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Neuronal central nervous system syndromes probably mediated by autoantibodies

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Abstract

In the last few years, a rapidly growing number of autoantibodies targeting neuronal cell-surface antigens have been identified in patients presenting with neurological symptoms. Targeted antigens include ionotropic receptors such as N-methyl-D-aspartate receptor or the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, metabotropic receptors such as mGluR1 and mGluR5, and other synaptic proteins, some of them belonging to the voltage-gated potassium channel complex. Importantly, the cell-surface location of these antigens makes them vulnerable to direct antibody-mediated modulation. Some of these autoantibodies, generally targeting ionotropic channels or their partner proteins, define clinical syndromes resembling models of pharmacological or genetic disruption of the corresponding antigen, suggesting a direct pathogenic role of the associated autoantibodies. Moreover, the associated neurological symptoms are usually immunotherapy-responsive, further arguing for a pathogenic effect of the antibodies. Some studies have shown that some patients' antibodies may have structural and functional in vitro effects on the targeted antigens. Definite proof of the pathogenicity of these autoantibodies has been obtained for just a few through passive transfer experiments in animal models. In this review we present existing and converging evidence suggesting a pathogenic role of some autoantibodies directed against neuronal cell-surface antigens observed in patients with central nervous system disorders. We describe the main clinical symptoms characterizing the patients and discuss conflicting arguments regarding the pathogenicity of these antibodies.

Keywords

antibodies; cerebellitis; encephalitis; NMDAR; synaptopathies

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Introduction

In the last few years, a rapidly growing number of patients with non-infectious, autoimmune encephalitis associated with autoantibodies targeting the central nervous system (CNS) have been described. The first anti-neuronal autoantibodies – anti-Hu (Szabo *et al.*, 1991), anti-Yo, anti-CV2/CRMP5 (Honnorat *et al.*, 1996) and anti-Ri (Pittock *et al.*, 2003) – were identified about 25 years ago in paraneoplastic neurological syndromes (PNSs). These anti-neuronal autoantibodies recognize intracellular antigens and therefore do not appear to be directly pathogenic, but may be used as diagnostic biomarkers of cancer (Honnorat, 2006; Raspotnig *et al.*, 2011). Cytotoxic neuronal damage and neuronal death are responsible for symptoms found in these PNSs and immunization with the paraneoplastic antigen does not induce disease in rodents, further supporting a non-pathogenic role of the respective autoantibodies (Sillevis Smitt *et al.*, 1995). Rather, the antibodies may reflect a T-cell-mediated immune response against neurons (Bien *et al.*, 2012). On the other hand, an increasing number of autoantibodies targeting neuronal cell-surface antigens have been identified recently in patients presenting with neurological symptoms resembling PNSs. Targets include ionotropic receptors including *N*-methyl-D-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid $(GABA)_AR$ and glycine receptor (GlyR); metabotropic receptors such as mGluR1, mGluR5 and $GABA_BR$; and proteins belonging to the voltage-gated potassium channel (VGKC) complex, namely Lgi1 and Caspr2. Several key features differentiate patients with cell-surface autoantibodies from patients with autoantibodies recognizing intracellular targets: (i) associated neurological symptoms are usually immunotherapy-responsive and reversible, suggesting a direct pathogenic effect of antibodies without cytotoxically induced neuronal loss; and (ii) tumour association is far less consistent. Encephalitis associated with antibodies directed against cell-surface antigens such as NMDAR or VGKC complex are much more common than PNSs with intracellular targets and were identified to account for ~8% of encephalitis cases in a population-based prospective study in England (Granerod *et al.*, 2010). The location of cell-surface antigens allows their recognition by autoantibodies on the intact cell and evidence suggests that these antibodies may play a direct pathogenic role in the neurological and psychiatric symptoms of patients with encephalitis. The purpose of this review is to present existing and converging evidence suggesting a pathogenic role of some autoantibodies directed against neuronal cell-surface antigens observed in patients with encephalitis. We describe the main clinical symptoms characterizing the patients and discuss conflicting arguments regarding the pathogenicity of these antibodies.

Encephalitis associated with antibodies directed against NMDAR

Definition and clinical presentation

Encephalitis associated with anti-NMDAR autoantibodies is a clinico-biological entity defined by a clinical presentation of encephalitis, and the presence of IgG antibodies in the cerebrospinal fluid (CSF) that are directed against the GluN1 subunit of the NMDAR (Dalmau *et al.*, 2008). Detection of anti-NMDAR antibodies relies on two tests: a specific immunohistochemical staining pattern on rat brain section with patients' IgG; and patients' IgG binding to NMDAR-expressing HEK cells in a cell-based assay (Dalmau *et al.*, 2008;

Gresa-Arribas *et al.*, 2014; Viaccoz *et al.*, 2014). Encephalitis with anti-NMDAR antibodies was initially described in 2007 in 12 women with associated ovarian teratoma (Dalmau *et al.*, 2007). The clinical presentation was more comprehensively described 1 year later in 100 autoantibody-positive encephalitis patients (Dalmau *et al.*, 2008). To date, several hundred cases have been published (Titulaer *et al.*, 2013), indicating a relatively frequent disorder. Accordingly, NMDAR encephalitis was identified as the most common cause of non-infectious encephalitis in patients under 30 years old (Gable *et al.*, 2012). Among all autoimmune encephalitides, NMDAR encephalitis is the most frequent (Thomas *et al.*, 2014). The clinical disorder, predominantly affecting young women, shows a progression of similar symptoms (Titulaer *et al.*, 2013), usually starting with a prodromal syndrome including headache, low-grade fever or non-specific viral-like illness followed by the development of psychiatric symptoms (anxiety, agitation, delusional thoughts, hallucinations, and personality or behavioural changes) and/or neurological symptoms (seizures, movement disorders, catatonia, alteration of mental state, speech impairment and rapid development of short-term memory loss) within the next days or weeks. During the course of the disease, patients often develop decreased responsiveness, abnormal movements (the most characteristic being oro-facial dyskinesia) and autonomic instabilities (Dalmau *et al.*, 2008, 2011). Only a few adult male patients have been described and tend to present with seizures as first symptoms whereas female patients usually present with psychiatric symptoms (Viaccoz *et al.*, 2014). Psychiatric symptoms and abnormal movements are more prominent in children (Florance *et al.*, 2009). A good recovery is generally observed in about 80% of patients but is typically slow, occurring in stages following the reverse order from symptom appearance (Dalmau *et al.*, 2011; Titulaer *et al.*, 2013; Gresa-Arribas *et al.*, 2014). In the largest published series, more than 75% of patients recovered fully or retained only mild deficits (Dalmau *et al.*, 2008). An underlying neoplasm is found in about 40% of patients, primarily in females aged between 12 and 45 years (Dalmau *et al.*, 2011; Titulaer *et al.*, 2013). More than 90% of all tumours associated with anti-NMDAR encephalitis are ovarian teratoma, while the frequency of an underlying tumour is less than 5% in men and children (Titulaer *et al.*, 2013). All immunopathological studies of teratomas associated with NMDAR encephalitis revealed the presence of GluN1-expressing nervous tissue (Dalmau *et al.*, 2008; Tüzün *et al.*, 2009). In more than 60% of cases, no tumour is found and mechanisms leading to the breaking of immunological tolerance remain unclear. In a few cases, anti-NMDAR antibodies have been observed a few weeks after a typical herpes simplex encephalitis, suggesting that viral encephalitis may sometimes trigger anti-NMDAR auto-immunity (Prüss *et al.*, 2012; Armangue *et al.*, 2013; Hacohen *et al.*, 2014) (Fig. 1).

Antigen

NMDAR belong to the family of ionotropic glutamate receptors (iGluRs). They are involved in excitatory neurotransmission and are the pivots of synaptic plasticity (e.g. long-term potentiation and long-term depression) underlying cognitive functions such as learning and memory. Functional NMDAR are heterotetramers consisting of two obligatory GluN1 subunits and GluN2 or GluN3 subunits. Antibodies of patients with anti-NMDAR encephalitis target the obligatory subunit GluN1 (Dalmau *et al.*, 2008; Gleichman *et al.*, 2012). Each NMDAR subunit comprises two extracellular domains, the amino-terminal domain (ATD) and the ligand-binding domain, one transmembrane domain and a large

intracellular domain (Paoletti *et al.*, 2013). Remarkably, this subunit structure is conserved for all members of the iGluR family (Traynelis *et al.*, 2010). Antibodies of patients with anti-NMDAR encephalitis target a conformational epitope located in the ATD of the GluN1 subunit, in a small region located near the hinge of a clamshell-like structure (Gleichman *et al.*, 2012). Within this region, the amino acid N368 was identified as crucial for patients' anti-NMDAR antibody binding (Gleichman *et al.*, 2012).

Antibody pathogenicity

Strong clinical arguments support the hypothesis of an antibody-mediated pathogenicity in anti-NMDAR encephalitis. First, pharmacological antagonists of NMDAR (e.g. ketamine) may induce specific clinical symptoms similar to those presented by patients with anti-NMDAR encephalitis. Moreover, the majority of patients respond well to plasma exchanges and intravenous immunoglobulins, often with full recovery (Titulaer *et al.*, 2013). Furthermore immunotherapy targeting an antibody producing CD20+ B-cells (e.g. Rituximab) improves patients' recovery (Titulaer *et al.*, 2013). Substantial evidence points toward an intrathecal synthesis of autoantibodies in anti-NMDAR encephalitis. Indeed, in patients with preserved blood–brain barrier integrity, antibody titres are higher in the CSF than in the serum (Dalmau *et al.*, 2007, 2008). Accordingly, several immunopathological studies reported deposits of IgG, B-cells and plasma cells cuffing in the brain perivascular spaces (Dalmau *et al.*, 2007, 2008; Tüzün *et al.*, 2009; Hughes *et al.*, 2010; Camdessanché *et al.*, 2011). Although anti-NMDAR antibodies are of the subclasses IgG1 and IgG3 that are capable of complement activation, no deposits of complement were found (Tüzün *et al.*, 2009; Hughes *et al.*, 2010). Taken together, these data support the hypothesis of an antibody-mediated pathogenicity, without major involvement of T-cells or complement-mediated cytotoxicity.

Incubation of neuronal cultures with patients' NMDAR autoantibodies caused a selective and reversible decrease in NMDAR surface density and synaptic localization without affecting other synaptic components, neuronal morphology or causing neuronal loss (Hughes *et al.*, 2010; Moscato *et al.*, 2014). The effect size correlated with patients' autoantibody titres. The mechanism of this decrease is selective antibody-mediated capping and internalization of surface NMDAR (Hughes *et al.*, 2010). NMDAR antibody binding does not appear to distinguish between excitatory and inhibitory neurons (Moscato *et al.*, 2014). Interestingly, patients' antibody-mediated decrease of NMDAR clusters relies upon the presence of the Fc domain of anti-NMDAR IgG that allows cross-linking of NMDAR (Hughes *et al.*, 2010; Moscato *et al.*, 2014) and suggests an antibody-mediated alteration of NMDAR surface diffusion. In accordance with those results, a subsequent study confirmed the effect of patients' NMDAR antibodies on NMDAR surface diffusion by disruption of NMDAR and EphrinB2 receptor (EPHB2R) interactions (Mikasova *et al.*, 2012) leading to NMDAR internalization. Activation of EPHB2R by its ligand EphrinB2 prevents patients' NMDAR antibodies' effects on their target (Mikasova *et al.*, 2012). Data from several electrophysiological recordings performed in *in vitro* and *ex vivo* studies point toward a functional effect of patients' NMDAR antibodies. Whole cell-patch clamp recordings showed that application of patients' CSF decreased the NMDAR-mediated component of excitatory currents (Hughes *et al.*, 2010). A decrease of the NMDAR-mediated current

seems to be caused only by internalization of NMDAR and not by an antagonistic effect (Moscato *et al.*, 2014). Acute application of patients' CSF also decreased neuronal network activity in neuronal cultures (Jantzen *et al.*, 2013). Finally, two studies reported an alteration of NMDAR-mediated plasticity by patients' NMDAR antibodies as they prevented induction of chemical long-term potentiation (LTP) (Mikasova *et al.*, 2012) and electrophysiologically induced LTP in neuronal cell cultures (Zhang *et al.*, 2012).

Independent studies reported a reduction of NMDAR clusters after intrathecal administration of NMDAR antibodies (Hughes *et al.*, 2010; Mikasova *et al.*, 2012; Planaguma *et al.*, 2014). Interestingly, this effect was partly reversed by co-injection of EphrinB2 (Mikasova *et al.*, 2012) confirming the above described *in vitro* studies. Microdialysis after hippocampal injection of patients' NMDAR antibodies in rodents revealed an increase in extracellular glutamate concentration (Manto *et al.*, 2010). Furthermore, injection of the motor prefrontal cortex with patients' NMDAR antibodies increased motor stimulation after high-frequency stimulation (Manto *et al.*, 2011a). Both studies support the hypothesis of induction of hyperactivity of glutamatergic pathways by patients' NMDAR antibodies. Recently, an *in vivo* study (Planaguma *et al.*, 2014) demonstrated that continuous intrathecal infusion of patients' CSF induced behavioural changes in mice (memory impairment, depressive-like and anhedonic behaviour; all symptoms also observed in patients). These effects were reversible upon cessation of patients' CSF infusion. No effect of patients' CSF infusion was observed on anxiety, aggressiveness and locomotor activity (Planaguma *et al.*, 2014).

To summarize, anti-NMDAR encephalitis is the best-described autoimmune encephalitis and appears to be a disorder much more common than initially expected. A direct pathogenic effect of NMDAR antibodies is suggested by altered behaviour in mice partly mimicking anti-NMDAR encephalitis symptoms after infusion with patients' CSF (Planaguma *et al.*, 2014), clinical data, patients' outcome, and other *in vitro* and *in vivo* studies. The possible mechanisms of NMDAR antibody action on NMDAR have started to be elucidated *in vitro* (Dalmau *et al.*, 2008; Hughes *et al.*, 2010; Gleichman *et al.*, 2012; Mikasova *et al.*, 2012), arguing for an antigenic modulation. Yet studies on the long-term effect of NMDAR antibodies on neuronal networks and pathways underlying synaptic plasticity are still lacking. Although clinical data such as treatment response and histopathological studies are not in favour of the involvement of cellular-mediated cytotoxicity, further experimental research is still needed to confirm this impression.

Encephalitis associated with antibodies directed against AMPAR

Definition and clinical presentation

Limbic encephalitis associated with antibodies directed against AMPAR was identified in 2009 in 10 of 109 patients with limbic encephalitis (Lai *et al.*, 2009). Subsequently, three studies describing a few cases were reported (Graus *et al.*, 2010; Hoftberger *et al.*, 2015; Joubert & Honnorat, 2015). The majority of patients were women (60%) with a median age around 60 years (Lai *et al.*, 2009; Graus *et al.*, 2010; Hoftberger *et al.*, 2015; Joubert & Honnorat, 2015). Clinical features are more variable than in anti-NMDAR encephalitis. The most common presentation reported is classical limbic encephalitis dominated by short-term memory loss, confusion and abnormal behaviour (Lai *et al.*, 2009; Hoftberger *et al.*, 2015).

Diffuse encephalitis with limbic dysfunction associated with various other symptoms (e.g. seizures, psychiatric manifestations, ataxia, abnormal movements, aphasia and neuropathy) has also been described (Spatola *et al.*, 2014; Hoftberger *et al.*, 2015). A few patients presented with fulminant encephalitis (Wei *et al.*, 2013; Joubert & Honnorat, 2015), and a few cases of atypical presentation with prominent psychiatric symptoms resembling acute psychosis have also been reported (Graus *et al.*, 2010; Hoftberger *et al.*, 2015). Additional associated antibodies recognizing cell-surface ($GABA_BR$, NMDAR, LGI1, VGCC), intracellular (SOX1, Hu) or synaptic (amphiphysin, GAD) targets have been identified in about 30% of these patients (Lai *et al.*, 2009; Hoftberger *et al.*, 2015; Joubert *et al.*, 2015). Overlapping immune responses may complicate clinical presentations and explain some aspects of the clinical heterogeneity observed in patients with anti-AMPAR encephalitis (Lai *et al.*, 2009; Hoftberger *et al.*, 2015). Associated tumours (thymus, lung, breast) were observed in 65% of patients with anti-AMPAR encephalitis (Lai *et al.*, 2009; Hoftberger *et al.*, 2015) and these tumours expressed AMPAR (Lai *et al.*, 2009). This finding supports the hypothesis of a break in immune tolerance induced by ectopic expression of AMPAR by the underlying neoplasm. However, anti-AMPAR encephalitis can occur without an identified tumour (Lai *et al.*, 2009). In these cases, the immune trigger remains unknown. Patients usually respond to immunotherapy although relapses may occur (Lai *et al.*, 2009). Aggressive immunotherapy significantly reduces risks of relapses (Hoftberger *et al.*, 2015). Regarding clinical presentation and severity, the outcome is heterogeneous and the presence of an underlying tumour seems to be associated with a poor outcome (Hoftberger *et al.*, 2015).

Antigen

Like NMDAR, AMPAR belong to the family of iGluRs. AMPAR mediate fast excitatory transmission in the brain. They are required for basal synaptic transmission and are involved in the mechanisms of synaptic plasticity (Santos *et al.*, 2009). AMPAR are heterotetramers composed of four subunits (GluA1 to GluA4) (Traynelis *et al.*, 2010). Patients' antibodies are IgG of uncharacterized subtype targeting GluA1 and/or GluA2 subunits of AMPAR, with a higher incidence of GluA2 antibodies (Lai *et al.*, 2009; Hoftberger *et al.*, 2015). Like NMDAR subunits, each AMPAR subunit is composed of two extracellular domains, the ATD and the ligand-binding domain, a transmembrane domain and an intracellular domain. The bottom lobe of the ATD is the main receptor epitope recognized by AMPAR antibodies (Gleichman *et al.*, 2014). This region matches the location of the epitope on the NMDAR in patients with anti-NMDAR encephalitis, suggesting that the bottom lobe of the iGluRs might be particularly antigenic (Gleichman *et al.*, 2014). The possible detection of AMPAR antibodies by western blot suggests a non-conformational epitope (Gleichman *et al.*, 2014).

Antibody pathogenicity

As in patients with anti-NMDAR encephalitis, clinical data tend to support the hypothesis of AMPAR-antibody-mediated pathogenicity. Clinical improvement after immune therapy occurred concurrent with a decline in CSF antibody titre, supporting a pathogenic role of the antibodies (Wei *et al.*, 2013). Some evidence indicates that patients' AMPAR antibody synthesis is intrathecal; antibody titres were higher in the CSF than in the serum (Lai *et al.*, 2009) and some patients have antibodies only detected in CSF (Hoftberger *et al.*, 2015).

Moreover, serum AMPAR antibodies differ in their epitope specificity from CSF antibodies (Gleichman *et al.*, 2014). Concerning the pathological effects of antibodies on affected brain structures, diffuse cortical atrophy was observed in a few patients with anti-AMPAR encephalitis (Joubert & Honnorat, 2015), suggesting a possible neuronal loss in these patients. However, neuropathological data to support this hypothesis are lacking.

Patients' CSF specifically decreases the number of AMPAR and alter their synaptic localization in cultured neurons. This effect is reversible upon removal of antibodies (Lai *et al.*, 2009). *In vitro*, patients' AMPAR antibodies do not seem to alter other components of glutamatergic synapses, or excitatory synapse density or cell viability (Lai *et al.*, 2009; Peng *et al.*, 2015). Cross-linking assay using patients' F(ab) fragment antibodies or full patient antibodies have not been published and the mechanisms leading to this AMPAR internalization have not yet been demonstrated. Functionally, patients' AMPAR antibodies specifically alter AMPAR-mediated synaptic transmission, as demonstrated by the reduction of amplitude and frequency of excitatory current recordings in cultured neurons treated with patients' CSF (Gleichman *et al.*, 2014; Peng *et al.*, 2015). Interestingly, patients' AMPAR antibodies also reduced inhibitory currents and increased neuronal excitability in cultured neurons, suggesting a compensatory decrease of inhibitory synaptic strength leading to a homeostatic increase in intrinsic neuronal excitability to counteract the effects of patients' AMPAR antibodies (Peng *et al.*, 2015). This imbalance between excitatory and inhibitory transmission has been suggested to account for seizures observed in some patients suffering from AMPAR encephalitis (Peng *et al.*, 2015). No published *in vivo* experimental data are available regarding a possible role of patients' AMPAR antibodies.

To summarize, contrary to anti-NMDAR encephalitis patients, the clinical presentations of anti-AMPAR encephalitis are more variable. This heterogeneity could reflect a wider diversity of pathological mechanisms in anti-AMPAR encephalitis that remains to be elucidated. While *in vitro* data strongly suggest a possible direct pathological effect of patients' AMPAR antibodies, the proof of their pathogenicity remains lacking and other immune factors such as T-cells or some cytokines could be also involved in the pathogenesis.

Encephalitis associated with antibodies directed against the $GABA_AR$

Clinical presentation

$GABA_AR$ antibodies have been recently described in patients with encephalitis and refractory seizures or status epilepticus (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014; Pettingill *et al.*, 2015). Two subgroups of patients can be differentiated based on immunological and clinical criteria. The first group presents with encephalitis and refractory seizures and high titres of serum and CSF $GABA_AR$ antibodies. The second group presents with diverse clinical features (encephalitis with seizures, stiff-person syndrome and opsoclonus–myoclonus) and low titres of $GABA_AR$ antibodies present only in the serum (Pettingill *et al.*, 2015). No strong tumour association has been reported in this disorder. These initial reports suggest a treatment-responsive disorder but the novelty of this discovery needs certitude regarding treatment response and patient outcome.

Antigen

GABA$_A$Rs belong to the family of heteropentameric ligand-gated ion channels, which also includes the glycine receptor. Various subunit combinations generate structurally and functionally distinct GABA$_A$R subtypes with different pharmacology and channel gating properties (Luscher *et al.*, 2011). Synaptic GABA$_A$Rs are composed of three α subunits (α1–3), two β subunits (β2 or β3) and a single γ2 subunit and mediate most fast inhibitory neurotransmissions in the adult brain (Jacob *et al.*, 2008). Mutations in GABA$_A$R subunits associate with genetic epilepsy syndrome in humans (Macdonald *et al.*, 2010). In patients with encephalitis and high GABA$_A$R anti-body serum titres, the antibodies are mainly of the IgG1 or rarely IgG3 subtype with subunit specificity (α1 or β3 or γ2) (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014; Pettingill *et al.*, 2015). No further epitope mapping has been reported. In patients with low GABA$_A$R antibody serum titre, the antibodies were mainly of the IgM subtype without subunit specificity (Pettingill *et al.*, 2015).

Antibody pathogenicity

Patients with anti-GABA$_A$R encephalitis tend to improve when treated with immunosuppressors and at least in one case clinical improvement was correlated with reduction of GABA$_A$R antibody titre in the serum (Pettingill *et al.*, 2015). Studies linking clinical evolution to CSF antibody titres are still lacking. Patients' CSF and sera reduce the synaptic density of GABA$_A$R when applied to neuronal culture with no effect on other synaptic components (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014; Pettingill *et al.*, 2015). This effect is not mediated by complement activation (Ohkawa *et al.*, 2014; Pettingill *et al.*, 2015). A functional effect of GABA$_A$R anti-bodies on inhibitory synaptic currents *in vitro* has been demonstrated by whole-cell patch clamp (Ohkawa *et al.*, 2014). However, effects of patients' antibodies on extrasynaptic GABA$_A$R are still unclear, with some contradictory data (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014) and there are as yet no *in vivo* studies published on the effect of GABA$_A$R antibodies.

To summarize, the clinical manifestation of encephalitis with anti-GABA$_A$Rs seem to be dependent on the CSF autoantibody titre. *In vitro* data suggest a potential structural and functional effect of the patients' CSF antibodies on their target antigen by a mechanism of antigenic modulation, similar to that demonstrated for other antibodies directed against the ionotropic channel receptor, but this effect must be confirmed by other studies.

Encephalitis associated with antibodies directed against Lgi1

Clinical presentation

Anti-Lgi1 antibodies were initially described in a cohort of patients with 'VGKC-Ab'-associated encephalitis (Shillito *et al.*, 1995; Lai *et al.*, 2010). Indeed, autoantibodies called 'anti-VGKC antibodies' were first described in patients with neuromyotonia, and later in patients with autoimmune limbic encephalitis and Morvan's syndrome (Lee *et al.*, 1998; Buckley *et al.*, 2001). Further studies revealed that the target of these autoantibodies was not the potassium channel itself but other proteins interacting with the channel, namely contactin-associated protein-like 2 (Caspr2) and leucin-rich, glioma inactivated 1 (Lgi1) (Irani *et al.*, 2010; Lai *et al.*, 2010; Lancaster *et al.*, 2011a).

Lgi1 antibodies are predominantly encountered in patients with a clinical picture of autoimmune encephalitis (Lai *et al.*, 2010; Klein *et al.*, 2013; Ohkawa *et al.*, 2013). Age of onset is usually in the sixth decade but can vary from 20 to 80 years (Lai *et al.*, 2010; Shin *et al.*, 2013; Malter *et al.*, 2014). Both limbic (anterograde amnesia, behavioural/psychiatric disturbances, seizures) and extra-limbic symptoms (motor, cerebellar, extrapyramidal involvement) can be observed. Epilepsy is found in 80% of the patients and may represent the initial symptom (Lai *et al.*, 2010; Klein *et al.*, 2013; Shin *et al.*, 2013; Malter *et al.*, 2014). Insomnia, paradoxical sleep disorders, severe bradyarrythmias and hyponatraemia are other typical features (Lai *et al.*, 2010; Klein *et al.*, 2013; Kim *et al.*, 2014; Malter *et al.*, 2014). Importantly, abnormal movements called facio-brachial dystonic seizures are closely associated with anti-Lgi1 encephalitis (Irani *et al.*, 2011, 2013). Interestingly, facio-brachial seizures respond only poorly to anti-epileptic drugs, but are highly responsive to immunotherapy (Irani *et al.*, 2011, 2013). Anti-Lgi1 encephalitis seems to be associated with a poor cognitive outcome and frequent evolution to hippocampal atrophy (Malter *et al.*, 2014), but no prospective studies are available. Relapses occur in 10% of patients (Lai *et al.*, 2010; Kim *et al.*, 2014; Malter *et al.*, 2014). Aggressive and prolonged immunotherapy seems important to relieve symptoms and prevent relapses (Irani *et al.*, 2013; Kim *et al.*, 2014). The prevalence of cancers varies among different studies but does not appear to exceed 20% of patients (Irani *et al.*, 2010; Klein *et al.*, 2013; Shin *et al.*, 2013; Malter *et al.*, 2014).

Antigen

Lgi1 is a secreted synaptic protein expressed in neural tissues. It interacts with the synaptic receptors ADAM22 and ADAM23 to create a trans-synaptic complex bridging post-synaptic glutamatergic AMPAR and pre-synaptic Kv1.1 (Fukata *et al.*, 2010). Lgi1 was proposed to act as a regulating factor for neuronal excitability at synapses. Indeed, Lgi1 mutations in humans are related to a hereditary epileptic syndrome (Ottman *et al.*, 1995) and Lgi1-knockout mice develop a phenotype of lethal epilepsy (Fukata *et al.*, 2010). Anti-Lgi1 antibodies are of the IgG4 type, as demonstrated by subclass-specific staining (Irani *et al.*, 2012). The results of epitope mapping performed using patients' serum antibodies suggest that different parts of the protein are recognized by these antibodies (Ohkawa *et al.*, 2013).

Antibody pathogenicity

The clinical symptoms of anti-Lgi1 encephalitis suggest CNS hyper-excitability, similar to what is reported in Lgi1 genetic deletion models (human hereditary epileptic syndrome and mutant mice), suggesting that patients' antibodies may alter Lgi1 functions leading to neuronal hyperexcitability. *In vitro*, Lgi1 antibodies were shown to impair Lgi1 binding to ADAM22 and to decrease surface expression of post-synaptic AMPAR in a reversible and dose-dependent manner (Ohkawa *et al.*, 2013). Although anti-Lgi1 antibodies are mainly of the IgG4 subtype (Irani *et al.*, 2012) and thus unlikely to fix complement, deposition of complement on neuronal membranes has been demonstrated in the brain of patients with anti-Lgi1 encephalitis, suggesting the involvement of complement-dependent cytotoxicity (Bien *et al.*, 2012). Moreover, Lgi1 antibodies fixed complement on the surfaces of Lgi1-transfected cells (Irani *et al.*, 2012). These observations might explain the more frequent occurrence of hippocampal atrophy associated with Lgi1 antibodies compared to other anti-

cell surface antigen antibodies associated with autoimmune encephalitis, such as anti-NMDAR or anti-Caspr2 antibodies. No *in vivo* experimental data arguing for Lgi1 antibody pathogenicity are available.

Encephalitis associated with antibodies directed against Caspr2

Clinical-resentation

Anti-Caspr2 antibodies (Caspr2 Abs) were initially described in eight 'VGKC Ab' patients with encephalitis and/or peripheral nervous system symptoms (Shillito *et al.*, 1995; Irani *et al.*, 2010). Caspr2 Abs correlate with the presence of peripheral symptoms, mostly neuromyotonia and Morvan's syndrome (Shillito *et al.*, 1995; Irani *et al.*, 2010; Lancaster *et al.*, 2011a; Klein *et al.*, 2013). By definition, CNS involvement is excluded in patients with pure neuromyotonia. Morvan's syndrome, by contrast, is a rare autoimmune disorder presenting neuromyotonia features together with marked dysautonomic symptoms (profuse sweating, tachycardia, genito-urinary dysfunction), complete disruption of sleep organization and encephalopathy (visual hallucinations, delusion and impaired vigilance) (Irani *et al.*, 2012). Caspr2 Abs are found in most of Morvan's syndromes, either alone or with moderately elevated anti-Lgi1 Abs (Irani *et al.*, 2012; Ohkawa *et al.*, 2013). Nevertheless, Caspr2 Abs can also be found in patients with pure limbic encephalitis, whose specific clinical pattern and prognosis remain to be precisely determined (Lancaster *et al.*, 2011a; Malter *et al.*, 2014). Differences in epitope specificities and location of the production of autoantibodies have been hypothesized to account for such a variety of clinical presentations. An associated malignant thymoma is observed in more than 50% of Caspr2 Ab-positive neuromyotonia/Morvan's syndrome patients (Irani *et al.*, 2012), while the prevalence of tumours is much lower in patients with pure limbic encephalitis (Lai *et al.*, 2010; Klein *et al.*, 2013; zShin *et al.*, 2013; Malter *et al.*, 2014). Patients with Caspr2 Ab-associated syndrome seem to have low titre of multiple autoantibodies such as Lgi1 Abs, anti-DCC or anti-DPP10 antibodies (Ohkawa *et al.*, 2013). The pathogenic role of these antibodies has not yet been evaluated.

Antigen

Caspr2 is a membrane cell adhesion molecule that clusters voltage-gated potassium channels (Kv1.1/1.2) at the juxtaparanodes of myelinated axons and may regulate axonal excitability (Poliak, 2003; Labasque & Faivre-Sarrailh, 2010). Experimental findings suggest that Caspr2 may also be present in the CNS at pre-synaptic sites where it may interact with the pre-synaptic Kv1 channels (Zweier *et al.*, 2009). Caspr2 was also suggested to play a role in synapse formation and dendritic arborization (Labasque & Faivre-Sarrailh, 2010). Polymorphisms of the CASPR2 gene (CNTNAP2) have notably been described in the autistic spectrum disorders (Anderson *et al.*, 2012).

Antibody pathogenicity

A recent *in vitro* study, using Caspr2 Abs from patients affected by pure limbic encephalitis, determined that Caspr2 Abs from patients' CSF mainly recognize the N-terminal Discoïdin and LaminiG1 modules of Caspr2 and strongly target inhibitory interneurons (Pinatel *et al.*, 2015). Functional assays indicated that limbic encephalitis with Caspr2 Abs may induce

alteration of Gephyrin clusters at inhibitory synaptic contacts (Pinatel *et al.*, 2015). This work provides new insight into the potential pathogenic effect of Caspr2 Abs in central hyperexcitability that may be related to perturbation of inhibitory interneuron activity. However, *in vivo* studies are still lacking to assess the potential pathogenic effects of Caspr2 Abs according to the different associated clinical presentations.

To conclude, despite the overlap of clinical syndromes, neurological symptoms specific to Lgi1 or Caspr2 Abs begin to emerge, but further work is needed to understand the exact role of the respective autoantibodies (Table 1).

Encephalitis associated with antibodies directed against $GABA_BR$

Clinical presentation

Antibodies against $GABA_BR$ were described in an initial series of 15 patients (Lancaster *et al.*, 2010) and subsequently followed by several case series (Boronat *et al.*, 2011; Höftberger *et al.*, 2013b; Jeffery *et al.*, 2013; Kim *et al.*, 2014). Patients with $GABA_BR$ antibodies usually present a pure limbic encephalitis with prominent severe seizures or status epilepticus (Lancaster *et al.*, 2010; Höftberger *et al.*, 2013b). Other rare clinical presentations such as opsoclonus–myoclonus or cerebellar ataxia have also been described (Lancaster *et al.*, 2010; Höftberger *et al.*, 2013b; Jarius *et al.*, 2013; Defelipe-Mimbrera *et al.*, 2014). About 50% of patients with $GABA_BR$ antibodies present an underlying small-cell lung carcinoma (Höftberger *et al.*, 2013b). In this paraneoplastic subgroup, the median age of patients is higher (around 60 years) with a shorter overall survival (Höftberger *et al.*, 2013b). Almost all patients achieve partial to complete neurological recovery with immunotherapy and appropriate oncological treatment (Lancaster *et al.*, 2010; Höftberger *et al.*, 2013b; Jeffery *et al.*, 2013; Kim *et al.*, 2014). As observed with anti-NMDAR encephalitis, recovery might be improved using more aggressive immunotherapy targeting B-cells and antibody production (e.g. rituximab) (Kim *et al.*, 2014). Interestingly, as observed in patients with $GABA_AR$ antibodies, a subset of patients with low titres of $GABA_BR$ antibodies in the serum or the CSF and with heterogeneous clinical syndrome has also been described (Lancaster *et al.*, 2010; Jeffery *et al.*, 2013). These patients present with additional antibodies (CV2/CRMP5, ANNA-1 or ANNA-3) revealing a larger antineuronal immunization and their prognosis is less favourable in spite of treatment (Jeffery *et al.*, 2013).

Antigen

The $GABA_BRs$ are transmembrane metabotropic G-protein coupled receptors that trigger cAMP cascades and thereby regulate specific ion channel properties. $GABA_BRs$ have been found to play a key role in regulating membrane excitability and synaptic transmission in the brain. Indeed, they can stimulate the opening of K^+ and Ca^{2+} channels and elicit both presynaptic and slow postsynaptic inhibition (Benarroch, 2012; Gassmann & Bettler, 2012). $GABA_BR$ is an obligatory heterodimer formed by 2 subunits ($GABA_B1$ and $GABA_B2$) (Bettler, 2004; Gassmann & Bettler, 2012). Patients' antibodies target the $GABA_B1$ subunit and are mainly of the IgG1 subtype, but IgG2 and IgG3 also occur (Lancaster *et al.*, 2010). Failure of $GABA_BR$ detection by patient antibody in immunoblots suggests that the

antibodies are directed against a conformational epitope (Höftberger *et al.*, 2013b). Recent deletion mapping experiments suggest that patients' anti-$GABA_BR$ antibodies bind to alternatively spliced Sushi domains present in the presynaptically localized $GABA_B1A$ isoform (Jain *et al.*, 2015).

Antibody pathogenicity

Aside from the good neurological outcome under immunosuppressive treatment, no *in vivo* experimental data are available on the direct neuronal pathogenicity of $GABA_BR$ antibodies. However, the above *in vitro* experiments by Jain *et al.* (2015) showed that patients' anti-$GABA_BR$ antibodies block baclofen-mediated activation of the $GABA_BR$ without decreasing $GABA_BR$ surface expression. These data suggest that anti-$GABA_BR$ antibodies interfere with GABA-mediated inhibition, thereby contributing to seizures.

Encephalomyelitis associated with antibodies directed against the glycine receptor

Clinical presentation

Glycine receptor (GlyR) antibodies were first described in association with progressive encephalomyelitis rigidity and myoclonus (Hutchinson *et al.*, 2008). Stiff-person syndrome (SPS), defined as axial rigidity with or without hyperreflexia and/or autonomic disturbances (Ciccotto *et al.*, 2013), progressive encephalomyelitis with rigidity and myoclonus (PERM or SPS with brainstem involvement) are the most common clinical presentations of patients with GlyR antibodies (McKeon *et al.*, 2013; Carvajal-González *et al.*, 2014). However, a strong phenotypic association is lacking, because GlyR antibodies could also be associated with demyelinating phenotypes including optic neuritis (Woodhall *et al.*, 2013; Martinez-Hernandez *et al.*, 2015). SPS and PERM symptoms are acute or subacute in 70% of cases (Carvajal-González *et al.*, 2014). In the largest described cohort of patients, median age at symptom onset was 50 years (range: 1–75 years) with equal male/female presence (Carvajal-González *et al.*, 2014). Contrary to patients with GlyR antibody-negative SPS/PERM, antibody-positive patients improved markedly with symptomatic treatment and immunotherapy (McKeon *et al.*, 2013; Carvajal-González *et al.*, 2014) although relapses and relapsing/remitting courses are frequent (Carvajal-González *et al.*, 2014). Associated tumours (mainly thymoma and lymphoma, but also malignant melanoma and metastatic breast cancer) have been reported in a few patients (Clerinx *et al.*, 2011; McKeon *et al.*, 2013; Bourke *et al.*, 2014; Carvajal-González *et al.*, 2014). A clear causality link is lacking and the majority of cases are not paraneoplastic.

Antigen

GlyRs are chloride pentameric channels composed of a variable arrangement of α and β subunits (Legendre, 2001; Betz & Laube, 2006). GlyRs are distributed mainly in the spine and brainstem and have a prominent role in the inhibitory modulation of motor, visual, auditory and autonomic networks (Lynch, 2004; Dutertre *et al.*, 2012). GlyR antibodies are predominantly of the IgG1 subclass, intrathecally synthesized and directed against an

extracellular epitope on the GlyRα subunit, probably common to the three isoforms of the subunit (Carvajal-González *et al.*, 2014).

Antibody pathogenicity

GlyR antibody titres in serum and CSF may correlate with the clinical course (Hutchinson *et al.*, 2008; Iizuka *et al.*, 2012). In one case, rituximab treatment (anti-CD20 antibody) led to a marked clinical improvement, suggesting a B-cell-mediated pathology. Interestingly, an increase in CSF GABA levels and a decrease in glutamate level suggestive of a compensatory mechanism have been reported in one patient (Carvajal-González *et al.*, 2014). Recently, the ability of patients' GlyR antibodies to induce GlyR internalization in HEK-transfected cells was reported (Carvajal-González *et al.*, 2014), but no *in vivo* experimental data arguing for GlyR antibody pathogenicity are available.

Other autoimmune encephalitis associated with pathogenic antibodies

Encephalitis associated with antibodies directed against mGluR5

Four patients with limbic encephalitis and antibodies against mGluR5 were recently described (Lancaster *et al.*, 2011b; Mat *et al.*, 2013; Pruss *et al.*, 2014). All presented with pure limbic encephalitis. This syndrome was previously described and named Ophelia syndrome by Carr (1982). The first described patients with mGluR5 antibodies were three patients with Hodgkin's lymphoma (Lancaster *et al.*, 2011b; Mat *et al.*, 2013), but no tumour was observed in a recently published case (Pruss *et al.*, 2014). Patients appear to respond well to immunosuppressive treatment (Lancaster *et al.*, 2011b; Mat *et al.*, 2013; Pruss *et al.*, 2014) and this recovery correlates with serum antibody titre reduction (Pruss *et al.*, 2014), indirectly arguing for a link between mGluR5 antibodies and pathogenicity. However, no *in vitro* or *in vivo* experimental data on the effect of mGluR5 antibodies have been reported.

Encephalitis associated with antibodies directed against DPPX

Antibodies against dipeptidyl-peptidase-like protein X (DPPX) (DPP6), an accessory subunit of Kv4.2 potassium channels, were detected in four patients with hallucinations and confusion associated with symptoms reflecting CNS hyperexcitability (e.g. myoclonus, tremor, hyperekplexia and seizures) (Boronat *et al.*, 2013). Subsequently, three additional patients with anti-DPPX antibodies were reported with a syndrome resembling PERM (Balint *et al.*, 2014). Until today, 21 patients with this disorder have been described (Tobin *et al.*, 2014; Piepgras *et al.*, 2015). Interestingly, half of the reported encephalitic patients with anti-DPPX had prominent gastrointestinal symptoms, mainly severe diarrhoea, but also constipation (Boronat *et al.*, 2013; Balint *et al.*, 2014; Tobin *et al.*, 2014). DPPX is a membrane glycoprotein that critically determines the conductance of neuronal Kv4.2 channels and thus regulates membrane excitability (Kim *et al.*, 2008; Kaulin *et al.*, 2009). DPPX expression is spread in the hippocampus, striatum and cerebellum, and remarkably in the myenteric plexus, which may explain the characteristic gastrointestinal symptoms of anti-DPPX encephalitis. DPPX-knockout mice have hyperexcitability of CNS neurons (Boronat *et al.*, 2013; Balint *et al.*, 2014). Recently, it was observed that patients' purified IgG reduced expression of DPPX and Kv4.2 channels on hippocampal neurons and demonstrated a significantly increased activity of enteric neurons after application of anti-

DPPX sera to myenteric plexus preparations (Piepgras *et al.*, 2015). These *in vitro* data suggest that downregulation of DPPX and Kv4.2 by a patient's anti-DPPX antibodies results in CNS and enteric neuron hyperexcitability, which may underlie the neuropsychiatric and gastrointestinal manifestations of anti-DPPX encephalitis. Therefore, these first *in vitro* data support a pathogenic role of anti-DPPX antibodies in this newly identified autoimmune encephalitis.

CNS syndromes associated with antibodies directed against amphiphysin

Amphiphysin antibodies were first described in patients with paraneoplastic SPS (Camilli *et al.*, 1993), although they can also be found in other neurological manifestations such as limbic encephalitis, dysautonomia and cerebellar dysfunction (Pittock *et al.*, 2005; Moon *et al.*, 2014). Classically, patients with SPS and anti-amphiphysin antibodies are female with a median age at symptom onset around 60 years and associated breast cancer (Murinson & Guarnaccia, 2008). These patients improve with immunotherapy and tumour removal (Murinson & Guarnaccia, 2008). An underlying tumour (lung cancer, ovarian cancer, gastric cancer) can also be found in some cases of non-SPS associated with amphiphysin antibodies and some clinical improvement can be achieved through immunotherapy (Moon *et al.*, 2014). Amphiphysin is an intracellular synaptic vesicle protein (Lichte *et al.*, 1992) involved in clathrin-mediated endocytosis. Alteration of GABAergic neurotransmission induced by patients' anti-amphiphysin antibodies has been reported (Geis *et al.*, 2010). Moreover, transfer of amphiphysin antibodies from patients to rodents causes stiffness and muscle spasms (Sommer *et al.*, 2005). Taken together, these data suggest that amphiphysin antibodies might be pathogenic although the mechanisms of antibody action on their intracellular target remain unknown.

Encephalitis and cerebellitis associated with antibodies directed against glutamate decarboxylase (GAD)

Clinical presentation

GAD autoantibodies associated with neurological syndromes were initially described by Solimena *et al.* (1988). Several neurological syndromes have been described in association with high titres of GAD autoantibodies, including SPS, cerebellar ataxia, epilepsy and limbic encephalitis (Saiz *et al.*, 2008; Ali *et al.*, 2011; Alexopoulos & Dalakas, 2013; Fouka *et al.*, 2015; Gresa-Arribas *et al.*, 2015). While GAD autoantibodies are generally not associated with cancer, they can occur as a paraneoplastic event (Saiz *et al.*, 2008; Ariño *et al.*, 2015). Patients with limbic encephalitis associated with GAD autoantibodies usually do not respond well to treatment (Malter *et al.*, 2010). Patients with cerebellar ataxia are mainly women with a median age around 55 years (Ariño *et al.*, 2014). Clinical presentation is insidious or subacute (Honnorat *et al.*, 2001; Ariño *et al.*, 2014) with the most common presenting symptom being gait ataxia, followed by limb ataxia, dysarthria and nystagmus (Ariño *et al.*, 2014). In contrast to limbic encephalitis patients, good outcome (modified Rankin scale < 3) with immunotherapy has been reported in 50% of patients with cerebellar ataxia (Ariño *et al.*, 2014). Finally, patients with SPS associated with GAD antibodies

appear to have the best probability of clinical improvement compared to patients who developed another GAD-associated neurological syndrome (Ariño *et al.*, 2015).

Antigen

GAD is the rate-limiting enzyme implicated in the synthesis of GABA, which is the major inhibitory neurotransmitter in the CNS (Buddhala *et al.*, 2009). Two isoforms of GAD (65 and 67 kDa) are expressed predominantly in the brain. GAD-65 can be found concentrated in presynaptic terminals and appears to be the dominant target of patients' autoantibodies that seem to recognize mainly the decarboxylase catalytic domain of GAD-65 (Gresa-Arribas *et al.*, 2015). Although GAD-65 is an intracellular enzyme, it has been suggested that autoantibodies may interact with their target during the synaptic release event (Gresa-Arribas *et al.*, 2015). GAD-65 antibody titres are significantly higher in patients with cerebellar ataxia than in patients with SPS associated with GAD antibodies (Gresa-Arribas *et al.*, 2015). Notably, GAD autoantibodies present in patients with SPS and cerebellar ataxia recognize an epitope distinct from that recognized by GAD autoantibodies present in patients with type 1 diabetes mellitus or limbic encephalitis (Manto *et al.*, 2015), arguing for GAD-65 antibodies recognizing disease-specific epitopes.

Antibody pathogenicity

In vitro and *in vivo* experiments with purified IgGs of patients with GAD-65 autoantibodies and SPS or cerebellar ataxia further supported the hypothesis that GAD-65 autoantibodies target and inhibit GAD-65 function in these diseases (Manto *et al.*, 2007, 2011b; Holmøy & Geis, 2011; Hampe *et al.*, 2013; Hansen *et al.*, 2013). Moreover, the administration of a monoclonal GAD-65 antibody directed against the epitope recognized by SPS patients disrupted *in vitro* the association of GAD with GABAergic synaptic vesicles and depressed the inhibitory synaptic transmission in cerebellar slices (Manto *et al.*, 2015). *In vivo*, this monoclonal antibody induced decreased exploratory behaviour and impaired locomotor function in rats (Manto *et al.*, 2007, 2015). These findings support a specific pathological role of GAD-65 autoantibodies in the pathogenesis of SPS and cerebellar ataxia. In contrast, no effect of GAD-65 antibodies from a patient with limbic encephalitis was observed *in vitro* on GABAergic neurotransmission (Stemmler *et al.*, 2015).

To summarize, numerous evidence suggests a direct role of GAD-65 antibodies in some associated neurological syndromes, but the antibodies may not always play a direct role. Differences in epitope specificities according the neurological syndromes may explain at least in part the spectrum of anti-GAD-associated neurological disorders (Mitoma *et al.*, 2016). Strong experimental evidence exists in favour of a pathogenic effect of GAD-65 antibodies in SPS and cerebellar ataxia.

Cerebellitis associated with antibodies directed against mGluR1

Clinical presentation

Since their first description in 2000, mGluR1 autoantibodies have been reported in five patients with cerebellitis. All patients experienced severe cerebellar ataxia with balance and gait disturbances, dysarthria and nystagmus. In two cases, mGluR1 cerebellitis was

associated with a Hodgkin's lymphoma (Sillevis Smitt *et al.*, 2000) and in one case with a prostate adenocarcinoma (Iorio *et al.*, 2013). In the two remaining published cases, no underlying tumours were found in spite of an extensive examination (Marignier *et al.*, 2010; Lancaster *et al.*, 2011b), raising the hypothesis of a 'primary' autoimmune-mediated disorder for which mechanisms leading to cross-reactivity remain unknown. Treatment allows only limited recovery (Sillevis Smitt *et al.*, 2000; Marignier *et al.*, 2010; Lancaster *et al.*, 2011b; Iorio *et al.*, 2013) (Fig. 2).

Antigen

mGluR1 is a metabotropic glutamate receptor localized postsynaptically in somatodendritic domains and strongly expressed in hippocampus and cerebellum (Martin *et al.*, 1992). In Purkinje cells, mGluR1 is critically involved in long-term depression (LTD) and motor coordination (Ichise *et al.*, 2000). Interestingly, mGluR1-knockout mice exhibit cerebellar symptoms and impaired cerebellar LTD (Aiba *et al.*, 1994). A role for mGluR1 in eye response movement adaption has also been reported (Shutoh *et al.*, 2002). The mGluR1 epitope is located extracellularly as indicated by the detection of patients' antibodies in cell-based assay experiments, but no further epitope mapping has yet been published. Although there is a strong sequence homology between mGluR1 and other members of the mGluR family (for instance mGluR5), antibodies do not cross-react (Lancaster *et al.*, 2011b). The IgG subtypes of patient antibodies have not been reported.

Antibody pathogenicity

The rarity of the disease does not allow a conclusion to be made regarding a pathogenic role of the associated autoantibody. Interestingly, antibodies to Homer-3, which co-localizes with and organizes mGluR1 at synapses in the dendritic spines of the Purkinje cells, have been reported in two exceptional patients who presented with clinical symptoms similar to patients with mGluR1-ab antibodies (Zuliani *et al.*, 2007; Höftberger *et al.*, 2013a). In one case of anti-mGluR1 cerebellitis, early immunosuppressive treatment led in one patient to a reduction of mGluR1 antibody titres in serum and CSF and recovery (Sillevis Smitt *et al.*, 2000) but the other described patients developed cerebellar atrophy and responded only partially to treatment (Coesmans *et al.*, 2003; Marignier *et al.*, 2010; Lancaster *et al.*, 2011b; Iorio *et al.*, 2013). In the only reported postmortem study of brain tissue, Purkinje cell loss was observed, suggesting involvement of cytotoxic mechanisms although no cytotoxic $CD8^+$ T-lymphocytes were observed (Coesmans *et al.*, 2003). Patients' antibodies are able to block mGluR1 activation in mGluR1-expressing CHO cells (Sillevis Smitt *et al.*, 2000). Accordingly, slice recordings and whole-cells patch clamp recordings indicate that patients' mGluR1 antibodies reduce Purkinje neuron excitability and spontaneous firing rate (Coesmans *et al.*, 2003). Extracellular bath application onto cultured embryonic Purkinje cells but not intracellular microinjection reduces LTD, further confirming that patients' mGluR1 antibodies are directed against the extracellular part of the receptor and that they can block mGluR1 activation and impair synaptic plasticity (Coesmans *et al.*, 2003). Passive transfer of patients' mGluR1 antibodies into mouse brain provoked transient ataxia and this behavioural effect was abolished by patients' CSF pre-absorption on CHO cells expressing mGluR1α, confirming that this effect was directly caused by mGluR1 IgG (Sillevis Smitt *et al.*, 2000). Moreover, antibody infusion into the flocculus of mice acutely and reversibly

decreases compensatory eye movements in a way similar to the impairment of saccadic eye movements observed in patients (Coesmans *et al.*, 2003). These experimental models provided the ultimate proof of the pathogenicity of patients' mGluR1 antibodies.

To summarize, cerebellitis associated with mGluR1 is an exceptional disorder for which the pathogenicity of the patients' antibodies has been clearly demonstrated. The metabotropic nature of the target of this antibody-mediated neurological disease is unique in this group of autoimmune encephalitides that generally share ion channel dysfunction as a common pathogenesis. Elucidation of the cellular consequences of this singular antibody-mediated metabotropic receptor dysfunction needs further investigation.

Cerebellitis associated with antibodies directed against the VGCC

Antibodies targeting the P/Q-type of the voltage-gated calcium channels (VGCC-Abs) are associated with Lambert-Eaton myasthenic syndrome, cerebellar ataxia or both (Lennon *et al.*, 1995). Cerebellar ataxia associated with VGCC-Abs is essentially paraneoplastic, associated with small cell lung carcinoma expressing functional VGCC (Meriney *et al.*, 1996). The accepted hypothesis for paraneoplastic cases proposes that the immune adapted reaction against the tumour triggers the autoimmune response. VGCC-Ab-associated cerebellar ataxia is usually subacute with symmetrical gait and limb ataxia, dysarthria and nystagmus. However, anti-VGCC cerebellar ataxia may sometimes develop progressively, mimicking idiopathic sporadic late-onset ataxia (Bürk *et al.*, 2010). Patients respond poorly to immunotherapy. This poor response is imputed to the early and diffuse loss of Purkinje cells observed in these patients (Fukuda *et al.*, 2003). In contrast, some case reports suggest that patients with the rare non-paraneoplastic VGCC-Ab-associated cerebellar ataxia may respond well to immunotherapy (Rigamonti *et al.*, 2014). Numerous observations support the hypothesis of a direct pathogenic role of VGCC-Abs in the development of cerebellar ataxia: P/Q-type VGCCs, which are involved in neurotransmitter release in the synaptic cleft (Simms & Zamponi, 2014), are prominent in the cerebellum (Hillman *et al.*, 1991), and mutations of P/Q VGCCs cause ataxia in mice (Hillman *et al.*, 1991; Fletcher & Lennon, 2003). Post-mortem brain examination revealed a diffuse loss of Purkinje cells along with Bergmann's gliosis, with only minor or absent lymphocytic perivascular infiltration (Fukuda *et al.*, 2003), arguing against a major role of cellular immunity. Furthermore, P/Q type VGCC density is decreased by 70–80% in the cerebellum of VGCC-Ab cerebellar ataxia patients compared to control subjects (Fukuda *et al.*, 2003). Indirect experimental arguments were provided by a study using a polyclonal antibody generated against a major epitope in the P/Q-type VGCCs that inhibited VGCC function in neuronal and recombinant VGCCs, altered cerebellar synaptic transmission, and conferred the phenotype of cerebellar ataxia (Liao *et al.*, 2008). More importantly, passive immunization of mice with antibodies from VGCC-Ab cerebellar ataxia patients induced acute ataxia in mice, demonstrating the pathogenic potential of VGCC-Abs (Martín-García *et al.*, 2013). Questions remain concerning the variability of the clinical manifestations associated with VGCC-Abs between patients. Differences in the production site of VGCC-Abs and in antibody epitope specificities may provide an explanation for this variability.

Cerebellitis associated with antibodies directed against Tr/DNER

Anti-Tr/Delta/notch-like epidermal growth factor-related receptor (DNER) antibodies are associated with paraneoplasic cerebellar degeneration and Hodgkin's lymphoma (Graus *et al.*, 1997; de Graaff *et al.*, 2012; Greene *et al.*, 2014). More than 40 patients have been reported with symptoms typically including progressive nystagmus, limb ataxia, dysarthria and gait ataxia (Trotter *et al.*, 1976; Graus *et al.*, 1997; Bernal *et al.*, 2003; de Graaff *et al.*, 2012; Greene *et al.*, 2014; Probst *et al.*, 2015). Even with successful Hodgkin disease treatment, ataxia correlated with cerebellar atrophy is irreversible in many patients (de Graaff *et al.*, 2012). DNER, the actual target antigen of anti-Tr antibodies, is a CNS-specific Notch ligand transmembrane protein expressed on Purkinje cells (de Graaff *et al.*, 2012). During development, DNER is involved in the crucial interaction between Purkinje cells and Bergmann's glia (Eiraku *et al.*, 2005). Anti-Tr/DNER antibodies are mainly of the IgG1 and IgG3 subclass (Bernal *et al.*, 2003) and intrathecally produced (Graus *et al.*, 1997). Their main epitopes have been mapped to an N-glycosylated extracellular region of DNER (de Graaff *et al.*, 2012). While it is plausible that DNER antibodies act by disrupting DNER-Notch signalling, this remains to be confirmed. Thus, proof of the pathogenicity of anti-DNER antibodies is still lacking and the exact pathogenic mechanisms of this disorder remain to be demonstrated.

Conclusions

The rapidly expanding types of autoimmune encephalitis have stimulated fruitful clinical and fundamental investigations, aiming to specify the role of the autoantibodies associated with these disorders (Table 1). Interestingly, some of these autoantibodies, in general targeting ionotropic channels or their partner proteins, define clinical syndromes that resemble the models of pharmacological or genetic disruption of the corresponding antigen, arguing for a pathogenic role of the associated autoantibodies. Different studies have shown that patients' antibodies may have structural and functional *in vitro* effects on the targeted antigens. However, definitive proof of the pathogenicity of these autoantibodies has been obtained for only a few antibodies by passive transfer experiments in murine models reproducing the human disease symptoms. Examples for autoantibodies with a direct effect are mGluR1R, NMDAR, amphiphysin, VGCC and GAD-65 antibodies. However, although strong evidence points toward a dysfunction of the targeted antigen's signalling and the synaptic apparatus that regulates it, the molecular cascades and cellular dynamics by which these autoantibodies induce pathological processes remain often poorly understood. In diseases for which no direct pathogenic role for associated autoantibodies has been demonstrated, patients often show great variability of the clinical presentations, which may possibly reflect a more complex pathogenicity. In these cases, the autoantibodies may serve as disease biomarkers and for characterization of the involvement of the immune system in the disease. However, they may present only one factor among other immune agents. Further clinico-biological correlation and experimental investigations will be necessary to understand the mechanisms of the underlying immune reaction.

Finally, these autoimmune encephalitides offer unique models of brain–immune interactions in which the targeted antigens have critical roles in synaptic transmission and plasticity.

Therefore, studies of the role of each associated autoantibody should open new avenues to understand the molecular mechanisms of some neurological and psychiatric disorders. These rare diseases with specific antibodies may provide novel experimental tools to decipher the role of the targeted synaptic proteins and their involvement in neurological and psychiatric dysfunctions observed in patients.

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Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ATD	amino-terminal domain
Caspr2	contactin-associated protein-like 2
CNS	central nervous system
CRMP5	collapsin response mediator protein 5
CSF	cerebrospinal fluid
DNER	Delta/notch-like epidermal growth factor-related receptor
DPPX	dipeptidyl-peptidase-like protein X
EPHB2R	ephrin B2 receptor
GABA	γ-aminobutyric acid
GAD	glutamate decarboxylase
GlyR	glycine receptor
iGluR	ionotropic glutamate receptor
Lgi1	leucine-rich glioma inactivated 1
LTD	long-term depression
LTP	long-term potentiation
mEPSC	miniature excitatory post-synaptic current
mGluR	metabotropic glutamate receptor
mIPSC	miniature inhibitory post-synaptic current
NMDA	*N*-methyl-D-aspartate

PERM	progressive encephalomyelitis with rigidity and myoclonus
PNS	paraneoplastic neurological syndrome
SPS	stiff-person syndrome
VGCC	voltage-gated calcium channel
VGKC	voltage-gated potassium channel

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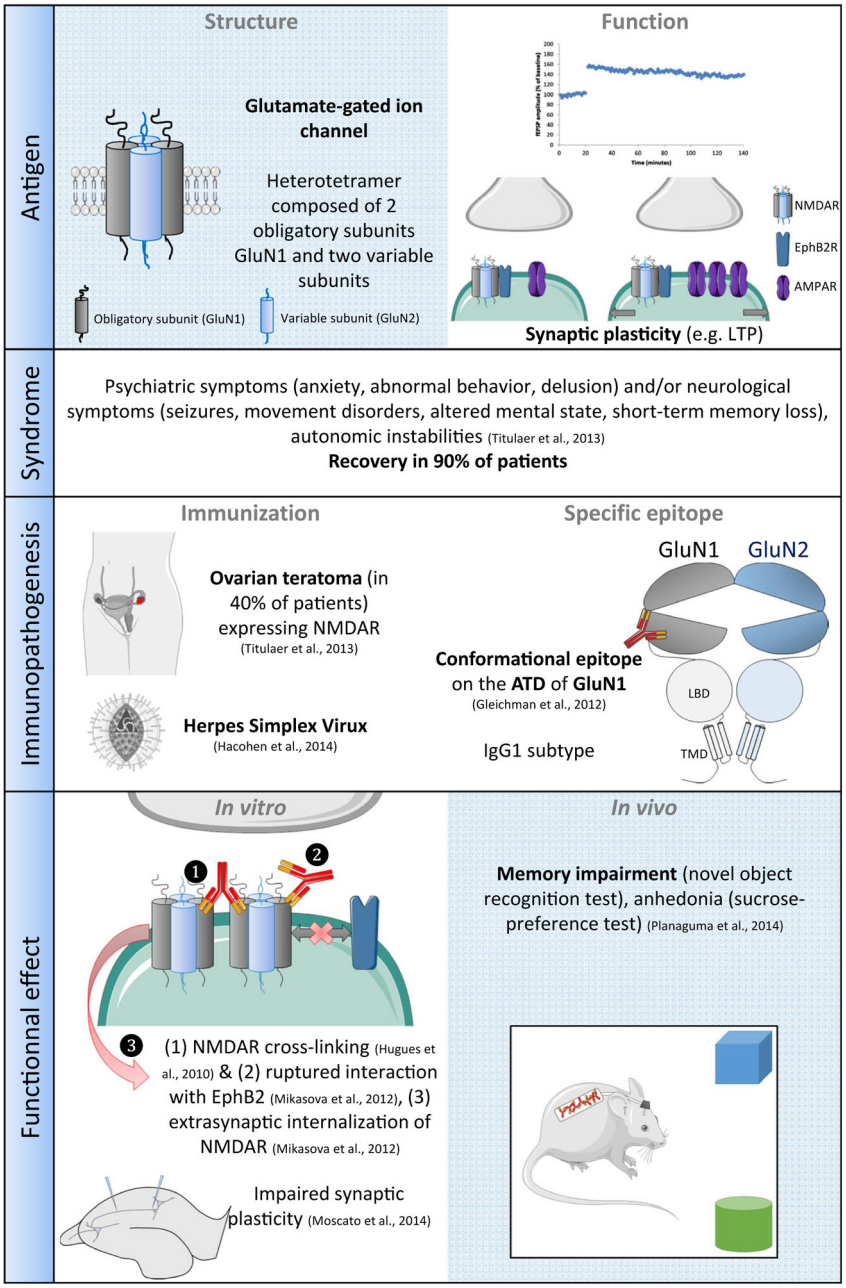

Fig. 1.
Example of encephalitis associated with anti-NMDAR autoantibodies.

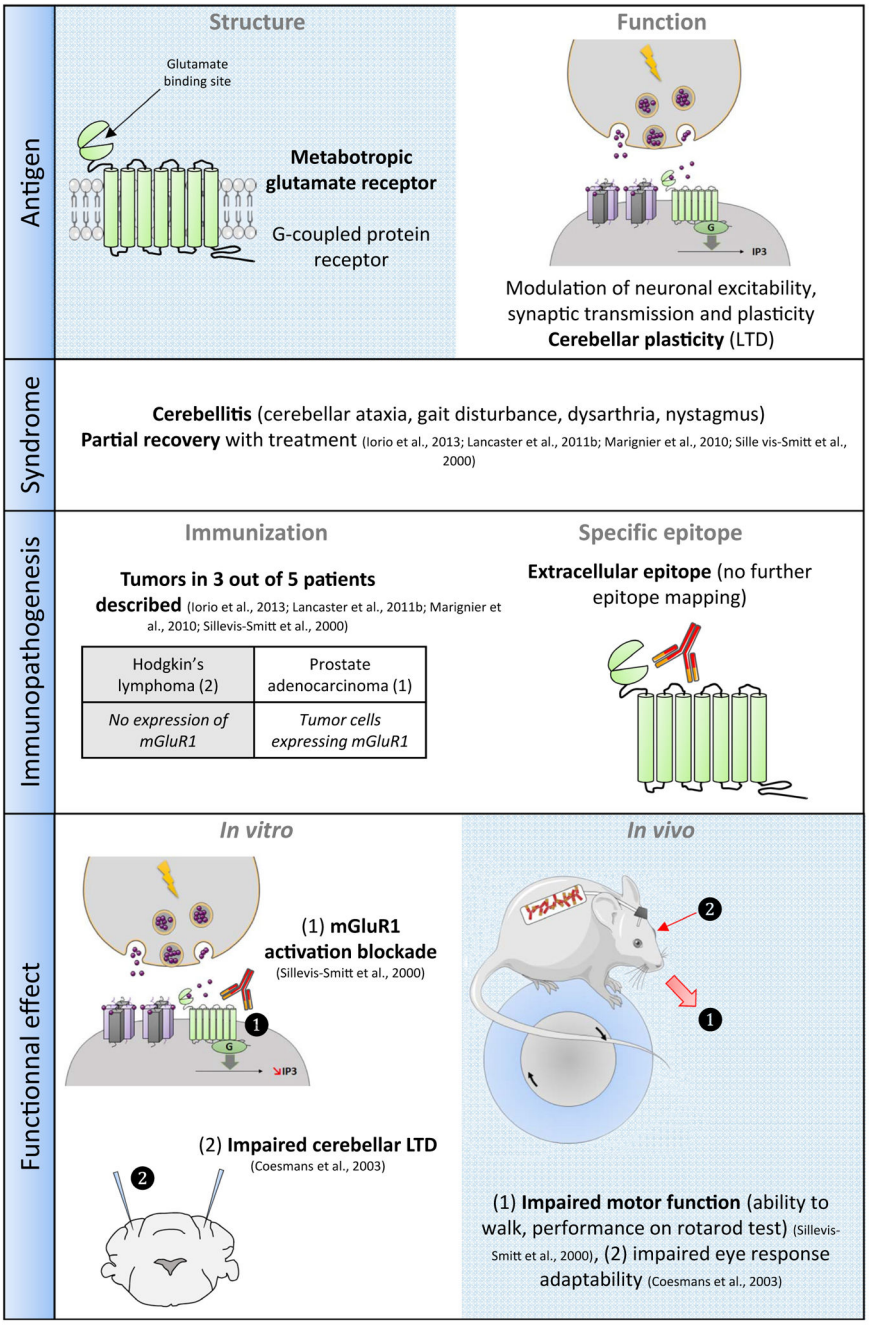

Fig. 2.
Example of cerebellitis associated with anti-mGluR1 autoantibodies.

Table 1

Main autoantibodies suspected to play a direct role in neurological symptoms

Antigen	Nature of the antigen	Number of described cases	Clinical syndrome	Tumour association	Described mechanisms
NMDAR	Ionotropic Glutamate Receptor	> 500 (Titulaer *et al.*, 2013)	Psychiatric symptoms (anxiety, abnormal behaviour, delusion) and/or neurological symptoms (seizures, movement disorders, altered mental state, short-term memory loss), autonomic instabilities (Titulaer *et al.*, 2013).	Age-dependent, up to 40% (ovarian teratoma) in young women (Titulaer *et al.*, 2013)	Antibodies disrupt NMDAR function by cross-linking and internalization of receptors (Hughes *et al.*, 2010; Mikasova *et al.*, 2012). *In vitro:* reduced surface expression (Hughes *et al.*, 2010), disrupted interaction with EphB2R (Mikasova *et al.*, 2012). *In vivo:* hyperactivity of glutamatergic pathway (Manto *et al.*, 2010), reduced number of NMDAR clusters (Hughes *et al.*, 2010), impaired memory and depression-like behaviour (Planaguma *et al.*, 2014).
AMPAR	Ionotropic Glutamate Receptor	≈58 (Lai *et al.*, 2009; Bataller *et al.*, 2010; Graus *et al.*, 2010; Wei *et al.*, 2013; Gleichman *et al.*, 2014; Spatola *et al.*, 2014; Hoftberger *et al.*, 2015; Joubert *et al.*, 2015)	Four distinct clinical presentations: classical limbic encephalitis, diffuse encephalitis, fulminant encephalitis, psychiatric presentation (Hoftberger *et al.*, 2015; Joubert *et al.*, 2015)	34% (thymus, breast, lung)	*In vitro:* antibody-induced internalization of AMPAR (Lai *et al.*, 2009; Peng *et al.*, 2015), reduced excitatory transmission (Gleichman *et al.*, 2014).
mGluR1	Metabotropic Glutamate Receptor	5 (Sillevis Smitt *et al.*, 2000; Marignier *et al.*, 2010; Lancaster *et al.*, 2011b; Iorio *et al.*, 2013)	Cerebellitis with cerebellar ataxia, balance and gait disturbances, dysarthria and nystagmus	2 cases with Hodgkin's lymphoma (Sillevis Smitt *et al.*, 2000), 1 case with prostate adenocarcinoma (Iorio *et al.*, 2013)	*In vitro:* blockage of mGluR1 activation (Sillevis Smitt *et al.*, 2000), reduced cerebellar LTD (Coesmans *et al.*, 2003). *In vivo:* severe but transient ataxia induced by patients' IgG infusion in mice (Sillevis Smitt *et al.*, 2000), impaired compensatory eye movement (Coesmans *et al.*, 2003).
mGluR5	Metabotropic Glutamate Receptor	4 (Lancaster *et al.*, 2011b; Mat *et al.*, 2013; Pruss *et al.*, 2014)	Limbic encephalitis	3 cases with Hodgkin's lymphoma (Lancaster *et al.*, 2011b; Mat *et al.*, 2013)	No experimental study available.
$GABA_AR$	Ligand-gated ion Channel	≈35 (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014; Pettingill *et al.*, 2015)	Encephalitis with refractory seizures	2 cases with thymoma (Ohkawa *et al.*, 2014), 1 case with a neuroepithelial tumour (Pettingill *et al.*, 2015)	*In vitro:* reduction of $GABA_AR$ synaptic density (Ohkawa *et al.*, 2014; Petit-Pedrol *et al.*, 2014; Pettingill *et al.*, 2015), reduced inhibitory currents (Ohkawa *et al.*, 2014).
$GABA_BR$	Metabotropic Receptor	≈67 (Lancaster *et al.*, 2010; Boronat *et al.*, 2011; Höftberger *et al.*, 2013a,b; Jeffery *et al.*, 2013; Kim *et al.*, 2014)	Limbic encephalitis with prominent seizures	50% (small-cell lung cancer) (Höftberger *et al.*, 2013a,b)	*In vitro*: blockage of $GABA_BR$ activation by baclofen without decrease of surface $GABA_BRs$ (Jain *et al.*, 2015)

Antigen	Nature of the antigen	Number of described cases	Clinical syndrome	Tumour association	Described mechanisms
GlyR	Chloride pentameric channel	≈77 (Hutchinson *et al.*, 2008; Clerinx *et al.*, 2011; Mas *et al.*, 2011; Turner *et al.*, 2011; Iizuka *et al.*, 2012; Damásio *et al.*, 2013; Kyskan *et al.*, 2013; McKeon *et al.*, 2013; Carvajal-González *et al.*, 2014; Kenda *et al.*, 2015; Bourke *et al.*, 2014; Carvajal-González *et al.*, 2014)	Stiff-person syndrome & progressive encephalomyelitis with rigidity and myoclonus	≈20% (thymoma, lymphoma, malignant melanoma, breast cancer)	*In vitro:* internalization of GlyR by GlyR in recombinant cellular model (Wuerfel *et al.*, 2014).
LGI1	Secreted Protein	> 150 (Irani *et al.*, 2010, 2011; Lai *et al.*, 2010; Ohkawa *et al.*, 2013; Shin *et al.*, 2013)	Encephalitis with limbic (amnesia, behavioural alterations, seizures) and extra-limbic symptoms	No consistent tumour association	*In vitro:* patients' LGI1 antibodies impair LGI1 binding to partner proteins and decrease synaptic AMPAR expression (Ohkawa *et al.*, 2013)
Caspr2	Adhesion Protein	95 (Irani *et al.*, 2010, 2012; Lancaster *et al.*, 2011a; Klein *et al.*, 2013)	Limbic encephalitis, Morvan's syndrome	50% (thymoma) (Irani *et al.*, 2012)	*In vitro:* Caspr2 antibodies from patients with limbic encephalitis alter gephyrin clusters (Pinatel *et al.*, 2015).
DPPX	Membrane glycoprotein	28	Pronounced gastrointestinal symptoms, agitation, hallucinations, confusion, myoclonus, tremor and seizures, sleep-disturbance, PERM-like syndrome	No tumour associations reported	*In vitro:* patient's IgG reduce expression of DPPX and Kv4.2 in cultured neurons (Piepgras *et al.*, 2015).
Amphiphysin	Synaptic vesicle protein	> 35 (Antoine *et al.*, 1999; Murinson & Guarnaccia, 2008; Moon *et al.*, 2014)	Stiff-person syndrome	≈90% (breast cancer)	*In vivo:* transfer of IgG from patients to rat causes muscles stiffness and spasms (Sommer *et al.*, 2005).
GAD	GABA synthesis enzyme	> 100 (Saiz *et al.*, 2008; Ariño *et al.*, 2015; Fouka *et al.*, 2015)	Limbic encephalitis, cerebellitis	Usually none. Associated with neuroendocrine tumours and lung cancer (Ariño *et al.*, 2014) in 2 case series (Saiz *et al.*, 2008; Ariño *et al.*, 2014).	*In vitro:* autoantibodies uptake in heterologous cell systems expressing GAD-65 (Hampe *et al.*, 2013). *In vivo:* altered behaviour induced by GAD antibodies transfer to rodents (Manto *et al.*, 2007, 2015; Hampe *et al.*, 2013).
VGCC	Calcium channel	> 40 (Mason *et al.*, 1997; Lorenzoni *et al.*, 2008; Bürk *et al.*, 2010; Ogawa *et al.*, 2011)	Cerebellar ataxia	Small cell lung carcinoma	*In vivo:* passive transfer of patients' antibodies to mice induces acute ataxia (Martín-García *et al.*, 2013).
Tr/DNER	Neuron-specific signalling protein	> 40 (Graus *et al.*, 1997; de Graaff *et al.*, 2012; Probst *et al.*, 2015)	Cerebellar ataxia	≈90% (Hodgkin's lymphoma)	No experimental study available.

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