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CLINICAL SPECTRUM OF MORVAN SYNDROME: A SINGLE CENTRE STUDY

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ABSTRACT **INTRODUCTION**: Morvan syndrome (MoS) is a rare autoimmune disorder characterised by peripheral nerve hyperexcitability, autonomic dysfunction and central nervous system symptoms. It has strong association with autoantibodies to voltage gated potassium channel complex. **METHODS**: This was a prospective observational study. We reported 6 cases of Morvan syndrome. Clinical features, investigations, treatment and outcome were described and review of literature was done. **RESULT**: All subjects were male. Myokymia and insomnia were present in all patients and no patient had seizure. Voltage gated potassium channel (VGKC) antibody was positive in 66% (n=4) of subjects, all four were positive for CASPER2 and 2 were also weakly positive for LGI1. All patients were treated with immunomodulation and we found good response to therapy. Pain was treated with carbamazepine and phenytoin. **CONCLUSION**: Morvan syndrome, a VGKC antibody spectrum disorder, is a clinical diagnosis. We found myokymia and insomnia in all patients and no patient had seizure. In our study, response to immunotherapy was good. Awareness about MoS is necessary, as it can be treated successfully.

KEYWORDS : CASPR2, Morvan syndrome, Myokymia, voltage gated potassium channel antibody

INTRODUCTION-

The first description of Morvan syndrome (MoS) or Morvan's fibrillary chorea was in 1890 by Augustin-Marie Morvan. [1] Morvan syndrome is a rare autoimmune disorder characterised by peripheral nerve hyperexcitability, autonomic dysfunction and central nervous system (CNS) symptoms. It has strong association with autoantibodies to voltage gated potassium channel complex that are CASPER2 (Contactin Associated Protein 2),LGI1 (Leucine rich Glioma Inactivated 1 Protein) and contactin 2.[2, 3] CASPR-2 lies in the hippocampal membrane and in the paranodal membrane in peripheral nerves, and anti-CASPR-2 antibodies give rise to the most of the clinical manifestations.[4] Variable and multifocal clinical presentation of MoS is due to selective binding of VGKC antibodies to various neural structures. Very few studies are available regarding MoS from India till now. [5] Being a treatable disease with high mortality, awareness and early diagnosis is important. Hence, we planned to study the clinical spectrum of Morvan syndrome.

METHODS:

This was a prospective observational study conducted from July 2017 to June 2020 a tertiary care teaching hospital of western India. We reported 6 cases of Morvan syndrome. The diagnosis of MoS was suspected based on characteristic central nervous, peripheral nervous and autonomic nervous system dysfunction. Demographic profile and clinical features were noted. Antibodies to voltage gated potassium channel complex, electromyography (EMG), electroencephalography (EEG), Magnetic resonance imaging (MRI) of brain, cerebrospinal fluid examination and whole body positron emission tomography (PET) were done in enrolled subjects. Treatment modalities used and response to therapy were observed. Patients were followed for relapse.

RESULTS:

All enrolled subjects were male and age ranged from 28 to 58 years (mean = 48). Features of CNS involvement as insomnia and peripheral nervous system hyperexcitability as myokymia were seen in all subjects. Autonomic dysfunction as orthostatic hypotension and hyperhydrosis were seen in 66% (n=4) subjects. No subject had seizure. Other clinical features noticed were agitation (16.66 %, n=1), hypertension (16.66 %, n=1), delirium (n=2, 33.33%) and neuropathic pain (n=2, 33.33%). Voltage gated potassium channel antibody was positive in 66% (n=4) of subjects and all four were positive for CASPER2. Out of these four, 2 were also weakly positive for LGI1. (Figure 1)

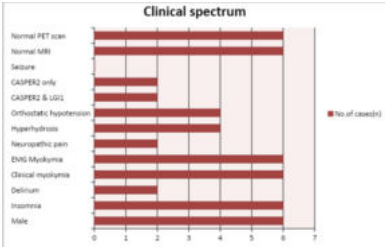

Figure 1: Clinical Spectrum of Morvan Syndrome patients

Neuromyotonia was observed in all patients and confirmed with electromyography. MRI Brain, EEG and cerebrospinal fluid examination were normal in all subjects. Whole body PET CT scan for primary tumour was normal.

Four subjects were treated successfully with injection methyl prednisolone 1 gm once a day for 5 days followed by oral steroid. Oral steroid was given (1mg/kg dose) for 6 weeks followed by slow taper and low dose oral steroid continued for 6 months. However, 2 subjects with LGI1 positive required additional treatment with intravenous immunoglobulin and in these subjects azathioprine was added to low dose steroid. In these patients, prolonged immunosuppression was considered. Pain was treated with phenytoin and carbamazepine. (Table 1) On follow up of about 1 to 3 years, no relapse was observed.

Table 1: Treatment modalities and outcome of Morvan Syndrome patients

Case no	Steroid/IVIG/ Plasma exchange	Response	Treatment of pain	Relapse	Follow up
1	IVIG + steroid+ azathioprine	Yes	CBZ	No	36 months
2	Steroid	Yes	CBZ + Phenytoin	No	34 months
3	Steroid	Yes	CBZ	No	27 months
4	IVIG + steroid+ azathioprine	Yes	CBZ+ Phenytoin	No	24 months
5	Steroid	Yes	CBZ	No	22 months
6	Steroid	Yes	CBZ	No	18 months

(IVIG- intravenous immunoglobulin, CBZ- carbamazepine)

DISCUSSION-

Morvan syndrome is a clinical diagnosis and it is characterized by central, autonomic and peripheral nervous system dysfunction. The central nervous system features include encephalopathy, insomnia, complex hallucinations, spatial and temporal disorientation, amnesia and agitation. The autonomic nervous system features are excessive sweating, salivation, and lacrimation, and fever, pruritus, constipation, arrhythmias, hypertension, and weight loss. The peripheral nervous system features are peripheral nerve hyperexcitability resulting in continuous muscle fiber activity (neuromyotonia, clinically manifest as myokymia), neuropathic pain and areflexia. Myokymia, insomnia and hyperhidrosis are usually present. Variable clinical presentation is due to presence of different antigens of VGKC antibody and selective binding. Neoplasia (56%), VGKC-antibody positivity (79%) and autoimmunity (41%) are frequent associations. [6]

Previously heavy metals were described in etiology of MoS; however recent evidences support an autoimmune etiology with strong association with autoantibodies to voltage-gated potassium channel complex (VGKC). It is probably autoantibody mediated but the nature

of the dysfunction and the targets for the antibodies are not clear. Recent study raises possibility of infectious trigger as they found four cases in short time span. [7] Similar to other studies [2, 8], all patients were male. High incidence in male is explained by rich source of antigen in male reproductive system, mainly prostate. Contrary to the available literature, recent study reported MoS in young girl with VGKC positive [9].

Morvan syndrome was not reactive to CASPR2 and LGI1 in our two patients, suggesting the existence of unknown antibodies against other antigens of VGKC complex. Diseases associated with VGKC antibodies with unknown antigen are peripheral neuropathy, neuropathic pain, fever-induced refractory epileptic encephalopathy (FIRES), rapidly progressing dementia, Creutzfeldt - Jakob disease and epilepsy. [10]

Association of CASPR2 with tumor (mainly thymoma) in 20% of cases has been described in literature [11], however we didn't find tumor our patients. There is a strong association of MoS with tumor. So, regular evaluation for tumor on follow up is needed to consider non-paraneoplastic MoS. In our study, due to limited resources we could not evaluate our patients for associated other autoimmune disorders.

Close differentials in MoS are limbic encephalitis and acquired neuromyotonia (Issac syndrome). Limbic encephalitis has memory disturbances, seizures (usually complex partial seizure), and temporal lobe structural abnormalities on neuroimaging. Limbic encephalitis patients have antibodies to LGI1. There is clinical overlap between MoS and limbic encephalitis. Issac syndrome has only peripheral nervous system involvement and no central or autonomic nervous system involvement like MoS.

Treatment of MoS is with immunosuppressive therapy with corticosteroids, azathioprine, methotrexate, cyclosporine, cyclophosphamide or rituximab. Refractory cases treated with plasma exchange (more effective) and intravenous immunoglobulin (IVIG). [12] In our study, response to immunosuppressive therapy was good. Available literature also observed favorable response (86%) to immunotherapy. [6] However, heterogeneous response to immunomodulation is reported in MoS. Although reason is unclear, it can be due to associated tumour or other autoimmune diseases. Recent study reported mortality of 22% in MoS. Prognosis is poor if associated with thymoma. In our study, after 1 to 3 years of follow up, we didn't observe relapse. Although no data is available about relapse in MoS, 25% had relapse in Caspr2 antibodies associate disease. [13]

Antiepileptic like carbamazepine, phenytoin, valproate, lacosamide and levetiracetam can be used for treatment of peripheral nerve hyperexcitability.

Recent studies described the need of prolonged immunotherapy in MoS to prevent relapse, although no guidelines are available about duration of therapy. VGKC antibody titers were correlated with clinical features and serial measurement of antibody titers may be useful for monitoring disease activity in MoS [14]. However, further research in this aspect and importance of role of antigens of VGKC complex other than CASPER2, LGI1 and contactin2 in MoS is needed.

CONCLUSION-

Morvan syndrome, a VGKC antibody spectrum disorder, is a clinical diagnosis. Voltage gated potassium channel antibody test can be negative as different antigens can be there. We found myokymia and insomnia in all patients and no patient had seizure. In our study, response to immunotherapy was good. Awareness about MoS is necessary, as it can be treated successfully. Duration of prolonged immunotherapy and serial measurements of VGKC antibody titers for monitoring disease activity in MoS need further research.

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