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Auto-antibodies against ion Channels in Guillan Barre Syndrome

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Introduction

Guillan Barre Syndrome (GBS) is a group of demyelinating, auto immune and rapidly progressive disorder, mediated by massive immune infiltration in the various parts of the peripheral nerve components.Based on the pathophysiological features there are different variant of GBS, which includes most commonly found Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and Acute Motor Axonal Neuropathy (AMAN),Acute Sensorimotor Axonal Neuropathy (AMSAN), Acute pandysautonomia and Miller fisher syndrome (MFS).This disease is called so far GBS because of the persons who defined the clinical features of GBS who are Guillan, Barre and Strohl in 1916[1-3]. Immune reactions either target the nodes of Ranvier or cell surface protein of Schwann cells and ganglioside antigen.It is characterized by muscle weakness, decreased or complete absence of muscle reflexes called areflexia, changes in sensation and pain, numbness, tingling feel which begin in the feet and leg which progress to the upper part of the body and also leads to paralysis and respiratory failure [4].The exact cause of this is not fully elusive however it is preceded by the certain infections like Epstein Barr virus, Cytomegalovirus, influenza virus, HIV virus and Campylobacter jejune infections, also triggered by certain immunizations, vaccines, stressful events and surgeries[4-6].Recent evidences indicated that infection with Zika virus also increase the possibility for the development of GBS [7-9] .GBS pathogenic conditions are rapidly progressing usually takes day to 2 weeks to reach the maximal effect.It can be diagnosed mostly with the help of CSF examination, electrophysiological study.Elevated concentration of CSF protein observed in the patients, these proteins are involved in the arrangements of axonal domain and certain cytokines secreted in response to the bacterial infections [10].

Pathogenesis of GBS

Molecular mechanism behind this GBS are the molecular mimicry or the cross reactivity between the neural antigen and pathogenic epitopes for instance LPS in the bacterial cell membrane has a huge similarity with the cell surface molecule of the peripheral nerve components.Immune response triggered in response to these viral and bacterial infections mistakenly target the neural antigens in Schwann cell surface membrane or myelin sheath which result in the demyelination.Even though it has been reported that both antibodies mediated humoral responses and T cell activated cell mediated immune responses involved in the pathogenesis of GBS, humoral responses contributing much higher in the disease pathogenesis [11]. Demyelinating such as damage of the myelin sheath is predominantly caused by the infiltration of activated T cells and macrophages into the basement membrane of nerve fibers and/or the presence of immunoglobulin.Neuronal antigenic epitope recognized by antigen presenting cells and present to T cells leads to the activation and effector T cells and in rare cases some of the epitope activate the suppressor T cells [12-15].However, GBS patients observed with the reduced number of Treg cells with CD4+ CD25+ expression [11,14].

Ganglioside also called N-acetyl muramic acid bearing glycosphingolipids present in the neuronal cell membrane micro domain called the lipid raft which mainly participate in neuronal transmission.Antibodies against this ganglioside antigen like GM1 and GD1a observed in the variant of GBS which mainly disrupts the peripheral nerve with the help of complement system which has been confirmed by the presence of complement protein in the cell surface of Schwann cell [11,12,16].It also has been corroborated by Nobile Orazio that treatment with the monoclonal antibody like eculizumab reduces the disability and clinical symptoms of GBS.These mAb particularly targets the complement protein C5 and it improves prognosis and walking ability of the person [13]. In addition, macrophages are also involved in the inflammation of myelin sheath and demyelination.These macrophages directly promote cellular cytotoxicity by the production of inflammatory

cytokines, chemokines, NO, MMPs (Matrix Metallo Proteinase)[18]. Moreover, presence of certain cytokines has a direct correlation with the severity of GBS for example concentrations of IL-6, IL-12 and IL-23increased during the inflammation, however certain cytokines play a dual role in disease pathogenesis such as IL-27 , TNF-α and IFN-γ [19,20]. Moreover, the complete pathogenic mechanism of this disease is not fully elusive however explaining the same is beyond the scope of this article.This review mainly aimed to describe the contribution of ion channels in the pathogenesis of GBS.

Ion Channelsin the Pathogenesis of GBS

Ion channels are the membrane protein involved in various cell metabolic functions like neuronal transmission, conduction, replication and neuronal damage, however malfunction of the same results in the numerous diseases mechanisms[21].As reported previously anti ganglioside antibodies secreted against GM1 also react with and inactivate voltage gated sodium channel present in the nerve fibers with complement activation.VGSC highly concentrated at the nodes of Ranvier in myelinated nerve fibers, mainly responsible for the influx of sodium currents, thereby cause the depolarization phase in the action potential thus antibodies against the same leads to the failure of neuronal transmission, changes in the action potential duration and muscle weakness [22-24].At the acute phase of the disease, sodium channel clusters fully disturbed and disappeared in the rangier node which was seen with the immunoglobulin and complement products [25]. These anti ganglioside antibodies like IgM-anti-G1b also react with voltage gated calcium channels expressed in the cerebellar granule cells, which results in the complete blockage of VGCC current and spontaneous muscle action potential, thus finally results in the nerve conduction failure and muscle weakness.Serum from AMAN patient significantly inhibited the Cav2.1 current, however it has not been observed with any changes in the activationand inactivation kinetics of VGCC current. These results could not be observed with the AIDP and healthy volunteer sera.

Moreover, presence of auto antibodies against the Voltage Gated Potassium Channel (VGKC) also has been observed in GBS variant in particular MFS.VGKC responsible for the efflux of potassium ion thereby render the cell to resting stage from the depolarized state. Thus, these auto antibodies responsible for prolonged refractory period and change in resting phase of the action potential [26-28].In addition to the antibodies react with the ion channels, auto antibodies also target the receptor which likely take place in the pre and post synaptic neurologic transmission[29-31].In particular, nAChR play an evitable role in the neuro muscular transmission such as Acetylcholine released from the motor neuron bind with nAChR expressed in muscle fibers.Auto antibodies react with this nAChR and inhibit this ionic current which is not observed with changes in the activation and desensitization kinetics, thus these antibodies disrupt the neuromuscular transmission that results in the limb and muscle weakness[32]. Previously mentioned that zika virus involved in the development of GBS which is mediated by the direct replication of zika virus in the neuronal cells and over activation of the NMDA receptor thereby cause the neuronal damage, inflammation and neuronal degeneration.Interestingly blockage of this receptor by memantine inhibits this receptor and thereby prevents the viral replication and reduces the neuronal damage in GBS [33].

Conclusion

Ion channels are the highly regulated, specialized membrane protein, involved in the maintenance of membrane potential, influx and efflux of ions and control the numerous metabolic processes. There are different subtypes of the ion channels which differ based on the cell types, developmental stage, amino acid composition and the specific function.Differential expression of these ion channels results in the dysregulation of the ionic transport and thereby leads to uncontrolled metabolic process and the incidence of various diseases.Altered expression of the ion channels have been involved in the all the diseases we have studied, however the studying the malfunction of the same in the disease pathology have not been elucidated fully.Similar to the blockage of NMDA receptor, modulator of the specific ion channels would pave the way for treating GBS diseases.Thus, detailed study of the ion channels in various metabolic processes of GBS will assist the understanding of the disease and also improve therapeutics.

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