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A REVIEW ON POTASSIUM CHANNEL ANTIBODY DISORDERS

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ABSTRACT

Voltage gated potassium channels is a group of tetrameric signalling proteins with several functions which includes modulation of neuronal excitability and neurotransmitter release. Potassium channel antibody disorder was first described in acquired neuromyotonia condition which is a syndrome of spontaneous and continuous muscle fibre contraction resulting from hyperexcitability of motor nerves. A syndrome from antibodies to voltage gated potassium channel includes Neuromyotonia, Morvan's syndrome, limbic encephalopathy. Neuromyotonia is a peripheral nerve hyperexcitability that causes spontaneous muscular activity resulting from repetitive motor unit action potential of peripheral origin with clinical presentations like Muscle cramps, Myotonia, Hyperhydrosis, Myokymia, Fasciculations, Fatigue, Exercise intolerance, Myoclonic jerks. Diagnosis includes needle electromyography, nerve conduction studies, chest CT, TSH, ESR, EEG. Morvan's syndrome is rarely characterised by peripheral and central system involvement with neuropathic pain, stocking type sensory loss and areflexia. Pathogenesis includes Antibodies against the voltage gated potassium channels which are detectable in neuromyotonia have been implicated in Morvan's syndrome Raised serum level of antibodies to voltage gated potassium channels binding of these raised antibodies to the voltage gated potassium channel causes central nervous system dysfunction which may also leads to the nerve hyperexcitability. Diagnosis includes needle electromyography, nerve conduction studies, chest CT, TSH, ESR, EEG, increased levels of antibodies against LGI-1,CASPR2, or both, detection of m-RNA. Limbic encephalopathy is most commonly seen in children characteristic feature found as cognitive impairment and seizures in anti-LGI-1positive patients, and peripheral motor hyperexcitability in anti- CASPR2 positive patients. Diagnosis includes neurpathological or neuroradiolgical examination.

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INTRODUCTION

Voltage gated potassium channels is a group of tetrameric signalling proteins with several functions which includes modulation of neuronal excitability and neurotransmitter release (Domenico plantone, 2016). Potassium channel antibody disorder was first described in acquired neuromyotonia condition which is a syndrome of spontaneous and continuous muscle fibre contraction resulting from hyperexcitability of motor nerves (John Raddiffe, ?). A syndrome from antibodies to voltage gated potassium channel includes

- Neuromyotonia
- Morvan's syndrome

- Limbic encephalopathy.

NEUROMYOTONIA

It is a diverse disorder and also known as Isaacs's syndrome or Isaac- Merton syndrome. It is a most severe phenotype of peripheral nerve hyperexcitability that causes spontaneous muscular activity resulting from repetitive motor unit action potential of peripheral origin (Maddison, 2006). It is paraneoplastic nature.

Causes of Neuromyotonia (Paul Maddison, 2002**)**

The three main causes for the occurrence of neuromyotonia are

- Hereditary
- Acquired
- Paraneoplastic

The acquired form is the most common which is usually caused by antibodies against the neuromuscular junction. Autoimmune neuromyotonia is typically caused by antibodies that bind to potassium channels on the motor nerves resulting in continuous hyper-excitability (Maddison, 2006). The acquired neuromyotonia is an immune mediated form associated with autoimmune diseases like Myasthenia Gravis, Addison's disease, Vitiligo, Hashimoto thyroiditis, pernicious anaemia, Celiac disease and rheumatoid arthritis (Irani et al., 2012).

Pathophysiology of Neuromyotonia (Morvan, 1890**).**

Neuromyotonia sometimes can be seen as a feature of genetically inherited disease. Most commonly it is associated with other disorders and mostly seems to be an autoimmune association. The following factors are paraneoplastic, Thymoma with or without myasthenia gravis, small cell lung carcinoma, Hodgkin's lymphoma, Plasmacytoma with IgM paraproteinaemia

- Potassium channel auto antibodies direct against a protein that is complexed with potassium channels in both peripheral and central nervous system.
- CASPR-2 present in 50%of patients with neuromyotonia these antibodies are common in individuals with paraneoplastic neurological diseases cause reduction in amplitude of voltage gate potassium channel currents.

Signs and symptoms of Neuromyotonia (Cottrell et al., 2004)

- Muscle cramps
- Muscle stiffness
- Myotonia (slow relaxation) associated with walking difficulties
- Hyperhydrosis
- Myokymia
- Fasciculations
- Fatigue
- Exercise intolerance
- Myoclonic jerks

Diagnosis of Neuromyotonia

The series of more specialised test including needle electromyography and nerve conduction studies.

Chest CT is used to ruled out paraneoplastic and specific blood potassium channel antibodies, acetylcholine receptors antibody and serum fixation, TSH, ESR, EEG etc. Neuromyotonia is characterised electromyographically by doublet, triplet or multiple single unit discharges that have a high, irregular intraburst frequency (Plazzi, 2002). Fibrillation potentials and fasciculation's are often also present with electromyography

Types of Neuromyotonia

There are three main types of neuromyotonia

- Chronic
- Monophasic
- Relapsing remitting

Co-morbid conditions: Thymoma, prostate adenoma, carcinoma of sigmoid colon (Maddison, 2006)

Treatment of Neuromyotonia

- The symptoms of peripheral nerve hyperexcitability respond well to membrane stabilising agents such as anticonvulsants such as phenytoin, carbamazepine, sodium valproate and lamotriazine which primarily reduces the neuronal repetitive firing through interaction with voltage gate sodium channel (Domenico plantone, 2016).
- patient with acquired neuromyotonia may require immuno suppressants such as methotrexate and azathioprine
- Plasma exchangers and IVIg treatment may provide short term relief (Domenico plantone, 2016).
- Voltage dependent potassium channels is one of the under lying issue for the hyperexcitability in auto immune neuromyotonia-BOTOX injection provides short term Relief (Linguri et al., 2001).

MORVAN'S SYNDROME

Morvan's syndrome was first described by French physician Augustin Marie Morvan in 1890 in patient who exhibited myokymia combined with excessive sweating and disordered sleep. It is rarely characterised by peripheral and central system involvement (Parthasarathi, 2006). It is mainly characterised by neuromyotonia along with neuropathic pain, stocking type sensory loss and areflexia (Domenico plantone, 2016). It is mostly predominant in males usually present with a slow insidious onset over months to years. Among them 90%of cases spontaneously goes to remission and remaining 10%leads to death. It indicates the paraneoplastic nature of the disease. It is a form of syringomyelia with tissue changes in the extremities, such as paraesthesia of the forearms and hands and progression painless ulceration of the fingertips (Buckley, 2015). This is characterised by involuntary and spontaneous muscle activity, muscle cramping, excessive perspiration and other neurological symptoms such as personality changes, insomnia and hallucinations (Lishman, 1998).

Pathogenesis of Morvan's syndrome

Antibodies against the voltage gated potassium channels which are detectable in neuromyotonia have been implicated in Morvan's syndrome (Morvan, 1890). Raised serum level of antibodies to voltage gated potassium channels binding of these raised antibodies to the voltage gated potassium channel causes central nervous system dysfunction which may also

leads to the nerve hyperexcitability by suppression of voltage gated k^+ outward currents (Graus et al., 2004).

Signs and symptoms of Morvan's syndrome

Muscle weakness, fatigue, muscle twitching, excessive sweating and salvation, small joint pain, itching, weight loss, confusional episodes with spatial and temporal disorientation, visual and auditory hallucinations, nocturnal insomnia, diurnal drowsiness, Hyperhydrosis (Abou- Zeid et al., 2012).

Co-morbid conditions: Thymoma, prostate adenoma, carcinoma of sigmoid colon

Diagnosis of Morvan's syndrome

- The diagnostic test follows to identify the Morvan syndrome includes needle electromyography and nerve conduction studies (Misawa et al., 2010).
- Chest CT is used to ruled out paraneoplastic and specific blood potassium channel antibodies, acetylcholine receptors antibody and serum fixation, TSH,, ESR, EEG etc (Cottrell et al., 2007).
- Morvan's syndrome is characterised electromyographically by doublet, triplet or multiple single unit discharges that have a high, irregular intraburst frequency. Fibrillation potentials and fasciculation's are often also present with electromyography (Cottrell et al., 2007). It includes the increased levels of voltage gated potassium channel complex antibodies in serum those are directed against the LGI-1, CASPR-2 or both and in other situations we observe contact between two antibodies the low levels of CASPR-2, m RNA is detected in the human prostate predominantly expressed in nervous system. Oligoclonal bands may be detected and also changes in the circadian serum levels of neuroharmones like melatonin and prolactin and without circadian release the nor-epinephrine was found to be high through the day without physiological nocturnal decrease or increased levels of cortisol was observed (Plazzi et al., 2002).
- Negative MRI is characteristic finding but in some conditions we observe frontal T2 hyper intensity and bilateral hippocampus T2 signal high (Plazzi et al., 2002).

Treatment for Morvan's syndrome

Morvan's syndrome is treated with plasmapheresis alone or in combination with steroids. Intravenous immunoglobulins, prednisolone, methyl prednisolone [3]. Haloperidol (6mg/kg) with some improvement in the psychomotor agitation and hallucinations, immuno-suppressive therapy with cyclophosphamide (Plazzi et al., 2002).

LIMBIC ENCEPHALITIS

It is not paraneoplastic in nature but it is an auto immune disorder. Anti-VGKC- complex encephalitis is caused by antibodies against the voltage gated potassium channel complex and is implicated in several autoimmune conditions including limbic encephalitis. It is most commonly seen in children (Sharma, 2013).

Pathophysiology of limbic Encephalitis: The voltage gated potassium channel like other channels belongs to a multiprotein complex. some of the which associates to the channel directly or indirectly induced, but are not limited to, LGI1, CASPR2, contactin2, DPPX, ADAM22 and ADAM23. LGI1 is secreted neuronal proteins which binds to ADAM22 and ADAM23 and thus cross links pre-synaptic VGKC with post synaptic AMPA receptor. An inherited form of human epilepsy known as autosomal dominant partial epilepsy with auditory features have been found to be caused by mutations of the LGI1 genes (Loscher et al., 2004). Mutation of CNTNAP2 have been reported to be associated with intellectual disability, most impairment and epilepsy**.**

Signs and symptoms of limbic encephalitis

Signs and symptoms depend on the targeted antigen, but the features in patients with different antibodies often overlap. The most characteristic feature found as cognitive impairment and seizures in anti-LGI-1positive patients, and peripheral motor hyperexcitability in anti- CASPR2 positive patients. Some patients have other coexisting autoimmune diseases.

- Anti-LGI-1encephalitis: patients with anti LGI1 encephalitis with amnesia and seizures other features include hyponatremia, movement disorders such as myoclonus/dyskinesia, sleep disorders and ataxia [10].
- Anti-CASPR2 nervous system manifestations: A patient with anti-CASPR2 antibodies develops symptoms from the CNS, hyperexcitability and limbic encephalitis [10].
- Patients with anti-DPPX encephalitis presents with symptoms of hyperexcitability such as agitation, tremor, muscle rigidity and gastrointestinal symptoms [18].

Diagnosis of limbic Encephalitis

The present diagnostic criteria followed for the evidence of limbic encephalopathy by neurpathological or neuroradiolgical examination (Ross, 2014).

Treatment for encephalitis

The treatment is largely based on the treatment of anti-NMDAR encephalitis. Treatment of an associated tumour is implicated in all neurological syndromes (Sinhas, 1991). Where treatment consists of combinations of IVIG, plasmapheresis, glucocorticoids and other immunosuppressant's drugs and rituximab (Buckley et al., 2015).

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