The Emerging Link Between Autoimmune Disorders and Neuropsychiatric Disease

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Abnormal autoimmune activity has been implicated in a number of neuropsychiatric disorders. In this review, the authors discuss a newly recognized class of synaptic autoimmune encephalitides as well as behavioral and cognitive manifestations of systemic autoimmune diseases.

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A role for autoimmune dysfunction in psychiatric illness has been actively investigated since at least the 1930s, when autoantibodies were first reported in a schizophrenia patient.[1] Since that time, there have been myriad reports of specific autoimmune responses to self-antigens in psychosis, affective dysregulation, and other behavioral abnormalities.[1–3] Despite these efforts, no autoantibody findings have remained so reproducible or ubiquitous as to become a biomarker for disease.[1,4] Recently, a number of syndromes characterized in part by global encephalopathy or even more focal psychiatric changes have been found to result from autoimmune dysfunction, at times with autoantibodies that guide both diagnosis and treatment.[5,6] Here, we review autoimmune encephalitides caused by antineuronal antibodies that attack proteins involved in synaptic function, and we examine systemic autoimmune diseases that have profound neuropsychiatric components.

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TABLE 1. Synaptic Autoimmune Encephalitides

Target Antigen	Primary Symptoms	Other Manifestations	Associated Tumor(s)	Demographic Data	Outcomes With Proper Therapy
NMDA receptor	Psychosis, seizures, autonomic instability, dyskinesias	Viral prodrome, changes in speech, catatonic features, hypoventilation	Ovarian teratoma*	75% women; 35% children and adolescents	75%–80% substantial improvement or full recovery
AMPA receptor	Memory loss, confusion, agitation, seizures	Psychotic symptoms, affective changes	Breast or lung cancer, thymoma	Predominates in women, ages 50–70	Most improve; frequent relapse
$GABA_B$ receptor	Seizures, memory loss, confusion	Hallucinations, paranoia, odd behaviors	Small-cell lung cancer	Either gender, middle-aged	~50% improve
LGI1	Amnesia, seizures, confusion, disorientation	Autonomic dysfunction, apathy/irritability, hyponatremia	Rare, thymoma	~2:1 male: female, middle-aged	~80% full recovery or mild deficits
Caspr2	Neuromyotonia, dysautonomia, confusion, insomnia	Amnesia, seizures, neuropathic pain, weight loss	Rare, thymoma	~4:1 male: female, middle-aged	~80% substantial improvement

*The association with teratomas is gender- and age-dependent. In women older than 18, ovarian teratomas occur in ~55% of cases. In women younger than 18, teratomas occur in 30% of cases. In women younger than 14, teratomas occur in 9% of cases. Only ~5% of men have an underlying tumor (germ-cell tumor of the testis, neuroblastoma, small-cell lung cancer).[11]

AUTOIMMUNE SYNAPTIC ENCEPHALITIS

Limbic encephalitides, which until recently were invariably thought to be viral or paraneoplastic in origin, commonly result from idiopathic autoimmune processes in the absence of any underlying cancer or infection. Classically, symptoms evolve over days to weeks and include psychiatric manifestations as diverse as irritability, depression, hallucinations, and personality disturbances, with neurocognitive changes in the form of short-term memory loss, sleep disturbances, and seizures.[7] Brain MRI usually demonstrates medial temporal lobe hyperintensities, and CSF analysis reveals a mild lymphocytic pleocytosis.[8] Antineuronal antibodies targeting synaptic proteins cause limbic encephalitis in some cases, often with a highly characteristic clinical picture.[7] The autoantibodies described below can be found in the CSF and serum of patients, and many have been shown to bind and interfere with postsynaptic receptor signaling, leading to abnormal synaptic transmission.[6]

Anti-NMDA Receptor Encephalitis

The NMDA-type glutamate receptor, long thought to be a crucial receptor in learning and memory, visual adaptation, synaptic plasticity, and disorders as diverse as schizophrenia, addiction, stroke, and Alzheimer's disease, is now also known to be a target of autoimmune dysfunction.[9] Anti-NMDA receptor encephalitis was first described several years ago in multiple large studies that characterized the clinical syndrome in detail.[9–12] Clinicians all over the world have begun to diagnose mysterious cases of sudden behavioral change followed by profound neurologic deterioration by identifying anti-NMDA receptor antibodies in patients' CSF, and some have postulated this syndrome to be the biological underpinning for what was historically described as "demonic possession."[13] Patients are usually young women or children (although men have also been identified) who first present to a psychiatric setting with paranoid and delusional thinking, perceptual disturbances, agitation, changes in speech, and bizarre behavior (Table 1).[9,11] A viral prodrome often precedes psychiatric symptoms by a few weeks, but otherwise there is usually sparse past medical history. In most cases, patients rapidly deteriorate neurologically, with symptoms such as seizures, autonomic instability, dyskinesias, altered levels of consciousness with catatonic-like features, and hypoventilation that can require intubation. CSF findings include mild-to-moderate pleocytosis, but nearly half of patients have no abnormalities on brain MRI studies.[9]

Although anti-NMDA receptor encephalitis is not by definition associated with cancer, ~50% of women with the disorder have an ovarian teratoma, with generation of antibodies in response to an antigen expressed by tumor cells.[9] In girls younger than age 18 and in male patients of any age, even fewer have an identifiable tumor of any kind (Table 1).[11] Regardless of the inciting factor, the effect of the autoantibodies has been well described and is uniform. NMDA receptors are expressed throughout the

brain, but immunostaining of rodent brain sections with patient antibodies demonstrates preferential labeling of hippocampus.[9] The antibody specifically recognizes the NR1 subunit of the NMDA receptor, which is the obligate subunit and thus is present in all NMDA receptors. Binding of patient antibodies to the receptor results in internalization from the neuronal surface and reduced glutamatergic transmission, although this effect is reversible with removal of the autoantibody.[9,14]

Despite the severity of neurologic symptoms, many patients respond well to treatment—likely a reflection of the reversible nature of the pathogenic cellular mechanisms. Thus, prompt recognition and diagnosis of anti-NMDA receptor encephalitis is essential. Patients with an ovarian teratoma or other tumor should have appropriate cancer care, usually with removal of the tumor and/or chemotherapy.[15] In the absence of cancer (or after tumor treatment), patients are treated with immunotherapy such as intravenous immunoglobulin, corticosteroids, cyclophosphamide, and rituximab.[9] Seventy-five to eighty percent of patients have full or substantial recovery, although usually after a prolonged hospital course. Behavioral and cognitive symptoms (disinhibition, poor attention, impulsivity) often persist for many months after the acute phase of illness, and about 20% of patients experience a relapsing course of disease.[7,9] Management of the acute and prolonged neuropsychiatric symptoms is receiving increased attention, and clinical experience suggests that despite a psychotic picture at times, high-potency dopaminergic blockade might not address symptoms as effectively as more sedating medications (MSK, JD, unpublished observations).[16]

Anti-AMPA Receptor Encephalitis

Dysfunction of glutamatergic signaling can also result in limbic encephalitis when the immune system attacks AMPA-type glutamate receptors. AMPA receptors mediate the majority of fast excitatory synaptic transmission in the CNS, and disrupted AMPA receptor function is thought to be involved in learning and memory abnormalities,[17] addiction,[18] and depression,[19] among other disorders. Anti-AMPA receptor autoantibodies bind the receptor, leading to a reversible internalization and removal from the synapse.[20] Patients are usually women older than 50 who present with subacute memory loss, confusion, agitated behavior, and seizures (Table 1); most also have an associated tumor of the breast, lung, or thymus.[20] MRI and CSF findings are typical of limbic encephalitis, and treatment is first oriented toward the tumor, followed by immunotherapy. Although patients respond well initially, this disorder is characterized by frequent relapse of short-term memory deficits and behavioral difficulties in the absence of detectable cancer recurrence, suggesting more prolonged autoimmune abnormalities.[20]

Remarkably, in both anti-NMDA receptor and anti-AMPA receptor encephalitis, specific cases have been identified in which neuropsychiatric symptoms predominate without focal neurologic signs or progression to severe neurologic compromise. One case involved a 19-year-old man who presented with subacute cognitive changes and behavioral symptoms most consistent with a manic episode. In retrospect, his parents had noticed excessive blinking (facial dyskinesias), which they attributed to anxiety. He was found to be anti-NMDA receptor antibody-positive and responded well to immunotherapy and valproic acid without further neurologic decline (MSK, JD, unpublished observations). Other case reports describe patients with anti-AMPA receptor antibodies who had only rapidly progressive behavioral changes consistent with atypical psychosis that responded to corticosteroid therapy.[21] Finally, Bataller and colleagues[22] report on a 67-year-old woman found to have anti-AMPA receptor encephalitis, who initially experienced confusion, hypersomnia, visual hallucinations, and combativeness after surgery for breast adenocarcinoma. Two weeks after discharge, she was readmitted with memory impairment and depressed affect. After treatment with high-dose intravenous immunotherapy and chemotherapy, her memory symptoms improved, although apathy and depressed mood persisted after 3 months. One year after the initial presentation, her mood and her neuropsychological symptoms were normal aside from partial amnesia of the illness and the previous 2 years. These cases highlight emerging evidence that autoimmune processes might masquerade as psychiatric illnesses and, given the vastly different treatment options, emphasize the renewed need for large studies to determine the frequency of these syndromes in the psychiatric population.[23]

Anti-GABA Receptor Encephalitis

In addition to modulation of glutamatergic signaling, recent work has described limbic encephalitis associated with anti-γ-aminobutyric acid type B ($GABA_B$) receptor autoantibodies (Table 1).[24] Disrupted $GABA_B$ receptor signaling in rodents has been shown to result in seizures, memory dysfunction, anxiety, and alterations in mood.[25] Consistent with these findings, patients with

anti-$GABA_B$ receptor encephalitis present with prominent seizures, severe memory dysfunction, and confusion; some also experience perceptual disturbances, paranoia, and behavioral changes.[24] Affected patients are usually in their 60s and are equally divided between sexes. Anti-$GABA_B$ receptor encephalitis occurs commonly with small-cell lung cancer, and more than half of patients improve with immunotherapy and tumor treatment. Interestingly, nearly half of these patients also harbor other autoantibodies, suggesting more generalized autoimmune dysfunction in this population.[24] Future work will help delineate the cellular mechanisms by which anti-$GABA_B$ receptor autoantibodies result in the observed clinical syndrome.

Antibodies Targeting *Trans*-Synaptic Cell Adhesion Molecules

Although multiple autoantibodies recognizing synaptic receptors have been described, recent work also implicates disruption of *trans*-synaptic scaffolding systems in certain autoimmune encephalitides. *Trans*-synaptic neuronal cell adhesion molecules are known to be crucial for proper synapse formation and adhesion, plasticity, and function.[26] In both developing and mature neurons, these molecules also serve to recruit and anchor pre- and postsynaptic proteins to appropriate synaptic localizations, allowing for normal synaptic transmission. In some instances, neuropsychiatric disorders such as autism and schizophrenia are postulated to result from genetic mutations in these neuronal cell-adhesion systems.[27,28] Recent discoveries now indicate that acquired autoimmune syndromes also target *trans*-synaptic signals. Leucine-rich glioma-inactivated 1 (LGI1) is a secreted protein that interacts with presynaptic ADAM23 and postsynaptic ADAM22 to create a *trans*-synaptic protein complex, which also includes potassium channels and AMPA-type glutamate receptors.[29,30] Mutations in LGI1 are known to cause autosomal-dominant partial epilepsy with auditory features,[31] a syndrome characterized by temporal lobe seizures with prominent auditory hallucinations (Table 1).[32] A classic limbic encephalitis previously thought to be caused by autoantibodies recognizing voltage-gated potassium channels (VGKC) is now known to result from autoantibodies targeting LGI1.[30,33] As described in detail as encephalitis attributed to anti-VGKC antibodies,[34] anti-LGI1 patients present most prominently with seizures, memory loss, and confusion. Other symptoms can include autonomic dysfunction (hyperhidrosis, hypersalivation) and behavioral changes such as apathy and irritability. MRI usually shows increased signal involving medial temporal lobes, although (uncharacteristic of classic limbic encephalitis) CSF is often normal. It is unclear why patients with anti-LGI1 antibodies do not often experience perceptual disturbances akin to those in patients with autosomal-dominant partial epilepsy with auditory features, although this difference is likely related to the acquired dysfunction of LGI1 later in life as opposed to a developmental abnormality. Like other autoimmune encephalopathies with extracellular antigen targets, anti-LGI1 encephalitis responds remarkably well to immunotherapy, with ~80% of patients showing either full recovery or mild disability.[34,35]

In addition to LGI1, current research suggests that another molecule involved in neuronal cell adhesion might be a target for autoimmune syndromes.[30,33] Contactin-associated protein-like 2 (Caspr2) has a role in clustering VGKC at the paranodal regions of myelinated axons.[36] Caspr2 is a member of the neurexin superfamily, which mediates cell–cell interactions in the CNS and in which mutations have been associated with schizophrenia, autism, and mental retardation.[37] Genetic-analysis experiments have described a cortical dysplasia/focal epilepsy syndrome caused by mutations in Caspr2.[38] Patients with these mutations present early in life (between ages 2 and 7) with intractable seizures, followed by diminished learning and social behaviors, with language regression. Other pervasive neuropsychiatric symptoms are autistic-like and include hyperactivity, inattention, and aggression. Autoantibodies recognizing Caspr2 have been described in autoimmune encephalitis, often in association with symptoms of peripheral nerve hyperexcitabilty such as neuromyotonia (difficulty in muscle relaxation), cramps, fasciculations, and muscle spasms (Table 1).[30,33,39] Taken together, these two autoimmune syndromes highlight the role of synaptic organizers in autoimmune encephalitis and open new avenues toward understanding the role of *trans*-synaptic signals in disease states.

ENCEPHALOPATHY IN LUPUS AND OTHER SYSTEMIC SYNDROMES

In addition to autoimmune synaptic encephalitides that tend to be idiopathic or paraneoplastic in nature, a number of systemic autoimmune disorders can affect the brain in isolation or along with multiple other organ systems, resulting in a range of neuropsychiatric defi-

TABLE 2. Neuropsychiatric Features of Systemic Autoimmune Disorders

Disorder	Proposed Target Antigen(s) in CNS Disease	Neurologic and/or Psychiatric Symptoms
Systemic lupus erythematosus	Ribosomal P; NR2 subunits of the NMDA receptor	Neuropsychiatric systemic lupus erythematosus: cognitive changes, affective disorders, anxiety, psychosis, delirium
Susac's syndrome	Endothelial cell	Branch retinal arterial occlusion, hearing loss, acute encephalopathy
CNS vasculitis	Unknown	Headache, encephalopathy (memory changes, confusion), other focal neurologic signs
CNS Whipple's disease	Unknown	Cognitive decline, personality/affective changes, oculomasticatory myorhythmia
Sjögren's syndrome	Ro, La, alpha-fodrin	Cognitive dysfunction, peripheral neuropathy, stroke- or multiple sclerosis-like symptoms
Behçet's disease	alpha B-crystallin, cardiolipin	Memory impairment (learning and recall), personality change/disinhibition

cits. One of the most clinically prevalent syndromes is neuropsychiatric systemic lupus erythematosus (SLE). Symptoms are variable and can run the spectrum of psychiatric dysfunction, including cognitive changes, delirium, anxiety disorders, mood disorders, and psychosis (Table 2).[40] Diagnosis of neuropsychiatric SLE remains clinically defined, without reliable imaging or laboratory criteria. Reflecting the historically variable diagnostic criteria, estimates of neuropsychiatric SLE incidence in lupus patients range widely, from ~15% to 80%.[41–43] Notably, psychiatric symptoms do not appear to be correlated with flare-ups in systemic disease,[44] further confounding diagnosis and emphasizing the need to rule out other potential etiologies (e.g., infection, steroid-induced psychiatric symptoms, and primary psychiatric disturbances).

A tremendous amount of research has centered on identifying causative autoantibodies in neuropsychiatric SLE for both diagnostic and treatment purposes, and while debate continues, a number of intriguing candidates have emerged (Table 2). In a seminal study published over 20 years ago, antiribosomal P autoantibodies were detected in 90% of patients with SLE and psychosis,[45] and recent work suggests that this antibody might cross-react with a neuronal surface protein to initiate calcium influx and apoptosis.[46] However, large clinical studies and meta-analyses have reached variable results with regard to the presence of antiribosomal P antibodies in neuropsychiatric SLE, with differences attributed to laboratory methodology, study population, fluctuating course of disease, and diagnostic discrepancies.[47,48] Other groups have reported that a subset of anti-DNA antibodies in SLE cross-react with NMDA receptors, potentially resulting in neuropsychiatric abnormalities.[49] In contrast with anti-NMDA receptor encephalitis, the autoantibodies in SLE recognized the NR2A and NR2B subunits of the NMDA receptor,[49] which are developmentally regulated and highly expressed in hippocampus.[50] These antibodies activate NMDA receptors and induce excitotoxic cell death;[50] mice exposed to the cross-reacting anti-DNA antibodies from human SLE patients demonstrate deficits in a particular memory task, although other cognitive tests remain normal.[51] Here too, clinical studies aiming to correlate manifestations of neuropsychiatric SLE with NMDA receptor antibodies have yielded inconsistent results.[5] Future work will undoubtedly continue to examine whether the aforementioned antibodies and others are pathogenic in neuropsychiatric SLE.

Susac's Syndrome, CNS Vasculitis, and Others

A number of other multi-organ diseases appear to have autoimmune pathogenesis, with protean clinical manifestations that often include neuropsychiatric changes. Susac's syndrome, first described in 1979, consists of the triad of branch retinal arterial occlusions, hearing loss, and acute encephalopathy (Table 2).[52–54] Neuropsychiatric symptoms may be less global, however, and include personality changes, paranoia, and affective dysregulation early in the course, with memory abnormalities and increasing confusion as the syndrome progresses.[54,55] Focal neurologic findings and headache are also commonly observed.[54] Susac's syndrome usually affects young women, and a viral prodrome can precede other symptoms. MRI shows disseminated lesions in white and gray matter, with a predilection for corpus callosum involvement. EEG often reveals diffuse slowing, whereas CSF only reliably shows elevated protein (no definitive autoantibody has been identified as

causative).[54,56] Fluorescein angiography and audiometry are normally part of the diagnostic process, as well. Susac's syndrome is thought to be a brain microangiopathy, with pathologic findings similar to those of autoimmune antiendothelial cell antibody syndromes.[53] Patients respond well if the syndrome is identified early and treated with immunosuppression,[54,55] further supporting the notion that Susac's syndrome is an autoimmune disorder.

Primary CNS vasculitis (also known as primary angiitis of the CNS) is a rare idiopathic vasculitis, with headache and encephalopathy as the most common initial symptoms (Table 2).[57–59] As with other vasculitides, this syndrome is thought to result from autoimmune dysfunction, based largely on the response to immunotherapy. Affected patients are usually middle-aged men (mean age, 50 years), with diffuse or focal neurologic findings resulting from injury to intracerebral vessels.[59] Psychiatric symptoms can include memory dysfunction, confusion, and affective changes.[57,59] Multifocal lesions or infarcts on MRI, inflammatory changes in CSF, and cerebral angiography showing vasculitic changes (alternating vessel narrowing and dilations) lead to diagnosis.[60] Although sensitivity varies among studies,[59] brain biopsy is generally considered the gold standard of diagnosis (particularly to rule out infectious processes) and often reveals granulomatous changes.[57,60] Treatment is with corticosteroids alone or in combination with cyclophosphamide.[59,60]

Finally, illnesses such as CNS Whipple's disease, Sjögren's syndrome, and Behçet's disease may have prominent neuropsychiatric symptoms (Table 2). Whipple's disease is caused by infection with *Tropheryma whipplei*, but immune dysfunction is thought to play a role.[61] With CNS involvement, oculomasticatory myorhythmia is pathognomonic,[62] and patients commonly have cognitive changes, although other psychiatric findings (depression, anxiety, psychosis, personality change) are often found.[63] Case reports have described a patient with an amnestic syndrome[64] and another with Klüver-Bucy-like symptoms[65] in CNS Whipple's disease, which highlights the variable presentation in this disease. Sjögren's syndrome[66–69] and Behçet's disease[70–72]—both autoimmune disorders—can involve the CNS as well, causing cognitive and personality changes (Table 2).

CONCLUSION

Although a link between behavior and immune function has been hypothesized for many decades, recent work provides some of the most compelling evidence thus far. In particular, autoimmune synaptic encephalitides demonstrate how abnormal autoimmune targeting of synaptic proteins can result in profound neuropsychiatric symptoms. Each syndrome is diagnosable by a set of laboratory tests and responds well to immunotherapy. These features provide a degree of clinical certainty rarely available to psychiatrists. Also, the high incidence of systemic autoimmune disorders with neuropsychiatric features reinforces the likely cross-reactivity of peripheral autoantibodies with brain antigens.

Future work in both synaptic encephalitides and systemic autoimmune disorders with cognitive and behavioral manifestations will no doubt add to our understanding of how autoimmunity and psychiatry are intertwined. Many significant questions remain: What stimuli trigger autoantibody formation in synaptic encephalitis in the absence of a paraneoplastic etiology? How do anti-NMDA receptor antibodies compare between SLE and anti-NMDA receptor encephalitis? Can neuropsychiatric symptoms in systemic autoimmune diseases be attributed to specific autoantibodies? Finally, and perhaps most significantly, new research will aim to determine whether a subset of what we currently diagnose as primary psychiatric disorders are in fact due to definable, treatable autoimmune syndromes.

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