Do Neuronal Autoantibodies Cause Psychosis? A Neuroimmunological Perspective

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In the last decade, autoantibodies targeting proteins on the neuronal surface and that are believed to be directly pathogenic have been described in patients with autoimmune encephalitis. Since then, new antigenic targets have been discovered, and new clinical phenotypes have been recognized. The psychotic disorders are one example of this expanding spectrum. Here, we consider the defining criteria of antibody-mediated central nervous system disease and the extent to which the psychiatric data currently satisfy those criteria. We discuss the implications these findings have for our understanding, nosology, and treatment of psychiatric disorders.

Key Words: Antibody-mediated disease, autoimmune encephalitis, psychosis, schizophrenia

At the beginning of the twentieth century, the dominating thought in immunology followed the Erlich paradigm (the "horror autotoxicus") that stated that autoimmune disease could not occur naturally in human beings. It took 50 years for the first evidence of an autoimmune human disease to be accepted, through the documentation of anti-thyroglobulin autoantibodies in thyroiditis. However, it was a neurological disease, myasthenia gravis (MG), that most clearly demonstrated the existence of naturally occurring autoimmunity and that remains the paradigm of antibody-mediated disease (1).

Myasthenia gravis patients are characterized clinically by muscle weakness that worsens on exertion and is due to a defect in neuromuscular transmission as defined by clinical neurophysiology. After years of research into a circulating neuromuscular blocking agent (2), a major discovery was made in 1973: the existence of serum acetylcholine receptor antibodies in an experimental model of MG (3) and in sera of patients (4). Other peripheral nervous system disorders associated with autoantibodies were later described, such as Lambert-Eaton myasthenic syndrome and acquired neuromyotonia, associated with antibodies to voltage-gated calcium channels (5) and voltage-gated potassium channels (VGKC) antibodies (6), respectively.

For a long time the brain was considered to be an immunologically privileged site, despite the accumulating evidence of autoantibodies directed against the peripheral nervous system. Under normal physiological conditions, the blood-brain barrier limits the access of antibodies, immune mediators, and immune cells from the systemic circulation into the brain. However, it is now accepted that this immune privilege is relative rather than absolute and can be disturbed under specific disease conditions (7). The first central nervous system (CNS) disorders associated with the presence of autoantibodies started to be recognized in the 1980s. In these disorders, antibodies targeting neuronal epitopes were present in patients with peripheral and central nervous system syndromes who had a cancer (paraneoplastic syndromes). The target antigens in those situations were cytoplasmic or nuclear proteins, and although commonly used as diagnostic markers, these onconeural antibodies are not thought to be causal; cytotoxic cells are thought to be the main pathogenic entity (8).

Rasmussen encephalitis, a rare disorder characterized by intractable epilepsy and progressive loss of function caused by chronic inflammation and atrophy of one cerebral hemisphere, was attributed in the 1990s to antibodies to the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor 3 (9). Yet, those antibodies were not found to be specific or sensitive for this disease (10,11) and are unlikely to be directly pathogenic.

In 2001 a CNS phenotype, limbic encephalitis, was described with autoantibodies that were believed to be directly pathogenic (12). Since then, a number of other CNS disorders, mainly with an encephalopathy-type phenotype, have been identified with autoantibodies targeting neuronal epitopes (Table 1). These disorders are most commonly not cancer-associated, despite earlier suggestions, and patients tend to respond favorably to timely immunotherapy. This field is currently expanding, both in terms of new antigenic targets discovered and in new clinical phenotypes associated with previously detected autoantibodies (13). The psychotic disorders are one example of this expanding spectrum, as reviewed by Deakin *et al.* in this issue of *Biological Psychiatry*. Here, we provide a wider context from the perspective of neuroimmunology. As well as outlining key aspects of pathophysiology, we consider the defining criteria of antibody-mediated CNS disease and the extent to which the psychiatric data currently satisfy those criteria.

Postulates of Koch/Witebsky and the Definition of Autoimmune Brain Diseases

In a broad sense, the definition of autoimmune disease requires that an abnormal adaptive immune response to a self-antigen causes the observed pathology. Conducting an experiment that would give absolute proof of this causal relationship is not possible; it would require the transfer of specific autoreactive T cells and/or autoantibodies into a healthy individual to see whether they induce disease. However, the autoimmune diseases can be defined according to principles that are similar to Koch's postulates in microbiology and that were adapted by Witebsky (14): 1) the autoantibody must be present with the clinical manifestation and detectable in the blood and/or affected tissue; 2) autoantibodies must target a receptor, ion channel, or other protein expressed on the membrane surface; 3) antibody transfer must replicate the disease in an animal experimental model or in humans (for instance, through placental transfer of antibodies to the fetus); 4) elimination or suppression of the autoimmune response (through plasma exchange or other immunotherapies) prevents disease progression or improves the clinical manifestations.

Although not required by these postulates, it also seems reasonable that, to assign pathogenicity to a specific autoantibody,

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Table 1. Main CNS Disorders Associated with Antibodies Targeting Neuronal Cell Surface Antigens

Antigen	Demographic Data	Clinical Phenotypes	Paraclinical Findings	Tumor Association	Outcome	Potential Importance for Psychiatry
NMDAR	80% female Age range: <12 months–85 yrs (median 21 yrs)	Psychiatric symptoms, memory and language deficits, seizures, movement disorders, autonomic instability, and decreased level of consciousness	CSF: lymphocytosis (70%) in the early stages and OCBs later (52%); EEG: generalized slowing; epileptiform discharges in early stages; MRI: normal or mild signs of inflammation (cortical or subcortical)	Teratoma (38%)	Good outcome with timely immunotherapy (± tumor removal); Cognitive and behavioral sequelae might persist	Case reports and small cohorts of patients with isolated psychosis reported; NMDAR hypofunction implicated in schizophrenia pathophysiology (pharmacological and experimental evidence)
VGKC-Complex Protein[a] LGI1	65% male Age range: 30–80 yrs old (median 60 yrs)	Limbic encephalitis; Faciobrachial dystonic seizures	Hyponatremia (60%); CSF: usually normal, occasional mirrored OCB; MRI: medial temporal lobe increase of FLAIR signal (60%)	Rare	Good outcome; relapses uncommon Good response to immunotherapy but absent or poor response with AED in faciobrachial dystonic seizures	Rare reports of pure psychiatric phenotype associated with VGKC complex antibodies (no target identified in those publications)
VGKC-Complex Protein[a] CASPR2	85% male Age range: 46–77 yrs (median 60 yrs)	Neuromyotonia; Morvan's syndrome; Limbic encephalitis; Idiopathic ataxia	MRI: medial temporal lobe increase of FLAIR signal (40%) in limbic encephalitis; EMG: spontaneous muscular hyperactivity in Neuromyotonia	Thymomas, SCLC (uncommon)	Good outcome, but can be complicated by tumor	Rare reports of pure psychiatric phenotype associated with VGKC-complex antibodies (no target identified in those publications)
AMPAR	90% female Age range: 38–78 yrs (median 60 yrs)	Limbic encephalitis	CSF: lymphocytosis with occasional raised protein and OCBs; MRI: medial temporal lobe increase of FLAIR signal (90%)	SCLC, thymoma or breast cancer (70%)	Tendency to relapse (50%), even in the absence of tumor	Prominent psychiatric manifestations; Sometimes isolated neuropsychiatric phenotype (abnormal behavior resembling acute psychosis)
GABAbR	50% female Age range: 24–75 yrs (median 62 yrs)	Limbic encephalitis (prominent seizures)	CSF: lymphocytosis with occasional raised protein and OCBs; MRI: medial temporal lobe increase of FLAIR signal (~66%)	SCLC (50%)	Good outcome; Relapses are rare	Isolated psychiatric phenotypes not described
GlyR	60% male Age range: 14 months–70 yrs (median 46 yrs)	Progressive encephalomyelitis, rigidity, and myoclonus; Classic and variant stiff-person syndrome	CSF: usually normal, occasional mild lymphocytosis; MRI: normal; EMG: continuous muscle activities in the agonist and antagonist muscles	Thymoma, Hodgkin lymphoma (rare)	Good outcomes; but relapses with immunotherapy taper	Isolated psychiatric phenotypes not described; Unlikely target in psychosis

AED, antiepileptic drugs; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; FLAIR, fluid-attenuated inversion recovery; GABAbR, γ-aminobutyric acid B receptor; GlyR, glycine receptor; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; OCB, oligoclonal bands; SCLC, small cell lung carcinoma; VGKC, voltage-gated potassium channel.

[a]Most VGKC antibodies, previously detected by immunoprecipitation of nervous tissue lysates containing the VGKC-complex labeled with radio-iodinated α-dendrotoxin, target components of the VGKC-complex (LGI1, CASPR2, and Contactin-2), and not the channel subunits.