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Autoimmune encephalopathies

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Abstract

Over the last 10 years the continual discovery of novel forms of encephalitis associated with antibodies to cell-surface or synaptic proteins has changed the paradigms for diagnosing and treating disorders that were previously unknown or mischaracterized. We review here the process of discovery, the symptoms, and the target antigens of twelve autoimmune encephatilic disorders, grouped by syndromes and approached from a clinical perspective. Anti-NMDAR encephalitis, several subtypes of limbic encephalitis, stiff-person spectrum disorders, and other autoimmune encephalitides that result in psychosis, seizures, or abnormal movements are described in detail. We include a novel encephalopathy with prominent sleep dysfunction that provides an intriguing link between chronic neurodegeneration and cell-surface autoimmunity (IgLON5). Some of the caveats of limited serum testing are outlined. In addition, we review the underlying cellular and synaptic mechanisms that for some disorders confirm the antibody pathogenicity. The multidisciplinary impact of autoimmune encephalitis has been expanded recently by the discovery that herpes simplex encephalitis is a robust trigger of synaptic autoimmunity, and that some patients may develop overlapping syndromes, including anti-NMDAR encephalitis and neuromyelitis optica or other demyelinating diseases.

Keywords

autoimmune encephalitis; limbic encephalitis; anti-NMDAR antibodies; psychosis; treatment

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Conflicts of interests

Dr. Dalmau holds patents for the use of Ma2, NMDAR, and GABAbR as autoantibody tests, and has patent applications for DPPX, GABAaR, and IgLON5 as autoantibody tests; he receives royalties for Ma2, NMDAR, and GABAbR diagnostic tests. Dr. Dalmau has a research grant from Euroimmun.

Introduction

The encephalitides associated with antibodies against cell-surface or synaptic proteins are a new category of diseases that occur with focal or widespread involvement of the nervous system in association with antibodies against extracellular epitopes of neuronal cell-surface or synaptic proteins.[1] The discovery of this group of disorders—referred in this review as *autoimmune encephalitis*—has affected many fields of medicine, resulted in changed paradigms for the diagnostic and treatment approaches to some neuropsychiatric disorders, and reclassified syndromes previously defined as *idiopathic* or with descriptive terms.[1] In addition, the study of these disorders has revealed novel mechanisms of how antibodies might alter memory, behavior, and cognition or cause psychosis, seizures, or abnormal movements (Fig. 1).[2,3]

The concept that autoimmunity mediated by antibodies or cytotoxic T-cell mechanisms can cause neurological symptoms is not new. The myasthenic syndromes are good examples of how autoantibodies can cause neurological symptoms; in myasthenic syndromes autoantibodies against acetylcholine receptor or voltage-gated calcium channels cause reversible muscle weakness by altering the normal function of the neuromuscular junction.[4,5] As another example, some paraneoplastic syndromes such as cerebellar degeneration or limbic encephalitis are associated with highly specific antibodies against intracellular neuronal proteins and aggressive cytotoxic T cell responses that usually lead to irreversible deficits.[6]

In contrast to classical paraneoplastic syndromes, the novelty of the autoimmune encephalitides reviewed here is that they can affect patients of all ages, some of them preferentially occurring in children and young adults;[7-9] they can develop with or without an underlying tumor; they are associated with antibodies that target extracellular epitopes of cell-surface or synaptic proteins; and for the disorders which underlying mechanisms have been investigated, the antibodies alter the structure or function of the target antigen.[2,10] In addition, the associated syndromes often respond to immunotherapy, resulting in substantial or complete recovery in 70–80% of the patients.[11] Owing to the severity and duration of symptoms, before these disorders were known the clinical recovery of similar patients was not expected, thus changing our concepts about supportive therapy today in cases that would have been considered futile in the past.[12,13]

Antibodies and target antigens

In 2005, the description of six patients with different forms of encephalitis, with antibodies against neuronal cell surface proteins, marks the beginning of the molecular identification and understanding of these disorders.[14] Until then, the only cell-surface antibodies associated with autoimmune encephalitis (specifically, limbic encephalitis and Morvan's syndrome) were attributed to antibodies specific for the Kv1.1 and Kv1.2 subunits of the Shaker family of voltage-gated potassium channels (VGKCs).[15,16] (This was later shown to be incorrect; discussed below). One of the six patients had been diagnosed with the Kv1.1- and Kv1.2-specific antibodies, but in the other five cases the neuronal targets were unknown. Remarkably, all of the patients improved substantially with immunotherapy and,

when appropriate, removal of the associated tumors (two had teratomas and two had tumors of the thymus).[14] This improvement, when compared with the limited treatment response of classic paraneoplastic syndromes[17-20] led investigators to distinguish a new category of autoimmune encephalitis. In subsequent studies, the unknown cell surface antigens were immunoprecipitated and found to be synaptic receptors, including the *N*-methyl-D-aspartate receptor (NMDAR),[21] the α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPAR),[22] or the γ-amino-butyric acid B-receptor (GABAbR).[23] Similar strategies showed that the antibodies originally attributed to the Shaker family of VGKCs were in fact directed against other proteins, including leucine-rich, glioma-inactivated 1 (LGI1)[24] and contactin-associated protein-like 2 (Caspr2).[25,26] Since 2005, the frequency of discovery of novel syndromes and their associated autoantigens has been 1–2 per year (Table 1).

Many patients with autoimmune encephalitis have a propensity to autoimmunity, including multiple serum antibodies that are unrelated to patients' symptoms (e.g., thyroid peroxidase (TPO) antibody or antinuclear antibodies (ANA)).[22,27] These encephalitis-irrelevant antibodies are usually absent in in the cerebrospinal fluid (CSF), which provides a clean source of disease-relevant antibodies for preliminary antigen characterization. Detection of CSF reactivity with the neuropil of brain along with immunolabeling of the cell surface of cultured neurons strongly suggests a pathogenic link between the antibodies and patients' symptoms. The techniques more frequently used to eventually characterize antigens include immunoprecipitation (nine of eleven antigens shown in Table 1, Fig. 1) [1,22] and screening of candidate antigens according either to patients' symptoms or the investigator's hypothesis (four of eleven; two of them, LGI1 and Caspr2, also identified by precipitation).[8,28]

General clinical features of autoimmune encephalitis

At disease onset, there is substantial overlap of symptoms among the different types of autoimmune encephalitis. The rapid development of symptoms in a few days or weeks, sometimes with headache or mild hyperthermia, and frequent CSF pleocytosis often lead to empiric antiviral or bacterial treatments while CSF and blood work for infectious, metabolic, and toxic causes are processed.[29,30] Alteration of mood, behavior, and memory, decreased level of consciousness, and seizures occur in most types of autoimmune encephalitis; however, the severity and predominance of some symptoms over others, and the presence of other features (e.g., dyskinesias, severe psychiatric manifestations, facio-brachial dystonic seizures, hyponatremia, diarrhea) along with demographic information (sex, gender, race), brain MRI findings, and presence or absence of a tumor can suggest a specific disorder. Sleep dysfunction, nearly constant in all forms of encephalitis, has been studied in detail in only two disorders, anti-LGI1 encephalitis[31] and the recently reported encephalopathy with IgLON5-specific antibodies[32] (discussed below).

The electroencephalogram (EEG) is almost always abnormal in all types of autoimmune encephalitis, showing focal or diffuse slow activity frequently associated with one or several foci of epileptic activity. Except for a pattern referred to as *extreme delta brush* that may occur in patients with anti-NMDAR encephalitis, there are no pathognomonic EEG abnormalities for any other forms of autoimmune encephalitis.[33,34] Magnetic resonance imaging (MRI) of the brain is very useful in patients with limbic encephalitis (see below),

usually showing increased FLAIR/T2 signal involving one or both temporal lobes, without contrast enhancement (Fig. 2). Similar findings can occur in patients with herpes simplex encephalitis (HSE) or medial temporal lobe seizures, but the pattern of highly selective medial temporal lobe involvement is limited to a few other disorders (e.g., paraneoplastic limbic encephalitis,[35] rare cases of lupus,[36] neurosyphilis,[37] Sjogren's syndrome,[38] or HHV6 infection[39]).

At symptom presentation, about 80% of patients with autoimmune encephalitis have mild-to-moderate CSF lymphocytic pleocytosis (usually <100 white blood cells/μl), 30% have mild-to-moderate increase of protein concentration, and 50–60% have oligoclonal bands. These bands can be present even when routine CSF studies are normal. In contrast to most autoimmune encephalitis, the limbic encephalitis associated with LGI1-specific antibodies frequently occurs with normal or minimal CSF findings.[40]

Specific syndromes

Anti-NMDAR encephalitis

The encephalitis associated with NMDAR-specific antibodies has been described in large series of patients[41-44] and a recent review.[45] This disorder is characterized by CSF IgG antibodies against the GluN1 subunit of the NMDAR. The disease usually occurs in young adults and children, predominantly women, although it can affect patients of all ages. In a population-based study in England examining causes of autoimmune encephalitis, anti-NMDAR encephalitis was second only to acute demyelinating encephalomyelitis (ADEM).[46] In a referral center focused in the study of encephalitis of unclear etiology, the incidence of anti-NMDAR encephalitis was higher than any individual viral encephalitis.[30] One percent of young patients (18–35 years) admitted to the intensive care unit of a large German center for encephalitis of unknown origin were in retrospect found to have NMDAR-specific antibodies.[47]

In a series of 577 patients (81% female), the median age was 21 years, 37% were younger than 18 years and 5% older than 45.[42] The frequency of males was higher in age groups below 12 years (39%) and above 45 (43%). Thirty eight percent of the patients (representing 46% of all women) had an underlying neoplasm. The presence of a tumor predominated in patients between 12 and 45 years. Only 6% of females younger than 12 years and 6% of males (all adults) had a tumor. Ninety four percent of the tumors were ovarian teratomas, 2% extraovarian teratomas, and 4% other tumors.

The syndrome was established in 2008 in a series of 100 patients,[41] and since then the spectrum of symptoms has not changed substantially (Fig. 3).[42,43] Approximately 70% of the patients develop prodromal symptoms, such as headache or fever, that are usually followed by rapid change of behavior that may include anxiety, agitation, insomnia, aggression, visual or auditory hallucinations, paranoia, grandiose delusions, hyper-religiosity, sexual disinhibition, mania, psychosis, or catatonia. The prominence of the psychiatric symptoms contributed to the initial identification of this disorder[48] and has recently led to a surge of interest in psychiatry[49,50] (discussed below in the section "Psychiatry"). These symptoms are usually followed by a wide range of abnormal

movements that may include orofacial dyskinesias, chorea, athetosis, ballismus, myorhythmia, stereotyped movements, rigidity, or opisthotonus.[7,51-53] As the symptoms progress there is decreased consciousness, stupor, coma, periods of agitation alternating with catatonia, autonomic dysregulation such as fluctuation of blood pressure, hyperthermia, sialorrhea, tachycardia, hypoventilation, and, less frequently, bradycardia, cardiac pauses, or ictal asystole that may require transient use of a pacemaker.[54-56] Seizures and complex status epilepticus may occur at any stage of the disease,[57] but almost always resolve after other symptoms improve, not requiring chronic antiepileptic therapy.[13] Seizures, as initial presenting symptom, are more frequent in adult male patients than in women.[43,58]

Brain MRI is normal in 66% of NMDAR encephalitis patients;[42] the other 34% have nonspecific cortical or subcortical FLAIR/T2 abnormalities, sometimes involving posterior fossa or medial temporal regions, often with small areas of demyelination, and in a few cases with extensive demyelinating abnormalities[59] (discussed in the section below "Overlapping syndromes").

The average hospital admission is 3 months, but many patients require longer admissions in rehabilitation centers.[60] During recovery and after the acute symptoms have resolved patients continue with deficits of memory and attention, impulsivity, behavioral disinhibition, and executive dysfunction that usually improve over many months. In a prolonged follow up of 501 patients, 81% had a modified Rankin scale score of 0–2 at 24 months, and some continued to improve thereafter.[42] The mortality rate is approximately 7%, with most deaths occurring during the stage of intensive care support.

The presentation of NMDAR encephalitis in children with behavioral abnormalities may initially suggest autistic regression, early onset schizophrenia, or childhood disintegrative disorder.[61,62] Compared with adults, children more often present initially with abnormal movements or seizures, and then in the ensuing days or weeks progress to develop a syndrome similar to that of the adults.[7,34,63] In patients older than 45 years, the clinical picture is similar to that of younger patients, but the outcome is less favorable. In this age group, 23% of patients had an underlying tumor (carcinomas instead of teratomas), and delays in diagnosis and treatment were more frequent than in younger patients.[64] For any age group, monosymptomatic cases such as isolated abnormal movements,[65,66] psychosis,[67] or seizures are extremely rare.[68]

Owing to the protracted clinical course, complexity of symptoms and complications, and loss of weight and deconditioning, many different specialists are involved in the care of these patients. Approximately 50% of patients respond to first line immunotherapies (intravenous immunoglobulins (IVIg), steroids, or plasma exchange) and the other 50% require second line therapies, such as rituximab or a combination of rituximab and cyclophosphamide.[42] Relapses occur in 12–20% of cases (12% during the first 24 months of the disease),often presenting as fragments of the syndrome (perhaps due to prompt diagnosis), and respond to immunotherapy.[69] Overall, these data, and the fact that patients that receive second line immunotherapies have fewer relapses, is leading many physicians to use rituximab initially. Patients who do not respond to treatment, or who have relapses,

should be reassessed for the presence of an underlying[12,13] contralateral or recurrent teratoma.[70]

Limbic encephalitis

Three neuronal cell–surface antibodies are associated with limbic encephalitis, anti-LGI1,[24,25] anti-GABAbR,[23] and anti-AMPAR.[22]

The encephalitis associated with LGI1 antibodies—This limbic encephalitis predominantly affects middle age or elderly patients, males more frequently than females (2:1), and presents with prominent short-term memory deficits, confusion, and frequent seizures.[24,25] About 60% of the patients have hyponatremia and some patients have preceding or concomitant myoclonic-like jerks in the face, arm, or leg—described as *facio-brachial dystonic* or *tonic* seizures.[71,72] Recognition and treatment of these seizures with immunotherapy may prevent development of the encephalitis and cognitive dysfunction.[73] A study showed that five of six patients with limbic encephalitis and LGI1-specific antibodies had rapid eye movement (REM) sleep behavior disorder; in three patients these symptoms improved along with those of limbic encephalitis after immunotherapy, while in two the sleep disorder persisted.[31] Some patients with LGI1-specific antibodies develop confusion and cognitive decline over a few months, suggesting more a rapidly progressive dementia than subacute encephalitis. Creutzfeldt-Jakob disease (CJD) has been suspected in some of these patients,[74] although CJD patients do not have LGI1-specific antibodies (see below).

The presence of LGI1 rarely associates with systemic tumors; when it does there is usually an associated thymoma.[24,25] Recent studies indicate the importance of differentiating LGI1 antibodies, as well as Caspr2 antibodies (both previously considered VGKC antibodies), from other antibodies referred to under the term *VGKC-complex antibodies*. While LGI1 and Caspr2 antibodies (discussed below) specifically associate with limited subsets of syndromes, the identity of other VGKC-complex antibodies is unknown (it is also unknown if the antigens are on the cell surface); the VGKC-complex antibodies also have limited specificity and may be found in non-autoimmune diseases, including Creutzfeldt-Jakob disease (CJD), among others.[75,76] In contrast, a study of CSF from 49 patients with pathologically confirmed CJD showed that none had anti-LGI1, anti-Caspr2 or other well-defined cell-surface antibodies.[77] The same study found that among 346 patients with suspected CJD, 6 (1.7%) had autoimmune disorders that responded well to immunotherapy.

The encephalitis associated with GABAbR antibodies—This limbic encephalitis usually develops as limbic encephalitis.[23] Two recent series,[78,79] including a total of 37 patients, showed in the majority of cases typical clinical and MRI involvement of the limbic region along with early and frequent seizures. This autoimmunity is the most frequent cause of limbic encephalitis in patients with small cell lung cancer (SCLC) and who are negative for Hu antibodies.[80] About 50% of patients with GABAbR antibodies have SCLC or neuroendocrine tumors; the other 50% do not have an underlying cancer. Among patients with SCLC and limbic encephalitis, those with GABAbR antibodies have a much better outcome than those with Hu antibodies,[81] reflecting the better response to immunotherapy

of patients with syndromes pathogenically associated with auto-reactive antibodies rather than cytotoxic T cell mechanisms.[78,82] There are only a few cases of patients with GABAbR antibodies and symptoms different from limbic encephalitis, including cerebellar ataxia[83] and brainstem encephalopathy;[84] and one child with overlapping GABAaR antibodies developed confusion, chorea, opsoclonus, and ataxia.[85]

The encephalitis associated with AMPAR antibodies—Anti-AMPAR limbic encephalitis was initially described in 2009.[22] Patients develop symptoms and MRI features of limbic encephalitis, but in some cases the presentation is purely psychiatric, with confusion, agitation, and aggressive behavior. In two patients with isolated psychiatric symptoms, the CSF and MRI were normal, but the EEG was abnormal.[86] In a series of 10 patients (9 women), 7 had thymoma or cancer of the lung or breast. Additional antibodies, such as anti-ANA, anti-TPO, anti-GAD65, or other autoimmune disorders (e.g., hypothyroidism) co-occur frequently.[22] Symptoms usually respond to immunotherapy, although relapses are frequent. The severe memory deficits and confabulations complicate the management of these patients, who may gradually develop cumulative deficits after each relapse.

Other syndromes and autoantibodies to cell surface antigens or synaptic receptors

Morvan's syndrome—This is a disorder that includes symptoms of encephalitis, such as amnesia, confusion, hallucinations, sleep and autonomic dysregulation, in association with peripheral nerve hyperexcitability, or *neuromyotonia*. Morvan's syndrome and neuromyotonia were previously considered associated with antibodies against the Shaker family of VGKCs,[15] but the serum and CSF of these patients do not react with Kv1.1 or Kv1.2 subunits of the these channels. Instead, many patients with Morvan's syndrome,[87,26] and only a few with neuromyotonia,[88] have antibodies against Caspr2, a protein expressed in the CNS and at the juxtaparanodal region of myelinated nerves where it is associated with potassium channels. Patients with Caspr2 antibodies may also develop neuropathic pain, encephalitis without symptoms of peripheral neuropathy, or, rarely, limbic encephalitis.[26,87] The frequency of an underlying tumor (thymoma) varies substantially (0–40%) among series, likely reflecting referral bias, and appears to depend more on the syndrome than the antibody. For example, among patients with Caspr2 antibodies, those with Morvan's syndrome appear to more frequently have thymomas[87] compared to those with encephalitis.[26] Immunotherapy is usually effective.

The Ophelia syndrome—This is a form of autoimmune encephalitis that occurs in patients with Hodgkin's lymphoma.[89] The syndrome is often described as limbic encephalitis, but in fact the clinical picture and MRI studies suggest a more diffuse encephalitis. Symptoms include depression, agitation, hallucinations, memory deficits, delusions, and bizarre behavior. The disorder is extremely rare, and all cases studied recently had antibodies against the metabotropic glutamate receptor 5 (mGluR5), which is highly expressed in the hippocampus.[90,91] A similar syndrome can occur without Hodgkin's lymphoma. The importance of recognizing this disorder is that patients have complete recoveries after treatment of the tumor or immunotherapy. Patients with Hodgkin's lymphoma can also develop cerebellar degeneration, in which case the antibodies are against

mGluR1, which is highly expressed in cerebellum.[92,93] It is unclear why these two mGluRs that belong to the same group of mGluR (group 1), and none of the six receptors that belong to other groups (group 2 and 3), associate with CNS autoimmune disorders and Hodgkin's lymphoma.

Progressive encephalomyelitis with rigidity and myoclonus (PERM)—PERM is a disorder that results from predominant brainstem and spinal cord dysfunction as a result of immune-mediated disruption of inhibitory pathways. Recent studies showed that patients with PERM often have antibodies to the α1 subunit of the glycine receptor (GlyR).[28,94] A few patients have been found to have thymoma or other tumors, but most patients do not have cancer. Different from patients with stiff-person syndrome who rarely have encephalopathy or prominent brainstem symptoms, 40–50% of patients with PERM have ocular movement deficits, cranial nerve paresis, brainstem dysfunction, and encephalopathy, and 30% have autonomic dysregulation. Hyperekplexia is also a frequent symptom of this disorder. In a retrospective study of 52 patients, the median age was 50 years, and four were younger than 15 years of age. After a median follow-up of 3 years most patients had substantially improved with immunotherapy, but four (9%) died during the course of the disease.[95] The authors concluded that GlyR antibodies strongly associate with spinal and brainstem dysfunction. However, studies with a large number of disease control groups show that these antibodies occur in a variety of disorders, including stiff-person syndrome, limbic encephalitis, cerebellar degeneration, or optic neuritis.[96] GlyR antibodies can overlap with GAD65 antibodies.[97,98]

The most recent neuronal cell–surface autoantigen associated with PERM is dipeptidyl-peptidase-like protein-6 (DPPX).[99] Patients with antibodies to DPPX more frequently develop a syndrome of CNS hyperexcitability (discussed below).[100] The three cases reported with PERM, all younger than 30 years of age, developed prominent hyperekplexia, a wide range of cerebellar-ocular movement abnormalities, ataxia, and muscle stiffness and spasms (triggered by acoustic and tactile stimuli sometimes as mild as a gentle breeze). Two of the patients had prominent gastrointestinal symptoms, a common feature of DPPX autoimmunity. Two patients responded to immunotherapy; the third patient was diagnosed retrospectively, developed spastic tetraparesis, and died of pneumonia that was a complication of severe dysphagia. PERM-like symptoms may occur in some patients with antibodies against the intracellular proteins Nova 1 and 2 (anti-Ri or ANNA2 antibodies).[101] These antibodies associate with brainstem encephalitis or encephalomyelitis frequently accompanied by opsoclonus, other ocular movement disorders,[102] and sometimes life threatening laryngeal spasms.[103] In contrast to GlyR and DPPX antibody-associated syndromes, anti-Ri associated encephalitis is likely mediated by cytotoxic T cells.

Stiff-person syndrome—This syndrome comprises a clinical picture characterized by muscle rigidity and spasms that may occur spontaneously or are triggered by several types of stimuli (e.g., tactile, auditory, emotional upset). The disorder predominantly affects axial, low back, and proximal muscles of the extremities. Electromyography (EMG) of the involved muscles shows continuous motor unit activity as a result of dysfunction of the inhibitory GABAergic system; symptoms and EMG findings improve with diazepam. Most

patients have high titers of GAD65 antibodies and may develop overlapping cerebellar symptoms in association with endocrinopathy (diabetes, thyroid dysfunction).[104] The reason why antibodies against GAD65 (an intracellular protein) associate with different symptoms, including seizures or limbic encephalitis, is unknown.[105,106] Patients with GAD65 antibodies usually do not have underlying tumors.

In addition to GAD65 antibodies, some patients with stiff-person syndrome develop GlyR antibodies.[98] In children the disorder is frequently misdiagnosed.[97] Another study identified four patients with stiff-person syndrome and low titer serum antibodies to GABAaR; three of the patients had been previously considered seronegative and one had coexisting GAD65 antibodies.[27] High CSF or serum GABAaR antibody titers associate with prominent seizures and status epilepticus (discussed below).

About 5% of patients with stiff-person syndrome have SCLC or breast cancer; these patients usually develop amphiphysin antibodies instead of GAD65 or GlyR antibodies.[107,108] Amphiphysin is a vesicular synaptic protein involved in endocytosis; although the protein is not expressed on the neuronal cell surface, it has been suggested that during the process of synaptic vesicle uptake amphiphysin is exposed on the cell surface and can be accessed by antibodies. Amphiphysin antibodies also occur with paraneoplastic myelitis or encephalomyelitis.[109]

Encephalitis associated with DPPX antibodies—Anti-DPPX encephalitis results in symptoms of CNS hyperexcitability, including agitation, hallucinations, paranoid delusions, tremor, myoclonus, nystagmus, seizures, and, sometimes, hyperekplexia.[100] The disorder was initially reported in four patients (45–76 years old, 2 males), three of whom had prodromal diarrhea that led to substantial loss of weight. The target antigen, DPPX, is a cell surface auxiliary subunit of the Kv4.2 Shal potassium channel family. DPPX increases the function of Kv4.2 channels, which are involved in somatodendritic signal integration and attenuation of dendritic back propagation of action potentials. Although the encephalopathy of patients with DPPX antibodies does not conform to a specific syndrome, the symptoms of CNS hyperexcitability are consistent with the increased excitability noted in electrophysiological studies of Dppx-deficient (*Dpp6*$^{-/-}$) mice.[110] The cause of the diarrhea and other gastrointestinal symptoms is unknown, but DPPX is expressed in neurons of the myentheric plexus that strongly react with patients' antibodies. Overall, the disorder is severe, resulting in lengthy hospitalization or multiple relapses that usually occur while immunotherapy is decreased.

Encephalitis with antibodies to γ-amino-butyric acid A-receptor (GABAaR)—Anti-GABAaR encephalitis associated with prominent seizures and status epilepticus with extensive cortical and subcortical FLAIR/T2 signal abnormalities that may appear, while other abnormalities resolve (Fig. 2D).[27] These MRI findings are rarely encountered in the other autoimmune encephalitis mentioned above. In a recent study of 18 patients, six with high CSF or serum antibody titers (ages 3–63 years, median 22, five males) developed refractory seizures, status epilepticus, or epilepsia partialis continua, four of them required pharmacological coma. Patients responded to immunotherapy, but two died of sepsis during intensive care management of the seizures. The 12 patients without CSF antibodies (all with

low serum titers) developed a broader spectrum of symptoms likely indicative of coexisting autoimmune disorders; six patients had encephalitis with seizures, two opsoclonus, and four stiff-person syndrome (discussed above).[27]

Basal ganglia encephalitis and antibodies to dopamine (D2) receptor—This encephalitis and anti-D2 antibodies were recently reported in 12 children who developed several types of movement disorders sometimes co-existing in the same patient, including dystonia, tremor, oculogyric crises, parkinsonism, and/or chorea.[8] Agitation, anxiety, psychosis, and sleep dysfunction were frequent accompaniments. The brain MRI was normal in 50% of the patients; when abnormal, the findings were localized to the basal ganglia. Responses to immunotherapy were observed, but residual motor, cognitive, and psychiatric deficits were common. Antibodies to the D2 receptor were also identified in a subset of patients with Sydenham chorea, as reported by other investigators.[111] The frequency of these antibodies in patients with encephalitis associated with abnormal movements is low; in our experience with 120 patients, mostly children, with encephalitis and abnormal movements or basal ganglia MRI abnormalities all were negative for D2 receptor antibodies (Armangue *et al.*, data unpublished).

A novel link between autoimmunity and neurodegenerative disorders: encephalopathy and IgLON5 antibodies

This disorder differs in many ways from the autoimmune encephalitides described above. In contrast to the subacute presentation of most encephalitis, the clinical picture of patients with IgLON5 antibodies may evolve over years.[32] The syndrome was recently described in eight patients (age 52–76 years of age, median 59 years; 5 women) and includes abnormal sleep movements and behaviors, with obstructive sleep apnea, and stridor. Accompanying symptoms preceding or developing after the core syndrome included dysarthria, dysphagia, ataxia, or chorea. In six patients, the median duration of the disease was 5 years (2–12 years); the other two patients had a subacute presentation and died within 6 months of symptom onset. In all cases studied, polysomnography revealed abnormal sleep architecture, undifferentiated non-REM sleep or poorly structured stage N2, simple movements and finalistic behaviors, normalization of non-REM sleep by the end of the night, and REM sleep behavior disorder. All patients had antibodies (IgG4) against IgLON5, a neuronal specific cell adhesion molecule with unknown function. Four of four Spanish patients had the HLA-DQB1*0501 and HLA-DRB*1001 alleles that are very uncommon among the Spanish population. Symptoms did not respond to immunotherapy, and six patients had died by the time of publication. Two patients had autopsy that showed an atypical neuronal tauopathy with predominant involvement of the hypothalamus and tegmentum of the brainstem, without signs of inflammation. Moreover, no inflammatory changes were identified in the patients' CSF, leaving it unclear at whether there is an inflammatory response that is subtle and transient or there is no inflammatory process at all. This disorder suggests an intriguing link between autoimmunity and neurodegeneration.

Mechanisms of disease

For anti-NMDAR encephalitis the pathogenic role of GluN1 IgG antibodies has been established in cultures of neurons and after hippocampal and cerebroventricular infusion into

rodents of patients' antibodies (Fig. 4).[41,112] Using cultured neurons, patients' antibodies caused crosslinking and selective internalization of NMDARs that correlated with the antibody titers; these effects were reversible after removing the antibodies.[113,114] In contrast to the intense effects on NMDAR, patients' antibodies did not alter the localization or expression of other synaptic proteins, number of synapses, dendritic spines, dendritic complexity, or cell survival. In other experiments, the density of NMDAR was also significantly reduced in the hippocampus of rats infused with patients' antibodies, a finding similar to that observed in the hippocampus of autopsied patients.[113] More recently, Mannara and colleagues developed a murine model of passive transfer of memory and behavioral deficits using continuous ventricular infusion (14 days via osmotic pumps) of CSF from patients with anti-NMDAR encephalitis. Analyses of hippocampus from the mice showed progressive antibody binding over time and a decrease of total and synaptic NMDARs, without affecting PSD95 or AMPAR. These effects gradually improved after stopping the antibody infusion, with reversibility of symptoms accompanied by restoration of NMDAR levels, establishing the pathogenicity of the antibodies (Fig. 4H).[115]

For the disorders associated with AMPAR or GABAaR antibodies, studies on pathogenicity have been conducted with cultured neurons, each antibody producing selective internalization of the corresponding receptor. Patients' AMPAR antibodies caused a decrease of the receptors at synaptic and extrasynaptic sites, along with reduction of AMPAR-mediated miniature excitatory postsynaptic currents using whole-cell patch recordings.[22,116] On the other hand, patients' GABAaR antibodies selectively eliminated the receptors from synapses but did not alter the number of extrasynaptic receptors.[27]

Different from the above cell membrane and synaptic receptors, LGI1 is a secreted protein that interacts with the presynaptic receptor ADAM23 and the postsynaptic receptor ADAM22, organizing a *trans*-synaptic complex that includes presynaptic Kv1.1 potassium channels and postsynaptic AMPAR (Fig. 5).[24] Lgi1-deficient ($Lgi^{-/-}$) mice develop a lethal epileptic phenotype characterized by myoclonic seizures.[117] In these mice, the increase of neuronal excitability has been attributed to a decrease in AMPAR function in inhibitory neurons, and to an increase in glutamate release.[117,118] Although it is unknown how LGI1 antibodies result in limbic encephalitis, a recent study using cultured neurons showed that patients' antibodies interfered with the LGI1–ADAM interaction and decreased the levels of postsynaptic AMPARs.[119]

The effects of patients' GlyR and dopamine D2 receptor antibodies have been examined *in vitro* in HEK cells expressing these receptors; the studies showed antibody-mediated internalization of the corresponding receptors.[8,95] It is not currently known if similar effects apply to neurons *in vivo*.

Autoimmune encephalitis in other disciplines

Information on autoimmune encephalitis in other disciplines is summarized in Figure 6.

Psychiatry

That patients with anti-NMDAR encephalitis and other autoimmune encephalitis frequently present with psychosis, affective dysregulation, and other behavioral abnormalities has fueled interest in autoimmunity as potential cause of some psychiatric illness.[49,50,120] One study reported finding NMDAR antibodies in serum of 3 of 46 (6%) patients with first onset of schizophrenia; the target subunit (e.g., GluN2 versus GluN1) was not determined and only one of the patients appeared to improve after immunotherapy.[121] Another study included serum obtained at symptom presentation by 80 patients with first onset psychosis who, one year later, met the DSM-IV-TR criteria for schizophrenia-spectrum illness. GluN1 IgG antibodies were not detected in any of the 80 cryopreserved sera;[122] these findings were consistent with those of another smaller study of patients with schizophrenia.[123]

Another study examined the prevalence of NMDAR antibodies in the sera from 121 patients with an initial diagnosis of schizophrenia, 108 with other psychiatric disorders, and 230 healthy subjects.[124] Two patients had GluN1 IgG antibodies, and retrospectively both were diagnosed with anti-NMDAR encephalitis (both had prominent dyskinesias, abnormal movements, autonomic dysfunction, and EEG abnormalities). None of the other patients had IgG GluN1 antibodies, though they did have other antibodies, mostly IgA or IgM against GluN1 identified in 8% of patients with schizophrenia and 3% with major depression. In a subsequent study, the same investigators found IgA or IgM antibodies in 16% of patients with several types of dementia and 7% of normal subjects.[125] More recently, Hammer and colleagues examined 2817 subjects, including 1325 healthy subjects and 1492 patients with schizophrenia, Parkinson disease, or affective-disorders, for the presence of serum antibodies against GluN1 subunit of the NMDAR.[126] In this study, 10.5% of all subjects (patients and healthy controls) were seropositive for IgA or IgM antibodies; only 0.6% had IgG antibodies. The authors hypothesized that schizophrenic individuals with history of blood–brain barrier (BBB) disturbance (e.g., neurotrauma at birth or thereafter) were more likely to have more pronounced neurological symptoms when NMDAR antibody positive; however, the authors did not show evidence of BBB disruption or the presence of antibodies in the CSF.[127]

Overall, these studies demonstrate limited clinical significance of serum IgA or IgM NMDAR antibodies in patients with psychiatric illness, given that a similar proportion of healthy subjects or disease controls had the same antibodies. In contrast, the absence or rare detection of GluN1 IgG antibodies suggests the specificity of these antibodies for anti-NMDAR encephalitis. Future investigations should include CSF analysis, comprehensive autoantigen characterization, and determination of antibody isotypes and subunit targets (e.g., GluN1 versus GluN2). The importance of antigen specification is shown in patients with antibodies attributed to VGKC-complex proteins but whose target antigens are in fact unknown. Antibodies to these unknown antigens have been detected in a few patients with schizophrenia,[121] though they were also found in a number of non-autoimmune disorders, raising the question of significance.[75]

Herpes simplex encephalitis (HSE) as trigger of synaptic autoimmunity

The clinical course of HSE is usually monophasic, but 14–26% of patients develop relapsing symptoms a few weeks after the infection has resolved.[128,129] These relapsing symptoms have been attributed to (1) viral relapse characterized by the demonstration of HSV by polymerase chain reaction (HSV-PCR) in the CSF, MRI findings of new necrotic lesions, and response to acyclovir or (2) a disorder of unclear etiology without evidence of HSV reactivation, absence of new necrotic lesions, and no response to acyclovir.[130] This complication occurs more frequently in children than in adults, and the clinical picture is usually different from that related to the initial episode of viral encephalitis. In fact, most children develop chorea, orofacial dyskinesias, dystonia, or ballismus, accompanied by agitation, aggression, sleep dysfunction, seizures, or decrease of level of consciousness.[131] This constellation of symptoms led physicians to coin the term *choreoathetosis post-HSVE* to describe this complication.[2,132] A similar disorder occurs in adults, but abnormal movements are infrequent.[132] The observation that some patients with HSE developed IgG antibodies against the GluN1 subunit of NMDAR,[133] and subsequent studies of children with choreoathetosis post-HSVE,[34] revealed that this complication is in fact anti-NMDAR encephalitis.[134] A recent study showed that patients who developed this complication were NMDAR antibody negative at the time HSE was diagnosed and then developed serum and CSF antibodies in the ensuing 2–6 weeks, leading to anti-NMDAR encephalitis.[135] The same study demonstrated that HSE is a robust trigger of autoimmunity to other cell surface or synaptic proteins (antigens still unknown), and another study showed antibodies to dopamine D2 receptor in two patients.[136] The identification of HSE as trigger of anti-NMDAR encephalitis has been confirmed by multiple investigators over a short period of time,[137-140] suggesting this complication may be more common than previously reported as choreoathetosis post-HSVE. Diagnosing anti-NMDAR encephalitis post-HSE is important because patients usually respond to immunotherapy.

Reclassification of disorders

In addition to choreoathetosis post-HSE, other disorders such as encephalitis lethargica with dyskinesias or abnormal movements[141] or encephalitis of unclear etiology with abnormal movements[29] are now identified as anti-NMDAR encephalitis. Archived serum or CSF samples of these patients confirm the presence of IgG antibodies to these receptors and retrospective assessment of the clinical picture is consistent with anti-NMDAR encephalitis.

Hashimoto's encephalitis is a term that continues to be in use even though the disorder was renamed steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT). The diagnosis is considered in patients who develop any type of encephalopathy of unclear etiology, with TPO antibodies, and response to steroids.[142] However, TPO antibodies are present in ~10% of healthy subjects[143,144] and they are also frequently encountered in patients with well-defined autoimmune encephalitis (e.g., NMDAR, GABAbR, and GABAaR, among others).[7,23,27,145] In our experience, patients with autoimmune encephalitis and relevant cell surface or synaptic antibodies are frequently misdiagnosed as Hashimoto's encephalitis, while patients without relevant autoantibodies that fulfill criteria of SREAT do not have antibodies reacting with the cell surface of neurons

(J. Dalmau, personal observation). This indicates that Hashimoto's encephalitis or SREAT should be a diagnosis of exclusion.

Overlapping syndromes: anti-NMDAR encephalitis and demyelinating disorders

Many patients with anti-NMDAR encephalitis have normal MRI scans (see anti-NMDAR encephalitis). A study of 691 patients with the disorder identified 23 (range 4–62 years of age, median 27; nine cases younger than 18 years of age), with clinical or MRI features suggesting a demyelinating disorder.[59] Twelve of these 23 patients developed anti-NMDAR encephalitis preceded or followed by one or more episodes of demyelination, and the other 11 developed both disorders simultaneously. Among the 12 patients with sequential development of syndromes, the demyelinating episode of five patients fulfilled criteria of neuromyelitis optica spectrum disorder (NMOSD) or NMO (four with aquaporin 4 antibodies); the other seven patients developed a a brainstem syndrome or multifocal demyelinating features (all with myelin-oligodendrocyte (MOG) antibodies). Among the 11 patients with concurrent anti-NMDAR encephalitis and demyelinating symptoms, five had aquaporin 4 antibodies (3 with features of NMOSD), and two had MOG antibodies, both with infratentorial abnormalities.

Most patients improved with immunotherapy, but compared with the episodes of anti-NMDAR encephalitis, the episodes of demyelination required more intensive therapy and resulted in more residual deficits.[59] Similar overlapping syndromes or autoantibodies have been identified by other investigators.[146-148]

Caveats in the diagnosis and treatment of autoimmune encephalitis

Autoantibodies to cell surface and synaptic proteins should be examined in both serum and CSF. A recent study showed that 14% of patients with anti-NMDAR encephalitis did not have detectable antibodies in serum using two different techniques, while all had antibodies in the CSF. For other disorders, the proportion of cases that are CSF positive and serum negative is unknown. In our experience, patients with encephalitis related to antibodies against NMDAR, AMPAR, GABAbR, DPPX, mGluR1, or mGluR5 always have antibodies in the CSF.

Other antibodies, such as anti-LGI1, anti-Caspr2, anti-GlyR, anti-GABAaR, may in rare instances be identified only in serum. In these cases the disease relevance of the serum antibodies is unclear, and sometimes the findings are not reproducible,[149] suggesting false positive results. Indeed, most of the atypical clinical associations of antibodies to neuronal cell surface antigens (e.g., NMDAR in patients with CJD or schizophrenia)[121,150] have been reported in patients who underwent limited serum testing using only cell-based assays without examining CSF, or whose CSF was negative. Although some investigators argue for a higher sensitivity of serum testing with the indicated cell-based assay, there is no data supporting this (e.g., CSF not tested, or comparison with other techniques not performed). In contrast, a study of Gresa-Arribas and colleagues[151] examining paired serum and CSF of 250 patients with anti-NMDAR encephalitis and 100 controls with three different assays,

showed that serum testing with any type of cell-based assay (live or fixed cells) leads to false negative results in at least 14% of the patients. We recently saw a patient that had been treated elsewhere for one year for anti-NMDAR encephalitis; the diagnosis had been based in a serum live cell-based assay without CSF analysis. The syndrome was surprisingly atypical for anti-NMDAR encephalitis; instead, the patient had narcolepsy-cataplexy that was confirmed by a compatible HLA and undetectable hypocretin in CSF. Comprehensive studies of the patient's serum sample (considered NMDAR-antibody positive elsewhere) and CSF (which had not been previously tested) were both antibody negative. In this case, the serum assay was not more sensitive than the CSF and it provided a false positive result (J. Dalmau, unpublished observation). In our experience, the problems that result from assessing autoimmune encephalitis by serum testing only can be avoided by including CSF testing. Moreover, the CSF findings show specific antibody–syndrome associations, and the results are comparable among different series and laboratories.[58]

There are no standard immunotherapy protocols for autoimmune encephalitis. Approaches to decrease the antibody levels (with plasma exchange or IVIg) are less effective than in antibody-mediated diseases of the peripheral nervous system such as myasthenia gravis or the Lambert-Eaton syndrome. The intrathecal production of antibodies that occurs in many types of autoimmune encephalitis, and the presence of CNS inflammatory infiltrates along with plasma cells,[21,152] likely explains the less frequent response to these immunotherapies. Interestingly, patients with anti-LGI1 associated symptoms (a disorder with infrequent intrathecal antibody synthesis) respond faster to steroids, plasma exchange, or IVIg than do patients with anti-NMDAR encephalitis (a disorder that associates with intrathecal antibody synthesis). However, the faster treatment response of patients with LGI1 antibodies does not lead to better long-term outcome; in fact, patients with anti-NMDAR encephalitis have full recoveries more frequently than do those with LGI1 antibodies (measured as ability to return to work or their original activities; Dalmau, personal observation).[42,153]

Experience with 501 patients with anti-NMDAR encephalitis demonstrated that rituximab and cyclophosphamide are usually effective in patients who do not respond to first-line immunotherapies.[42] Although this approach is increasingly being used for other autoimmune encephalitis, it is unclear whether it has the same effects.

Follow-up of serum antibody titers is an unreliable biomarker of disease activity in many types of autoimmune encephalitis. A recent study showed that in patients with anti-NMDAR encephalitis, the CSF antibody titers associate better with the course of the disease and relapses than do serum titers.[151] In our experience, serum antibody titers (or even CSF titers) should not be used as the main guide for treatment decisions, instead they should be predominantly based on clinical assessment. As examples, patients with anti-NMDAR encephalitis may be comatose for several months and have low or undetectable serum antibody titers, while their CSF titers are persistently elevated.[151] Conversely, patients may have recovered, sometimes for several years, and still have antibodies in serum or CSF.[154,155] The limited usefulness of antibody titers is not surprising if one considers that the same problem applies to other well-established antibody-mediated disorders such as myasthenia gravis.

Future directions

The discovery of autoimmune encephalitis has changed paradigms in the diagnosis and treatment of disorders that were previously unknown or mischaracterized. The increasing interest and number of studies in the field are raising interesting questions on multiple fronts. For example, it is unclear whether the clinical and basic mechanisms of anti-NMDAR encephalitis (the best studied of this group of disorders) are applicable to the other disorders. There are important differences among them, not only clinical but also in the function and structure of the target antigens (some are ion channels, others metabotropic receptors, and one is a secreted protein). A critical question is how and where the immunological response is initiated, and which mechanisms are involved in the activation and expansion of the immune response within the CNS. It is unclear why some disorders appear to be consistently associated with intrathecal synthesis of antibodies, while others less so. What is the mechanism of action of rituximab in these CNS disorders? Despite the limited ability to cross the BBB, this drug can eliminate plasmablasts (which express CD20) or interfere with the process of B cell expansion and maturation into plasma cells (which are not directly affected by rituximab). These postulated mechanisms may explain why patients with anti-NMDAR encephalitis who receive early and aggressive immunotherapy have faster improvement and better outcome than those with delayed or less aggressive therapies (perhaps allowing development of more extensive infiltrates of plasma cells in patient's brain; Fig. 7). Other prognostic factors, such as severity of symptoms[42] or, perhaps, compensatory mechanisms of synaptic function,[156] should be investigated and may explain differences in patients' outcomes.

Most neuronal cell–surface or synaptic autoantibodies are IgG1 or IgG3 subtypes that potentially fix complement; but in the disorders thus far studied (mainly anti-NMDAR encephalitis) there is no evidence of complement-mediated mechanisms of cell injury.[21,152,157] This is different from NMO and aquaporin 4 antibodies, where symptoms are less reversible and complement-mediated brain injury is more visible in MRI.[158] On the other hand, IgLON5 antibodies are IgG4, which do not fix complement; but in general, disorders associated with IgG4 antibodies appear to respond frequently to rituximab (an observation to consider in future studies).[32,159,160]

The underlying mechanisms involved in antibody-mediated changes in the structure and function of the target antigen have been elucidated in some autoimmune encephalitis, but the effects at the circuit level are unknown. Upcoming animal models/studies will provide strategies on how to neutralize the antibody effects, not only using immunotherapy but perhaps optimizing compensatory synaptic mechanisms. In line with potentially novel therapeutic strategies, a study showed that Ephrin-B2 ligand prevents the destabilizing NMDAR crosslinking effects of patients' antibodies.[114]

The disorders discussed here provide natural models of human disease along with unique tools (patients' antibodies) to understand the link between selective alteration of specific cell surface proteins or receptors and plasticity, memory, learning, and behavior.

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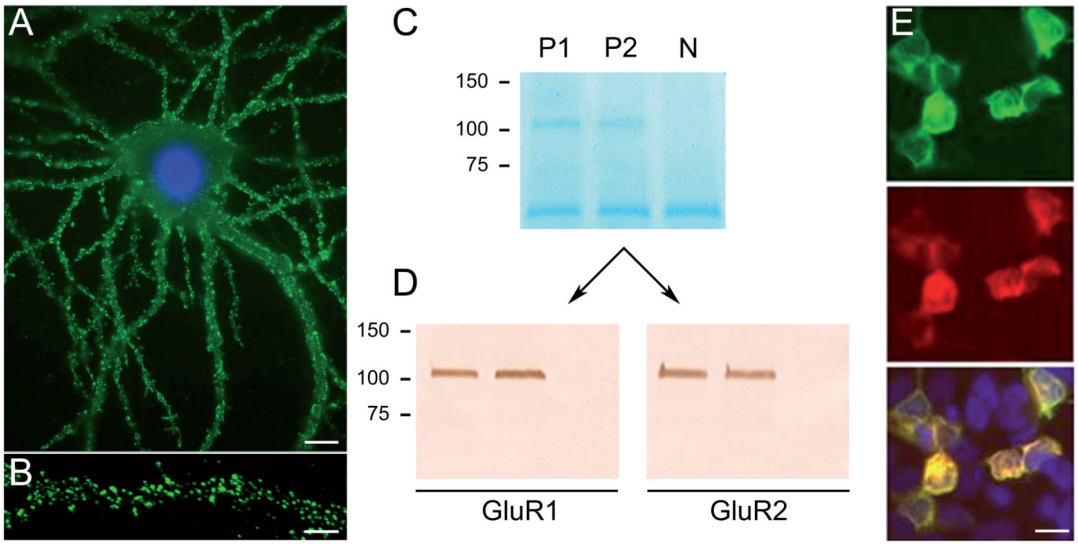

Figure 1.

Process of discovery, antigen immunoprecipitation, and development of a diagnostic test. Dissociated rat hippocampal neurons maintained *in vitro* and incubated (live, non-permeabilized) with CSF of a patient. Note the intense reactivity of patient's antibodies with cell surface antigens (A); scale bar = 10 μm. Confocal microscopy suggests that the antigens are concentrated in clusters along dendrites (B); scale bar = 5 μm. Precipitation of these antigens using two patients' CSF antibodies is shown in a gel in which proteins are visualized with EZBlue (C). Note that patients' antibodies (P1, P2) precipitated a single band at ~100 kDa; this band is not seen in the precipitate of a control individual (N). Analysis of the 100 kDa band by mass spectrometry demonstrated sequences derived from GluR1/GluR2 subunits of the AMPAR. The ~50 kDa band across all samples corresponds to IgG. Transfer of the proteins to nitro-cellulose and Western blot with GluR1 and GluR2 antibodies confirmed that the 100 kDa band contained both GluR1 and GluR2 subunits (panels in D). Further validation of the antigen was done in heterologous cells expressing GluR1/2, showing reactivity with patient's antibodies (green), a monoclonal antibody (red), and the merged reactivities (yellow). Adapted from Lai and colleagues[22] with permission.

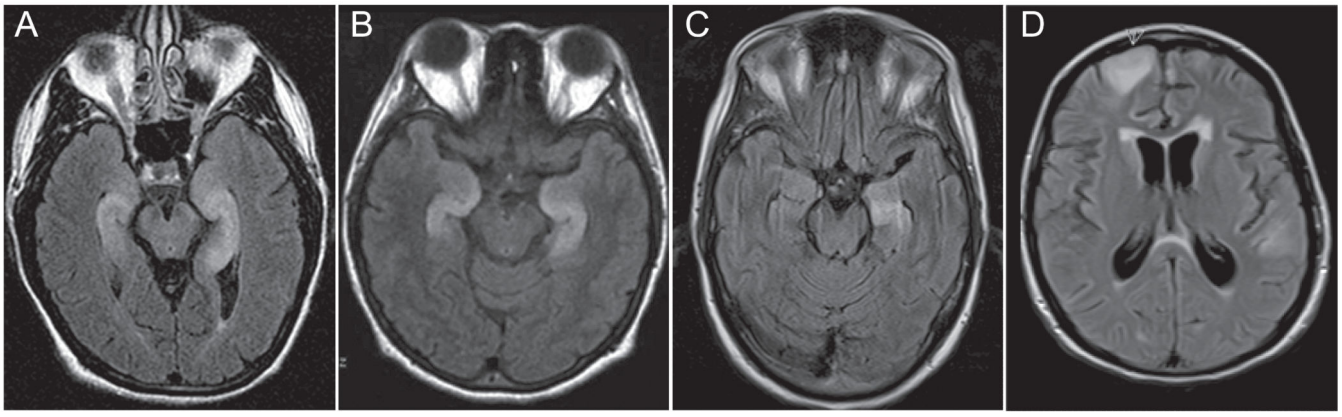

Figure 2.

Comparison of MRIs of patients with limbic encephalitis and different cell surface autoantibodies with the MRI of a patient with multifocal encephalitis and GABAaR receptor antibodies. The MRIs of the three cases with limbic encephalitis correspond to a patient with LGI1 antibodies (A), a patient with AMPAR antibodies (B), and a patient with GABAb-R antibodies (C). In contrast, note that the MRI of the patient with GABAaR antibodies shows multifocal cortical-subcortical FLAIR abnormalities (D). Panels A–C, from Lancaster and colleagues,[11] with permission; panel D from Petit-Pedrol and colleagues[27] with permission.

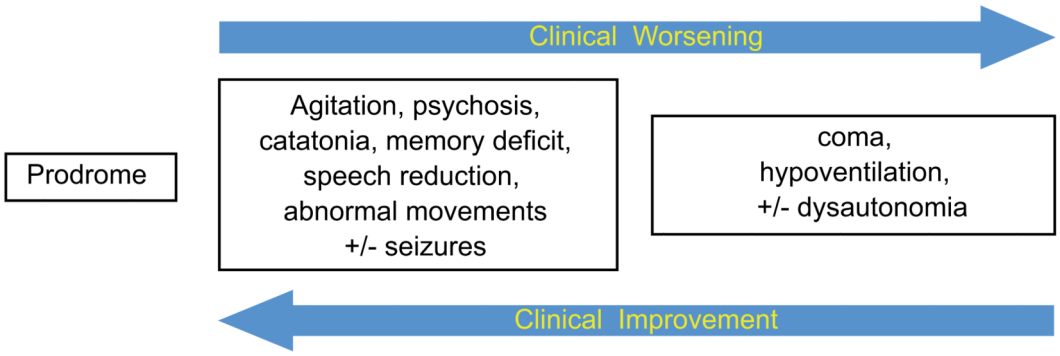

Figure 3.

Sequence of syndrome development in patients with anti-NMDAR encephalitis. During the first month of the disease most patients with anti-NMDAR encephalitis progressively develop the sequence of symptoms shown in the graph.[42] Adapted from Dalmau and colleagues.[45]

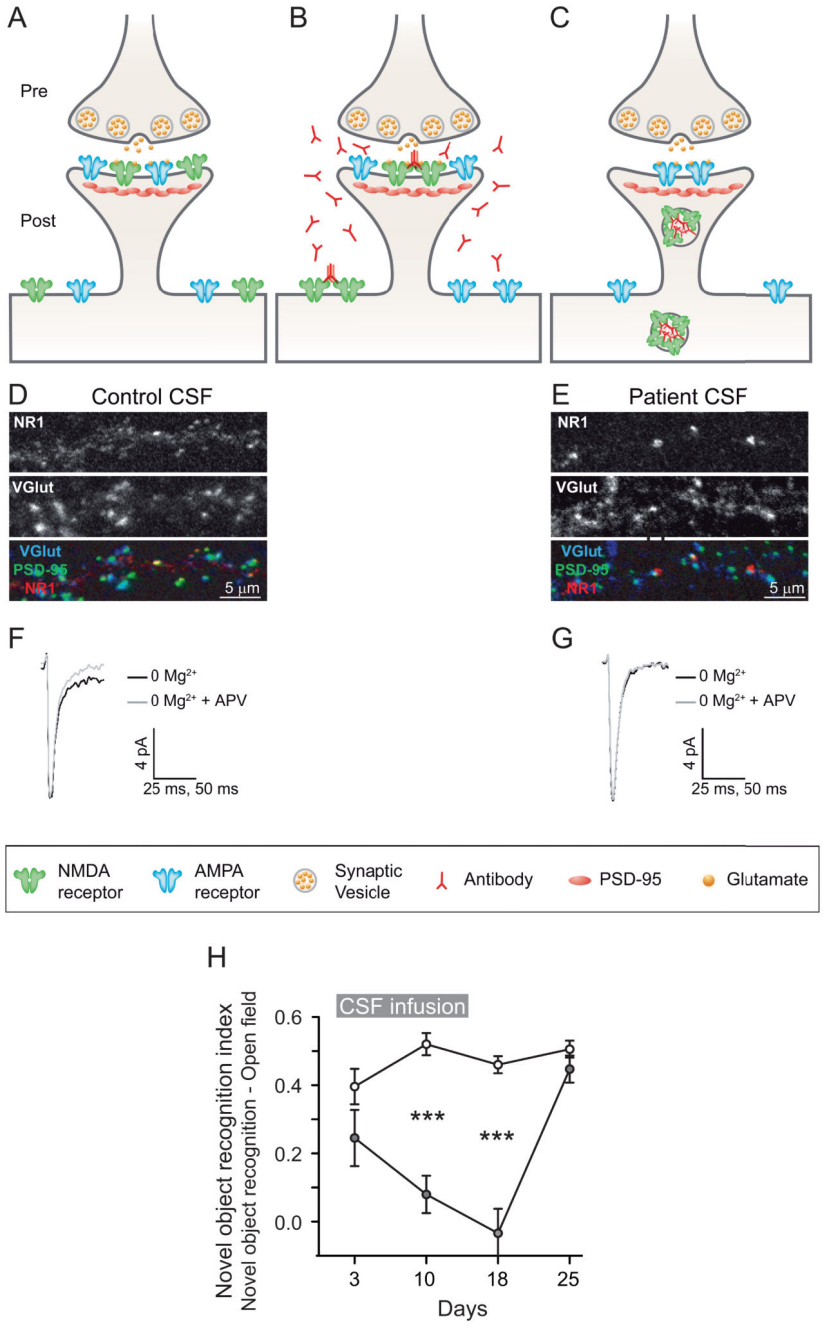

Figure 4.

Synaptic and behavioral effects of antibodies from patients with anti-NMDAR encephalitis. **(A–C)** AMPA and NMDA receptors are localized in the postsynaptic membrane and are clustered at the postsynaptic density A. Patient antibodies in the CNS bind selectively to NMDA receptors at the synapse as well as extrasynaptic receptors. This binding leads to receptor cross-linking B. NMDA receptors that have been bound and cross-linked by antibodies are internalized, resulting in a decrease of surface, synaptically localized NMDA receptors. Other synaptic components, such as postsynaptic AMPA receptor clusters,

PSD-95, as well as presynaptic terminals, dendrite branches, dendritic spines and cell viability, are unaffected C. Thus patient anti-NMDA receptor antibodies lead to a rapid, selective excision of NMDA receptors from neuronal membranes. This effect is titer-dependent and reverses after antibody titers are reduced (not shown). **(D–E)** Rodent cultured neurons treated with control CSF or patient's CSF for 3 days, and subsequently stained for postsynaptic GluN1 to label NMDA receptor clusters, VGlut to label presynaptic sites, and PSD-95 as a postsynaptic marker. Note that patient's CSF cause a decrease in dendritic GluN1 cluster density, while VGlut and PSD-95 cluster density remain unchanged. **(F–G)** Whole-cell patch recordings of miniature excitatory postsynaptic currents (mEPSCs) that consist of a fast AMPA receptor–mediated component and a slower later component mediated by NMDA receptors and is APV sensitive. Compared with neurons incubated with CFS control F, those treated with CSF from a patient with NMDA receptor antibodies show a loss of the APV-sensitive NMDA receptor component E. **H**: Progressive memory deficit assessed by standard object recognition test, in a group of 5 mice treated with cerebroventricular infusion of CSF from patients with anti-NMDAR encephalitis (grey circles) compared with a group of 5 mice treated with CSF from control subjects without NMDAR antibodies (white circles). Antibodies were continuously infused for 14 days; the peak of memory deficit was on day 18, followed by progressive clinical recovery. Panels (A–G) obtained from Moscato and colleagues,[2] with permission. Panel H provide by Planaguma and colleagues (unpublished data).

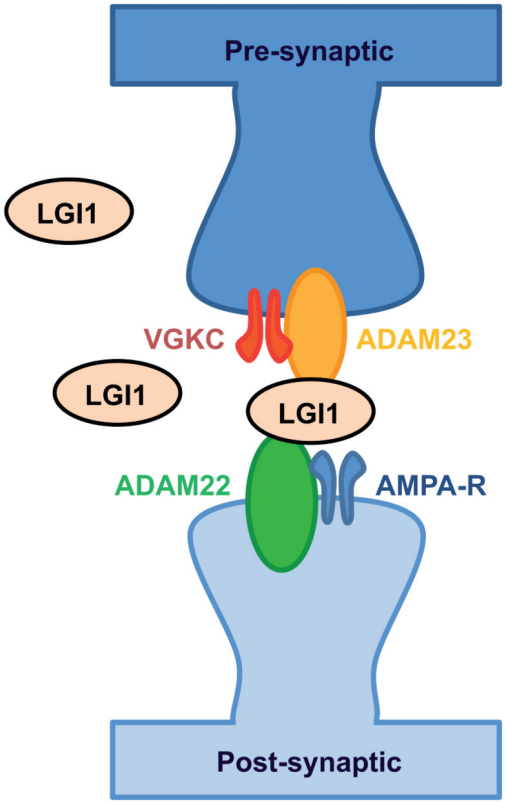

Figure 5.

Interaction of LGI1 with synaptic proteins. Secreted LGI1 interacts at the presynapse with ADAM23 and at the postsynapse with ADAM22. The figure is based on studies indicating that LGI1 co-precipitates with other proteins including the presynaptic Kv1 potassium channels and a variety of pre- and post-synaptic scaffolding proteins. Adapted from Lancaster and colleagues,[11] with permision.

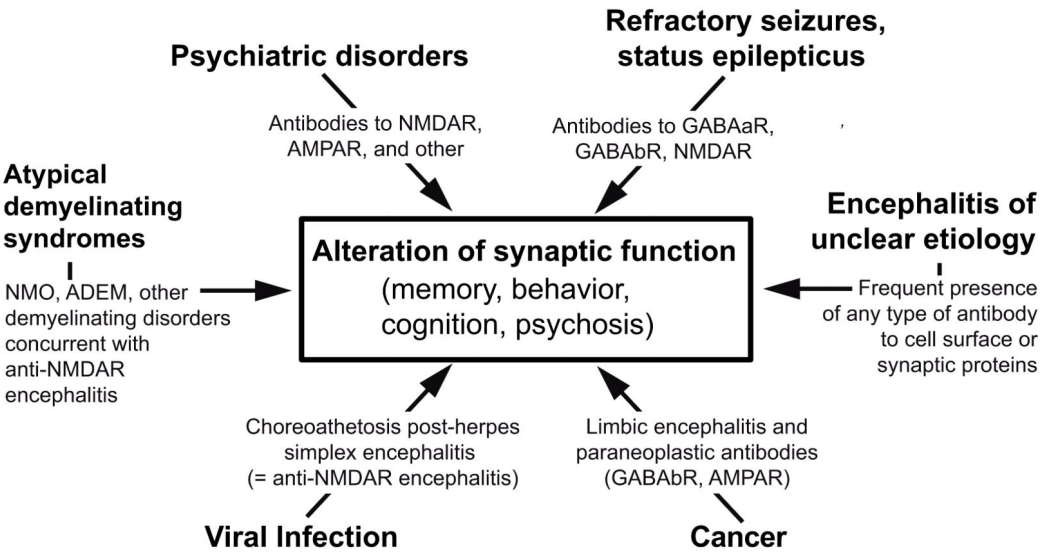

Figure 6.

Associations, trigers, and common symptoms of autoimmune encephalitis: impact on multiple disciplines

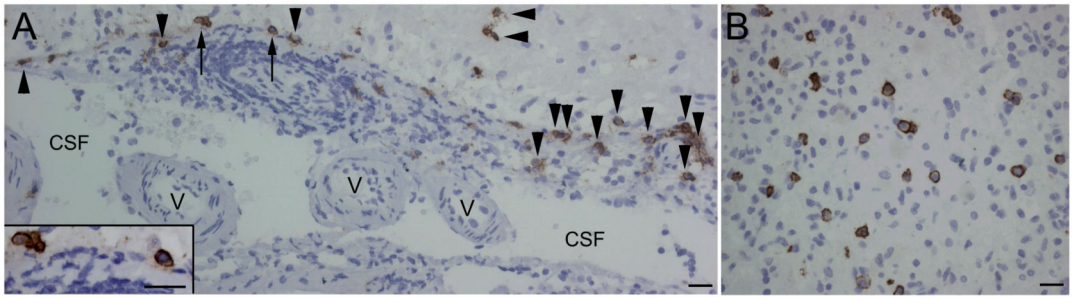

Figure 7.

Plasma cell infiltrates in the brain of a patient with anti-NMDAR encephalitis. Paraffin embedded sections of brain biopsy of a patient with anti-NMDAR encephalitis. $CD138^+$ cells (plasma cells/plasmablasts) are present in perivascular, Virchow-Robin (A), and interstitial spaces (B). In Virchow-Robin spaces (A) the $CD138^+$ cells are in perivascular regions (arrows) and along the tissue surface (arrow heads) that delineates spaces containing CSF and small vessels (v). The plasma cells/plasmablasts indicated with arrows are amplified in the inset in A. Scales = 20 μm. Adapted from Martinez-Hernandez and colleagues,[152] with permision.

Table 1

Autoimmune encephalitis with antibodies against cell surface and synaptic proteins

Antigen	Clinical syndrome	Tumor
NMDAR (GluN1)	Anti-NMDAR encephalitis: prodromal symptoms, psychiatric, seizures, amnesia, movement disorders, catatonia, autonomic instability, coma	Age-dependent 10–45% ovarian teratomas, infrequently carcinomas
AMPAR	Limbic encephalitis, psychiatric symptoms	70% (lung, breast, thymoma)
GABAbR	Limbic encephalitis, prominent seizures	50% lung, neuroendocrine
LGI1	Limbic encephalitis, 60% hyponatremia, occasional focal faciobrachial seizures prior to encephalitis	<10% (lung, thymoma)
CASPR2	Encephalitis, Morvan syndrome, neuromyotonia	0–40% thymoma
mGluR5	Limbic encephalitis (reported in less than 10 patients)	Frequently, Hodgkin lymphoma
D2R	Basal ganglia encephalitis, Sydenham chorea.	Infrequent
DPPX	Diarrhea, encephalitis with CNS hyperexcitability: confusion, psychiatric symptoms, tremor, myoclonus, nystagmus, hyperekplexia, PERM-like symptoms, ataxia.	No tumor association
GABAaR	Refractory seizures, status epilepticus, or epilepsia partialis continua, stiff-person, opsoclonus	Infrequent
GlyR	Stiff-person, PERM, limbic encephalitis, cerebellar degeneration, optic neuritis	Infrequent
IgLON5	Abnormal sleep movements and behaviors,obstructive sleep apnea, stridor, dysarthria, dysphagia, ataxia, chorea (reported in less than 10 patients)	No tumor association