



9-2017

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### Recommended Citation

Saeed, Mohammad and Ahmad, Arsalan (2017) "Neuroimmunology: An expanding frontier in 21st century neurology," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 12 : Iss. 3 , Article 1.

Available at: <https://ecommons.aku.edu/pjns/vol12/iss3/1>

# Neuroimmunology: An expanding frontier in 21st century Neurology

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**Date of submission:** May 22, 2017 **Date of revision:** June 29, 2017 **Date of acceptance:** June, 2017

The recent discovery of functional lymphatic vessels lining the dural sinuses shattered the long held view of the absence of CNS lymphatic vasculature and provided solid neuroanatomical ground for Neuroimmunology<sup>1</sup>. 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 macrophages and T-cells via specialized cholinergic receptors<sup>2</sup>. 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 gastrointestinal tract (GIT) in a manner similar to prion diseases<sup>3</sup>. 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<sup>4</sup>. GIT microbiome has been shown to be a key component of this spread by release of mediators affecting inflammation<sup>3</sup>. The prion-like mechanism of spread has previously been demonstrated for ALS as well<sup>5</sup>, where mutant SOD<sup>1</sup> converts normal mitochondrial SOD<sup>1</sup> into an abnormal protein leading to mitochondrial aggregations and dysfunction<sup>5</sup>.

In the brain, the astrocytes maintain the blood-brain-barrier (BBB) while the microglia directly contribute to immune defense mechanisms. Alzheimer's disease (AD) is characterized by plaques and neurofibrillary 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 microglia with consequent reduction of release of inflammatory mediators and ensuing neuroinflammation<sup>6</sup>. Thus such a strategy could have immune-therapeutic effects on AD.

Multiple sclerosis (MS) has seen rapid immunotherapeutic advances with the advent of monoclonal antibodies. Natalizumab (an integrin inhibitor preventing lymphocyte extravasation) 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<sup>7</sup>. Teriflunomide, a hepatic metabolite of an old anti-rheumatic drug - Leflunomide, was also approved by FDA for MS<sup>8</sup>. 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 anti-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.

## REFERENCES:

1. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015 Jul 16;523(7560):337-41. PubMed PMID: 26030524
2. Pavlov VA, Tracey KJ. Neural circuitry and immunity. *Immunol Res*. 2015 Dec;63(1-3):38-57. PubMed PMID: 26512000.
3. Sampson TR, Debelius JW, Thron T, et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell*. 2016 Dec 1;167(6):1469-1480 e12. PubMed 27912057.
4. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Parkinsons Dis*. 2017 Jan 11;3:3. PubMed PMID: 28649603.
5. Deng HX, Shi Y, Furukawa Y, et al. Conversion to the amyotrophic lateral sclerosis phenotype is associated with intermolecular linked insoluble aggregates of SOD1 in mitochondria. *Proc Natl Acad Sci U S A*. 2006 May 2;103(18):7142-7. PubMed PMID: 16636275.
5. Deng HX, Shi Y, Furukawa Y, et al. Conversion to the amyotrophic lateral sclerosis phenotype is associated with intermolecular linked insoluble aggregates of SOD1 in mitochondria. *Proc Natl Acad Sci U S A*. 2006 May 2;103(18):7142-7. PubMed PMID: 16636275.
6. Lee SH, Le Pichon CE, Adolfsson O, et al. Antibody-Mediated Targeting of Tau In Vivo Does Not Require Effector Function and Microglial Engagement. *Cell Rep*. 2016 Aug 9;16(6):1690-1700. PubMed PMID: 27475227.
7. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017;376:209-220.
8. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *New Engl J Med* 2011;365:1293-1303.

Conflict of interest: Author declares no conflict of interest.

Funding disclosure: Nil

Author's contribution:

Mohammad Saeed; concept, data collection, data analysis, manuscript writing, manuscript review

Arsalan Ahmed; data collection, data analysis, manuscript writing, manuscript review