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NATIVE MEDICATION INDUCED ANTI-VGKC AUTOMMUNITY AND NEUROMYOTONIA: A CASE SERIES OF 4 PATIENTS FROM A TERTIARY CARE CENTRE.

Neurology

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ABSTRACT

Isaac's syndrome or Neuromyotonia is a disorder characterized by continuous muscle fiber activity with peripheral nerve hyperexcitability and typical electromyography features . The acquired form occur with autoimmune diseases, paraneoplastic syndromes and toxins. We describe 4 patients in whom Neuromyotonia was diagnosed after consumption of ayurvedic medications and was confirmed by presenting symptoms, physical examination , electrophysiologic findings and auto-antibody results. There could be suboptimal or undetectable levels of heavy metals/ elements triggering autoimmunity in these ayurvedic preparations. They expose VGKC channels on nerve endings leading to prolonged repolarization and Neuromyotonia. Immediate identification and withdrawl of drug is needed for amelioration of symptoms with prompt immunosuppressive therapy.

KEYWORDS

Neuromyotonia; ayurvedic medication; VGKC channels.

INTRODUCTION:

Isaac's syndrome/Neuromyotonia, initially described by Isaac[1] in 1961 is a rare disorder characterized by muscle twitching, stiffness, and cramps of extremity muscles. The symptoms of continuous muscle fiber activity persist in wakefulness and sleep. Other symptoms include weakness , hyperhidrosis/ paresthesias and weight loss along with sleeplessness and restlessness. There have been reports of patients having neuromyotonia with encephalopathy manifesting as confusion, hallucinations, agitation and insomnia. The triad of neuromyotonia, encephalopathy, and hyperhidrosis is referred to as Morvan syndrome. This could be due to either genetic or acquired causes. The acquired form occurs with autoimmune diseases, paraneoplastic syndromes and toxins. On electrophysiologic studies, nerve conduction studies in Isaacs' syndrome is usually normal . The diagnosis is made on EMG, which reveals continuous firing of motor unit potentials even at rest and myokymic discharges occurring in duplets, triplets, or multiplets with characteristic high intra-burst frequency of 150-300Hz[2]

The primary interest of this review is to describe Neuromyotonia syndrome caused by intake of indigenous medications. There are various reports in the literature linking neuromyotonia to native medicine intake. We describe four patients ,who were admitted in neurology unit in our tertiary care centre, in whom Neuromyotonia was diagnosed following consumption of ayurvedic medicinal preparations for different ailments. The diagnosis was confirmed by the presenting symptoms, physical examination , electrophysiologic findings along with auto-antibody results.

Case 1:

A 52 year old right handed male, a chronic smoker and case of T2 Diabetes mellitus for the last 6 years on regular medications p/w 2 months history of pain and burning paresthesia's in both feet along with visible calf muscle twitching and hyperhydrosis. He had taken local ayurvedic medicine in the form of tablets for 3-4 months prior to the onset of these symptoms. These symptoms started after 3 months of starting of consumption of this medication. On examination, positive findings included intermittent myokymic contractions of gastrocnemius muscle with hyperhidrosis with diminished reflexes. On electrical testing, nerve conduction studies were normal. The needle portion of his study revealed frequent fasciculations and myokymic discharges in distal leg muscles. Laboratory findings included elevated Anti-VGKC/ Caspr2 antibodies. Heavy metal screening was negative. The diagnosis of Isaac's syndrome was based on the clinical presentation/ EMG findings and elevated VGKC antibodies. Initially he was managed with Tab. Carbamazepine and Tab.Pregabalin, but did not find any relief. Hence he was administered IVIG injection following which he showed improvement in his symptoms within 4 months.

Case 2

A 22 year right handed female presented with 4 months history of pain and cramps in lower limb every 15-20 days. For the last 2 months ,she had visible twitching in both calf region and arm region along with burning dysesthesia's and excessive sweating in palms and soles. She received some ayurvedic powder for last 6 months for well being. On examination there was myokymia in both calf and arm region. Nerve conduction studies were normal and EMG was suggestive of myokymic discharges. Heavy metal screen was negative. Anti- VGKC / anti-caspr2 antibody results were positive. She was managed with injection Methyl Prednisolone 1gm for 5 days and Tablet carbamazepine. Patient had good improvement with considerable relief in symptoms over a period of 2 months.

Case 3

A 40 year old right handed male, a chronic alcoholic for the last 8 years, received local ayurvedic powder for last 4 months as deaddiction therapy following which he developed weakness with visible calf muscle twitching/ burning dysaesthesia's in both feet for last 1 month. On examination, myokymic twitchings were seen in widespread distribution in calf muscle region . No weakness or sensory deficits were noted. Deep tendon reflexes were hypoactive. EMG studies revealed myokymic discharges in multiple muscles. Patient had received IV Methyprednisolone injection in a private hospital but his symptoms kept increasing. Computed tomography scans of the chest, thorax, and abdomen were negative. His heavy metal screening was negative. Laboratory screen showed Anti- VGKC antibody/ caspr-2 to be positive. He was given IVIG Injections after which he showed significant improvement over the next 2 months.

Case 4:

A 66 year old male, a chronic smoker came with history of sudden onset weakness in the right upper limb with full recovery in one month, after which he was put on ayurvedic treatment for 2 months. Now

patient had developed abnormal twitching movement of muscles of whole body, restlessness,decreased sleep and irritability. On examination fasciculation and rippling of muscles was present in whole body. There was also facial flushing. MRI Brain showed sub acute infarct in left parietal area with chronic periventricular ischaemic changes. EMG showed triplets and quadruplets s/o neuromyotonia. His heavy metal screen was negative. So serum for VGKC Antibodies was sent which was positive. Patient was started on IVIG therapy after which he improved in a month .

DISCUSSION :

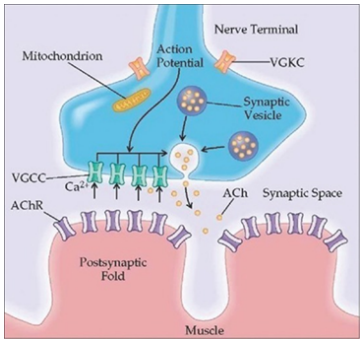
The involvement of immune system in Neuromyotonia has been demonstrated in earlier reports[3,4] and they put forward that autoimmune antibodies to the VGKC channels, present in the peripheral nerve terminals are central to the origin of these continuous discharges in muscle fibres. Furthermore the association between thymoma; LEMS[5] and other paraneoplastic syndromes support the autoimmune phenomenon. Increase in CSF proteins does provide an indirect evidence and positive autoimmune antibodies in serum strongly support the involvement of immune system. There are various reported case studies , where in toxin/ heavy metal and drug induced neuromyotonia's have been recorded with a temporal association of intake of these preparations and onset of Neuromyotonia. Zhou et al[6] described 3 patients with subacute onset of motor neuron hyperexcitability with mercury poisoning. Pencillamine administration and Gold in rheumatoid arthritis has been associated with acquired neuromyotonia[7]

India is a diverse country even in the aspect of existing medicinal systems. There are many forms like Ancient ayurvedic medicine, Homeopathic medicine , siddha medicine , naturopathy etc co-existing with the modern medicine. These indigenous medicines contain complex mixture of heavy metals / minerals and other herbal extracts. Heavy metals and minerals in native form are toxic to the human body. They undergo a purification process where in they are subjected to high heat and melting processes to alter their physical and chemical nature. One modified powdered form famously called Bhasma is widely used in ayurvedic medicine[8].It is a form of Powdered ash which is prepared in two stages: shodhan(purification) and maaran (incineration). In Shodhan, the metals are mixed with various herbal extracts, cow urine, milk, ghee, and so forth and subjected to trituration. Then they undergo repeated cycles of incineration called Maaran(incineration) thus forming final powdered ash that is Bhasma[9,10]

There was history of ayurvedic medicine (tablet form in1 ; bhasma in two patients and nature unknown in 1 patient) intake for around 3-6 months in all 4 of our patients for various ailments. There was a lag period of 2-4 months before the onset of undulating muscle twitchings. These drugs were withdrawn after hospital admission. Meanwhile, all causes were excluded to establish a temporal association between the ayurvedic preparation intake and the onset of neuromyotonia.

The mechanisms by which these ayurvedic preparations induce autoimmunity is being tried to put forward in this paper, with background studies in mind and theories proposed earlier are indirectly being consolidated. These native medications contain some elements in suboptimal levels which target the peripheral nerves and expose the VGKC channels . The VGKC channels lying exposed on the nerve endings become vulnerable to the body's immune mechanism and the body produces antibodies against these channels causing peripheral nerve excitability followed by the myokymic discharges seen in the muscles. Normally, action potential is generated in the peripheral nerve terminal by opening of the Voltage -gated calcium channels. Repolarization of peripheral nerve terminal occurs due to opening of the VGKC [Figure 1[11]]. Antibodies to VGKC causes incomplete opening of potassium channels[12], hence poor repolarization, and prolonged opening of calcium channels result in excessive entry of calcium in the nerve terminal along with excessive release of acetylcholine ultimately causing continuous muscle fibre activity. Also studies have been done where patient's plasma or purified IgG was injected into mice and it enhanced in-vitro resistance to d-tubocurarine at the neuromuscular junction of diaphragm muscle preparations[3]. It further adds that increase in neurotransmitter release is due to reduction in number of functional potassium channels.

Figure 1[12]:



Motor nerve terminal showing voltage-gated potassium channels and voltage-gated calcium channels

Similar observations were made by G. Gnanashanmugam et al[12] where in mercury toxicity was seen due to unauthorized siddha medicine intake in a case series of 32 patients with NMT and 12 patients had positive antibodies to VGKC Channels. In all four of our patients, the blood heavy metal screen was negative. This indicates that there could be suboptimal levels/ doses of metal compounds which can induce autoimmunity against VGKC channels. Also there could be many other extracts ,in these indigenous medicines which are capable of inducing autoimmunity against these medications.

The initial lag period noted which may be needed to trigger autoimmunity / positive serum anti-VGKC(CASPR2 antibodies) in all 4 patients along with excellent response to IVIG and Methylprednisolone further more supports the theory of these ayurvedic preparations as a causative agent in triggering autoimmunity by exposing the VGKC channels. One of the largest 20 patient case series jotted down by Pangariya et al[2] from north west India also strikingly demonstrated the association between ayurvedic drug intake and Neuromyotonia.

An important point that should be stressed upon is the treatment. In all four of our cases, there was poor response to conventional drugs (Carbamazepine and Pregabalin in their optimal dosages) .There was excellent response seen to IVIG administration in 3 of our patients and 1 patient responded to initial IV MPS administration. All patients ultimately needed immunosuppressive therapy along with withdrawl of the offending drug. Intravenous Immunoglobulin was given in 3 patients and IV MPS in 1 patient. They improved significantly with reduction in these myokymic discharges over a period of 4-6 months. Similar response with IV MPS injection was seen in the case series of Pangariya et al. where they noted significant EMG and clinical response to IV MPS injections which was not used in earlier studies .Similar results were reported by Gnanashanmugam et al[13] in patients of neuromyotonia triggered by mercury toxicity caused by siddha medicine intake. Significant response to plasmapheresis is published in earlier literature.

CONCLUSIONS :

Indigenous medicine intake, specifically ayurvedic preparations in powdered form called Bhasma and other forms can induce acquired Neuromyotonia. There could be suboptimal or undetectable levels of elements/ metals that can trigger autoimmunity and there still could be many enigmatic entities yet to be discovered in these ayurvedic preparations. They expose VGKC channels on these nerve endings and lead to prolonged repolarization and increased acetylcholine release at the neuromuscular junction leading to continuous muscle fibre activity. Immediate identification and withdrawl of the drug is needed for amelioration of symptoms. Another important issue was poor response noted to conventional symptomatic medications. They promptly need immunosuppressive therapy. Considering IVIG / MPS as therapy in auto-antibody positive patients early can lead to quicker resolution of symptoms. Other point which we would like to add is that the lacunaes in the preparation and dispensing of these indigenous medications, have to be identified sooner than later with making of strict protocols.

Limitations of our study:

Larger studies are required to elucidate in detail, the theory of autoimmunity put forward ,as we had limited number of cases. Further more we could not chemically analyse and look for heavy metal

content of these ayurvedic preparations by standard methods, as there was no facility available. Follow up antibody levels after withdrawl of drug and immunosuppressive therapy could not be obtained because of limited resources , which could have added weightage to the study.

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