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The immunobiology of autoimmune encephalitides

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ABSTRACT

Autoimmune encephalitides, with an estimated incidence of 1.5 per million population per year, although described only 15 years ago, have already had a remarkable impact in neurology and paved the field to autoimmune neuropsychiatry. Many patients traditionally presented with aberrant behavior, especially of acute or subacute onset, and treated with anti-psychotic therapies, turn out to have a CNS autoimmune disease with pathogenic autoantibodies against synaptic antigens responding to immunotherapies. The review describes the clinical spectrum of these disorders, and the pathogenetic role of key autoantibodies directed against: a) cell surface synaptic antigens and receptors, including NMDAR, GABAa, GABAb, AMPA and glycine receptors; b) channels such as AQP4 water-permeable channel or voltage-gated potassium channels; c) proteins that stabilize voltage-gated potassium channel complex into the membrane, like the LGI1 and CASPR2; and d) enzymes that catalyze the formation of neurotransmitters such as Glutamic Acid Decarboxylase (GAD). These antibodies, effectively target excitatory or inhibitory synapses in the limbic system, basal ganglia or brainstem altering synaptic function and resulting in uncontrolled neurological excitability disorder clinically manifested with psychosis, agitation, behavioral alterations, depression, sleep disturbances, seizure-like phenomena, movement disorders such as ataxia, chorea and dystonia, memory changes or coma. Some of the identified triggering factors include: viruses, especially herpes simplex, accounting for the majority of relapses occurring after viral encephalitis, which respond to immunotherapy rather than antiviral agents; tumors especially teratoma, SCLC and thymomas; and biological cancer therapies (immune-check-point inhibitors). As anti-synaptic antibodies persist after viral infections or tumor removal, augmentation of autoreactive B cells which release autoantigens to draining lymph nodes, molecular mimicry and infection-induced bystander immune activation products play a role in autoimmunization process or perpetuating autoimmune neuroinflammation. The review stresses the importance of early detection, clinical recognition, proper antibody testing and early therapy initiation as these disorders, regardless of a known or not trigger, are potentially treatable responding to systemic immunotherapy with intravenous steroids, IVIg, rituximab or even bortezomid

1. Introduction

The field of autoimmune neurology comprises a large number of disorders affecting both the central and peripheral nervous system. A major subset, recently recognized encompasses the group of autoimmune encephalitides, based on the presence of pathogenic autoantibodies against synaptic CNS autoantigens which cause a wide spectrum of clinical phenotypes by affecting fundamental brain functions [1–3]. The impetus of this discovery has been remarkable not only to neurology but also to psychiatry because many of these patients present with neuro-psychiatric manifestations that effectively respond not to anti-psychotic sedatives but to immunotherapies, generating the conceptual field of "autoimmune neuropsychiatry" [4,5].

Encephalitis is a severe and often deadly condition that refers to inflammation of the brain parenchyma. The most common causes are infectious agents directly invading the CNS, such as viruses, bacteria, fungi or paracites, causing encephalitis or, when with meningeal involvement, meningoencephalitis. Patients with acute infectious encephalitis present with rapid onset of fever, headache, nausea, seizures, respiratory symptoms, confusion, focal neurological deficits and impaired level of consciousness leading to coma [6]. The overall incidence of encephalitis is estimated to be 5–7 per 100,000 *per annum*. The last decade however, it has become evident that a large number of patients presenting with acute or subacute CNS disorders similar to infectious

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encephalitides or even with wider clinical spectrum, do not have a CNS infection requiring anti-infectious agents but an immune-mediated process that starts *de novo* against CNS antigens [2,7,8].

The main discovery in the field is that these patients, bear neuronal-specific, often pathogenic, autoantibodies which by targeting synaptic antigens alter neuronal circuit function [9] leading to neuronal hyperexcitability. These discoveries have revolutionized the field, as many of the syndromes associated with these antibodies are treatable with immunotherapies. The clinical manifestations of autoimmune encephalitides vary but often include acute behavioral alterations, psychosis and sleep disturbances leading patients to psychiatric units and initiation of treatment with anti-psychotic sedatives. Patients also exhibit various neurological manifestations including seizures, memory changes, movement disorders such as ataxia, chorea and dystonia, or even coma. Although, it is clearly evident that in these patients an immune activation process, either cellular or humoral, takes place at disease onset, it is still uncertain how autoimmunization emerges or tolerance is broken and how these antibodies transverse the blood brain barrier to affect specific neurons or glial cells. Evolving data indicate that viruses and tumors play a role, as many of these antibodies emerge as a response to a co-existing tumor (paraneoplastic antibodies), or following a diagnosed viral encephalitis [10].

The review is timely considering the major recent advances in the field. It aims to: highlight the main clinical spectrum of these disorders, especially the neuropsychiatric aspects, in connection with the identified autoantibodies; address the pathogenic role of these antibodies and how they disrupt synaptic transmission leading to abnormal neuronal excitability; present the convergence of autoimmune neurology to the evolving field of "autoimmune neuro-psychiatry"; elaborate on the auto-immunization mechanisms discussing possible triggers that break tolerance; and outline the most effective immunotherapeutic schemes.

2. Clinical syndromes of autoimmune encephalitis related to specific antibodies

Anti neuronal antibodies affecting the central nervous system can be broadly placed in two main categories; those that target *cell surface or synaptic antigens* in neurons and glia, and those targeting *intracellular* antigens [11]. Cell surface antigens, include receptors like the NMDA [12], GABAa, GABAb [13], AMPA [14] and glycine, and channels like the AQP4 water-permeable channel [15]. The definition of synaptic antigens in this context is somewhat broader and includes proteins that stabilize receptors or channels into the membrane, like the LGI1 and CASPR2 proteins associated with voltage-gated potassium channels (VGKC) [16], or enzymes that catalyze the formation of neurotransmitters like Glutamic acid decarboxylase (GAD) [17]. The most important shared characteristic of these antigens is that they are directly and readily accessible to all the immune system components; accordingly, the antibodies generated against them are considered pathogenic, as confirmed by *ex vivo* assays or animal passive transfer models.

The neurological manifestations of autoimmune encephalitides, have common overlapping denominators, such as epileptic seizures and prodromes of fever and headaches, probably representing early signs of blood brain barrier dysfunction. They have however, in addition, distinctive clinical characteristics according to the type of affected synapses and brain regions e.g. hippocampus, brainstem or spinal cord, against which these antibodies are directed [18]. The encephalitic syndromes and their associated antibodies include the following (Table 1A and B):

A. *Anti*-NMDAR encephalitis. This is the most common autoimmune encephalitis caused by IgG1 antibodies against the excitatory NMDAR receptor [19]. The antibodies, when especially found in the CSF, are directed against the NR1 subunit [20] of the post-synaptic NMDA receptor in synapses altering synaptic function in the limbic system, basal ganglia or brainstem [21] Accordingly, these patients

Table 1A
Common antibodies directed against intracellular antigens

ANTIBODY (antigen)	CLINICAL PICTURE	TUMOR ASSOCIATION (> 90% of cases)	INFECTIOUS TRIGGERS	THERAPY
Yo (CDR2)	Cerebellar ataxia, brainstem encephalitis	Ovarian adenocarcinoma (> 60%), breast carcinoma	–	Oncological therapy combined with immunotherapy
Hu (HuD)	Limbic & brainstem encephalitis, autonomic & peripheral neuropathy	Small cell lung carcinoma (> 75%), non-small cell lung carcinoma	–	Oncological therapy combined with immunotherapy
Ri (NOVA1)	Limbic & brainstem encephalitis, opsoclonus	Breast adenocarcinoma (> 50%), Small cell lung carcinoma	–	Oncological therapy combined with immunotherapy
CV2 (CRMP5)	Encephalomyelitis, neuropathy	Small cell carcinoma (> 75%), thymoma	–	Oncological therapy combined with immunotherapy
Ma1, 2	Limbic & brainstem encephalitis	Testicular cancer (~50%), lung and other cancers	–	Oncological therapy combined with immunotherapy
PCA-2 (MAP1B)	Encephalomyelitis and/or peripheral neuropathies	Small cell lung carcinoma, non-small cell carcinoma	–	Oncological therapy combined with immunotherapy
Amphiphysin	Stiff person syndrome, limbic encephalitis	Small cell carcinoma, breast adenocarcinoma	–	Oncological therapy combined with immunotherapy
SOX1	Ataxia, Lambert-Eaton myasthenic syndrome	Small cell lung carcinoma (> 95%)	–	Oncological therapy combined with immunotherapy
GFAP	Meningo-encephalomyelitis	Ovarian teratoma (in only 35% of cases)	–	Oncological therapy combined with Immunotherapy
Zic4	Cerebellar ataxia	Small cell lung carcinoma	–	Oncological therapy combined with immunotherapy

Table 1B
Common antibodies directed against synaptic antigens.

ANTIBODY (Ig class)	CLINICAL PICTURE	TUMOR ASSOCIATION	INFECTIOUS TRIGGERS	THERAPY
NMDA receptor (IgG1)	Psychosis, seizures, choreoathetosis, dyskinesias	Ovarian teratoma (50% in women)	Post-Herpes Simplex virus infections	Oncological & immunotherapy
LGI1 (IgG4/IgG1)	Limbic encephalitis, faciobranchial dystonic seizures	Up to 20%, small cell lung carcinoma, thymoma	–	Oncological & immunotherapy
CASPR2 (IgG4/IgG1)	Limbic encephalitis, neuromyotonia	Up to 20%, small cell lung carcinoma, thymoma	–	Oncological & immunotherapy
AMPA receptor (IgG1)	Limbic encephalitis, seizures	Small cell lung carcinoma, thymoma	–	Oncological & immunotherapy
GABAb receptor (IgG1)	Limbic encephalitis	Small cell lung carcinoma	–	Oncological & immunotherapy
GABAa receptor (IgG1)	Limbic encephalitis, Refractory seizures, Stiff person syndrome (rare)	Thymoma, lung carcinoma	–	Oncological & Immunotherapy
Glycine receptor (IgG4)	Progressive encephalomyalitis with rigidity and myoclonus, stiff person syndrome	Thymoma, lymphoma (rare)	West Nile virus infection, Brucella sp.	Immunotherapy
DPPX (IgG4/IgG1)	Encephalitis with CNS hyperexcitability	Rare	–	Immunotherapy
Tr-DNER (IgG1)	Cerebellar ataxia	Hodgkin lymphoma (> 90% of cases)	–	Oncological & Immunotherapy
GAD (IgG1/IgG2)	Stiff person syndrome, phobias, seizures, limbic encephalitis	Rare	West Nile virus infection	Symptomatic & Immunotherapy
mGlyR5 (IgG1)	Limbic encephalitis, Ophelia Syndrome	Hodgkin lymphoma	–	Immunotherapy

have a very characteristic clinical picture of excitability, initially presented with neuropsychiatric symptoms of insomnia, irritability, abnormal behavior, agitated confusion, psychotic and paranoid ideations, and hypoventilation. Because of the predominantly abnormal behavior many of these patients may be initially referred to psychiatrists but they often show intolerance to administered neuroleptics. These symptoms are quickly followed by, or co-exist with, primarily movement disorders, such as chorea and dystonic movements, seizures, focal deficits (paresis, ataxia), speech impairment, amnesia or coma [22].

The patients's NMDAR antibodies despite being of the IgG1 subtype, do not fix complement on the targeted synapses, but instead they lower the surface density of NMDA receptors of the post-synaptic neurons [23]. This alters their firing properties and disrupts the interaction of the NMDAR with ephrin receptor 2 leading to excess levels of glutamate and excitotoxicity [24] (Fig. 1). In most cases, if the antibodies are rapidly suppressed or removed, the synaptic density recovers and the patients' symptoms dramatically improve [25]. On the other hand, chronic exposure to the antibodies results in irreversible neurological deficits due to excessive neuronal death and the ensuing brain atrophy as demonstrable by MRI imaging. NMDAR-antibody encephalitis can be associated with ovarian teratomas, especially in young women, with impressive resolution of symptoms upon tumor removal in conjunction with immunotherapy [26].

B. *Anti*-AMPA and *anti*-GABAa receptor encephalitis. These antibodies have a mode of action similar to the *anti*-NMDAR antibodies, i.e. altering receptor density, which is clinically manifested like the NMDAR-encephalitis with prominent cognitive decline, memory problems, psychotic episodes and seizures (Fig. 1) [22,27].

C. The spectrum of Voltage-Gated Potassium Channel-associated syndromes (VGKC)-associated encephalitis. Patients with antibodies against the VGKC- complex, as measured with RadioImmunoAssay (RIA), do not have in reality antibodies directed against the channel itself but against the channel-associated proteins LGI1 and CASPR2 [28,29]. Patients with *anti*-LGI1 antibodies present with limbic encephalitis, typically manifested with acute confusional state, hallucinations, anxiety, depression, irritability, personality change, seizures and anterograde amnesia, but the pathogenetic mechanism is somewhat different. The LGI1 plays a role in bridging the pre-synaptic voltage-gated potassium channel protein Kv1.1 with the post-synaptic AMPA receptor through interaction with the synaptic anchor molecules ADAM22 and ADAM23 (Fig. 1). The *anti*-LGI1 antibodies, which are of the IgG4 subclass (therefore non-complement fixing), alter the binding of LGI1 with ADAM22 and decrease the post-synaptic levels of AMPA receptors [30].

Patients that harbour *anti*-CASPR2 autoantibodies, apart from the classical encephalopathy symptoms [31,32] may also develop exclusively peripheral symptoms with predominant neuromyotonia, or a mixture of peripheral and central symptoms as typically represented by the so-called Morvan's syndrome [33]. CASPR2 is a protein localized in the juxtaparanodal region in the nodes of Ranvier both in peripheral and central nervous system axons and function to stabilize the VGKC channels. How these antibodies exert their function causing diverse symptomatology is not fully understood but it is thought to alter gephyrin clusters at inhibitory synaptic contacts [34].

D. The spectrum of GAD-antibody syndromes. GAD65 is an enzyme in pre-synaptic inhibitory neurons that converts glytamate to GABA. Anti-GAD autoimmunity is associated with a variety of syndromes, including Stiff Person Syndrome, cerebellar ataxia, epilepsy, nystagmus and encephalitis [35,36]. GAD is mostly found intracellularly but it is probably exposed during neurotransmitter release and re-uptake or it may be transiently exhibit an extracellular domain during the dynamic process of neurotransmission and exocytosis [37] (Fig. 2). GAD is not only synthesised in GABAergic neurons in the CNS but also in the β-cells of the pancreas. Unlike NMDAR or VGKC encephalitis however, the pathogenetic role of anti-GAD antibodies is unclear. In support of the notion that GAD antibodies are pathogenic,

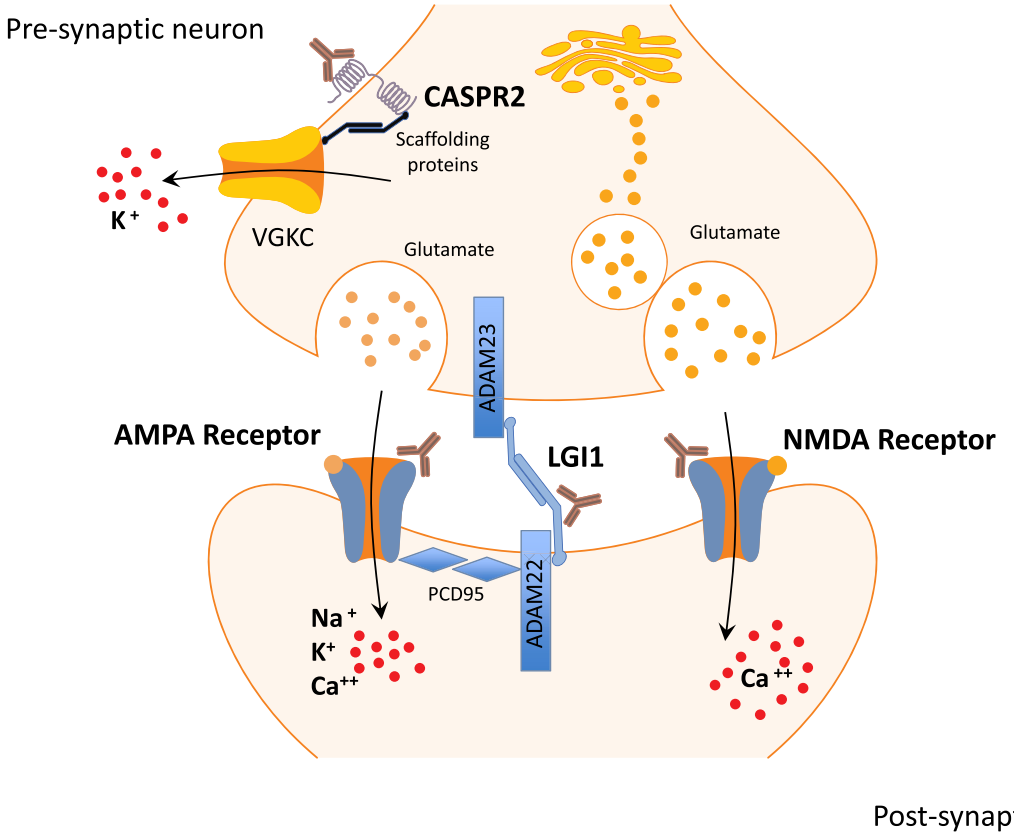

Fig. 1. Pathophysiological mechanism of excitatory central nervous system synapses represented by the Voltage-Gated Potassium Channel complex (LGI1 and CASPR2), NMDAR and AMPA. Leucine-rich glioma-inactivated-1 (LGI1) IgG interacts with presynaptic ADAM23 and postsynaptic ADAM22 forming a complex that includes presynaptic Kv1.1 potassium channel and postsynaptic AMPA receptor. LGI1 IgG effects this complex, potentially altering postsynaptic AMPA receptors and presynaptic Kv1 channels, leading to increased neuronal excitability. Within this complex, *anti*-CASPR2 antibodies also affect the stability of the VGKC presynaptic channel. N-methyl-D-aspartate (NMDA) receptor IgG predominantly binds to an epitope on NR1 subunit, disrupts the interaction between NMDA receptor and EphB2, causing internalization of the NMDA receptor. The same mechanism applies for antibodies targeting directly the AMPA receptor.

anti-GAD specific IgG from SPS patients inhibits GAD enzymatic activity *in vitro* and impairs GABA synthesis [38,39]. The degree of inhibition, although dose dependent, is not however related to anti-GAD antibody titers [39]. The anti-GAD antibodies can be also produced intrathecally [40], but there is no correlation between the serum or the cerebrospinal fluid GAD-specific IgG index to disease severity or symptom duration, even within individual patients followed over time [41]. Additional concerns casting doubt on the pathogenic role of GAD antibodies, include: a) GAD65 antibodies do not transfer the disease from mothers to infants despite the fact that the infants may also acquire high anti-GAD titres for up to 24 months after birth [42]; b) GAD65 is cytosolic and the fundamental mechanism by which antibodies can recognize intracellular targets causing disease, is not clear [43–46] and c) antibodies, although associated with different GAD-related syndromes, as mentioned earlier, share the same antigenic epitopes while their titres, either in CSF or serum, do not correlate with disease severity.

E. Anti gamma-aminobutyric acid receptor-B (GABAb)- a G-protein-coupled receptor-autoimmune encephalopathies. In two large series of more than 35 *anti*-GABAb-seropositive patients, the most common symptoms were limbic encephalitis, seizures, ataxia and opsoclonus-myoclonus [47–49]; while a single case presented with brainstem encephalitis [50]. The GABAb-associated syndrome can be paraneoplastic in up to 35% of the cases, most often associated with small-cell lung cancer, and it often presents in conjunction with another paraneoplastic antibody [13,51] (Fig. 2).

F. Anti-Glycine receptor-associated autoimmunity. These antibodies are primarily associated with Progressive encephalomyelitis with rigidity and myoclonus (PERM) syndrome, consisting of abnormal autonomic features, hyperekplexia, severe brainstem myoclonus or excessive startle, painful spasms and breathing problems [52,53]. Glycine is a key neurotransmitter in spinal inhibitory interneurons and Gly-α1 receptors are primarily expressed in spinal cord, brainstem and cerebellum. Symptoms can be explained by the disruption of the inhibitory glycinergic synaptic transmission, which is prominent in the spinal cord and brainstem. The documented presence in serum and CSF of *anti*-GlyR antibodies suggests an antibody-mediated pathogenesis with good response to immunotherapies if initiated early. These antibodies have also been described in a subset of SPS patients [54]. The *anti*-GlyR antibodies are thought to exert their effect via receptor internalization, disrupting the normal function of the receptor, which forms a ligand-gated chloride channel, generating inhibitory currents (Fig. 2) [55].

G. *Anti*-DPPX-associated encephalitis. Apart from the CNS symptoms that overlap with those described earlier for all the other limbic encephalitis patients, *anti*-DPPX-positive patients also manifest characteristic non-CNS symptoms like diarrhea due to co-expression of the DPPX in the myoenteric plexus [56].

H. Paraneoplastic-associated encephalitis. These patients harbour antibodies against intracellular antigens shared by both the tumor and the nervous tissue and include Hu, Ri, Yo, MAP1B, Ma2, CV2, SOX1, mitochondrial IP3 receptor-1, and Zic4 (Table 1A and B) [57,58]. These patients present with encephalitis, cerebellar ataxia and peripheral neuropathy, either alone or in combination. The most common paraneoplastic-antibody associated encephalitis is with *anti*-Hu antibodies which are mainly produced as a reaction to small-cell

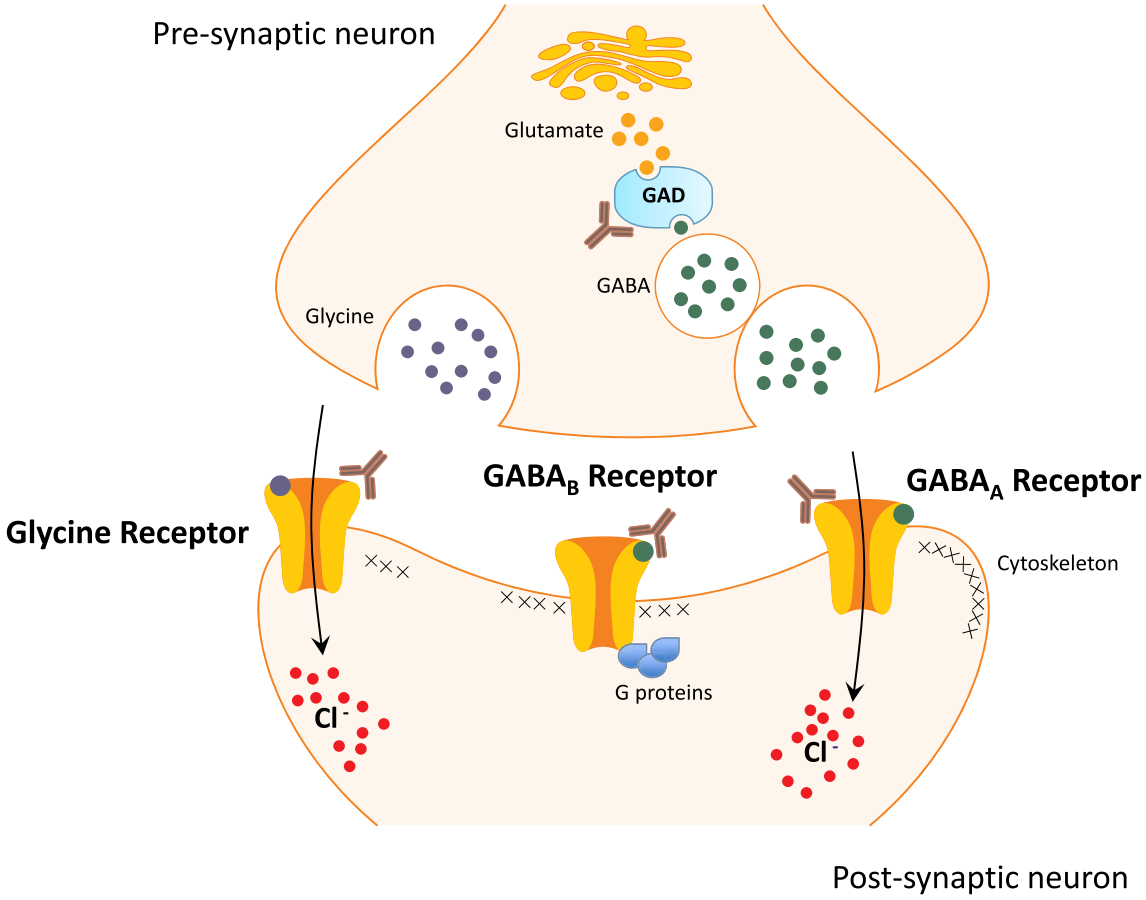

Fig. 2. Pathophysiological mechanism of inhibitory CNS synapses represented by GlycineR, GABAaR GABAbR and GAD. Antibodies affect glycine, GABAa and GABAb receptors in the post-synaptic neuron altering Cl^- influx and G-protein downstreem signalling. In the pre-synaptic neurons, anti-GAD antibodies may effect GABA synthesis changing synaptic potential.

lung carcinomas [59] and they are directed against a group of 35-40kD neuronal RNA binding proteins, including HuD, PLE/HuC and Hel-N1 [60]. The role of these antibodies has been however elusive [61], as described below.

3. General principles of autoimmunity in connection with intracellular or anti-synaptic antibodies

The aforementioned anti-synaptic antibodies are either produced intrathecally or cross the blood brain barrier from the periphery. The migration of B-cells into the CSF occurs across the choroid plexus, while migration from the blood into the brain parenchyma is safeguarded by the blood-brain barrier (BBB). Because BBB is more stringent than the blood-CSF barrier, most of the intrathecal autoantibody production seems to stem from within the CSF-residing B-cells or B-cells that form ectopic germinal centers in the meninges [62]. In a fully intact BBB very little IgG is allowed to pass through, but when this is disrupted under various conditions, like injury, infection, inflammation or strokes, the barrier allows for IgG to transverse [25,63].

Intracellular antigens, such as the RNA-binding proteins Hu (mostly HuD) and Ri, transcription factors such as Yo protein, or intracellular receptors like the mitochondrial IP3 receptor 1, are considered inaccessible by their respective autoantibodies [64]. The neurological phenotypes associated with such antigens are almost exclusively paraneoplastic as these antibodies are produced in response to a comorbid tumor. Since these autoantigens are intracellular, the neurological symptoms are most likely mediated by $CD8^+$ cytotoxic T-cells, and these antibodies serve as diagnostic biomarkers [65].

In contrast, the antibodies against synaptic antigens, effectively target excitatory or inhibitory synapses and alter synaptic function on the affected brain areas of the limbic system, basal ganglia or brainstem, resulting in the aforementioned complex encephalitic symptomatology. Because some of these antigens are also expressed in non-CNS synapses, several of these patients, apart from the classic limbic encephalitis, also exhibit additional symptomatology. For example, LGI1 encephalitis, may also manifest a unique type of faciobrachial dystonic seizures; the DPPX-associated encephalitis may be associated with diarrhea due to co-expression of the DPPX in the myoenteric plexus; and GAD associated autoimmunity may manifest diabetes because GAD is expressed in pancreatic cells and a spectrum of CNS or PNS symptoms including excessive muscle stiffness (stiff person syndrome), cerebellar ataxia, nystagmus or myoclonus [66].

The fundamental clinical importance of the antibodies against synaptic circuitry, such as GABAa, GABAb and Glycine receptors [67], or against enzymes i.e GAD, is that early suppression with immunotherapy leads to symptom amelioration or complete recovery [3]. This is because antibodies against synaptic components cause functional synaptic disruption responsible for the described symptomatology, without causing an associated tissue destruction, demonstrable by MRI imaging, at least for some time after disease onset. In a sense, these disorders, are analogous to the prototypic synaptic autoimmune disease, Myasthenia gravis, where many different synaptic antigens expressed at the neuromuscular junction (such as the acetylcholine receptor and MuSK [68]) are targeted, but the disruptive synaptic transmission is successfully reversed with immunotherapy. When structural damage is however concurrently inflicted in neurons or glia, permanent neurologic deficits and demonstrable brain lesions with cortical atrophy ensue and persist.

4. Autoimmune neuro-psychiatry

Immune neuro-psychiatry [69] is an emerging field that links hyper- or hypo-activation of the immune system with the development of neuropsychiatric symptoms, such as psychosis, schizophrenia or major depression, in the context of an organic neurological disease [5,70]. This concept emerged only recently with the discovery of autoimmune encephalitides especially NMDAR, which uncovered that patients presenting with rapidly progressive psychiatric symptoms, such as psychosis, agitation, paranoias, phobias or depression either alone or in combination with cognitive impairment, seizures and abnormal movements, had an autoimmune disease responding to immunotherapy [71]. Because psychosis is often the presenting, though not always the only symptom, it was proposed that *anti*-NMDAR antibodies can cause psychosis [72,73]. This insightful observation has lead to a highly rewarding concept that all acute psychotic episodes or psychoses as a presenting symptom, even in a patient thought to have schizophrenia, should be tested for the aforementioned anti-synaptic autoantibodies to consider immunotherapy [74]. Distinguishing however autoimmune organic disease from a primary functional psychiatric disorder can be at times challenging especially since 90% of autoimmune patients have prominent psychiatric or behavioral symptoms at disease onset [4,75,76]. Screening the CSF for NMDAR antibodies is of major diagnostic help as discussed below.

At the immunobiological level, studies have now demonstrated that the patients' *anti*-NMDAR antibodies reduce the synaptic levels of NMDAR [77,78] in a pattern similar to the synaptic mechanistic theory of NMDAR hypofunction proposed in schizophrenia [79]. Many clinical studies in patients with psychosis hospitalized in psychiatric clinics or exclusively attended by psychiatrists, have now identified a small percentage of patients (ranging from 3 to 9% in several series) positive for *anti*-NMDAR antibodies [80]. Considering that even in typical autoimmune encephalitis, 20% of the patients can be seronegative, the incidence in the psychiatric population may theoretically be higher requiring the need for heightened suspicion and awareness. On the other hand, it is also possible that chronic schizophrenia may lead to a secondary *anti*-NMDAR immune response as a result of antigen release following a synaptic neurodegenerative process. In such a setting, the search for antibodies in the CSF is of fundamental importance because positive titers in the CSF are clearly diagnostic for an autoimmune chronic encephalitis that can respond to immunotherapy and the main test distinguishing doubtful cases of autoimmune vs. functional psychosis. Low-titers of IgM and IgA but not IgG *anti*-NMDAR antibodies, have been also found in healthy individuals corresponding to natural autoantibodies, but never in the CSF [81]. Testing however in our own laboratory of various commercial IVIg preparations for natural autoantibodies have not detected *anti*-NDMAR or any of the aforementioned synaptic antibodies (Dimitriadou et al., *in press*).

A connection between autoimmunity and phobic neurosis has been also entertained by us in patients with anti-GAD autoimmunity. This stems from the observation that excessive phobias in addition to hyperexcitabillity are commonly seen in GAD-positive patients with Stiff Person Syndrome. Detailed psychiatric and neuropsychological testing however revealed that these patients' phobic neurosis was probably related to their physical ailment rather than to a primary autoimmune GAD-related psychiatric component because when the patients somatic symptoms improved with immunotherapy the phobias also improved [82]. In our mind, this issue has not been however settled, because excessive phobias and obsessive-compulsions are very prominent in these patients and, in our experience, disproportionate to their physical disability compared to other non-GAD-positive patients with similar degree of neurological involvement like progressive multiple sclerosis.

Apart from the aforementioned organic autoimmune neurological disorders presenting with psychiatric symptoms, links between autoimmunity and pathogenesis of some clearly psychiatric disorders such as autism, bipolar disorder, obsessive-compulsive anxiety disorder and schizophrenia, have been also entertained over the years but never clearly delineated. The main evidence linking autoimmunity to some of these psychiatric diseases has been based on epidemiological and cytokine studies. An increased risk, of still unclear significance, has been observed in patients with schizophrenia and various autoimmune diseases, like Type 1 diabetes [83], celiac disease [84] and Systemic Lupus Erythematosus. This most likely represents common risk factors such as infections, co-existing autoimmunity [83,85] or shared risk genes for both, autoimmunity and schizophrenia, associated within the major histocompatibility complex [86]. There are also reports that in schizophrenia, various inflammatory biomarkers, such as cytokines, acute-phase proteins [87–89] endothelial cell and glial activation [90–92] are increased but whether the adaptive or innate immunity plays any role in disease pathogenesis has never been demonstrated [93,94].

A plausible link may also exist between inflammation and depression based on the assumption that infections drive increased expression of cytokines such as IL-1β, IL-6 and TNF which in turn influence mood, social behavior and cognitive abilities [95]. Chronic inflammation may also be associated with or contribute to depressive symptoms during the course of a chronic inflammatory disease like rheumatoid arthritis or multiple sclerosis [96–98], possibly influenced by increased levels of pro-inflammatory cytokines and acute phase reactants, including C-reactive protein [99–103]. It is likely however, that co-existent complex comorbidities and the burden of chronic illness and disability are contributing factors. Immunotherapeutic drugs may also exert an effect; for example, treatment with anti-cytokine drugs such as IFNβ for multiple sclerosis or chronic viral hepatitis, has been associated with depressive symptoms, while steroids, by disturbing the HPA axis homeostasis, may also trigger altered behavior and depression [104]. The cause of neuropsychiatric systemic lupus erythematosus or the rare incidents of lupus psychosis remains still unsettled [105]. It is of interest, that in a subset of lupus patients with neuropsychiatric or psychotic symptoms, antibodies against the NMDAR have been found but to a different subunit compared to the *anti*-NMDAR encephalitis antibodies discussed earlier [105].

5. Functional consequences of anti-synaptic antibodies & animal models

The functional effect of anti-synaptic antibodies has been explored in cultured cells and animal models. Application of patient sera or CSF or purified antibodies to primary mouse hippocampal or cerebellar cells has been used to explore alterations in neuronal electrophysiological properties, complement mobilization, modulation of antigen expression and modulation of global gene expression. Application of CSF from *anti*-NMDAR patients onto cultured hippocampal neurons revealed that the antibodies diminish the NMDAR expression on the cell surface [23]. A similar effect has been also observed for *anti*-AMPA and *anti*-GABAa receptor antibodies [67]. These antibodies can cross-link their receptors via their two Fab fragments with one Fab fragment binding to the one receptor and the other to the adjacent receptor. Such antibody-linked receptors can be endocytosed, internalized and decomposed. A decrease of receptor surface density lessens the neuronal ability to respond to physiological levels of released neurotransmitter.

The pathophysiology of the autoimmune encephalitic syndromes has been also studied with passive transfer of antibodies to experimental animals providing additional evidence that the antibodies against NMDAR, LGI1, CASPR2 and AMPAR encephalitis are pathogenic. The most convincing results are the following:

A. NMDAR encephalitis model: Continuous infusion of cerebrospinal fluid from NMDAR-positive patients or controls with ventricular catheters placed intracerebrally into C57BL6/J mice showed that animals infused with patients' cerebrospinal fluid, developed progressive memory deficits, and anhedonic and depressive-like behaviours, but without psychotic or locomotor effects. Pathology of issue sections showed progressive increase of brain-bound human antibodies,

predominantly in the hippocampus where a progressive decrease in the density of the synaptic NMDAR clusters and the total NMDAR protein concentration was noted. Overall, these findings have established a link between memory and behavioral deficits with antibody-mediated reduction of NMDAR [106,107].

B. LGI1 encephalitis model: Patient-derived IgG *anti*-LGI antibodies where used in cerebroventricular transfer experiments in a mouse model to determine whether these antibodies disrupt the interaction of LGI1 with ADAM23 and ADAM22 or have an effect on Kv1.1, AMPA receptors and the animals' memory. It was found that the patients' antibodies prevented the binding of LGI1 to ADAM23 and ADAM22. Confocal analysis of hippocampal slices showed a decrease of total and synaptic levels of Kv1.1 and AMPA receptors. In acute slice preparations of hippocampus, patch-clamp analysis from dentate gyrus granular cells and CA1 pyramidal neurons showed neuronal hyperexcitability with increased glutamatergic transmission. Analysis of synaptic plasticity by recording field potentials in the CA1 region of the hippocampus showed a severe impairment of long-term potentiation. In parallel with these findings, mice infused with patient-derived IgG showed severe memory deficits in a novel object recognition test. Overall, these findings have demonstrated that patient-derived IgG disrupts presynaptic and postsynaptic LGI1 signalling, causing neuronal hyperexcitability, decreased plasticity, and reversible memory deficits [108].

C. AMPA receptor model: Using electrophysiology, imaging and passive transfer studies it was shown that antibodies against the GluA2 subunit of the AMPA receptor provoked a rearrangement of synaptic receptors in mice. This involved the insertion of inwardly rectifying compensatory non-GluA2 AMPA receptors. Confocal and super resolution imaging in primary neurons confirmed the loss only of synaptic GluAs subunits. Combining recordings from cultured neurons and brain slices from antibody-injected animals, it was concluded that the *anti*-AMPA antibodies, similarly to the NMDAR antibodies, lead to receptor internalization, followed by synaptic recruitment of available receptors by insertion of different subunits. At the behavioral level, continuous infusion of IgG fractions into the lateral ventricles or stereotaxic injections of IgG into the CA1 and CA3 region of the hippocampus caused memory impairment and increased anxiety-like behavior, which constitute typical signs of the human disease [109].

D. CASPR2 antibody model: Purified plasma IgG from either a CASPR2 antibody-positive patients or healthy individuals was injected intraperitoneally in mice on a daily basis for 8 days. Lipopolysaccharide was also injected intraperitoneally to cause a temporary breach in the blood brain barrier. Mice exposed to CASPR2-IgG, compared with control-IgG injected mice, displayed reduced working memory and, in the reciprocal social interaction test, CASPR2-IgG injected mice showed more freezing behavior and reduced non-social activities of rearing and grooming. Neuropathology showed more IgG deposited in the brains of CASPR2-IgG injected mice and increased c-fos expression in the piriform-entorhinal cortex and hypothalamus with a modest loss of Purkinje cells. Although patients with CASPR2 antibodies have, as already mentioned, a range of clinical features, only mild clinical defects were observed in the injected mice [110].

6. Factors triggering CNS autoimmunity

6.1. Infectious and parainfections triggers

Various viral, bacterial, fungal or parasitic infections may directly infect the brain most commonly resulting in meningitis, infectious encephalitis or meningoencephalitis. Herpes simplex virus-1 & 2 infections accounts for the majority of viral encephalitides, followed by *Varicella zoster*, Japanese encephalitis virus, West Nile virus (WNV), tick-borne (*Borrelia burgdorferi*) virus, Eastern Equine encephalitis and others. The same infectious agents however can also trigger an immune-mediated inflammatory process [111]. There is long-standing evidence that infectious pathogens (either bacterial, viral or protozoan) can trigger neurological autoimmunity with the most typical example being the Guillain Barre Syndrome following a gastrointestinal infection with *Campylobacter jejuni* [112]. In these cases, owing to identical sequence homology between the Campylobacter and ganglioside myelin antigens, pathogenic autoantibodies against gangiosides are generated resulting in demyelination. Similarly, certain forms of Guillain Barre syndrome have occurred following Zika virus infection (a flavivirus) owing to molecular mimicry between gangliosides and surface molecules of the Zika virus [113] Less well studied, is the development of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), where a subset of children present with rapid onset of obsessive-compulsive disorder [114]. An autoinflammatory cascade possibly triggered by latent viral infections has been also postulated for some chronic autoimmune CNS conditions like multiple sclerosis, where Epstein Bar virus (EBV) sequences have been found inserted into the genome [115].

Similar, but more convincing observations, have been made for some of the autoimmune encephalitis discussed earlier with the best studied example the NMDAR encephalitis triggered by Herpes simplex-1 infection, in both children and adults [116,117]. Herpes simplex virus encephalitis has been known to have a relapsing course in up to 12% of adults and 14–35% of children [118], despite anti-viral treatment. The pathogenesis of these relapses was until recently unclear because in most relapsing patients, PCR for HSV-1 or HSV-2 was negative. It is now evident, that in these patients most of the encephalitis relapses are not due to a latent virus reactivation, as had been thought, but due to a post-infectious autoimmune process, that followed the HSV-induced brain damage [119,120]. More than 50 cases of post-HSV autoimmune encephalitis have been now reported associated with *anti*-NMDAR antibodies produced in the CSF rather than the serum in a pattern similar to idiopathic or paraneoplastic NMDAR encephalitis [116]. Similarly to idiopathic NMDAR encephalitis [121,122], long-term antibody persistence is also evident in post-infectious NMDAR encephalitis suggesting that certain B-cell clones, probably long-lived plasmablasts, persist in the circulation; whether these represent negative prognostic factors for future relapses, if gain access into the CNS, remains unclear. The most clinically important observation is that the post-HSV- induced NMDAR encephalitis responds to immunotherapy with IVIg, steroids or rituximab, providing the impetus for the clinicians to shift therapeutic attention from anti-viral to anti-immune therapies [123].

Apart from *anti*-NMDAR, rare cases of *anti*-GABAb and anti-voltage-gated calcium channel antibodies have also been described following HSV infection [124]. The reason why the *anti*-NMDAR cases are more frequent, is probably because NMDAR is more abundant in the CNS, compared to other receptors or channels, and this antigen is released at greater levels post-destruction from HSV. It seems therefore more likely that the post-HSV anti-synaptic antibodies do not develop as a result of molecular mimicry but rather due to self-immunization following the release of antigens from the damaged brain tissue. Interestingly, however, in a recent study of young patients with NMDAR encephalitis without clinical history of previous herpetic encephalitis, an increased frequency of HSV-1 antibodies was found implying the possibility that molecular mimicry may occur in the periphery [125].

WNV is a mosquito-borne single-stranded RNA flavivirus that infects humans, causing symptoms ranging from fever to severe encephalitis, flaccid paralysis, and death. Reports of WNV patients who subsequently developed myasthenia gravis, indicate a possible-although yet disputed-link between WNV infection and autoimmunity [126]. A recent report has also identified a case of a West Nile Virus (WNV) infected patient who developed autoimmune encephalitis with autoantibodies against Glycine receptor [127]. Post-infectious GlyR autoimmunity has also been reported, in a patient who developed PERM, the most common clinical manifestation of these antibodies, following an infectious brucellosis [128]. Post-infectious anti-GAD autoimmunity has been also observed after WNV infection in a patient who developed Stiff person

syndrome with anti-GAD antibodies [129].

These observations raise several possibilities as to how the two seemingly separate events, namely the viral and autoimmune encephalitis, are etiologically connected. Augmentation of naturally occurring autoreactive B cells could result from tissue destruction, following brain parenchyma infection, which in turn releases autoantigens to draining lymph nodes. Considering that the elicited synaptic antibodies persist in both, autoimmune and post-viral encephalitis, a similar autoimmunization process or perpetuation of autoimmunity is likely. Molecular mimicry, based on sequence homology or structural similarities between microbial and CNS autoantigenic epitopes, is also a possibility in a pattern similar to the immunological reaction and evolved autoimmunity in GBS triggered by *Campylobacter jejuni* and Zika virus infection [113]. Finally, superantigens and cryptic antigens, apoptotic and necrotic host cell death and infection-induced bystander immune activation products may also play additional role in triggering or perpetuating CNS autoimmune inflammation.

6.2. Neoplasms as triggers of autoimmunity

Paraneoplastic neurological disorders can affect any part of the nervous system. These are not caused by metastatic or local effects of cancer but from an immune response against neuronal antigens expressed by the tumors. The mounted immune response against tumor antigens cross-reacting with the same neural-specific antigens is both cellular, involving $CD4^+$ and $CD8^+$ lymphocytes, but also humoral involving autoantibodies [130]. CNS paraneoplastic autoimmunity can manifest as cortical, limbic or brainstem encephalitis, as cerebellar ataxia or as complex multiple level dysfunction affecting cortical and myelinated CNS or PNS structures. Many types of tumors can induce paraneoplastic neurological autoimmunity, most often small cell lung cancer (SCLC), thymoma, breast, ovarian and testicular cancer, teratomas, melanomas and lymphomas [131].

In cancer-related autoimmunity, antigens can be intracellular or synaptic, with autoimmunity against intracellular antigens being associated with a tumor in over 90% of the cases. The intracellular antigens shared by both the tumor and the nervous tissue include, as already mentioned, Hu, Ri, Yo, MAP1B [132], Ma2, CV2, SOX1 and Zic4 (Table 1A and B). These patients most often present with encephalitis, cerebellar ataxia, and peripheral neuropathy. Cancer autoimmunity against synaptic antigens is more variable, ranging from 10 to 90%, and include among others: a) *LGI1,* where only 10% of cases are paraneoplastic presenting as limbic encephalitis, b) *NMDAR*, where up to 50% of cases are paraneoplastic (especially associated with teratomas in young women presenting as encephalitis with neuropsychiatric symptoms); c) *Tr/DNER* where 90% of the cases are paraneoplastic presenting as cerebellar ataxias [133]; and d) rare antigens where a tumor association is extremely rare (< 1%) or has not been found as in cases of AQP4 spectrum disorders and in *IgLON5*, an antigen found in patients presenting with sleep disorder, ataxia, chorea and neurodegeneration [134]. The noted percentages may be however misleading as many of these syndromes are rare with only few described cases (Table 1A and B).

In a prospective series of 264 consecutive patients with SCLC, 9.4% developed paraneoplastic neurological syndromes; the most common among them was Lambert-Eaton myasthenic syndrome (3.8%), sensory neuronopathy (1.9%) and limbic encephalitis (1.5%) [135]. Overall, the most notable associations are of SCLC with the intracellular antigens Hu, Ri and CV2; of thymoma with *anti*-AChR antibodies and myasthenia; and ovarian teratomas with NMDAR-encephalitis. The frequency and type of cancer also vary according to the autoantibody. For example, 60% of patients with neurological syndromes associated with GABAbR antibodies have an underlying SCLC, whereas 60% of those with AMPAR autoantibodies have non-small-cell lung cancer, breast cancer or thymic tumors [136]. Almost all patients with limbic encephalitis and Hu autoantibodies have an underlying SCLC, wheras those with LGI1 autoantibodies rarely have cancer [137]. A recent case of LGI1 encephalitis associated with SCLC seems to stem from molecular mimicry as LGI1 appears expressed in the tumor (Dalakas et al., *in preparation*).

Regarding the pathological effect of the immune response to the nervous system, post-mortem studies in patients harboring autoantibodies against intracellular targets e.g. *anti*-Hu, have revealed neuronal loss, microglial proliferation and cellular inflammatory infiltrates consisting of both T-cells and B-cells. The presence of cytotoxic T-cells in proximity to neurons and the expression of membranolytic enzymes such as perforin or granzyme B strongly suggest T-cell-mediate neuronal damage. In patients with antibodies against synaptic antigens such as NMDAR antibodies and ovarian teratoma, biopsy and autopsy studies revealed mild inflammatory infiltrates, limited or absent neuronal loss, frequent B-cell or plasma cell infiltrates and IgG deposits without complement [138].

6.3. Biological cancer therapies (immune checkpoint inhibitors) as triggers of autoimmunity

There is overwhelming evidence that patients receiving treatment with immune checkpoint inhibitors (ICI's) are at a risk for developing immune-related neurological diseases [139]. It is now clear that apart from the risk of developing paraneoplastic autoimmunity, cancer patients may also suffer from autoimmune neurological syndromes after cancer immunotherapy, when unrestrained T-cells attack neuronal antigens necessitating the initiation of traditional immunotherapy to halt the unfolding neurological events [140]. The main FDA-approved ICI's are against CTLA-4 (Ipilimumab) and PD-1 (Pembrolizumab and Nivolumab). These drugs result in positive co-stimulation and T-cell activation which can kill tumors, but in this process also disrupt immune tolerance. The exact mechanism by which autoimmunity occurs is unclear. These drugs enhance Th1 and Th17 responses and the production of pro-inflammatory cytokines such as IL-6 and IL-17 which lead to altered T-regulatory cell function [140]. The dysregulation of the Treg/Th17 axis is implicated in many autoimmune neurological diseases. Further, the ICI's stimulate autoantibody production, especially in patients with autoimmune susceptibility [139,140]. It has been calculated that these drugs can also precipitate pre-existing autoimmune neurological diseases with an estimated 27–42% risk for mild to moderate exacerbations. A classic example is the severe exacerbation of myasthenia gravis and multiple sclerosis during ipilimumab therapy [141].

The overall incidence of neurological complications in treated patients ranges from 2 to 4%, even though most of them are mild. Autoimmune encephalitis may occur in 0.1–0.2% of patients within days or weeks after therapy initiation (as a few case reports illustrate) [142–144], but especially with combined therapy of ipilimumab with nivolumab [139]. The larger reported number of patients have *anti*-NMDAR antibodies or *anti*-Hu antibodies which also represent the most commonly encountered intracellular or synaptic antibodies. NMDAR subunit GluN2A is encoded by the GRIN2A gene and is expressed in melanocytes, where it is highly mutated in melanoma. In these patients, the encephalitis could be due to molecular mimicry, as antibodies against the tumor might also attack the nervous system [140]. These patients respond to high-dose steroids and immunotherapy. In addition, in a phase II trial, in SCLC patients treated with ipilimumab and chemotherapy, *anti*-Hu and *anti*-Yo autoantibodies were detected in 45% of the patients suggesting that ICI's can also exacerbate paraneoplastic autoimmunity [145]. Such a situation is arguably complex for the clinician as it might be difficult to distinguish whether a neurological manifestation is due to treatment or to cancer itself [140].

7. Treatment strategies

Immunotherapy is the most effective treatment for autoimmune encephalitides, irrespective of cause; it has made a major impact in the

field leading to improvement, complete clinical remission or even cure of patients with previously lethal or untreated diseases. Immunotherapy has been also changing the approach for some erroneously treated acute psychotic disorders (prior receiving only symptomatic therapies with neuroleptics or antiepileptics) or for post HSV-encephalitis relapses (prior receiving a second anti-viral therapy course) [146].

First line therapies consist of intravenous steroids, 1 g daily for 3–5 days, followed by intravenous immunoglobulin (IVIg). After 4 weeks if there is no response, plasma exchange may be considered or a transition to second line therapies with rituximab or cyclophosphamide. Third line treatments with bortezomib (a proteasome inhibitor) or tocilizumab (an IL6 receptor antagonist) might be last options. The same immunotherapeutic treatment strategies also apply to autoimmune encephalitides associated with viral or tumor triggers with better response when the antigens are synaptic.

The prognosis and response to immunotherapy may however differ in patients with tumors where cancer treatment is always a priority. There are characteristic cases where only the surgical removal of an ovarian teratoma had effectively cured NMDAR encephalitis. In patients with cancer and tumors, immunotherapy may also vary according to the immunological subtype of encephalitis and the associated autoantibody. For example, in patients with paraneoplastic antibodies against intracellular antigens, that often precede cancer detection, the autoimmune tissue damage is thought to be primarily cell-mediated; in these patients targeting antibodies or removing them from the circulation i.e. with plasmapheresis or *anti*-B cells therapies, may not be as successful as treating them with IVIg, steroids or *anti*-T cell therapies. On the other hand, when antibodies against synaptic antigens are implicated, targeting autoantibodies with plasmapheresis or *anti*-B cells agents is more promising.

When paraneoplastic antibodies are detected as part of general screening, it is of paramount importance for patients to undergo thorough search for cancer detection. Even if this proves negative, increased awareness is needed and, accordingly, cancer screening may be repeated for the first 3 years. Whether in cancer patients the presence of onconeuronal antibodies is a marker of survival is an unsettled matter. In two progressive clinical studies the presence of *anti*-Hu antibodies, correlated with increased survival, but in two other studies, there was no difference between seropostive and seronegative patients supporting the notion -which we strongly favor-that onconeuronal antibodies are just biomarkers of a CTL-mediated antitumour immune response [139].

In patients with immune-related encephalitis due to treatment with immune checkpoint inhibitors, early application of immunotherapy with IVIg, steroids or plasmapheresis is essential while consideration to stopping cancer immunotherapy or changing to a different agent i.e. from an *anti*-CTLA-4 to anti- PD-1, might be entertained [140].

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