Review

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Autoantibodies to Neurotransmitter Receptors and Ion Channels in Psychotic Disorders

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ABSTRACT:

Autoantibodies to neurotransmitter receptors and ion channels in psychotic disorders

Cell surface antibody–associated central nervous system disorders have emerged in the last decade as a novel field in neuroimmunology. It is now well known that patients with antibodies to ion channels such as N-methyl-D-aspartate receptor and voltage-gated potassium channel-complex manifest with prominent psychiatric symptoms and particularly psychosis early in the disease course. In this review, major neuronal cell surface autoantibodies related with neuropsychiatric symptoms were discussed with a special emphasis on their potential pathogenicity in neuropsychiatric disorders. Presence of neuronal cell surface antibodies in patients with isolated first episode psychotic disorder, schizophrenia and systemic lupus erythematosus were also discussed. Moreover, a list of diagnostic criteria that might help recognition of neuronal cell surface antibody positive psychosis patients has been proposed.

Keywords: psychosis, encephalitis, NMDAR, potassium channel, antibody, immunotherapy

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INTRODUCTION

Autoimmune disorders of the nervous system are now well recognized. After the establishment of autoimmune pathogenic mechanisms in myasthenia gravis (MG), a paradigm of antibody-mediated diseases mostly related with acetylcholine receptor (AChR) antibody, other antibody-mediated peripheral nervous system disorders, such as voltage-gated calcium channel (VGCC) antibody associated Lambert-Eaton myasthenic syndrome and voltage-gated potassium channel (VGKC) complex antibody associated neuromyotonia have been described[1].

Once thought to be resistant to autoimmune disorders due to the blood-brain barrier, central nervous system (CNS) is now also known to be a major target for pathogenic autoantibodies. The first recognized antibodies associated with autoimmune encephalitis with or without psychosis were targeting cytoplasmic and nuclear proteins and were almost always related with an underlying tumor expressing the target neuronal antigens. Although these antibodies (e.g., Hu, Yo, Ma2, CV2, Ri, amphiphysin antibodies) are still commonly used as diagnostic markers, several

Table 1: Main psychotic disorders associated with antibodies targeting neuronal cell surface antigens

Antigen	Demographic features	Clinical syndromes	Tumor association	Importance for psychiatry
NMDAR	Women > men; Median age: 21	Limbic encephalitis, movement disorders, autonomic instability	Teratoma (40-50%)	Prominent psychiatric manifestations, sometimes isolated psychosis
LGI1	Men > women; Median age: 60	Limbic encephalitis	Thymoma (rare)	Rare reports of isolated psychosis
CASPR2	Men > women; Median age: 60	Limbic encephalitis, Morvan syndrome	Thymoma, SCLC (30-40%)	Rare reports of isolated psychosis
AMPAR	Women > men; Median age: 60	Limbic encephalitis	SCLC, thymoma, breast cancer (70%)	Prominent psychiatric manifestations, sometimes isolated psychosis
GABABR	Men = women; Median age: 62	Limbic encephalitis	SCLC (50%)	Isolated psychiatric phenotypes not described
GlyR	Men > women; Median age: 46	Progressive encephalomyelitis, rigidity, myoclonus (PERM)	Thymoma, Hodgkin lymphoma (rare)	Isolated psychiatric phenotypes not described
Kv4.2 DPPX	Men = women; Median age: 55	Limbic encephalitis, diarrhea, rigidity	None	Isolated psychiatric phenotypes not described
D2R	Men = women; Median age: 9	Psychosis, movement disorder (parkinsonism, chorea, dystonia)	None	Prominent psychiatric manifestations, isolated psychiatric phenotypes not described

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CASPR2: contactin-associated protein-like 2, $GABA_BR$: γ-aminobutyric acid B receptor, GlyR: glycine receptor, LGI1: leucine-rich glioma inactivated 1, NMDAR: N-methyl-D-aspartate receptor, SCLC: small cell lung carcinoma, VGKC: voltage-gated potassium channel, D2R: dopamine 2 receptor, DPPX: dipeptidyl-peptidase-like protein-6

experimental studies have shown that they have no pathogenic action and develop as a byproduct of the ongoing CNS inflammation and brain destruction predominantly mediated by cytotoxic T cells. These so called onconeural antibodies were also indicative of poor response to immunotherapy[2,3].

An antibody mediated disorder of the CNS, limbic encephalitis associated with VGKC complex antibodies measured by iodinated dendrotoxin radioimmunoprecipitation assay, was first described in 2001[4]. Since then a plethora of antibodies directed against neuronal membrane/synapse proteins and ion channels have been described in association with a diversity of autoimmune encephalitis phenotypes (Table 1). In contrast with onconeural antibodies, these so called neuronal surface antibodies (NSAb) often display pathogenic alterations in the functions of target neurons, they are less frequently associated with an underlying cancer and patients with these antibodies tend to respond favorably to immunotherapy[3,5]. Moreover, brain specimens of encephalitis patients with NSAb display much lower amounts of cytotoxic T cells as compared to those related with onconeural antibodies and show an abundance of IgG deposits particularly concentrated in limbic regions[6]. While, these NSAb associated syndromes comprise a large group of neurological symptoms including memory loss, seizures, movement disorders, autonomic symptoms and loss of consciousness, psychotic disorders also stand out as a major component of anti-neuronal autoimmunity[7]. In this review, major autoantibodies related with neuropsychiatric symptoms will be discussed with a special emphasis on their potential pathogenicity. Patients with isolated first episode psychotic disorder or classical schizophrenia and NSAb will also be discussed.

Psychosis in Specific Syndromes Associated with NSAb

Antibody mediated CNS disorders are characterized with an acute onset encephalopathy

presenting with seizures, memory loss and psychiatric symptoms, inflammation findings in cerebrospinal fluid (CSF) (increased lymphocyte count, protein concentration, oligoclonal bands, and high IgG index), signal changes in magnetic resonance imaging (MRI) (mostly in medial temporal lobes) and focal or generalized EEG findings (temporal or global slow waves and epileptic discharges)[8-10]. Additionally, these patients display serum/ CSF antibodies directed against N-methyl-D-aspartate receptor (NMDAR) (Figure 1), leucine-rich glioma-inactivated 1 (LGI1), γ-aminobutyric acid B receptor ($GABA_BR$), contactin associated protein-like 2 (CASPR2) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR). NMDAR and VGKC-complex (LGI1, CASPR2) antibodies constitute around 80% of NSAb mediated autoimmune encephalitis population[11]. Antibodies that are less frequently associated with autoimmune encephalitis and psychotic features are those directed against glycine receptor (GlyR), DPPX component of the VGKC Kv4.2 subunit and dopamine 2 receptor[12-14]. Some of the reported autoimmune encephalitis patients have presented with isolated (and often first-onset) seizures, movement disorders or psychosis. In these cases, a positive response to immunotherapies has been observed, corroborating the autoimmune origin of these monosymptomatic episodes[15-17].

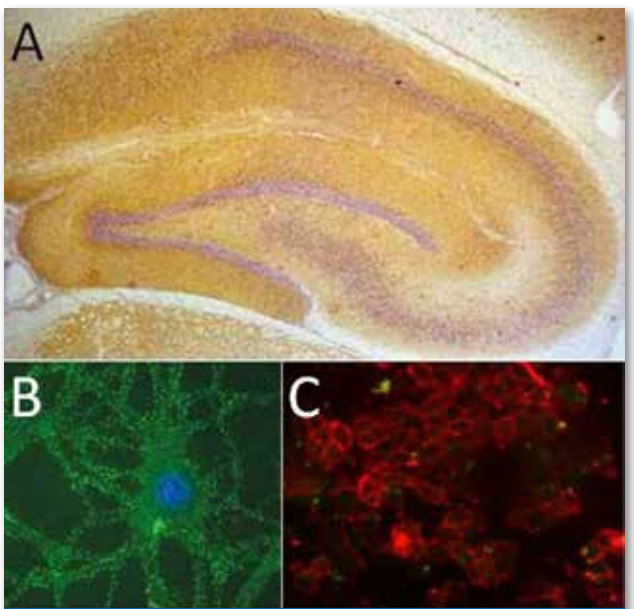

Figure 1: Representative illustration of the immunoreactivity pattern of an autoimmune encephalitis patient with psychotic symptoms and N-methyl-D-aspartate receptor (NMDAR) antibody. Serum IgGs of the patient react with neuropil of the hippocampus (A), cultured live hippocampal neurons (B) and human embryonal kidney cells transfected with NR1 and NR2 subunits of the NMDAR (C).

NMDAR encephalitis patients are mostly young women and less than half of the patients have teratomas. Two thirds of NMDAR encephalitis patients present with psychiatric symptoms, including psychosis and behavioral change[11,18-20]. Some of these patients may also display catatonia[18]. More than three quarters of NMDAR encephalitis patients initially present with psychiatric symptoms and no accompanying neurological findings and thus might mistakenly be diagnosed as a primary psychiatric disorder[19]. These patients develop memory loss, seizures, movement disorders and autonomic symptoms shortly after the initial psychiatric symptoms[19,20]. NMDAR antibody has also been detected in patients with schizophrenia, lethargic encephalitis, Hashimoto's encephalopathy, and major depressive disorder with psychotic features[15,21-23].

VGKC complex antibodies are more often detected in over 40-year-old men. They initially present with amnesia, seizures, and medial temporal lobe hyperintensity on MRI. During the course of the disease they may develop hyponatremia, agitation, confusion, hallucinations, personality change, depression, anxiety, REM-sleep behavior disorder and autonomic symptoms[24]. LGI1 antibody is more frequently associated with limbic encephalitis, whereas CASPR2 antibody is mostly found in Morvan syndrome and neuromyotonia patients. VGKC complex antibody positive patients might display thymoma or small cell lung cancer[25]. Patients with AMPAR antibodies may present with limbic encephalitis and isolated psychiatric symptoms[26]. Encephalitis associated with $GABA_BR$, Kv4.2 DPPX subunit and dopamine 2-receptor typically present with behavioral disturbance, paranoia, hallucinations, and delusions[8,13,14].

Evidence for Pathogenicity of NSAb

The definition of autoimmune disease requires an immune response to a self antigen to generate an observable pathology. In this context, pathogenic NSAb (i) should be present in blood, CSF or affected nervous system tissue, (ii) target a protein expressed by neuronal membrane, (iii) induce pathological and clinical features of a disease upon transferring to animals and (iv) elimination of antibodies through plasma exchange, intravenous immunoglobulin (IVIg) or other immunotherapies must improve the clinical symptoms in parallel to a decline in serum/CSF antibody levels[27]. Notably, all of the major NSAb related with psychotic features satisfy most of these criteria corroborating the concept of autoimmune psychosis.

NSAb target ionotropic or metabotropic neurotransmitter receptors and neuronal adhesion molecules that are involved in excitatory transmission (NMDAR, AMPAR), inhibitory transmission ($GABA_BR$, GlyR), and regulation of neuronal excitability (VGKC-complex proteins LGI1 and CASPR2)[28]. In vitro studies conducted with neuronal cell cultures have shown that NMDAR, AMPAR and GlyR antibodies reduce the expression of their target receptors thereby decreasing excitatory or inhibitory neurotransmission in widespread CNS regions[26,29,30]. Furthermore, electrophysiological studies have shown that administration of NMDAR and AMPAR antibodies have significantly reduced relevant ion currents in cultured neurons[26,29]. Reduced NMDAR expression has also been demonstrated in the brain samples of autoimmune encephalitis patients with NMDAR antibodies and experimental animals treated with NMDAR antibodies[29,31]. Moreover, intraventricular administration of serum/CSF IgG of NMDAR encephalitis patients into rat hippocampus increase extracellular glutamate concentrations[32] and corticomotor hyperexcitability[33]. LGI1 antibody does not reduce the expression of the target neuronal membrane protein but instead decreases the flow of K currents through VGKCs and Ca currents through AMPAR by as yet not entirely known mechanisms[34]. Complement dependent neuronal destruction has also been proposed as a potential pathogenic mechanism for VGKC- and GlyR-antibody mediated encephalitis[30,35].

Notably, NMDAR is expressed by frontostriatal circuit structures and thus psychiatric symptoms, catatonia, rigidity and dystonia, common manifestations of NMDAR encephalitis, are attributed to reduced NMDAR function in this circuit. Other pscyhosis-related autoantigens AMPAR and $GABA_BR$ are highly expressed in the hippocampus, which is important for memory, learning, and behavior[8,26]. Likewise, antibodies to LGI1, which predominantly has a hippocampal localization, is more profoundly associated with psychosis and other CNS symptoms as compared to antibodies to another VGKC complex protein CASPR2, which is expressed in the juxtaparanodes of myelinated neurons[25]. Moreover, NMDAR antagonists phencyclidine and ketamine induce psychosis like behavioral changes and mice with NMDAR subunit NR1 mutations display cognitive and behavioral disturbances[36,37]. Similarly LGI1 and CASPR2 mutations are associated with epilepsy, autism, and schizophrenia[38,39]. Overall, the correlations of target antigens and clinical syndromes give support to autoimmune origin of acute psychosis and imply that these patients might respond favorably to immunotherapies.

Currently there are no reported IgG passive transfer studies producing full-blown clinical findings of autoimmune encephalitis in experimental animals. However, a few NMDAR encephalitis patients with pregnancy (a natural model for passive transfer of IgG from mother to fetus) have been reported. Surprisingly, none of the newborns of these pregnant mothers displayed neurological symptoms or serum NMDAR antibodies. This might be explained by the fact that NMDAR antibodies are often found only in CSF of NMDAR encephalitis patients[40].

An important source of supporting evidence for the autoimmune basis of psychosis is treatment responses of encephalitis patients. Psychotic features can be encountered in patients

with or without well-characterized autoimmune encephalitis symptoms. Visual hallucinations and paranoid delusions occurring in the setting of autoimmune encephalitis patients give remarkable response to antibody depleting treatment methods such as pulse IV methylprednisolone, IVIG, plasma exchange, and rituximab. There are also reports of cases with isolated first-onset psychosis that give prompt response to steroid and/ or IVIG treatment. Some of these cases display NSAb, whereas some do not display any of the well-characterized NSAb suggesting that there might be additional psychosis-related anti-neuronal antibodies or immunological factors pending to be delineated[4,17,20,41,42]. Unfortunately, reported treatment results are mostly from retrospective series and no clinical trials have taken place for autoimmune encephalitis as yet.

Psychosis and NSAb in Systemic Lupus Erythematosus (SLE)

A proportion of SLE patients present with neuropsychiatric symptoms including psychosis. NSAb that are commonly detected in autoimmune encephalitis patients can not be found in SLE patients and no other reliable and specific antibodies have been defined for SLE. Antinuclear antibodies (ANA) and ribosomal P antibodies are commonly detected in SLE patients with or without neuropsychiatric symptoms and therefore do not represent a specificity for psychotic symptoms[43,44]. Antibodies to a small pentapeptide sequence (DWEYS) found on the NR2A and NR2B subunits of the NMDAR have been measured by small peptide ELISA. However, this ELISA method may often yield nonspecific results and no direct clinical correlations between these antibodies and psychosis has been found implying that the clinical relevance of these antibodies is unclear[45]. Injection of these antibodies into the hippocampus of experimental animals has induced neuronal apoptosis and memory loss but no behavioral symptoms have been described in these animals[46].

NSAb in Primary Psychotic Disorders

The NMDAR hypofunction model of schizophrenia provides support for the relevance of NMDAR antibodies in primary psychotic disorder[36,37]. However, patients with psychosis with or without additional neurological findings and NSAb generally do not satisfy the relevant Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia or other primary psychotic disorders. So far there are only 11 patients with schizophrenia or schizophreniform disorders reported to have serum NMDAR or VGKC complex antibodies of the IgG isotype[15,16,47]. However, some of these patients had atypical features such as seizures and accompanying tumors bringing forward the possibility that these patients genuinely had autoimmune encephalitis mimicking a primary psychotic disorder. Also, absence of CSF studies in schizophrenia patients may lead to an underestimation of prevalence of NSAb.

Movement disorders and memory loss can occur in primary psychiatric disorders and whether these patients represent an encephalopathic subtype of schizophrenia need to be further studied. Anti-NMDAR IgA and IgM antibodies have also been detected in schizophrenia patients[16]. However, these antibodies can also be detected in non-autoimmune neurological disorders and their significance and specificity for schizophrenia are uncertain. Antibodies to M1, M2 subunits of the muscarinic AChR and α7 subunit of the nicotinic AChR have been defined in small proportions of schizophrenia patients[48,49]. However, these results have not been replicated by others and the clinical significance of these antibodies needs to be further scrutinized.

Diagnostic Implications: When and Whom to Screen for NSAb

The diagnosis is quite straightforward in patients with psychosis developing in the context of an acute encephalitis episode. However, in isolated psychosis patients and in encephalopathies with

Table 2: Criteria and supportive features to suspect psychosis of autoimmune origin

1. Acute or subacute (<12 weeks) onset of symptoms.
2. Exclusion of other causes (nervous system infection, trauma, toxic, tumor, metabolic).
3. At least one of the following supportive features:
   a. The presence of a well-defined clinical syndrome such as limbic encephalitis
   b. CSF pleocytosis, oligoclonal bands, elevated IgG index
   c. MRI abnormality that is typical for autoimmune encephalitis (e.g. increased signal in the medial temporal lobe)
   d. Inflammatory neuropathology on biopsy
   e. History of a coexisting autoimmune disease.
   f. Response to immunotherapy.

psychotic and atypical features, diagnosis might be complicated even in the presence of well-characterized NSAb, especially because low titers of these antibodies have been detected in normal individuals and neurodegenerative disorders[50-52]. In these cases additional criteria and in particular the condition of response to immunotherapy must be satisfied. The proposed criteria listed in Table 2 have been adopted from diagnostic algorithms prepared for autoimmune encephalitis and autoimmune epilepsy patients[9,10]. However, there is little doubt that diagnostic criteria specific for psychosis patients with autoimmune etiology need to be urgently settled.

Concluding Remarks

There are few studies that have investigated the prevalence of NSAb in purely psychiatric presentations. One epidemiologic study has suggested that autoimmune encephalitis incidence is greater than herpes simplex virus encephalitis[53], emphasizing the urgent requirement for describing the prevalence and characteristics of NSAb in psychotic patients. Also much work remains to be done on the etiology and pathogenic mechanisms of NSAb. The relevance of different clinical phenotypes (e.g., full-blown autoimmune encephalitis versus isolated psychosis, major depressive disorder with psychotic features, and catatonia) and the exact target epitopes of different NSAb requires further studies. The optimal diagnostic algorithms and treatment methods of patients with different NSAb should also be determined by randomized clinical trials. Development and validation of biomarkers (e.g., novel brain imaging methods) for discrimination of autoimmune vs non-autoimmune psychosis are needed.

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