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Neuroimmunology: An expanding frontier in 21st century Neurology

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The recent discovery of functional lymphatic vessels lining the dural sinuses shattered the long held view of the absence of CNS lymphatic vas culature and provided solid neuroanatomical ground for Neuroimmunology[1]. Moreover, it has been shown that there is the presence of what is known as the inflammatory reflex. This is mediated by sensory neurons and transmitted directly to immune cells such as the macro phages and T-cells via specialized cholinergic receptors[2]. These findings demonstrate a strong interaction between the nervous and immune systems.

One of the major proteins that contribute to the pathogenesis of Parkinson's disease (PD) is alpha-synuclein (aSyn). Surprisingly, alpha-synuclein pathogenic inclusions were recently shown spread to the brain from the gastro intestinal tract (GIT) in a manner similar to prion diseases[3]. With the vagus nerve tracking through the GIT, it plays a key role in the interaction of the brain with the immune system. Inflammation in the GIT leads to over expression and aggregation of aSyn in the enteric nervous system and spreads to the vagal dorsal motor nucleus in the brainstem via the nerve[4]. GIT micro bio me has been shown to be a key component of this spread by release of mediators affecting inflammation[3].The prion-like mechanism of spread has previously been demonstrated for ALS as well[5], where mutant SOD[1] converts normal mitochondrial SOD[1] into an abnormal protein leading to mitochondrial aggregations and dys function[5].

In the brain, the astrocytes maintain the blood-brain-barried (BBB) while the micro glia directly contribute to immune defense mechanisms. Alzheimer's disease (AD) is characterized by plaques and neuro fibrillary tangles (NFT), the latter being composed predominantly of the misfolded protein Tau. In a mouse model it was shown that antibodies directed against Tau prevented the spread of NFTs. Modulation of the Fc portion of the antibodies led to absence of binding to micro glia with consequent reduction of release of inflammatory mediators and ensuing neuroinflammation[6]. Thus such a strategy could have immune-therapeutic effects on AD.

Multiple sclerosis (MS) has seen rapid immun other apeutic advances with the advent of monoclonal antibodies. Nataluzimab (an integrin inhibitor preventing lymphocyte extra vasation) and Rituximab (B-cell inhibitor) showed remarkable success in disease management. Recently Ocrelizumab, a humanized form of Rituximab, was recently approved by FDA for treatment of Primary progressive MS[7]. Teriflunamide, a hepatic metabolite of an old anti-rheumatic drug - Leflunomide, was also approved by FDA for MS[8]. In resource limited countries such as Pakistan, Leflunomide has been successfully used for treatment of MS, though formal studies to assess its efficacy are currently lacking.

Several neuropsychiatric syndromes and immune encephalitis are now yielding to the power of Neuroimmunology and being routinely diagnosed to be mediated by antibodies such as the anit-GABA, anti-NMDA, anti-VGKC (CASPR2& LGI1) and the more familiar dsDNA. This has opened doors to treatments which were previously impossible. Now chemical or biological immunomodulators are helping to bring such vague diseases under excellent clinical control. Furthermore the recent introduction of onco-neural antibodies is an added tool in the diagnosis of previously elusive paraneoplastic neurological syndromes.

These pathobiologic advances, combined with immunotherapeutics and a broad range of available antibody tests has made Neuroimmunology a major diagnostic and therapeutic field of immense clinical significance.

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