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A REVIEW ON MULTIPLE SCLEROSIS AND PERSISTENT HICCUPS MANAGEMENT

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ABSTRACT

Multiple sclerosis (MS) is a Central Nervous System (CNS) demyelinating disease. The pathological hallmark is the presence of plaques. The paroxysmal symptoms of MS can be managed by gabapentine and carbamazepine. Disease modifying drugs can be employed to decrease the frequency of relapses. The hiccups of long term nature (longer than 48 hours) are termed as persistent hiccups. It's mainly caused due to the irritation or damage of vagus or phrenic nerve. Gabapentine agonist baclofen and anti-psychotic drug chlorpromazine are the primary choices of treatment for the management of persistent hiccups. The aim of this review is to discuss the Etiopathogenesis, clinical features and all newer treatment strategies for the rational management of multiple sclerosis and persistent hiccups.

KEYWORDS: Multiple sclerosis, Persistent hiccups, Demyelinating disease, Gastroesophageal reflux disease.

INTRODUCTION

Multiple sclerosis is a demyelinating disease that affects the Central Nervous System. It's characterized by the destruction of the myelin sheath and followed by the degeneration of the axon.[1] Peripheral nervous system may also be affected due to the demyelination.[2] Around 4,00,000 people in USA is suffering from multiple sclerosis and 2.1 million people worldwide.[1] Multiple sclerosis literally means "many scars". These scars or lesions are the areas in which myelin has been damaged. The lesions of the multiple sclerosis can be broadly classified into three acute lesions, active chronic lesions, chronic lesions. Acute lesions contains numerous T cells (CD 3+ cells) and macrophages (CD68+) throughout. In active chronic lesions the majority of T cells and macrophages were present at the border between demyelinated and normally myelinated tracts, a few T cells and macrophages were present at the centre. Chronic lesions were characterized with few or no T cells and macrophages at the centre or periphery of the lesion.[3] Hiccups consists of brief bursts of inspiratory activity involving diaphragm and intercoastal muscles.[4] Hiccups that lasts for more than 48 hours are termed as persistent hiccups. The hiccups that generally lasts for more than one month are called intractable hiccups and they may be associated with lesions of medulla including infarctions in cerebral artery, tumour, tuberculoma, abscess formation, haematoma and demyelination.[5]

Multiple sclerosis

Pathophysiology

Multiple sclerosis is a T cell (CD4+) mediated autoimmune inflammatory demyelinating disease. The T cells have a molecule on their surface called α_4 integrin. α_4 integrin has a vital role in the migration of T cells into CNS through the Blood Brain Barrier. The autoreactive T cells will bind with the antigen presenting cell in the CNS and initiates inflammatory reactions, these will further activate macrophages to release harmful mediators like metalloproteinases, reactive oxygen species, excitotoxins which destroys the myelin sheath of oligodendrocytes and structural damage to axons.[6]

Etiopathogenesis

Defects in myelin metabolism(leucodystrophies)
Virus diseases of oligodendrocytes(progressive multifocal leucoencephalopathy)
Exposure to toxins(central pontine myelinolysis)
Vitamin D deficiency
Smoking.[1,2]

Defects in myelin metabolism(leucodystrophies)

It refers to the destruction or loss of previously acquired myelin in individuals which is more often seen in infancy than in adulthood. Clinical features associated with leucodystrophies includes optic atrophy, retinal degeneration, cataract, peripheral neuropathy, cerebral ataxia, migraine, stroke and macrocephaly.[7]

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy is a demyelinating disease which is seen in association with human immunodeficiency virus (HIV)infection. Its mainly caused by a polyomavirus namely JC virus. The virus starts replicates in oligodendrocytes and astrocytes which causes demyelination of oligodendrocytes and structural damage to axons.[8]

Central pontine myelinolysis
Central pontine myelinolysis is a neurological demyelinating disorder that affects the brainstem portion pons. Apart from the pons these may also affect cerebellum, thalamus, cortex and subcortex which is collectively termed as Extra Pontine Myelinosis(EPM).[9,11]

Vitamin D deficiency
Vitamin D helps to prevent Experimental Autoimmune Encephalomyelitis, an autoimmune disease seen in animals which is used as a model for multiple sclerosis.[12] According to Munger et al, a 40% reduction in risk of Multiple Sclerosis was found in women who use vitamin D supplements compared to women who haven't used vitamin D supplyments.[13]

Smoking
Smoking increases the risk of multiple sclerosis due to the formation of nitric oxide from cigratte smoke which may trigger the demyelination of oligodendrocytes.[14,15]

Therapeutic management of Multiple Sclerosis
According to Lawrence M Sankoff and Andrew D Goodman et al Treatments of multiple sclerosis include treating paroxysmal symptoms which includes bowel dysfunction, bladder dysfunction, spasticity, pain, tremor, depression, sexual dysfunction.[1]

Bladder dysfunction
Around 70% of the multiple sclerosis patients are affected by neurogenic bladder. The demyelination of cerebral hemispheres, pons will affect the normal contraction and relaxation of detrusor and sphincter muscles respectively which helps in micturition.[1]

Treatment measures include administration of anti cholinergic agents
Oxybutynin(Ditropan)
Tolterodine(Detrol)
Trospium(Sanctura)
Festerodine(Toviaz)
Darifenacin(Enablex)
Solifenacin(VeSIcare)

Bowel dysfunction
Bowel dysfunction are common in multiple sclerosis. Around 29-50% multiple sclerosis are experiencing constipation and faecal incontinence. Gastrointestinal transit is controlled by cerebral and spinal cord pathways, hence in multiple sclerosis the demyelination results in bowel dysfunction.[1]

Treatment includes administration of stool softeners, laxatives, rectal stimulants, enemas Lubiprostone, a bowel motility agent is now widely studied for its use in MS associated constipation and faecal incontinence.[1]

Spasticity
Trigeminal Neuralgia(TN)facial pain is experienced in multiple sclerosis patients. Paroxysmal dystonic spasms of limbs are common in multiple sclerosis patients. Treatments for the management includes. 80% of the MS patients experiences severe spasticity.[1]

Treatment measures includes administration of Baclofen Tizanidine Gabapentine Clonazepam.

Newer therapy includes Intrathecal (IT) baclofen pump which directly delivers baclofen into lower cord through Cerebro Spinal Fluid. It's FDA approved method for the treatment of spasticity.[1]

Tremor
Tremor associated with multiple sclerosis are arrested by use of benzodiazepenes(carbamazepine) and beta blockers(propranolol). Stereotactic implantation of microelectrodes in Ventral Intermediate Nucleus (VIN) has shown beneficial effects in multiple sclerosis patients but the side effects are reported to be in the higher side including dysphasia, dysphagia, hemiparesis.[1]

Sexual dysfunction
Spasticity, cognitive dysfunction, neurogenic bladder, pain of multiple sclerosis will affect the sexual activity of patient including reduced libido, erectile dysfunction and ejaculatory or orgasmic disturbances.[1]

Treatment remedies include administration of following medications
Sildenafil
Tadanafil
Vardenafil

Newer therapeutic measures includes treatment with disease modifying drugs including Immunosuppresants, Glucocorticoids, Cytokines(Interferones) And Monoclonal Antibody(Natalizumab).[1]

α_4 integrin is a molecule found on the surface of the autoreactive Tcells which aids the T cells to migrate through the BBB into CNS. Natalizumab binds with the α_4 integrin and prevents the demyelination of oligodendrocytes and axons.[1,16,17,18]

Persistant Hiccups
Pathophysiology
Hiccups consists of brief bursts of inspiratory activity involving diaphragm and intercoastal muscles.[4] The

pathophysiology of persistent hiccups can be explained with the help of 3 components.

Afferent limb
Brain
Efferent limb

The afferent limb receives the stimulation from the central or peripheral lesions and it is passed to brain were the signals are processed and the responded signals are conveyed to diaphragm and intercoastal muscles though efferent limb.[19,22]

Etiopathogenesis

Cerebrovascular accidents

Persistent or intractable hiccups may be observed in patients with brain ischemia or stroke, hence initiating anti coagulant therapy can subside hiccups to a great extend. Hence the doctor must properly examine for infarcts in brain or stroke if a patient develops persistant or intractable hiccups.[19,22,25]

Central nervous system tumour, lesions Patients with CNS tumour has an increased risk of developing persistant and intractable hiccups. Astrocytoma, carvernoma, and brain stem tumours are reported to trigger hiccups in patients. Surgical removal of tumours have subsided associated hiccups, cerebellar aneurysm also have a tendency to induce hiccups.[19,26,29]

Gastrointestinal and abdominal disorders

Studies have confirmed that 7.9% male and 10% female GERD patients had hiccups. The excess acid produced due to GERD may cause lesions in the stomach and diaphragm muscles. The role of *helicobacter pylori* infection in hiccups onset was confirmed after the successful eradication of the bacteria. The hyper acidity followed by bacterial infection will irritate the vagus nerve, triggering hiccups.[30,31]

Anaesthetic and post operative hiccups

Persistant hiccups was reported in an infant associated with epidural ropivacaine injection.[32] Patients undergone surgeries like colectomy and whoople operation have developed postoperative hiccups.[33,34]

Hiccups in cancer patients

In cancer patients hiccups might be secondary to chemotherapy. Hiccups was observed in individuals undergone with chemotherapeutic treatment with cisplatin, carboplatin and etoposide.[35] Steroids combined with ramosetron have shown beneficial results in management of persistant hiccups.[36]

Instrument Related Hiccups

Irritation of phrenic nerve was reported to induce hiccups. Catheter insertion in patients with atrial fibrillation was reported to initiate hiccups.[37,38] Respiratory tract procedures like bronchoscopy and tracheostomy were reported to cause serious hiccups.[39,40]

Therapeutic Management of Persistent Hiccups

According to Nancy L Friedman, et al the drugs administered for the treatment generally act by blocking the transmitting nerve signals.[41] Treatment measures include administration of Baclofen Chlorpromazine Metoclopramide Valproic acid Baclofen GABA(γ-Amino Butyric Acid) which is an inhibitory neurotransmitter reduces the transmission of interneurons in the brain. Baclofen is a $GABA_B$ agonist drug which promotes the action of GABA and it helps to reduce the hiccups stimulus.[42]

Chlorpromazine

Dopamine, Norepinephrine and 5-hydroxy triptamine are the vital neurotransmitters present in the hypothalamus, pons, brain stem. Chlorpromazine is a dopamine antagonist, since dopamine is an excitatory neurotransmitter, the blocking of dopamine will be useful in the management of hiccups.[43]

Metoclopramide

Metoclopramide serves as D3 antagonist at the same time 5-HT4 agonist which finds its use as a central anti emetic drug and peripheral prokinetic agent respectively. Metoclopramide promotes gastric emptying and reduces GERD which is one of the main underlying cause of hiccups.[41,44]

Valproic acid

Valproic acid acts similar to baclofen, it promotes the inhibitory effect of GABA neurotransmitter and blocks the transmission of nerve impulses in the interneurons of the brain. Also it initiates presynaptic inhibition in the spinal cord.[43,45,46]

CONCLUSION

Multiple sclerosis is an autoimmune T cell mediated disease of Central Nervous System in which demyelination of oligodendrocytes followed by structural damage of axons takes place. Treatment measures includes symptomatic treatment of associated paroxysmal symptoms and newer techniques including administration of monoclonal antibodies like Natalizumab, Immunosuppresant drugs and glucocorticoids. It is evident that intake of Vitamin D supplyments reduces the risk of multiple sclerosis.

Persistent hiccups consists of spontaneous bursts of inspiratory activity between diaphragm and intercoastal muscles. The drugs administered for the therapy of persistent hiccups mainly promotes the action of inhibitory neurotransmitter GABA which blocks the transmission of nerve signals to the brain. Untreated persistent hiccups may cause severe complications like post surgical wound bleeding, respiratory depression.

Recommendation

Long term treatment of multiple sclerosis in patients may lead to a condition called multiple sclerosis reflux, a condition in which the closure of the sphincter muscles of diaphragm are affected and excess acid flows to the oesophagus causing severe heartburn and indigestion.

One of the major underlying causes of persistent hiccups is the GERD(Gastroesophageal reflux disease)abdominal disturbances. Hence combination of a proton pump inhibitor drug along with the first line drug indicated for multiple sclerosis and persistent hiccups in a single medication will be highly beneficial and will improve the patient compliance to a great extend.

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