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Letter to Editor Open Access

Autoimmunity in Neurological and Psychiatric Disorders: Participation of Antibodies and Cytokines in the Immunopathogenesis of these Diseases

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Letter to the Editor

Glutamatergic function deficits are hypothesized to contribute to the pathogenesis of neuropsychiatric disorders, including schizophrenia. In autoimmune encephalitis is thought that the receptors and proteins involved in glutamatergic neurotransmission are the antigen targets: N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptors [1]. Glutamate receptor antibodies such as anti-AMPA and anti-NMDA can be found in some neurological and autoimmune disorders including systemic lupus erythematosus (SLE), Sjogren's syndrome, schizophrenia, seizure disorder and mania. They can down regulate cerebral functions leading to brain damage that induces behavioural, psychiatric and cognitive abnormalities in animal models and they can be reverted in some patients by the use of immunotherapy [2-3].

Controversially autoantibodies (Ab's) to the "B" peptide (amino acids 372-395) of glutamate/AMPA receptor subtype 3 (GluR3) were found in serum and cerebrospinal fluid of some patients with different types of epilepsy but not association was found between the presence of such antibodies and patients suffering from epilepsy that accompanies anti-phospholipid syndrome (APS) or Sneddon's syndrome (SNS), which are two autoimmune disorders [4]. Anyway these findings are important because some of these neurological disorders may fall in the field of clinical immunology and therefore it may be needed the realization of a screening for specific autoimmune antibodies and immune cells, complement proteins and cytokines. If the autoimmune nature of this neurological or psychiatric problems is confirmed the patient could be treated with immunotherapy including intravenous immunoglobulins, immunosuppressors, plasmapheresis, rituximab and cytostatic agents. We cannot forget that in SLE neurological and psychiatric manifestations are present as evidence of the interrelation between both immune and central nervous systems [5].

The biological basis of depression in SLE has been recently confirmed. The participation of biochemical and neurophysiological changes, induced by cytokines, in the development of neuropsychiatric symptoms has been demonstrated. Cytokines are capable of causing mood swings and depression. Down regulation of the hypothalamic-pituitary-adrenal (HPA) axis correlates with neurophysiological changes involved in depression. In addition to that cerebro-reactive autoantibodies present in the cerebrospinal fluid (CSF), such as anti-NMDA and anti-ribosomal P, can cause significant damage to neurons which are relevant to humor and behaviour, leading to depressive symptoms [6]. Epilepsy is a complex and multifactorial phenomenon. Accumulating evidence suggests that the immune system may play an important role in neuronal excitability and epileptogenesis. In epilepsy patients studies (including ex vivo) show elevated levels of IL-1β, IL-2, IL-5, IL-6 or TNF-α after carbamazepine, valproic acid and phenytoin treatment [7]. In Table 1 we summarized the association of certain autoantibodies with specific diseases of the central nervous system, and therefore they can be classified as autoimmune disorders and this has implications in the management of these problems where immune-therapy could be used. Table 2 shows a cytokine involvement in neuropsychiatric diseases that can be interpreted as a pathogenic role of these molecules in the genesis of these problems or the result of interactions between the immune and/or endocrine system with the brain.

Disease	Autoantibody	Reference
Cognitive and affective dysfunctions in autoimmune thyroiditis	Anti-thyroid peroxidase Ab, anti-central nervous system Ab	[8]
Hashimoto's encephalopathy (HE)	Anti-α-enolase Ab, anti-thyroid peroxidase Ab	[8,9]
Limbic encephalitis in multiple sclerosis	Anti-N-methyl D-aspartate-type glutamate receptor Ab	[1,10]
Complex regional pain syndrome	Anti-nuclear Ab (ANA), anti-neuronal Ab	[11]
Idiopathic and symptomatic epilepsies	Neurotropic Abs to NF-200, GFAP, MBP and S100β, and to receptors of neuromediators (glutamate, GABA, dopamine, serotonin and choline-receptors	[12]
Schizophrenia	Autoantibodies against glutamate, dopamine, acetylcholine and serotonin receptors, and antineuronal antibodies against synaptic biomolecules	[13-16]
Lambert-Eaton myasthenic syndrome	Autoantibodies against P/Q-type voltage-gated calcium channels	[17]
Myasthenia gravis	Auto-Ab to muscle-specific tyrosine kinase	[18]

Table 1: Presence of auto-antibodies in neurological and psychiatric disorders

Disease	Cytokine involved	Reference
Neuropsychiatric systemic lupus erythematosus	Elevated interleukin (IL)-17, IL-2, interferon- gamma (IFN-γ), IL-5, basic	[19]

	fibroblast growth factor (FGF) and IL-15	
Relapsing remitting multiple sclerosis	Elevated IL-17 and INF-gamma and decreased transforming growth factor-beta (TGF-beta 1) levels	[20]
Guillain-Barre syndrome	Elevated TNFα and IL-10	[21]
Schizophrenia	Increased interleukin (IL)-1, IL-6, and TGF-β appear to be state markers, whereas IL-12, interferon-gamma (IFN-γ), TNF-α, and soluble IL-2 receptor appear to be trait markers	[22,23]
Multiple sclerosis (MS)	IL-17 plays an important role in the inflammatory phase of relapsing-remitting MS	[24]

Table 2: Cytokine involvement in neuropsychiatric diseases.

Diseases	References
Guillain-Barré syndrome	[25-29]
Chronic inflammatory demyelinating polyneuropathy	[25-29]
Multiple motor neuropathy	[26,27]
Multiple sclerosis	[26,27]
Myasthenia gravis	[26-28]
Acute disseminated encephalomyelitis	[27]
Diabetic neuropathy	[27]
Lambert-Eaton myasthenic syndrome	[27]
Opsoclonus-myoclonus	[27]
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	[27]
Polymyositis	[27,30-32]
Rasmussen's encephalitis	[27]
Multiple sclerosis	[33]

Table 3: List of neurological diseases where the use of intravenous immunoglobulins (IVIG) has been used successfully.

In Table 3 we listed neurological disorders where IVIG [34] has proven effective. The possible mechanisms of action are not yet well established, but it is believed that IVIG has immunosuppressive activity on B cells, T cells and antigen presenting cells, down-regulation of complement proteins, suppression of NFkB activation and IkB degradation [35-37] and actions on the idiotypic-anti-idiotypic network [38], enhances the expansion of T regulatory cells [39], neutralizes pathogenic autoantibodies [40,41], remyelinisation, release of cytokines and cytokine antagonists and modulation of cell proliferation and apoptosis [42-44]. IVIG was not recommended for 8 conditions including paraproteinemic neuropathy (IgM variant), intractable childhood epilepsy, inclusion body myositis, amyotropic lateral sclerosis, adrenoleukodystrophy, autism, critical illness polyneuropathy and POEMS syndrome characterized by polyneuropathy, organomegaly, endocrinopathy or edema, M-protein and skin abnormalities [45].

We do not want to conclude this letter without speaking about the blood-brain barrier (BBB) as shown in Figure 1. It is a complex structure lining the capillaries throughout the brain. In normal conditions the BBB denies the traffic of large molecular weight molecules such as proteins [46]. A breach in the BBB can allow circulating antibodies that cross-react with neurological tissues to infiltrate the brain causing tissue damage as it is seen in autoimmune disorders including neuropsychiatric systemic lupus erythematosus (NSLE). It may also cause neurotoxicity. Autoantibodies and cytokines once inside the brain can cause inflammatory reactions that can be amplified by the damaging effects of TH1 and TH17 lymphocytes. Multiple sclerosis is characterized by a disruption in the BBB that allow myelin-specific lymphocytes to induce demyelination, as evidenced by the appearance of gadolinium (gd)-enhancing lesions on magnetic resonance (MR) imaging [47-49]. Table 4 shows experimental therapy and mechanisms of actions in neurological autoimmune disorders.

Disease	**Experimental drug**	**Mechanism of action**	**Reference**
Multiple sclerosis	Oral fingolimod	It Inhibits egress of lymphocytes from lymph nodes and their recirculation	[50,51]
Multiple sclerosis	Daclizumab	It is a humanized neutralizing monoclonal antibody against the α-chain of the interleukin-2 receptor	[52-54]
Chronic inflammatory demyelinating polyradiculoneuropathy	Corticosteroids, plasma exchange, and high-dose IVIG	Immunosuppressor (corticosteroids), immunomodulator (IVIG and plasma)	[55,56]
Experimental autoimmune encephalomyelitis	Laquinimod	Modulates adaptive T cell immune responses via its effects on cells of the innate immune system and may not influence T cells directly	[57]
Myasthenia gravis	Rituximab	A chimeric IgG k monoclonal antibody that target CD20 on B cells	[58,59]
Guillain-Barré syndrome	Plasma exchange	Deplete pathogenic autoantibody	[60]
Paraneoplastic neurological disorders	IVIG, plasma exchange	Immunomodulator, deplete auto-Ab	[61]

Table 4: Experimental therapy and mechanisms of actions in neurological autoimmune disorders.

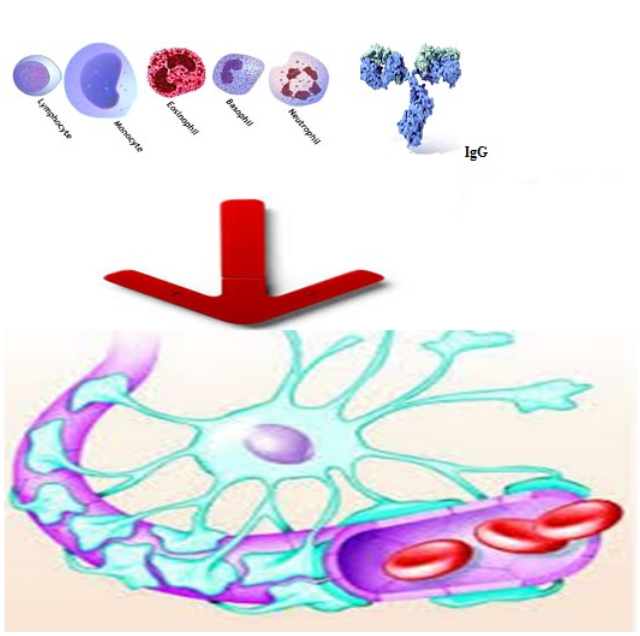

Figure 1: Representation of a damage to the blood-brain barrier.

When it is damaged immune and accessory cells go through and reach the brain, which is an immunological privileged organ, and after that these immunological components infiltrate the extracellular compartments and cause neuronal damage and neurotoxicity. Autoantibodies with specificity for neuron cells and other components of the central nervous system react with their targets, causing for example, demyelination as it is seen in several neurological diseases including multiple sclerosis, neuromyelitis optica, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy that are autoimmune diseases, where the damaged myelin impairs the conduction of signals in the affected nerves.

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