal MUAP and complete interference pattern. Normal EMG is seen in bilateral biceps & right TA muscles.

Impression:- EPS study is showing of neurogenic pattern with evidence of active dennervation & reinnervation , suggestive of myokemia peripheral nerve hyperextremity.
Please correlate clinically.

1 gram for three days, showing clinical improvement and then again for 2 more days to a total of 5 days. It was then switched to oral steroids that were tapered off in a span of 2 weeks. Patient was also started on plasma exchange therapy for 5 days on alternate days. After the full course of treatment, the patient showed clinical improvement and recovered significantly.

DISCUSSION

Acquired neuromyotonia also known as ISSAC Syndrome is described as persistent generalized muscle twitching and stiffness associated with spontaneous motor unit action potential on needle electromyograph. ISSAC Syndrome is a peripheral nerve hyperexcitability syndrome of spontaneous muscle fiber activity resulting in hyperexcitability of peripheral nerve origin. It is reported to be twice as common in males than females and the average age of onset is the mid-40s.

The pathological Hallmark of ISSAC syndrome is the anti VGKC complex antibody binding to LGI 1 and CASPR 2 which are the components of VGKC complex [6]. Among these, LGI 1 is a neuronal protein which is expressed predominantly in hippocampus and associates specifically with Kv1.1 subunits in CNS presynaptic terminals [7]. LGI 1 is strongly associated with encephalitis, specifically limbic encephalitis.

The CASPR 2 is a transmembrane protein which is required for localization of Kv1.1 and 1.2 at the juxtaparanodes [8]. CASPR 2 antibodies are found in ISSAC syndrome or Morvan's Syndrome. Morvans Syndrome is a rare condition which presents with neuromyotonia plus autonomic disturbance and CNS involvement that includes insomnia and confusion [9]. Our Patient is both CASPR 2 and LGI 1 positive and has no autonomic disturbance.

ISSAC Syndrome presents with muscle twitching, cramps, hyperhidrosis, slow relaxation of muscle after muscle contraction [10]. Diagnosis can also be made by EMG showing high intraburst of irregular frequency. The abnormal EMG is characterized by doublet, triplet ad multiplet single unit discharges which is also seen in our present case [10,11]. These changes are also known as myokymic and neuromyotonic discharges [11].

Clinically ISSAC syndrome patients show improvement in symptoms with Immunosuppressive and Immunomodulatory therapy, this improvement is reflected in the antibody levels as well. In some reported cases the antibody levels become undetected with the Immunomodulatory therapy [4].

ISSAC Syndrome 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. A PET scan is therefore may be sometimes required in case of doubt and no signs and symptoms. Sometimes this syndrome is presented years before the neoplasm is discovered [12-14]. Certain studies have shown association of neoplasm to be as high as 31.6% with CASPR 2 antibody positivity [7].

CONCLUSION

Management of Issac Syndrome includes symptomatic treatment at first with Carbamazepine, phenytoin, sodium valproate, which can be used in combination if necessary. Suggested treatment includes steroid pulse dose along with plasmapheresis in cases not responding to steroids alone. Refractory cases can be managed with an immunomodulator's, mainly azathioprine or methotrexate. In some refractory cases, Rituximab showed to be effective. In cases associated with neoplasms, improvement after removal of an underlying neoplasm is reported.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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None.

CONSENT OF PUBLICATION

Written consent is obtained for the paper.

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