Autoantibodies and Psychosis

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Abstract Research into antibody-mediated disease, in response to immune dysfunction or to tumour development, has rapidly expanded in recent years. Antibodies binding to neuroreceptors can cause psychiatric features, including psychosis, in a minority of patients as well as neurological features. The responsiveness of some of these cases to immunotherapy supports the hypothesis that antibody-associated mechanisms play a role in the pathogenesis of psychotic diseases. The purpose of this chapter is to review autoantibodies that are most likely to be relevant for patients with psychotic symptoms. Herein, we describe receptor structure and mechanism of action, clinical and psychiatric features for the growing number of neuronal surface antibodies, including those to the N-methyl-D-aspartate (NMDA) receptor. The identification of a subgroup of patients with psychiatric features having antibody-mediated disease highlights the importance of considering the diagnosis, particularly in those patients presenting with a first episode of psychosis.

Keywords Autoimmune encephalitis · First episode psychosis · NMDA encephalitis · Organic psychosis · Psychoneuroimmunology

1 Background

Inflammation is increasingly recognised as a risk factor for psychosis (Cannon et al. 2014; Khandaker et al. 2015; Kelleher and Corvin 2013). The influence of inflammation was recognised as early as schizophrenia was conceptualised, with Kraepelin suggesting that dementia praecox was a disease of the brain caused by 'an autointoxication' from the body (Kraepelin 1899; Noll 2004). The study of immunity and psychosis incorporates many landmark studies of psychiatric research. Examples include Wagner-Jauregg's treatment of 'general paralysis of the insane' (in fact neurosyphilis) with induced *Plasmodium vivax* malaria (Wagner-Jauregg and Bruetsch 1946) and the systematic reviews examining the association between winter or spring birth and schizophrenia (Davies et al. 2003; Mcgrath and Welham 1999), maternal infection during pregnancy and schizophrenia (Brown et al. 2004; Mortensen et al. 2007; O'Callaghan et al. 1991), childhood infection and schizophrenia (Khandaker et al. 2018, 2012; Dalman et al. 2008; Benros et al. 2011), childhood/adolescent inflammatory markers and risk of schizophrenia and related psychoses (Khandaker et al. 2014; Metcalf et al. 2017; Kappelmann et al. 2019) and

maternal infections and inflammation in animal models and their effects on neurodevelopment (Cotter et al. 1995; Farrelly et al. 2015). From a genetic perspective, genome-wide association studies (GWAS) have identified that several common variants of the locus for the major histocompatibility complex (MHC), a group of cell surface proteins that regulate the adaptive immune system, are strongly associated with schizophrenia (Purcell et al. 2009; Shi et al. 2009; Stefansson et al. 2009). Most recently, emerging evidence suggest that the effects of antibodies binding to neuroreceptors, generated in response to immune dysfunction or in response to tumour development, can lead to psychiatric features, providing additional evidence of this interplay. While research has linked schizophrenia with dysfunction in various aspects of immune system, the purpose of this chapter is to review autoantibodies that are most likely relevant for pathogenesis of psychoses.

2 History of the Influence of Antibodies on Psychosis

Early work by Oppenheim (Schulz and Pruss 2015), Lehmann-Facius (Deakin et al. 2014) and Deny-Brown (Denny-Brown 1948) examined links between the immune system, malignancy, circulating antibodies and subsequent neuropsychiatric features. In 1960, Brierley and colleagues reported three patients with 'subacute encephalitis of later adult life, mainly affecting the limbic areas' (Brierley et al. 1960). Corsellis et al. (1968) later described 'limbic encephalitis' in a case series of patients with either short-term memory loss or dementia in association with bronchial carcinoma. All those affected had degenerative changes concentrated in the temporal parts of the limbic grey matter. In the 1980s, paraneoplastic limbic encephalitis associated with antibodies targeting neuronal epitopes (the part of the antigen the antibody binds to) was identified in patients with central nervous system (CNS) and peripheral nervous system (PNS) syndromes who had an underlying cancer (Graus et al. 1985). Subsequently the concept of an immune-mediated pathogenesis gained relevance after anti-Hu (Dalmau et al. 1992) and other onconeuronal antibodies against intracellular antigens were identified (Dalmau and Bataller 2006), some of them with more syndrome specificity for limbic dysfunction than the anti-Hu immune response (Table 1).

Later work identified that, from a psychiatric perspective, the most relevant antibodies are antibodies to the N-methyl-D-aspartate receptor antibody (NMDAR-Ab) and to a lesser extent leucine-rich glioma-inactivated protein (LGI1-Ab) and contactin-associated protein-2 (CASPR2-Ab). These can present with prominent neuropsychiatric features particularly in the early stages of illness (Dalmau et al. 2007, 2008; Irani et al. 2010a, b; Lai et al. 2010; Vitaliani et al. 2005; Zandi et al. 2011). While most are rare, other autoantibodies that have been linked to encephalitis with psychiatric features include dopamine 2 receptor (D2R) (Dale et al. 2012), gamma-aminobutyric acid (GABA) (Lancaster et al. 2010) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor (AMPAR) (Lai et al. 2009)

Table 1 Paraneoplastic antibodies that may associate with limbic encephalitis (Dalmau and Bataller 2006)

Antibody	Syndrome	Cancer
Hu	Limbic encephalitis, encephalomyelitis	SCLC, other
Ma	Limbic, hypothalamic and brainstem encephalitis	Testis, lung, other
CV2/ CRMP5	Limbic, striatal encephalitis (chorea), cerebellar ataxia, peripheral neuropathy, uveitis	SCLC, thymoma
Amphiphysin	Limbic encephalitis, stiff-person syndrome	Breast, SCLC

SCLC small cell lung cancer

amongst others. A summary of relevant paraclinical data linking these autoantibodies with psychiatric features is outlined in Table 2.

3 N-Methyl-D-Aspartate Receptor Antibody (NMDAR-Ab)

Since at least 1995, there have been case reports of women with ovarian teratomas presenting with reduced consciousness, psychiatric symptoms and neurological disease whose symptoms improved following tumour removal (Nokura et al. 1997; Okamura et al. 1997). Initially this was believed to be a paraneoplastic process due to an antibody to an unknown antigen expressed in the hippocampus (Vitaliani et al. 2005). In 2007, antibodies were identified as binding to the N-methyl-D-aspartate receptor (NMDAR) in a case series of four females who presented with initial psychotic/altered behaviour and then developed progressive neurological features. This condition was termed anti-NMDA or NMDAR-Ab encephalitis (Dalmau et al. 2007; Irani et al. 2010b), an immune-mediated disorder that occurs when IgG antibodies bind to the GluN1 subunit of the NMDA receptor causing it to be internalised and destroyed (Hughes et al. 2010).

Due to prominent psychiatric symptoms early on in the course of this illness, psychiatry is the specialty that is often in contact with these patients in early stages of their presentation, in approximately 75% of cases according to one report (Dalmau et al. 2011). As highlighted in the first report in the psychiatric literature by Barry et al. (2011), psychosis features prominently. NMDAR-Ab encephalitis supports the influence of glutamatergic dysregulation and has revitalised efforts into whether specific autoantibody syndromes might explain a subset of patients with schizophrenia or psychosis.

Table 2 Clinical features and associations of antibodies relevant to patients with psychiatric features

Antibodies	Psychiatric clinical features	Associated features/ symptoms	Gender/age associations	Paraclinical information	Malignancy associations	Clinical course
NMDAR (to NR1 subunit)	Behavioural change (psychosis and mood changes) follows a viral 'prodromal period'. Catatonia and movement disorders, e.g. dyskinesia may then follow the 'psychiatric' phase, usually within 1 month (Titulaer et al. 2013). Autonomic features	'Viral symptoms' prodromal period (1–2 weeks) Altered conscious level Memory deficits New seizures Autonomic instability Dyskinesias Speech disturbance (including mutism)	Young (median age 21) female (Dalmau et al. 2008; Titulaer et al. 2013; Irani et al. 2010b)	Delta brush sign on EEG in 30% of cases (Schmitt et al. 2012) Abnormal EEG in 90% of patients (Dalmau et al. 2008; Irani et al. 2010b; Titulaer et al. 2013) CSF lymphocytosis in 80% of cases (Irani et al. 2010b; Dalmau et al. 2008) CSF oligoclonal bands in 60% cases (Dalmau et al. 2011) Non-specific MRI brain changes in 30% cases (Titulaer et al. 2013; Irani et al. 2010b, Dalmau et al. 2008)	Ovarian teratoma in 30–50% (Irani et al. 2010b; Titulaer et al. 2013)	10–15% patients relapse (Titulaer et al. 2013) and relapses likely monosymptomatic (Kayser et al. 2013) Cognitive deficits (impaired processing speed, episodic memory, executive functioning) reported several years later (Finke et al. 2012; Mckeon et al. 2017) Estimated mortality rate of 4–6% (Dalmau et al. 2011; Titulaer et al. 2013) up to 12% if untreated (Titulaer et al. 2013)
LGI1	Broad range of psychiatric features including mood and anxiety symptoms (depression, apathy, disinhibition and compulsive behaviour) Psychotic features (hallucinations) also	Seizures (initially subtle focal seizures or faciobrachial dystonic seizures later tonic-clonic seizures) followed by memory deficits Confusion Insomnia Autonomic	Median age 60 years, males more likely affected (Van Sonderen et al. 2016c)	Hyponatraemia in ~60% (Irani et al. 2010a, 2013) Abnormal MRI brain (hippocampal T2 hyperintensity) in~56–75% (Irani et al. 2010a, 2013; Lai et al. 2010; Celicanin et al. 2017)	Usually thymoma in ~10%	35% of patients experience a relapse 2-year case fatality rate of 19% (Van Sonderen et al. 2016c)

(continued)

Table 2 (continued)

Antibodies	Psychiatric clinical features	Associated features/ symptoms	Gender/age associations	Paraclinical information	Malignancy associations	Clinical course
	described Spatial disorientation	dysfunction Morvan's syndrome Isolated epilepsy		EEG abnormal 56–89% (Celicanin et al. 2017, Irani et al. 2011; Van Sonderen et al. 2016c) Normal CSF in 75% of cases (Irani et al. 2013, Van Sonderen et al. 2016c)		
CASPR2	Behavioural disturbance Hallucinations Psychosis	Limbic encephalitis Morvan syndrome (peripheral nerve hyperexcitability) Neuromyotonia Muscle spasms/fasciculations Cognitive impairment Seizures Insomnia Autonomic disturbance	Middle-aged (median age 57)/ elderly males (Irani et al. 2010a, 2012; Lancaster et al. 2011a)	Hyponatremia in 10% MRI brain: 25% cases had T2 hyperintensities of medial temporal lobes (Irani et al. 2010a, 2012; Lancaster et al. 2011a) CSF abnormal in 35%–50% of cases (raised WCC, raised protein and/or unmatched oligoclonal bands) (Van Sonderen et al. 2016c; Irani et al. 2012) EEG abnormal in ~60% cases (epileptic	0–32% have malignancy (usually thymoma) (Irani et al. 2010a; Lancaster et al. 2011a; Klein et al. 2013)	Full recovery in ~40% of cases and partial recovery ~12% cases Approximately 25% of cases with >1-year follow-up relapse (median 19 months) (Van Sonderen et al. 2016c)

				or slow waves) (Lancaster et al. 2011a)		
AMPA receptor (GluA1 or GluA2 subunit)	Behavioural change Psychosis, hallucinations/delusions	Short-term memory loss, confusion and abnormal behaviour Seizures, ataxia, abnormal movements	Middle-aged (median age 60, range 38–87) females (Lai et al. 2009)	Rarely hyponatremia (Hoftberger et al. 2015) MRI brain may show increased signal in bilateral or unilateral mesiotemporal lobes (~75% of cases) EEG: 75% of cases abnormal (diffuse slow activity, theta activity or short waves) (Lai et al. 2009) CSF pleocytosis in 50–90% of cases (Lai et al. 2009; Hoftberger et al. 2015)	Thymoma, breast, small cell lung carcinoma in ~70% of cases (Lai et al. 2009)	Immunotherapy and oncological treatment lead to improvement in 70–90% of cases Relapses occur in approximately 16% of cases (Lai et al. 2009; Hoftberger et al. 2015)
$GABA_a$ receptor	Affective problems (mood and anxiety) Behavioural changes, psychotic features (hallucinations)	Limbic encephalitis, status epilepticus, refractory seizures	Median age 22 years, males more likely affected (Petit-Pedrol et al. 2014)	Extensive cortical-subcortical MRI abnormalities in antibodies in CSF/high serum titres EEG may be abnormal in up to 100% of cases CSF abnormal in 84% of cases (Petit-Pedrol et al. 2014)	Hodgkin's lymphoma	Immunotherapy improves outcomes in 50% of cases (Petit-Pedrol et al. 2014)

(continued)

Table 2 (continued)

Antibodies	Psychiatric clinical features	Associated features/ symptoms	Gender/age associations	Paraclinical information	Malignancy associations	Clinical course
$GABA_B$ receptor	Behavioural changes, hallucinations	Limbic encephalitis (memory loss, confusion, seizures) Severe seizures/status epilepticus Rarely opsoclonus-myoclonus or cerebellar ataxia prior to limbic encephalitis (Kim et al. 2014)	Typically middle aged (median age 62) (M/F, 1:1) (Lancaster et al. 2010; Kim et al. 2014)	MRI brain abnormal in ~70% of cases (usually unilateral/ bilateral increases in medial temporal lobe FLAIR/T2 signal) CSF demonstrates lymphocytic pleocytosis in 80% of cases EEG invariably abnormal ~90% of cases (Lancaster et al. 2010)	~50% of cases have small cell lung carcinoma	75% have partial or complete response to immunotherapy and oncological treatment where indicated (Hoftberger et al. 2013) 30% mortality rate (due to malignancy or chemotherapy treatment) (Lancaster et al. 2010)
D2R	Psychosis, depression, agitation (Dale et al. 2012; Pathmanandavel et al. 2015)	Basal ganglia encephalitis (parkinsonism, chorea, dystonia)	Children, mean (range) age at onset 6.7 (0.4–15) years	MRI basal ganglia changes in 50% of cases CSF abnormal in 75% of cases EEG either normal or non-specific slowing (Dale et al. 2012)	Unclear, not all patients tested	Limited data Variable recovery with and without treatment
DPPX	Depression/apathy initially Psychosis	Cognitive impairment Diarrhoea/weight loss Hyperexcitability Progressive encephalomyelitis with	Median age 53, males more affected (Boronat et al. 2013; Hara et al. 2017; Tobin et al. 2014)	CSF: Abnormal in 55–100% cases EEG: Slowing or epileptiform activity in 85–100% cases MRI brain: May show white matter changes	Rarely B-cell tumours	60% of cases respond to immunotherapy 20% had died Relapses may occur in 23% (Hara et al. 2017)

		rigidity and myoclonus (PERM) (Balint et al. 2014)		in 33% cases (Hara et al. 2017; Boronat et al. 2013)		
MgluR5	Depression, anxiety, delusions, hallucinations, anterograde amnesia	Limbic encephalitis	Median age 25.5 (range 15–46) M/F 1:1 (Lancaster et al. 2011c; Mat et al. 2013)	MRI brain: May show increased signal in mesiotemporal lobes or hyperintensities in posterior parietal-occipital cortex CSF: May show lymphocytosis (Lancaster et al. 2011c; Mat et al. 2013)	Hodgkin's lymphoma	May have complete recovery with immunotherapy/chemotherapy treatment

CSF cerebrospinal fluid, *EEG* electroencephalogram, *F* female, *M* male, *MRI* magnetic resonance imaging, *WCC* white cell count

3.1 Structure of the NMDA Receptor

The NMDA receptor is essential to the development and function of the nervous system and plays a central role in synaptic plasticity and memory formation (Bliss and Collingridge 1993). It is an ionotropic type of receptor with eight alternatively spliced GluN1 isoforms and two GluN3 subunits (A–B), which bind glycine, and four GluN2 subunits (A–D), which bind glutamate. Target epitopes are located in extracellular regions of NR1–NR2B NMDA receptors (Dalmau et al. 2007) with the crucial epitopes in NMDAR-Ab encephalitis present in the more widely expressed NR1 subunit (Dalmau et al. 2008).

In healthy NMDA receptors, glutamate is released from the presynaptic terminal into the synaptic cleft to act on postsynaptic glutamate receptors. Subsequent activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors by glutamate depolarises the postsynaptic membrane and removes a magnesium block on the NMDA receptor (Mayer et al. 1984; Nowak et al. 1984). This allows cations, including calcium ions (Ca2+), to flow into the postsynaptic dendrite, leading to excitatory transmission and synaptic plasticity (Mayer and Westbrook 1987). The strengthening of the impulse between the two neurons is an essential process in synaptic plasticity, cognition and memory formation. The hippocampus contains the highest density of NMDARs which are important for shaping the strength of synaptic connections through involvement in long-term potentiation (LTP) and long-term depression (LTD) (Newcomer and Krystal 2001; Waxman and Lynch 2005).

3.2 Mechanism of NMDAR-Ab Encephalitis

Blockade of the NMDA receptor through NMDA antagonists such as phencyclidine (PCP) and ketamine is well known to cause both positive- and negative-type symptoms of schizophrenia (Javitt 2007) as well as agitation and dissociation (Javitt and Zukin 1991). Psychotic features due to ketamine are proportional to glutamate levels, suggesting a mechanism of action that may lead to psychosis (Stone et al. 2012).

Approximately 50% of adult women presenting with NMDAR-Ab encephalitis have an underlying teratoma, which may contain nervous tissue (Titulaer et al. 2013). In a paraneoplastic model, it is proposed that an antigen, released by tumour cells undergoing apoptosis, is taken up by antigen-presenting cells (Martinez-Hernandez et al. 2011; Moscato et al. 2014). This breaks down immune tolerance by a sequence of mechanisms including antigen presentation by T or dendritic cells generating memory B cells and antibody-producing plasma cells. Systemically synthesised antibodies can bind to NMDA receptors present in the tumour. It is postulated that antibodies can also pass through a disrupted blood-brain barrier

(BBB) or reach the brain through the choroid plexus. The memory B cells (also activated T cells) undergo restimulation (resident antigen-presenting cells or T cells), antigen-driven affinity maturation, clonal expansion and differentiation into NMDA receptor antibody-secreting plasma cells (Moscato et al. 2014). Antibodies bind to extracellular epitopes of the NMDA receptor causing subsequent dysfunction and internalisation.

Greater than 90% of young girls or males with the disorder have no identified trigger, although it may be associated with herpes simplex virus 1 (HSV-1) infection (Irani et al. 2010b; Titulaer et al. 2013; Armangue et al. 2014). Approximately 10–25% of patients with HSV-1 encephalitis have an immune-mediated relapse associated with GluN1-specific antibodies and NMDAR-Ab encephalitis symptoms.

NMDAR-Ab have been shown to cause reversible reduction in neuronal surface NMDA receptors without causing cell death (Hughes et al. 2010; Moscato et al. 2014) leading to reduction in NMDAR-mediated currents and synaptic plasticity. Removal of the pathogenic antibodies through tumour removal and treatment with immunosuppression (see below) leads to clinical improvement (Titulaer et al. 2013). Antibody titres may decline (months or even years) after recovery or in some cases remain detectable (Gresa-Arribas et al. 2014).

3.3 Incidence and Clinical Characteristics of NMDAR-Ab Encephalitis

The incidence of NMDAR-Ab encephalitis has been estimated at 0.85 per million children per year in the UK (Wright et al. 2015). While it can affect both men and women of any age, it appears to predominantly affect young women (median age 21 [range 1–95], 81% female) (Titulaer et al. 2013). As mentioned previously, in women over 18 years of age, ~50% have an underlying tumour (overwhelmingly found to be ovarian teratoma) compared to only 5% of men (Dalmau et al. 2011).

About 70% of cases have prodromal symptoms including headache, fever, nausea and respiratory tract infections (Dalmau et al. 2008). Within 2 weeks they can develop psychiatric symptoms characterised by psychotic features, e.g. delusions, hallucinations, paranoia and, less commonly, anxiety and mood symptoms. These are the presenting symptoms in over 65% of cases (Titulaer et al. 2013). Children are more likely to have abnormal movements, e.g. chorea earlier in the disease course, and to experience seizures compared to adults. Psychosis is less common compared to adults, but behavioural regression is frequently noted (Titulaer et al. 2013).

During the first month of the disease, the majority of patients (87%) developed four or more of eight categories of symptoms (see Table 3) (Dalmau et al. 2008). Short-term memory loss is common early in the disease process but can be underestimated because psychopathology and language deficits can dominate the

Table 3 Features of NMDAR-Ab encephalitis

Behavioural change
Memory dysfunction
Speech disorder/mutism
Seizures
Decrease in level of consciousness
Movement disorder
Autonomic dysfunction
Central hypoventilation

clinical presentation. Following this, abnormal movements such as catatonia, chorea, akathisia, dystonia and orofacial dyskinesia manifest (Baizabal-Carvallo et al. 2013; Duan et al. 2016; Mohammad et al. 2014). Features may progress and include autonomic instability leading to cardiac/respiratory arrest or refractory status epilepticus. Patients are often (75%) transferred to the intensive care unit (ICU) at this stage for ventilation, intravenous antiepileptic medication and inotropic support (Titulaer et al. 2013).

3.4 Diagnosis of NMDAR-Ab Encephalitis

Criteria to aid the early diagnosis of NMDAR-Ab encephalitis have been published by lead researchers in the field based primarily on clinical features and the results of investigations (Graus et al. 2016) (see Table 4). Techniques that identify NMDAR-Ab in serum and CSF are cell-based assays (CBAs) (used by most clinical laboratories) using live or fixed cells, immunohistochemistry of brain sections adapted to membrane proteins (commercially available; sometimes used as a confirmatory test) and immunocytochemistry of cultures of dissociated rodent live hippocampal neurons (used in research laboratories) (Graus et al. 2016).

Electroencephalogram (EEG) is abnormal in approximately 90% of patients, usually showing non-specific, slow and disorganised activity (Dalmau et al. 2008). Slow rhythmic activity in the delta-theta range (the so-called ‘delta brush’ sign) was initially thought to predominate in the catatonic-like stage (Schmitt et al. 2012); however this feature was later shown to appear in other neurological disorders (Baykan et al. 2018). CSF analysis is abnormal in about 80% of patients, demonstrating lymphocytic pleocytosis (Dalmau et al. 2008; Irani et al. 2010b). Other findings include normal or mildly increased protein concentration and, in 60% of patients, CSF-specific oligoclonal bands (Dalmau et al. 2011). Importantly, CSF abnormalities may be the only remarkable clinical finding (Scott et al. 2018), hence the importance of offering lumbar puncture to patients found to be seropositive for NMDAR-Ab.

Clinical routine brain magnetic resonance imaging (MRI) is abnormal in only 30% of patients approximately, despite patients being significantly unwell at the

Table 4 Diagnostic criteria for anti-NMDA receptor encephalitis (Graus et al. 2016)

Probable anti-NMDA receptor encephalitis Diagnosis can be made when all three of the following criteria have been met: Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms: • Abnormal (psychiatric) behaviour or cognitive dysfunction • Speech dysfunction (pressured speech, verbal reduction, mutism) • Seizures • Movement disorder, dyskinesias or rigidity/abnormal postures • Decreased level of consciousness • Autonomic dysfunction or central hypoventilation At least one of the following laboratory study results: • Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity or extreme delta brush) • CSF with pleocytosis or oligoclonal bands Reasonable exclusion of other disorders • Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma
Definite anti-NMDA receptor encephalitis Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, after reasonable exclusion of other disorders. Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (e.g., live neurons or tissue immunohistochemistry, in addition to cell-based assay)

time of imaging (Titulaer et al. 2013). Changes may include white matter hyperintensities. Follow-up brain MRI has been shown to remain normal or show minimum change despite the severity and duration of symptoms (Dalmau et al. 2011). Brain biopsy may show normal or non-specific signs of inflammation. These include perivascular lymphocytic cuffing (predominantly of B cells), sparse parenchymal T-cell infiltrates or microglial activation (Camdessanche et al. 2011).

Patients who have had NMDAR-Ab encephalitis identified should undergo screening for malignancies associated with these occasional paraneoplastic antibodies. In the largest study of patients with NMDAR-Ab encephalitis ($N = 571$) (Titulaer et al. 2013), 38% of patients were found to have underlying malignancy, invariably ovarian teratomas. While teratomas and carcinoma located elsewhere (lung, breast, testicular; ovarian carcinoma, thymic carcinomas and pancreatic cancer) can occur, they are uncommon.

Given the prominent psychiatric, especially psychotic, features, there is significant interest by the psychiatric community in what has been described as a new 'identifiable treatable subtype of psychosis' (Kayser and Dalmau 2016). Therefore, a key issue for psychiatrists is whether patients with NMDAR-Ab encephalitis may have psychiatric features alone and whether patients with psychosis and NMDAR-Ab require a different treatment pathway (Lennox et al. 2012).

3.5 *Psychiatric Features Associated with NMDAR-Ab Encephalitis*

As outlined above, psychiatric features appear prominently in the early course of NMDAR-Ab encephalitis, and psychiatrists are usually the first clinicians to assess such cases, who usually do not have a previous psychiatric history (Peery et al. 2012). Patients with psychotic disorders such as first episode psychosis (FEP) and schizophrenia would seem a natural cohort to assess for NMDAR antibodies. There has been much debate as to the most robust methodologies used to identify NMDAR-Ab, the relevance of NMDAR-Ab in serum only in the absence of CSF and the significance of IgM and IgA antibodies amongst others.

A study (Kayser et al. 2013) reviewed the presentations of 571 patients with NMDAR-Ab encephalitis, who were identified as having NMDAR-Ab both in serum and CSF with a fixed cell-based assay and immunohistochemistry. The authors found that 23 (~4%) of these had isolated psychiatric symptoms – at the time of presentation (0.9%, 5/571) or at relapse (3.2%, 18/571). When considering that only 64 individuals (11.2%) experienced a relapse, the proportion of patients with psychiatric features at relapse increases (28%, 18/64). Seventy-four percent had some form of delusional thinking, 43% had abnormal perceptions (auditory or visual hallucinations) and 57% had aggressive behaviour. Seventy percent had a mood element to their presentation usually mania, mood lability and impulsivity. Depressive symptoms were less common (Kayser et al. 2013). Psychotic phenomena in presenting cases have been described as fragmented in comparison with those typically found in functional psychoses, with delusions being poorly formed and non-systematised (Barry et al. 2015).

Several screening studies have examined NMDAR-Ab in psychosis populations. A landmark study (Zandi et al. 2011) identified that 3/46 (6.5%) patients with first episode psychosis but without traditional encephalopathic features were seropositive using a cell-based assay with live Human Embryonic Kidney (HEK) cells (Irani et al. 2010b). All three cases met DSM-IV criteria for schizophrenia, and one responded to immunotherapy treatment. Similar results were found in a later study (Pathmanandavel et al. 2015) of 43 children experiencing a first episode of psychosis (FEP) (median age 15 years), which identified antibodies to NMDAR using a flow cytometry live cell-based assay and none in a paediatric control cohort ($N = 43$). Studies utilising fixed and permeabilised CBAs found no difference in the seroprevalences of NMDAR antibodies in patients and in controls (Dahm et al. 2014; Hammer et al. 2014). While some studies (de Witte et al. 2015; Masopust et al. 2015) which used both fixed cell-based assay and immunohistochemistry did not identify any NMDAR-Ab in serum of cohorts of patients with schizophrenia and first episode psychosis, other studies have identified seropositive cases in post-partum psychosis, using this 'double validation' method (Bergink et al. 2015).

In 2014, a meta-analysis by Pollak and colleagues examined the seroprevalence of NMDAR-Ab in 1441 patients with psychotic illnesses and 1,598 healthy controls from several screening studies (Hammer et al. 2014; Haussleiter et al. 2012;

Masdeu et al. 2012; Rhoads et al. 2011; Steiner et al. 2013; Tsutsui et al. 2012; Zandi et al. 2011). This identified 115 individuals [7.98%, 95% confidence interval (CI) 6.69–9.50] who were anti-NMDA receptor antibody positive. Of these, 21 patients (1.46%, 95% CI 0.94–2.23) were positive for antibodies of the IgG subclass. Prevalence rates were greater in cases than controls only for IgG antibodies. A meta-analysis of NMDAR-Ab seropositivity in patients with schizophrenia, schizoaffective disorder, bipolar affective disorder (BPAD) or major depressive disorder (MDD) demonstrated a higher odds ratio of 3.1 compared to healthy controls (Pearlman and Najjar 2014).

Scott et al. (2018) screened all inpatients (children as well as adults up to age 45 years old) admitted with a first episode psychosis for autoantibodies. Importantly, they endeavoured to recruit every FEP case including those who had a drug-induced psychosis, and each participant had a clinical assessment and was investigated with EEG, MRI brain and antibodies both in serum and CSF. The authors identified that approximately 5% (6/113) of participants had autoimmune encephalitis. Four of these cases (3.5%, 4/113) were diagnosed with NMDAR-Ab encephalitis. Two other recent studies (Lennox et al. 2017; Gaughran et al. 2018) which identified an NMDAR-Ab seroprevalence rate of ~3% in first episode psychosis services, with the prevalence in controls varying between 0 and 1%, using a live cell-based assay (L-CBA) only. Although the results of clinical investigations were not described, none of the cases were reported as having developed NMDAR-Ab encephalitis at 6-month follow-up in one study (Lennox et al. 2017). The prevalence of autoimmune encephalitis may be underestimated in research cohorts or community cohorts (who are capacitous, prescreened for organic red flags and often in at least partial remission) (Pollak and Lennox 2018). Therefore, the study by Scott and colleagues is important as they recruited participants as early as possible, clinically investigated them and obtained CSF which is often challenging in psychosis populations and a criticism of studies that use serum only (Leypoldt et al. 2017).

NMDAR-Ab in serum has also been identified in patients with treatment-resistant psychosis with an identified point prevalence of 7% (3/43) using a live cell-based assay (Beck et al. 2015). NMDAR-Ab has also been identified in serum in cases of autism (Creten et al. 2011), bipolar affective disorder (Choe et al. 2013), eating disorders (Perogamvros et al. 2012) and post-partum psychosis (Bergink et al. 2015).

Differences between current assays suggest examining for NMDAR-Ab with at least two techniques, e.g. both a CBA and immunohistochemistry, or binding to cultured neurons, sampling both CSF and serum for NMDAR-Ab whenever possible, and cross-laboratory comparative assays should help understand the differences described (Varley et al. 2015). Recent consensus criteria by Graus et al. (2016) which utilise much of this will ideally lead to clarity for clinicians in the diagnosis of NMDAR-Ab encephalitis. However, such an approach does exclude those patients who have psychotic symptoms alone and are seropositive for NMDAR-Ab but who do not have abnormal investigative findings or who have declined investigations. Yet there are reports that such patients can respond to treatment with immunotherapy and research into this is ongoing (Zandi et al. 2014).

Table 5 Overview of immunotherapy treatment in NMDAR-Ab encephalitis

First-line immunotherapy	Oral/IV steroids (methylprednisolone)
	Intravenous immunoglobulins (IVIG)
	Plasmapheresis
	Plasma exchange
Second-line immunotherapy	Rituximab
	Cyclophosphamide
Other immunotherapy	Azathioprine, mycophenolate mofetil, tacrolimus, methotrexate

3.6 Treatment of NMDAR-Ab Encephalitis

A framework for treatment of NMDAR-Ab encephalitis has emerged (see Table 5) (Titulaer et al. 2013). Utilising this, approximately 50% of patients that are treated with first-line immunotherapy or tumour removal will experience improvement within 4 weeks of treatment, reaching an mRS [modified Rankin Scale, which runs from no symptoms (0) to death (6) (Quinn et al. 2008)] of 0–2 by 24 months (Titulaer et al. 2013). Notably patients with psychosis due to NMDAR-Ab encephalitis may experience worsening of autonomic dysfunction with neuroleptic treatment (Lejuste et al. 2016), and psychiatric symptoms can resolve in response to immunotherapy (Kayser et al. 2013; Zandi et al. 2011, 2014). 70% of those who do not improve with first-line treatment receive second-line immunotherapy (Dalmau et al. 2008; Irani et al. 2010b; Titulaer et al. 2013). Approximately 10–15% of patients relapse in a 2-year period (Titulaer et al. 2013). Relapses are more likely to be monosymptomatic (including psychiatric symptoms only) (Kayser et al. 2013) and result in fewer admissions to ICU (Titulaer et al. 2013). NMDAR-Ab can persist for a prolonged period following recovery (Gresa-Arribas et al. 2014).

3.7 Clinical Course and Relapse

Delays in treatment are associated with cognitive and functional impairment as well as death (Finke et al. 2012; Titulaer et al. 2013). The estimated mortality from NMDAR-Ab encephalitis is 4% with the median time from disease onset to death estimated at three and a half months (Dalmau et al. 2011). Female patients need to be monitored with yearly ultrasound scanning in case ovarian pathology develops. Screening protocols for males and prepubescent (<12) females are unknown (Titulaer et al. 2013). A recent systematic review of cognitive outcomes identified that, while intellectual functioning was more impaired within the acute recovery period than in the later phase of convalescence (Mckeon et al. 2017), rates of impaired processing speed, episodic memory and aspects of executive functioning were consistent across time points. Adverse neuropsychological outcomes occurred at higher frequency in patients where immunotherapy was delayed. Persistent

cognitive deficits are reported up to several years post-clinical remission (Finke et al. 2012; Mckeon et al. 2016).

4 Voltage-Gated Potassium Channel Complex Antibodies (VGKCC-Ab)

In 2001, a type of limbic encephalitis characterised by neuropsychiatric features including psychosis, seizures, amnesia and hyponatremia was described in patients with antibodies to the voltage-gated potassium channel receptor (VGKC-Ab) (Buckley et al. 2001). Later work (Irani et al. 2010a; Lai et al. 2010) demonstrated that most VGKC-Ab were directed towards cell surface proteins complexed to the voltage-gated potassium channel subunits (Kv), predominantly leucine-rich glioma-inactivated-1 (anti-LGI1 antibody) and contactin-associated protein-2 (anti-CASPR2 antibody) and more rarely contactin-2. Antibodies to this entire complex were termed voltage-gated potassium channel *complex* antibodies (VGKCC-Ab). However patients positive for LGI1-Ab and CASPR2-Ab accounted for almost all of the immunotherapy-responsive cases, and many VGKC-Ab patients including those without anti-LGI1 antibody and anti-CASPR2 antibody (so-called 'double-negative' VGKC-Ab cases) were tested and were less clearly immunoresponsive (Varley et al. 2017; Grain et al. 2017). Recently, double-negative autoantibodies have been shown to be directed against intracellular aspects of the channel itself as well as against the non-neuronal protein dendrotoxin (DTX). These are both unlikely to be pathogenic autoantibodies (Lang et al. 2017). At present, direct testing for anti-LGI1 antibody and anti-CASPR2 antibody is recommended instead of testing for VGKC-Ab.

Anti-LGI1 antibodies are more often associated with limbic encephalitis and epilepsy, whereas anti-CASPR2 antibodies are associated with movement disorders such as peripheral nerve hyperexcitability, neuromyotonia and Morvan's syndrome. Neuromyotonia is a syndrome of peripheral nerve hyperexcitability (PNH) with fasciculations and cramps (Shillito et al. 1995). Morvan's syndrome is characterised by neuromyotonia, encephalopathy, autonomic dysfunction, insomnia and complex nocturnal behaviours (Klein et al. 2013; Liguori et al. 2001).

LGI1 and CASPR2 antibodies are identified through cell-based assays examining the binding of IgG immunoglobulins to human embryonic kidney (HEK) cells, transfected with complementary DNA encoding the relevant autoantigen. This binding is then visualised using a fluorescence-labelled secondary antibody (Irani et al. 2010a).

4.1 Leucine-Rich Glioma-Inactivated-1 Antibody (LGI1-Ab)

4.1.1 Structure of LGI1

LGI1 is a neuronal secreted synaptic protein expressed mainly in the hippocampus and neocortex (Irani et al. 2010a). It forms a complex with presynaptic disintegrin and metalloproteinase domain-containing protein 23 (ADAM23) and postsynaptic disintegrin and metalloproteinase domain-containing protein 22 (ADAM22). LGI1 may interact with postsynaptic AMPA receptors, postsynaptic density protein 95 (PSD95) and presynaptic shaker Kv1-potassium channels. Through interacting with pre- and postsynaptic proteins, LGI1 may have a role in the regulation of neurotransmitter release (Fukata et al. 2010). It is known that murine mutations of LGI1 disrupt the formation of this complex and alter AMPA-mediated signalling (Fukata et al. 2010; Varley et al. 2017). Mutations in the LGI1 gene are associated with lateral temporal lobe epilepsy and psychiatric features including psychosis (Striano et al. 2011).

4.1.2 Mechanism of Action of LGI1-Ab

LGI1 antibodies cause reversible CNS synaptic dysfunction by several mechanisms (Lancaster and Dalmau 2012). The antibodies may prevent binding of LGI1 to the receptors that it regulates, or they might act on the LGI1-ADAM protein complex. Alternatively, LGI1 antibodies could disrupt currents mediated by Kv1.1 and Kv1.2 and/or impair AMPAR function, either indirectly by blocking LGI1-mediated regulation of these proteins or directly by disrupting the entire protein complex. Binding of antibodies to LGI1 leads to secondary channel dysfunction, caused by a reversible reduction of synaptic AMPA receptors and a loss of function of inhibitory interneurons, with consequent excess neuronal network excitation and seizures (Ohkawa et al. 2013).

A study involving application of serum from a patient with LGI1 antibodies to a hippocampal slice preparation showed increased nerve hyperexcitability, effects similar to application of a Kv1.1 and Kv1.2 antagonist (Lalic et al. 2011). Antibody titres appear to correlate with clinical presentation, with immunotherapy treatment resulting in clinical improvement in patients (Malter et al. 2014). LGI1 antibodies are strongly associated with Human Leukocyte Antigen-DR 7 isotype (HLA-DR7) and HLA-DRB4 in nontumour patients, supporting the autoimmune hypothesis (Kim et al. 2017; Van Sonderen et al. 2017).

4.1.3 Clinical Characteristics of LGI1-Ab Encephalitis

The median age of onset of LGI1-Ab encephalitis is around 60 years and most often occurs in males (Irani et al. 2010a; Lai et al. 2010). Cases may develop

neuropsychiatric features, including mood disturbances, psychosis, amnesia and disorientation (Zandi et al. 2011; Irani et al. 2013; Navarro et al. 2016). 80% of patients with limbic encephalitis due to LGI1 antibodies present with a variety of seizures, including faciobrachial dystonic seizures (FBDS) (Irani et al. 2013). These are brief (<3 s) unilateral contractions of the arm, often involving the ipsilateral face (or leg) and occurring up to 100 times a day. Subsequently, patients develop subacute onset amnesia and behavioural/psychiatric disturbances. Seizures may develop into tonic clonic type (Irani et al. 2010a; Lai et al. 2010).

Hyponatremia is present in at least 60% of patients which may be due to the syndrome of inappropriate antidiuretic hormone (SIADH) (Van Sonderen et al. 2016b, c). One possible mechanism is inflammation of the hypothalamic-pituitary neuraxis (Newey and Sarwal 2014). Brain MRI shows T2 high signal of the medial temporal lobe in approximately two-thirds of patients (Irani et al. 2010a; Lai et al. 2010; Shin et al. 2013). EEG can be abnormal in up to 90% of cases (Celicanin et al. 2017; Zandi et al. 2011; Van Sonderen et al. 2016c). CSF cell count and protein are unremarkable in 75% of cases (Van Sonderen et al. 2016c). Tumour screening is positive in up to 11% of the patients with thymoma and lung cancer being the most common; however other malignancies have been associated (Irani et al. 2010a; Lai et al. 2010; Malter et al. 2014).

4.1.4 Psychiatric Features Associated with LGI1-Ab

Both mood and psychotic symptoms are described in association with LGI1 antibodies (Pruss and Lennox 2016). Additional psychiatric features include apathy, disinhibition and compulsive behaviour (Van Sonderen et al. 2016c). The prevalence of LGI1 antibodies has been found to be 0.1% in patients with established schizophrenia in one study and none were identified in patients with affective disorders or borderline personality disorder (Dahm et al. 2014). A more recent study of patients with first episode psychosis ($N = 228$) and controls ($N = 105$) routinely screened for LGI1-Ab found no significant difference between both cases and controls (Lennox et al. 2017). Anti-LGI1 encephalitis is reported occurring post-partum with prominent anxiety features that responded to immunotherapy (Gotkine et al. 2011). Psychotic features with LGI1-Ab encephalitis show a response to treatment with immunotherapy (Klein et al. 2013). New psychotic illness have also been described in individuals following treatment for LGI1-Ab encephalitis (Pollak and Moran 2017).

4.1.5 Treatment of LGI1-Ab Encephalitis and Follow-Up

Treatment pathways are similar to those utilised in NMDAR-Ab encephalitis with first- and second-line immunotherapies. In refractory cases, rituximab and cyclophosphamide may be used (second-line therapies) (Lancaster et al. 2011b). Treatment with first-line immunotherapy in 32 patients with anti-LGI1 encephalitis was considered effective in 80% of cases (Van Sonderen et al. 2016c). Shorter time to

start immunotherapy allows resolution of FBDS and recovery of basal functions (Irani et al. 2011).

At 2-year follow-up of 21 patients with LGI1-Ab encephalitis, 67% of cases had a favourable outcome (measured by mRS of 0–2). Six of seventeen (35%) patients with available data had a relapse of symptoms, with a median time to relapse of 35 months (range 21–98 months) (Van Sonderen et al. 2016c). Cognitive assessment of 11 immunotherapy treated individuals at median 44 months (range 25–95) follow-up showed reduced spatial recognition, but they were otherwise normal compared to normative data (Van Sonderen et al. 2016c). Other studies have reported that patients may develop hippocampal atrophy and memory deficits (Butler et al. 2014; Malter et al. 2014).

4.2 Contactin-Associated Protein-2 Antibody (CASPR2-Ab)

4.2.1 Structure of CASPR2

CASPR2 is a transmembrane axonal protein of the neurexin IV superfamily that is localised to the juxtaparanode of myelinated axons (Poliak et al. 1999). It's extracellular domain interacts with contactin-2, and it connects with the cytoskeleton via protein 4.1B. CASPR2, contactin-2 and protein 4.1B are necessary to concentrate Kv1.1 and Kv1.2 channels in the juxtaparanode, which is important for the proper electrical functioning of axons in both the CNS and PNS (Lancaster and Dalmau 2012; Zhou et al. 1999).

4.2.2 Mechanism of Action of CASPR2-Ab

CASPR2 antibodies are widely thought to act by disrupting axonal potassium currents. Factors such as differences in time to establish intrathecal antibody synthesis, or in the structure of tight, septate-like junctions of myelinating cells around the axons, may explain the variability of PNS and CNS symptoms in patients with CASPR2 antibodies (Lancaster and Dalmau 2012). Genetic variation in the human gene encoding CASPR2 (CNTNAP2) is associated with autism (Jackman et al. 2009; Whalley et al. 2011), epilepsy (Strauss et al. 2006), Tourette syndrome, obsessive-compulsive disorder (Verkerk et al. 2003), schizophrenia (Malhotra and Sebat 2012), Pitt-Hopkins syndrome (Zweier et al. 2009) and other mental disabilities (Gregor et al. 2011).

4.2.3 Clinical Characteristics of CASPR2-Ab-Related Disease

Patients typically are males with age of onset later in life, e.g. approximately 66 years (Lai et al. 2010; Lancaster et al. 2011a; Irani et al. 2010a; Van Sonderen et al. 2016a). Clinical syndromes include neuromyotonia alone, a purely CNS-based limbic encephalitis or symptoms of both in Morvan's syndrome (Varley et al. 2017). They can also experience peripheral nerve hyperexcitability (PNH). Limbic encephalitis with CASPR2-Ab can be associated with autonomic features, pain or cerebellar symptoms (Irani et al. 2010a) and can potentially mimic Creutzfeldt-Jakob disease (CJD). Indeed some patients with a positive CASPR2-Ab have been subsequently diagnosed with CJD (Rossi et al. 2015).

In a case series of 38 patients with CASPR2 antibody-associated disease (Van Sonderen et al. 2016a), the most common presenting symptoms were cognitive disturbance, seizures, PNH or neuropathic pain. During the disease course, approximately 80% of patients experienced cognitive dysfunction, and 53% had seizures. Paraclinical data is outlined in Table 2. CASPR2 antibodies are associated with malignancy in approximately 20% of cases (Van Sonderen et al. 2016a). These are usually thymomas, found in 40% of cases of Morvan's syndrome and 10% of other presentations (Vincent and Irani 2010; Lancaster et al. 2010).

4.2.4 Psychiatric Features Associated with CASPR2-Ab

Behavioural disturbances, persecutory delusions, hallucinations and psychosis have been reported in cases with CASPR2 antibodies (Irani et al. 2012; Lancaster et al. 2011a; Van Sonderen et al. 2016a). Rare mutations of the CNTNAP2 gene that codes for CASPR2 protein (Ottman et al. 2004) can cause a clinical presentation of auditory hallucinations and partial epilepsy. CASPR2-Ab have been estimated at 0.9% in one large study of 2,533 seropositive patients with a variety of neuropsychiatric illness including schizophrenia (Dahm et al. 2014), although the seroprevalence rate in FEP in another study was not significantly different to healthy controls (Lennox et al. 2017).

4.2.5 Treatment of CASPR-Ab-Related Disease and Follow-Up

Treatment of CASPR2-Ab disease includes identifying and treating any malignancy and treatment with first- and second-line immunotherapy. Full recovery can be achieved in ~40% of cases and partial recovery with 12%. Approximately 25% of cases with >1-year follow-up had relapses presenting at a median of 19 months post initial episode (Van Sonderen et al. 2016a).

5 α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor Antibody (AMPAR-Ab)

5.1 Structure and Mechanism of Action

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) is a gated ion channel which consists of GluA 1–4 tetrameric subunits and is part of the family of glutamate receptors. They mediate fast excitatory synaptic transmission, necessary for learning, memory and synaptic plasticity (Henley and Wilkinson 2016). Antibodies target the extracellular domains of GluA1 and GluA2 subunits of the AMPA receptor and were first described in ten patients with limbic encephalitis (Lai et al. 2009). They cause a selective reversible decrease in the total surface amount and synaptic location of GluA1 and GluA2 through increased internalisation and degradation. This leads to a decrease of AMPAR-mediated currents (Lai et al. 2009).

5.2 Clinical Features of AMPAR-Ab-Related Disease

AMPAR antibody-associated disease mostly affects older females in response to malignancy (lung, breast, thymus) in approximately 65% of cases (Hoftberger et al. 2015; Lai et al. 2009). Clinical features vary but may include those of limbic encephalitis (short-term memory deficits, confusion, abnormal behaviour and seizures). Seizures are frequently present. Insomnia, lethargy and decreased level of consciousness have also been described (Graus et al. 2010; Hoftberger et al. 2015). Paraclinical data is available in Table 2.

5.3 Psychiatric Features Associated with AMPAR-Ab

Almost one in three patients (27%) in a case series of AMPAR-Ab encephalitis ($N = 22$) had psychotic features as part of their presentation (Hoftberger et al. 2015). One of these cases had a background history of BPAD. Recent screening studies however have identified no differences in the seroprevalence of AMPAR-Ab in FEP compared to healthy controls (Lennox et al. 2017). An earlier study reported that AMPAR-Ab were not found in a cohort of schizophrenia, affective disorders or borderline personality disorders (Dahm et al. 2014). However an additional study described that 3 of 4,819 patients with neuropsychiatric presentations had GluR2 AMPAR antibodies and that all had memory deficits and mood symptoms (Dogan Onugoren et al. 2015). Additional case reports of atypical psychosis (Graus et al. 2010) and mood and psychotic symptoms (Elamin et al. 2015) responding to immunotherapy treatment are described. Antibodies to AMPAR have been identified

in patients with Turner's syndrome with co-morbid bipolar disorder and psychotic features (Quaranta et al. 2015).

5.4 Treatment and Clinical Course

Treatment with immunotherapy or oncological treatment leads to an improvement in the majority (70–90%) of cases (Hoftberger et al. 2015; Lai et al. 2009). Relapses occur in approximately 16% of cases which may be reduced by the use of more aggressive forms of treatment (chemotherapy or rituximab).

6 γ-Aminobutyric Acid A Receptor ($GABA_AR$) and γ-Aminobutyric Acid B Receptor ($GABA_BR$) Antibody Disease

6.1 Structure and Mechanism of Action

GABA receptors act as inhibitory receptors in the central nervous system through mediation of GABA (γ-Aminobutyric acid), the major inhibitory neurotransmitter. $GABA_A$ receptor ($GABA_AR$) is a ligand-gated chloride channel that mediates fast inhibitory synaptic transmission in the CNS. At the synapse, most $GABA_ARs$ contain 2 α subunits, 2 β subunits and 1 γ subunit, arranged as γ-β-α-β-α (Sieghart 2006). Genetic or pharmacological alteration of the $GABA_A$ receptor has been associated with seizures (Baulac et al. 2001; Sun et al. 2013). $GABA_B$ receptors are heterodimers comprising of the $GABA_BR$ subunits 1 and 2 with $GABA_B1$ subunits containing the ligand-binding domain (Pagano et al. 2001). $GABA_BRs$ are G-protein-coupled receptors coupled indirectly to either calcium or potassium channels to produce prolonged inhibitory responses (Bowery 2010) and are found in both the CNS (cortex, cerebellum, thalamus and hippocampus) and the PNS (autonomic ganglia, visceral tissue) (Benarroch 2012). GABAB1R polymorphisms are associated with temporal lobe epilepsy (Xi et al. 2011), schizophrenia and obsessive-compulsive disorder (Zai et al. 2005, 2009).

6.2 Clinical and Psychiatric Features of GABA Antibody-Related Disease

Anti-$GABA_AR$ antibody encephalitis has been described relatively recently, and the spectrum of symptoms has not been fully defined. One study (Pettingill et al. 2015) identified autoantibodies against the α1 and/or γ2 subunits of the GABA receptors in

40 of 2046 patients whose serum was negative for other neuronal surface antibodies. Features of 15 representative patients included seizures (47%), memory impairment (47%), hallucinations (33%) and anxiety (27%). Notably one of these patients had pre-existing obsessive-compulsive disorder, and diagnoses for other cases included paranoid schizophrenia. The majority of patients in this study were not treated with immunotherapy. Antibodies to the GABA α1/β3 subunits were identified at high serum titres as well as in the CSF of patients with limbic encephalitis, status epilepticus or epilepsia partialis continua (Petit-Pedrol et al. 2014). Their presentations included affective problems, behavioural changes and/or psychotic features. All cases developed extensive cortical-subcortical MRI abnormalities and had a high mortality and a variable response to immunotherapy. Forty percent of patients with anti-$GABA_AR$ encephalitis have tumours, mostly thymomas and, less commonly, other neoplasms (e.g. Hodgkin lymphoma, multiple myeloma). See Table 2 for paraclinical data.

Anti-$GABA_B$ receptor encephalitis was first described in 15 cases with limbic encephalitis with a tendency towards severe seizures (Lancaster et al. 2010). Behavioural disturbances and psychotic features (delusions, paranoia, gustatory and visual hallucinations) formed part of the presenting complaint in 4 of these 15 cases (~25%) and in 5% (1/20) of another series (Hoftberger et al. 2013). Additional studies since then (Lancaster et al. 2010, 2011a; Hoftberger et al. 2013; Kim et al. 2014) show that the majority of patients present with seizures, confusion and memory deficits. Ataxia and opsoclonus-myoclonus have also been reported (Hoftberger et al. 2013). $GABA_B$ receptor antibodies have been identified in 0.3% of affective disorders (Dahm et al. 2014). About 50% of $GABA_B$ receptor encephalitis cases have lung cancer (mainly small cell lung cancer) (Hoftberger et al. 2013; Lancaster et al. 2010). Underlying carcinoid of the thymus (Lancaster et al. 2011a) and melanoma (Jarius et al. 2013) have also been reported.

6.3 Treatment and Clinical Course

Immunotherapy and treatment of malignancy resulted in substantial improvement in 18/21 (86%) patients with $GABA_A$ receptor encephalitis. Fourteen percent of cases died from status epilepticus or sepsis (Spatola et al. 2017). Approximately 75% of patients with $GABA_B$ receptor encephalitis show a partial or complete response to immunotherapy and oncological treatment (Hoftberger et al. 2013).

7 Dopamine 2 Receptor Antibody (D2R-Ab)

7.1 Structure and Mechanism of Action

Dopamine signalling is mediated through dopamine receptors. These are G-protein-coupled seven-transmembrane domain receptors. Five receptors are divided into two groups: D1- (D1R and D5R) and D2-class receptors (D2R, D3R and D4R) (Dale et al. 2012). The dopamine 2 receptor (D2R) has long isoforms (located on the postsynaptic membrane) and short isoforms (on presynaptic membrane) coded by alternative splicing of the same D2R gene (Usiello et al. 2000). D2R are highly expressed in the basal ganglia, cortex, hippocampus and substantia nigra and involved in synaptic plasticity and memory formation (Beaulieu and Gainetdinov 2011). D2R expression modulation has been associated with schizophrenia, depression and movement disorders (Beaulieu and Gainetdinov 2011).

7.2 Clinical and Psychiatric Features

Clinical features of D2R antibody disease include prominent movement disorders (parkinsonism, dystonia and chorea). Psychiatric features including psychotic features can occur in 25% of cases from one series (Dale et al. 2012). Where MRI brain was abnormal, findings were localised to the basal ganglia. EEG was abnormal in a minority of cases. D2R antibodies were also reported in 3 of 43 (7%) children with FEP (Pathmanandavel et al. 2015) using a live CBA. They were not identified in patients with schizophrenia, major depression or borderline personality disorder (Muller et al. 2014). D2R antibodies have been found in PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) (Cox et al. 2013).

7.3 Treatment and Clinical Course

There is limited data on treatment of patients with D2R antibodies. In a follow-up of 12 cases with D2R antibodies who received first-line immunotherapy, 5/12 are described as returning to baseline at 5-year follow-up; however residual motor, cognitive and psychiatric deficits were common in other cases (Dale et al. 2012).

8 Dipeptidyl-Peptidase-Like Protein 6 Antibody (DPPX-Ab)

8.1 Structure

DPPX (dipeptidyl-peptidase-like protein 6) is an auxiliary subunit of Kv4.2 potassium channels. It is a membrane glycoprotein involved in increasing the surface expression and channel conductance of Kv4.2 channels (Kaulin et al. 2009). Kv4.2 channels and DPPX are distributed throughout the nervous and enteric system (Boronat et al. 2013; Tobin et al. 2014).

8.2 Clinical Features

Hara et al. (2017) reviewed 39 known cases to date (median age 57 years); of these the majority (67%) developed weight loss/diarrhoea, behavioural disturbances and cognitive dysfunction and CNS hyperexcitability. DPPX antibodies have been associated with progressive encephalomyelitis with rigidity and myoclonus (PERM) (Balint et al. 2014). Psychiatric manifestations may occur with prominent psychotic features or behavioural disturbances that may lead to admission under psychiatry (Boronat et al. 2013) or neuropsychiatry (Hara et al. 2017). Forty-four percent of cases may have mood symptoms (appetite loss, depression and apathy) at the time of presentation (Hara et al. 2017). See Table 2 for paraclinical data.

Routine screening in a cohort of patients with first episode psychosis and high-risk psychosis did not reveal any seropositive cases (Mantere et al. 2017). The prevalence of DPPX antibodies in a cohort of patients with schizophrenia was reported as less than 1% (Dahm et al. 2014).

8.3 Treatment and Clinical Course

Sixty percent of cases had moderate-substantial improvement in response to treatment with immunotherapy. At follow-up, 20% of anti-DPPX encephalitis cases had died. Relapse occurred in 8 of 35 patients (23%) and was responsive to immunotherapy (Hara et al. 2017).

9 Rare Autoimmune Syndromes

Antibodies to the metabotropic glutamate receptor 5 (mGluR5), highly expressed in the hippocampus, are associated with Hodgkin's lymphoma (Carr 1982; Lancaster et al. 2011c; Mat et al. 2013; Pruss et al. 2014). Symptoms include depression, agitation, hallucinations and bizarre behaviour. Patient can have complete recovery from this rare syndrome following immunotherapy/oncological therapy (Leypoldt et al. 2015). Although glycine receptor and voltage-gated calcium channel (VGCC) antibodies are associated with characteristic neurological symptoms, they are rarely associated with psychiatric symptoms (Pollak et al. 2016).

10 Summary and Future Directions

The concept and emerging evidence of antibodies driving psychiatric symptoms particularly psychosis are important. This may lead to a better understanding of the mechanisms of schizophrenia and improved treatment pathways in a proportion of individuals found to have antibody-related disease. Early identification of such and treatment with immunotherapy lead to improved cognitive and functional outcomes. Autoimmune encephalitis frequently affects individuals with no previous psychiatric history, and behavioural change and psychosis are some of the earliest features. Careful history taking (including collateral history where available) and clinical examination for sometimes subtle neurological signs, CSF and paraclinical investigations, e.g. MRI brain and EEG, lead to diagnosis and guide treatment decisions (Midgley et al. 2018). Routine serum screening for such antibodies in patients with first episode psychosis is recommended (Lennox et al. 2017). For patients with isolated psychosis and NMDAR-Ab in serum, there appears to be no difference in psychopathology compared to other patients with psychosis (Lennox et al. 2017).

Examining for autoantibodies (in particular NMDAR-Ab) in several large cohorts of patients with first episode psychosis, treatment-resistant psychosis, established schizophrenia and healthy controls has shown that autoantibodies are identified in a small proportion of patients with psychosis. The lack of paired CSF samples in some studies has been criticised; however performing lumbar puncture in patients with new psychiatric symptoms can be challenging as patients may refuse and in those who are not neurologically ill it may be hard to justify. However, it is important that the seropositive patients are offered this investigation which may in some cases be the only abnormal finding (Scott et al. 2018).

This approach does however leave patients who present with psychotic symptoms and who have a positive serum neuronal autoantibody test result but who do not have EEG, neuroimaging or CSF abnormalities with diagnostic uncertainty. While rare, there is evidence that patients with psychosis and NMDAR-Ab in serum who are refractory to regular psychiatric treatment and receive immunotherapy may

demonstrate clinical improvement (Zandi et al. 2014). Such patients have been designated 'synaptic and neuronal autoantibody-associated psychiatric syndromes' (SNAps) by Al-Diwani et al. (2017). Whether such antibodies identified in serum alone affect isolated psychotic symptoms is currently under investigation.

The SINNAPS2 trial (clinical trial number NCT03194815) is a randomised phase II double-blinded placebo-controlled trial designed to explore the utility of immunotherapy for patients with acute psychosis associated with anti-neuronal antibodies including NMDAR and LGI1 (Lennox et al. 2018). This trial may answer whether patients with psychosis and cell surface antibodies improve with immunotherapy treatment. If so, it could fundamentally change how we screen and treat patients with psychosis in the future.

For the present, awareness by psychiatrists of the features of autoimmune encephalitis is essential. Psychiatric features are early clinical signs of NMDAR-Ab encephalitis and neurological features may only evolve when the patient is already under psychiatric care (Barry et al. 2015). Hence, psychiatrists and psychiatry services need to be aware of emerging clinical signs which may be subtle or when the individual fails to respond to standard treatment or potentially has an adverse reaction to treatment with antipsychotics. Training and education of staff on the features of encephalitis is especially important in a time when psychiatric services are becoming increasingly demedicalised (Craddock et al. 2008; Oyebode and Humphreys 2011). In addition to considering the diagnosis, discussing such cases with clinical neurology and agreeing joint management strategies between psychiatrists and neurologists provide the best opportunity to enhance patient care at present.

References

Al-Diwani A, Pollak TA, Langford AE, Lennox BR (2017) Synaptic and neuronal autoantibody-associated psychiatric syndromes: controversies and hypotheses. Front Psych 8:13

Armangue T, Leypoldt F, Málaga I, Raspall-Chaure M, Marti I, Nichter C, Pugh J, Vicente-Rasoamalala M, Lafuente-Hidalgo M, Macaya A, Ke M, Titulaer MJ, Höftberger R, Sheriff H, Glaser C, Dalmau J (2014) Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 75(2):317–323

Baizabal-Carvallo JF, Stocco A, Muscal E, Jankovic J (2013) The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord 28:543–547

Balint B, Jarius S, Nagel S, Haberkorn U, Probst C, Blöcker IM, Bahtz R, Komorowski L, Stöcker W, Kastrup A, Kuthe M, Meinck HM (2014) Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology 82(17):1521–1528

Barry H, Byrne S, Barrett E, Murphy KC, Cotter DR (2015) Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. BJPsych Bull 39:19–23

Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, Cotter DR, Murphy KC (2011) Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. Br J Psychiatry 199(6):508–509

Baulac S, Huberfeld G, Gourfinkel-An I, Mitropoulou G, Beranger A, Prud'homme JF, Baulac M, Brice A, Bruzzone R, LeGuern E (2001) First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. Nat Genet 28(1):46–48

Baykan B, Gungor Tuncer O, Vanli-Yavuz EN, Baysal Kirac L, Gundogdu G, Bebek N, Gurses C, Altindag E, Tuzun E (2018) Delta brush pattern is not unique to NMDAR encephalitis: evaluation of two independent long-term EEG cohorts. Clin EEG Neurosci 49(4):278–284

Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63:182–217

Beck K, Lally J, Shergill SS, Bloomfield MA, Maccabe JH, Gaughran F, Howes OD (2015) Prevalence of serum N-methyl-D-aspartate receptor autoantibodies in refractory psychosis. Br J Psychiatry 206:164–165

Benarroch EE (2012) GABAB receptors: structure, functions, and clinical implications. Neurology 78:578–584

Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB (2011) Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry 168:1303–1310

Bergink V, Armangue T, Titulaer MJ, Markx S, Dalmau J, Kushner SA (2015) Autoimmune encephalitis in postpartum psychosis. Am J Psychiatry 172:901–908

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39

Boronat A, Gelfand JM, Gresa-Arribas N, Jeong HY, Walsh M, Roberts K, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R, Graus F, Rudy B, Dalmau J (2013) Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol 73:120–128

Bowery NG (2010) Historical perspective and emergence of the GABAB receptor. Adv Pharmacol 58:1–18

Brierley JB, Corsellis JAN, Hierons R, Nevin S (1960) Subacute encephalitis of later adult life. Mainly affecting the limbic areas. Brain 83:357–368

Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, Perrin M, Gorman JM, Susser ES (2004) Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry 161:889–895

Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, Vincent A (2001) Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 50:73–78

Butler CR, Miller TD, Kaur MS, Baker IW, Boothroyd GD, Illman NA, Rosenthal CR, Vincent A, Buckley CJ (2014) Persistent anterograde amnesia following limbic encephalitis associated with antibodies to the voltage-gated potassium channel complex. J Neurol Neurosurg Psychiatry 85:387–391

Camdessanche JP, Streichenberger N, Cavillon G, Rogemond V, Jousserand G, Honnorat J, Convers P, Antoine JC (2011) Brain immunohistopathological study in a patient with anti-NMDAR encephalitis. Eur J Neurol 18:929–931

Cannon M, Clarke MC, Cotter DR (2014) Priming the brain for psychosis: maternal inflammation during fetal development and the risk of later psychiatric disorder. Am J Psychiatry 171(9):901–905

Carr I (1982) The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet 1:844–845

Celicanin M, Blaabjerg M, Maersk-Moller C, Beniczky S, Marner L, Thomsen C, Bach FW, Kondziella D, Andersen H, Somnier F, Illes Z, Pinborg LH (2017) Autoimmune encephalitis associated with voltage-gated potassium channels-complex and leucine-rich glioma-inactivated 1 antibodies – a national cohort study. Eur J Neurol 24:999–1005

Choe CU, Karamatskos E, Schattling B, Leypoldt F, Liuzzi G, Gerloff C, Friese MA, Mulert C (2013) A clinical and neurobiological case of IgM Nmda receptor antibody associated encephalitis mimicking bipolar disorder. Psychiatry Res 208:194–196

Corsellis JA, Goldberg GJ, Norton AR (1968) "Limbic encephalitis" and its association with carcinoma. Brain 91:481–496

Cotter D, Takei N, Farrell M, Sham P, Quinn P, Larkin C, Oxford J, Murray RM, O'Callaghan E (1995) Does prenatal exposure to influenza in mice induce pyramidal cell disarray in the dorsal hippocampus? Schizophr Res 16:233–241

Cox CJ, Sharma M, Leckman JF, Zuccolo J, Zuccolo A, Kovoor A, Swedo SE, Cunningham MW (2013) Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol 191:5524–5541

Craddock N, Antebi D, Attenburrow MJ, Bailey A, Carson A, Cowen P, Craddock B, Eagles J, Ebmeier K, Farmer A, Fazel S, Ferrier N, Geddes J, Goodwin G, Harrison P, Hawton K, Hunter S, Jacoby R, Jones I, Keedwell P, Kerr M, Mackin P, Mcguffin P, Macintyre DJ, Mcconville P, Mountain D, O'donovan MC, Owen MJ, Oyebode F, Phillips M, Price J, Shah P, Smith DJ, Walters J, Woodruff P, Young A, Zammit S (2008) Wake-up call for British psychiatry. Br J Psychiatry 193:6–9

Creten C, Van Der Zwaan S, Blankespoor RJ, Maatkamp A, Nicolai J, Van Os J, Schieveld JN (2011) Late onset autism and anti-Nmda-receptor encephalitis. Lancet 378:98

Dahm L, Ott C, Steiner J, Stepniak B, Teegen B, Saschenbrecker S, Hammer C, Borowski K, Begemann M, Lemke S, Rentzsch K, Probst C, Martens H, Wienands J, Spalletta G, Weissenborn K, Stocker W, Ehrenreich H (2014) Seroprevalence of autoantibodies against brain antigens in health and disease. Ann Neurol 76:82–94

Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, Ben-Pazi H, Varadkar S, Aumann TD, Horne MK, Church AJ, Fath T, Brilot F (2012) Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 135:3453–3468

Dalman C, Allebeck P, Gunnell D, Harrison G, Kristensson K, Lewis G, Lofving S, Rasmussen F, Wicks S, Karlsson H (2008) Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. Am J Psychiatry 165:59–65

Dalmau J, Bataller L (2006) Clinical and immunological diversity of limbic encephalitis: a model for paraneoplastic neurologic disorders. Hematol Oncol Clin North Am 20:1319–1335

Dalmau J, Graus F, Rosenblum MK, Posner JB (1992) Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 71:59–72

Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25–36

Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:1091–1098

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-Nmdar encephalitis. Lancet Neurol 10:63–74

Davies G, Welham J, Chant D, Torrey EF, Mcgrath J (2003) A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. Schizophr Bull 29:587–593

De Witte LD, Hoffmann C, Van Mierlo HC, Titulaer MJ, Kahn RS, Martinez-Martinez P, European Consortium of Autoimmune Mental D (2015) Absence of N-methyl-D-aspartate receptor IgG autoantibodies in schizophrenia: the importance of cross-validation studies. JAMA Psychiatry 72:731–733

Deakin J, Lennox BR, Zandi MS (2014) Antibodies to the N-methyl-D-aspartate receptor and other synaptic proteins in psychosis. Biol Psychiatry 75:284–291

Denny-Brown D (1948) Primary sensory neuropathy with muscular changes associated with carcinoma. J Neurol Neurosurg Psychiatry 11:73–87

Dogan Onugoren M, Deuretzbacher D, Haensch CA, Hagedorn HJ, Halve S, Isenmann S, Kramme C, Lohner H, Melzer N, Monotti R, Presslauer S, Schabitz WR, Steffanoni S, Stoeck K, Strittmatter M, Stogbauer F, Trinka E, Von Oertzen TJ, Wiendl H, Woermann FG, Bien CG (2015) Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. J Neurol Neurosurg Psychiatry 86:965–972

Duan BC, Weng WC, Lin KL, Wong LC, Li ST, Hsu MH, Lin JJ, Fan PC, Lin MI, Chiu NC, Lin YC, Wang HS, Hung KL, Lee WT (2016) Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis: a nationwide study in Taiwan. Medicine (Baltimore) 95: e4365

Elamin M, Lonergan R, Killeen RP, O'riordan S, Tubridy N, Mcguigan C (2015) Posterior cortical and white matter changes on Mri in anti-Ampa receptor antibody encephalitis. Neurol Neuroimmunol Neuroinflamm 2:e118

Farrelly L, Focking M, Piontkewitz Y, Dicker P, English J, Wynne K, Cannon M, Cagney G, Cotter DR (2015) Maternal immune activation induces changes in myelin and metabolic proteins, some of which can be prevented with risperidone in adolescence. Dev Neurosci 37:43–55

Finke C, Kopp UA, Pruss H, Dalmau J, Wandinger KP, Ploner CJ (2012) Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 83:195–198

Fukata Y, Lovero KL, Iwanaga T, Watanabe A, Yokoi N, Tabuchi K, Shigemoto R, Nicoll RA, Fukata M (2010) Disruption of LGI1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. Proc Natl Acad Sci U S A 107:3799–3804

Gaughran F, Lally J, Beck K, McCormack R, Gardner-Sood P, Coutinho E, Jacobson L, Lang B, Sainz-Fuertes R, Papanastasiou E, Di Forti M, Nicholson T, Vincent A, Murray RM (2018) Brain-relevant antibodies in first-episode psychosis: a matched case-control study. Psychol Med 48(8):1257–1263

Gotkine M, Ben-Hur T, Vincent A, Vaknin-Dembinsky A (2011) Limbic encephalitis presenting as a post-partum psychiatric condition. J Neurol Sci 308:152–154

Grain R, Lally J, Stubbs B, Malik S, Lemince A, Nicholson TR, Murray RM, Gaughran F (2017) Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: a systematic review, meta-analysis, and case series. Psychiatry Clin Neurosci 71:678–689

Graus F, Cordon-Cardo C, Posner JB (1985) Neuronal antinuclear antibody in sensory neuronopathy from lung cancer. Neurology 35:538–543

Graus F, Boronat A, Xifro X, Boix M, Svigelj V, Garcia A, Palomino A, Sabater L, Alberch J, Saiz A (2010) The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology 74:857–859

Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Hoftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Pruss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostasy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15:391–404

Gregor A, Albrecht B, Bader I, Bijlsma EK, Ekici AB, Engels H, Hackmann K, Horn D, Hoyer J, Klapecki J, Kohlhase J, Maystadt I, Nagl S, Prott E, Tinschert S, Ullmann R, Wohlleber E, Woods G, Reis A, Rauch A, Zweier C (2011) Expanding the clinical spectrum associated with defects in CNTNAP2 and NRXN1. BMC Med Genet 12:106

Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, Mccracken L, Leypoldt F, Gleichman AJ, Balice-Gordon R, Rosenfeld MR, Lynch D, Graus F, Dalmau J (2014) Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 13:167–177

Hammer C, Stepniak B, Schneider A, Papiol S, Tantra M, Begemann M, Siren AL, Pardo LA, Sperling S, Mohd Jofrry S, Gurvich A, Jensen N, Ostmeier K, Luhder F, Probst C, Martens H, Gillis M, Saher G, Assogna F, Spalletta G, Stocker W, Schulz TF, Nave KA, Ehrenreich H (2014) Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. Mol Psychiatry 19:1143–1149

Hara M, Arino H, Petit-Pedrol M, Sabater L, Titulaer MJ, Martinez-Hernandez E, Schreurs MW, Rosenfeld MR, Graus F, Dalmau J (2017) DPPX antibody-associated encephalitis: main syndrome and antibody effects. Neurology 88:1340–1348

Haussleiter IS, Emons B, Schaub M, Borowski K, Brune M, Wandinger KP, Juckel G (2012) Investigation of antibodies against synaptic proteins in a cross-sectional cohort of psychotic patients. Schizophr Res 140:258–259

Henley JM, Wilkinson KA (2016) Synaptic AMPA receptor composition in development, plasticity and disease. Nat Rev Neurosci 17:337–350

Hoftberger R, Titulaer MJ, Sabater L, Dome B, Rozsas A, Hegedus B, Hoda MA, Laszlo V, Ankersmit HJ, Harms L, Boyero S, De Felipe A, Saiz A, Dalmau J, Graus F (2013) Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology 81:1500–1506

Hoftberger R, Van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, Paredes M, Sabater L, Saiz A, Titulaer MJ, Graus F, Dalmau J (2015) Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. Neurology 84:2403–2412

Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, Parsons TD, Lynch DR, Dalmau J, Balice-Gordon RJ (2010) Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 30:5866–5875

Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, Peles E, Buckley C, Lang B, Vincent A (2010a) Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 133:2734–2748

Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese MA, Galea I, Kullmann DM, Beeson D, Lang B, Bien CG, Vincent A (2010b) N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 133:1655–1667

Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, Zuliani L, Watanabe O, Lang B, Buckley C, Vincent A (2012) Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol 72:241–255

Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, Schott JM, Armstrong RJ, S Zagami A, Bleasel A, Somerville ER, Smith SM, Vincent A (2011) Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 69(5):892–900

Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schneider SA, Pettingill P, Pettingill R, Waters P, Thomas A, Voets NL, Cardoso MJ, Cash DM, Manning EN, Lang B, Smith SJ, Vincent A, Johnson MR (2013) Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 136:3151–3162

Jackman C, Horn ND, Molleston JP, Sokol DK (2009) Gene associated with seizures, autism, and hepatomegaly in an Amish girl. Pediatr Neurol 40:310–313

Jarius S, Steinmeyer F, Knobel A, Streitberger K, Hotter B, Horn S, Heuer H, Schreiber SJ, Wilhelm T, Trefzer U, Wildemann B, Ruprecht K (2013) GABAB receptor antibodies in paraneoplastic cerebellar ataxia. J Neuroimmunol 256:94–96

Javitt DC (2007) Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol 78:69–108

Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308

Kappelmann N, Khandaker GM, Dal H, Stochl J, Kosidou K, Jones PB, Dalman C, Karlsson H (2019) Systemic inflammation and intelligence in early adulthood and subsequent risk of schizophrenia and other non-affective psychoses: a longitudinal cohort and co-relative study. Psychol Med 49:295–302

Kaulin YA, De Santiago-Castillo JA, Rocha CA, Nadal MS, Rudy B, Covarrubias M (2009) The dipeptidyl-peptidase-like protein DPP6 determines the unitary conductance of neuronal Kv4.2 channels. J Neurosci 29:3242–3251

Kayser MS, Dalmau J (2016) Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Schizophr Res 176:36–40

Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J (2013) Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. JAMA Neurol 70:1133–1139

Kelleher E, Corvin A (2013) In: Mitchell KJE (ed) The genetics of neurodevelopmental disorder. Wiley, Cambridge

Khandaker GM, Zimbron J, Dalman C, Lewis G, Jones PB (2012) Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. Schizophr Res 139:161–168

Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB (2014) Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry 71:1121–1128

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2:258–270

Khandaker GM, Dalman C, Kappelmann N, Stochl J, Dal H, Kosidou K, Jones PB, Karlsson H (2018) Association of childhood infection with IQ and adult nonaffective psychosis in Swedish men: a population-based longitudinal cohort and co-relative study. JAMA Psychiatry 75:356–362

Kim TJ, Lee ST, Shin JW, Moon J, Lim JA, Byun JI, Shin YW, Lee KJ, Jung KH, Kim YS, Park KI, Chu K, Lee SK (2014) Clinical manifestations and outcomes of the treatment of patients with GABAB encephalitis. J Neuroimmunol 270:45–50

Kim TJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, Shin YW, Jun JS, Lee HS, Lee WJ, Yang AR, Choi Y, Park KI, Jung KH, Jung KY, Kim M, Lee SK, Chu K (2017) Anti-LGI1 encephalitis is associated with unique Hla subtypes. Ann Neurol 81:183–192

Klein CJ, Lennon VA, Aston PA, Mckeon A, O'toole O, Quek A, Pittock SJ (2013) Insights from LGI1 and CASPR2 potassium channel complex autoantibody subtyping. JAMA Neurol 70:229–234

Kraepelin E (1899) Psychiatrie: Ein lehrbuch fur studierende und aerzte. JA Barth, Leipzig

Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, Mata S, Kremens D, Vitaliani R, Geschwind MD, Bataller L, Kalb RG, Davis R, Graus F, Lynch DR, Balice-Gordon R, Dalmau J (2009) AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 65:424–434

Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, Cowell JK, Dalmau J (2010) Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol 9:776–785

Lalic T, Pettingill P, Vincent A, Capogna M (2011) Human limbic encephalitis serum enhances hippocampal mossy fiber-CA3 pyramidal cell synaptic transmission. Epilepsia 52:121–131

Lancaster E, Dalmau J (2012) Neuronal autoantigens–pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 8:380–390

Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, Friedman D, Skeen MB, Grisold W, Kimura A, Ohta K, Iizuka T, Guzman M, Graus F, Moss SJ, Balice-Gordon R, Dalmau J (2010) Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 9:67–76

Lancaster E, Huijbers MG, Bar V, Boronat A, Wong A, Martinez-Hernandez E, Wilson C, Jacobs D, Lai M, Walker RW, Graus F, Bataller L, Illa I, Markx S, Strauss KA, Peles E, Scherer SS, Dalmau J (2011a) Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 69:303–311

Lancaster E, Martinez-Hernandez E, Dalmau J (2011b) Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 77:179–189

Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulos M, Weaver S, Antoine JC, Liebers E, Kornblum C, Bien CG, Honnorat J, Wong S, Xu J, Contractor A, Balice-Gordon R, Dalmau J (2011c) Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology 77:1698–1701

Lang B, Makuch M, Moloney T, Dettmann I, Mindorf S, Probst C, Stoecker W, Buckley C, Newton CR, Leite MI, Maddison P, Komorowski L, Adcock J, Vincent A, Waters P, Irani SR (2017) Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies. J Neurol Neurosurg Psychiatry 88:353–361

Lejuste F, Thomas L, Picard G, Desestret V, Ducray F, Rogemond V, Psimaras D, Antoine JC, Delattre JY, Groc L, Leboyer M, Honnorat J (2016) Neuroleptic intolerance in patients with anti-NMDAR encephalitis. Neurol Neuroimmunol Neuroinflamm 3:e280

Lennox BR, Coles AJ, Vincent A (2012) Antibody-mediated encephalitis: a treatable cause of schizophrenia. Br J Psychiatry 200(2):92–94

Lennox BR, Palmer-Cooper EC, Pollak T, Hainsworth J, Marks J, Jacobson L, Lang B, Fox H, Ferry B, Scoriels L, Crowley H, Jones PB, Harrison PJ, Vincent A (2017) Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. Lancet Psychiatry 4:42–48

Lennox BR, Tomei G, Vincent SA, Yeeles K, Pollard R, Palmer-Cooper E, Jones P, Zandi MS, Coles A (2018) Study of immunotherapy in antibody positive psychosis: feasibility and acceptability (SINAPPS1). J Neurol Neurosurg Psychiatry. pii: jnnp-2018-318124. https://doi.org/10.1136/jnnp-2018-318124

Leypoldt F, Armangue T, Dalmau J (2015) Autoimmune encephalopathies. Ann N Y Acad Sci 1338:94–114

Leypoldt F, de Witte L, Lancaster E, Titulaer MJ (2017) Serum neuronal cell-surface antibodies in first-episode psychosis. Lancet Psychiatry 4(3):186–187

Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P, Baruzzi A, Carey T, Gambetti P, Lugaresi E, Montagna P (2001) Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 124:2417–2426

Malhotra D, Sebat J (2012) CNVS: harbingers of a rare variant revolution in psychiatric genetics. Cell 148:1223–1241

Malter MP, Frisch C, Schoene-Bake JC, Helmstaedter C, Wandinger KP, Stoecker W, Urbach H, Surges R, Elger CE, Vincent AV, Bien CG (2014) Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol 261:1695–1705

Mantere O, Saarela M, Kieseppa T, Raij T, Mantyla T, Lindgren M, Rikandi E, Stoecker W, Teegen B, Suvisaari J (2017) Anti-neuronal anti-bodies in patients with early psychosis. Schizophr Res 192:404–407

Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J (2011) Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 77:589–593

Masdeu JC, Gonzalez-Pinto A, Matute C, Ruiz De Azua S, Palomino A, De Leon J, Berman KF, Dalmau J (2012) Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia. Am J Psychiatry 169:1120–1121

Masopust J, Andrys C, Bazant J, Vysata O, Kuca K, Valis M (2015) Anti-NMDA receptor antibodies in patients with a first episode of schizophrenia. Neuropsychiatr Dis Treat 11:619–623

Mat A, Adler H, Merwick A, Chadwick G, Gullo G, Dalmau JO, Tubridy N (2013) Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology 80:1349–1350

Mayer ML, Westbrook GL (1987) Permeation and block of N-methyl-D-aspartic acid receptor channels by divalent cations in mouse cultured central neurones. J Physiol 394:501–527

Mayer ML, Westbrook GL, Guthrie PB (1984) Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature 309:261–263

Mcgrath JJ, Welham JL (1999) Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. Schizophr Res 35:237–242

Mckeon GL, Scott JG, Spooner DM, Ryan AE, Blum S, Gillis D, Langguth D, Robinson GA (2016) Cognitive and social functioning deficits after anti-N-methyl-D-aspartate receptor encephalitis: an exploratory case series. J Int Neuropsychol Soc 22:828–838

Mckeon GL, Robinson GA, Ryan AE, Blum S, Gillis D, Finke C, Scott JG (2017) Cognitive outcomes following anti-N-methyl-D-aspartate receptor encephalitis: a systematic review. J Clin Exp Neuropsychol 40:1–19

Metcalf SA, Jones PB, Nordstrom T, Timonen M, Maki P, Miettunen J, Jaaskelainen E, Jarvelin MR, Stochl J, Murray GK, Veijola J, Khandaker GM (2017) Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: a prospective birth cohort study. Brain Behav Immun 59:253–259

Midgley L, Kelleher E, Zandi MS (2018) Autoimmune encephalitis. Br J Hosp Med (Lond) 79(9): C134–C137. https://doi.org/10.12968/hmed.2018.79.9.C134

Mohammad SS, Sinclair K, Pillai S, Merheb V, Aumann TD, Gill D, Dale RC, Brilot F (2014) Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-methyl-D-aspartate receptor or dopamine-2 receptor. Mov Disord 29:117–122

Mortensen PB, Norgaard-Pedersen B, Waltoft BL, Sorensen TL, Hougaard D, Yolken RH (2007) Early infections of Toxoplasma gondii and the later development of schizophrenia. Schizophr Bull 33:741–744

Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ (2014) Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 76:108–119

Muller UJ, Teegen B, Probst C, Bernstein HG, Busse S, Bogerts B, Schiltz K, Stoecker W, Steiner J (2014) Absence of dopamine receptor serum autoantibodies in schizophrenia patients with an acute disease episode. Schizophr Res 158:272–274

Navarro V, Kas A, Apartis E, Chami L, Rogemond V, Levy P, Psimaras D, Habert MO, Baulac M, Delattre JY, Honnorat J (2016) Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. Brain 139:1079–1093

Newcomer JW, Krystal JH (2001) NMDA receptor regulation of memory and behavior in humans. Hippocampus 11:529–542

Newey CR, Sarwal A (2014) Hyponatremia and voltage gated potassium channel antibody associated limbic encephalitis. J Neurol Neurophysiol 5:195

Nokura K, Yamamoto H, Okawara Y, Koga H, Osawa H, Sakai K (1997) Reversible limbic encephalitis caused by ovarian teratoma. Acta Neurol Scand 95:367–373

Noll R (2004) Historical review: autointoxication and focal infection theories of dementia praecox. World J Biol Psychiatry 5(2):66–72

Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307:462–465

O'Callaghan E, Sham P, Takei N, Glover G, Murray RM (1991) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. Lancet 337:1248–1250

Ohkawa T, Fukata Y, Yamasaki M, Miyazaki T, Yokoi N, Takashima H, Watanabe M, Watanabe O, Fukata M (2013) Autoantibodies to epilepsy-related Lgi1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptors. J Neurosci 33:18161–18174

Okamura H, Oomori N, Uchitomi Y (1997) An acutely confused 15-year-old girl. Lancet 350:488

Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley TA, Hauser WA (2004) LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology 62:1120–1126

Oyebode F, Humphreys M (2011) The future of psychiatry. Br J Psychiatry 199:439–440

Pagano A, Rovelli G, Mosbacher J, Lohmann T, Duthey B, Stauffer D, Ristig D, Schuler V, Meigel I, Lampert C, Stein T, Prezeau L, Blahos J, Pin J, Froestl W, Kuhn R, Heid J, Kaupmann K, Bettler B (2001) C-terminal interaction is essential for surface trafficking but not for heteromeric assembly of GABA(b) receptors. J Neurosci 21:1189–1202

Pathmanandavel K, Starling J, Merheb V, Ramanathan S, Sinmaz N, Dale RC, Brilot F (2015) Antibodies to surface dopamine-2 receptor and N-methyl-D-aspartate receptor in the first episode of acute psychosis in children. Biol Psychiatry 77:537–547

Pearlman DM, Najjar S (2014) Meta-analysis of the association between N-methyl-d-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. Schizophr Res 157:249–258

Peery HE, Day GS, Dunn S, Fritzler MJ, Pruss H, De Souza C, Doja A, Mossman K, Resch L, Xia C, Sakic B, Belbeck L, Foster WG (2012) Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 11:863–872

Perogamvros L, Schnider A, Leemann B (2012) The role of NMDA receptors in human eating behavior: evidence from a case of anti-NMDA receptor encephalitis. Cogn Behav Neurol 25:93–97

Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, Mccracken L, Martinez-Hernandez E, Mason WP, Kruer MC, Ritacco DG, Grisold W, Meaney BF, Alcala C, Sillevis-Smitt P, Titulaer MJ, Balice-Gordon R, Graus F, Dalmau J (2014) Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol 13:276–286

Pettingill P, Kramer HB, Coebergh JA, Pettingill R, Maxwell S, Nibber A, Malaspina A, Jacob A, Irani SR, Buckley C, Beeson D, Lang B, Waters P, Vincent A (2015) Antibodies to GABAA receptor alpha1 and gamma2 subunits: clinical and serologic characterization. Neurology 84:1233–1241

Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, Trimmer JS, Shrager P, Peles E (1999) Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels. Neuron 24:1037–1047

Pollak TA, Lennox BR (2018) Time for a change of practice: the real-world value of testing for neuronal autoantibodies in acute first-episode psychosis. BJPsych Open 4(4):262–264

Pollak TA, Moran N (2017) Emergence of new-onset psychotic disorder following recovery from LGI1 antibody-associated limbic encephalitis. BMJ Case Rep 2017. https://doi.org/10.1136/bcr-2016-218328

Pollak TA, Beck K, Irani SR, Howes OD, David AS, Mcguire PK (2016) Autoantibodies to central nervous system neuronal surface antigens: psychiatric symptoms and psychopharmacological implications. Psychopharmacology (Berl) 233:1605–1621

Pruss H, Lennox BR (2016) Emerging psychiatric syndromes associated with antivoltage-gated potassium channel complex antibodies. J Neurol Neurosurg Psychiatry 87:1242–1247

Pruss H, Rothkirch M, Kopp U, Hamer HM, Hagge M, Sterzer P, Saschenbrecker S, Stocker W, Harms L, Endres M (2014) Limbic encephalitis with mGluR5 antibodies and immunotherapy-responsive prosopagnosia. Neurology 83:1384–1386

Purcell SM, Wray NR, Stone JL, Visscher PM, O'donovan MC, Sullivan PF, Sklar P (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752

Quaranta G, Maremmani AG, Perugi G (2015) Anti-AMPA-receptor encephalitis presenting as a rapid-cycling bipolar disorder in a young woman with turner syndrome. Case Rep Psychiatry 2015:273192

Quinn TJ, Dawson J, Walters M (2008) Dr John Rankin; his life, legacy and the 50th anniversary of the Rankin Stroke Scale. Scott Med J 53:44–47

Rhoads J, Guirgis H, Mcknight C, Duchemin AM (2011) Lack of anti-NMDA receptor autoantibodies in the serum of subjects with schizophrenia. Schizophr Res 129:213–214

Rossi M, Mead S, Collinge J, Rudge P, Vincent A (2015) Neuronal antibodies in patients with suspected or confirmed sporadic Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 86:692–694

Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D (2012) Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 79:1094–1100

Schulz P, Pruss H (2015) "Hirnsymptome bei Carcinomatose" – Hermann oppenheim and an early description of a paraneoplastic neurological syndrome. J Hist Neurosci 24:371–377

Scott JG, Gillis D, Ryan AE, Hargovan H, Gundarpi N, McKeon G et al (2018) The prevalence and treatment outcomes of antineuronal antibody-positive patients admitted with first episode of psychosis. BJPsych Open 4(2):69–74

Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Crowe RR, Oksenberg JR, Mirel DB, Kendler KS, Freedman R, Gejman PV (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460:753–757

Shillito P, Molenaar PC, Vincent A, Leys K, Zheng W, Van Den Berg RJ, Plomp JJ, Van Kempen GT, Chauplannaz G, Wintzen AR et al (1995) Acquired neuromyotonia: evidence for autoantibodies directed against K+ channels of peripheral nerves. Ann Neurol 38:714–722

Shin YW, Lee ST, Shin JW, Moon J, Lim JA, Byun JI, Kim TJ, Lee KJ, Kim YS, Park KI, Jung KH, Lee SK, Chu K (2013) VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neuroimmunol 265:75–81

Sieghart W (2006) Structure, pharmacology, and function of Gabaa receptor subtypes. Adv Pharmacol 54:231–263

Spatola M, Petit-Pedrol M, Simabukuro MM, Armangue T, Castro FJ, Barcelo Artigues MI, Julià Benique MR, Benson L, Gorman M, Felipe A, Caparó Oblitas RL, Rosenfeld MR, Graus F, Dalmau J (2017) Investigations in GABAA receptor antibody-associated encephalitis. Neurology 88(11):1012–1020

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietilainen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Borglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Bottcher Y, Olesen J, Breuer R, Moller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Rethelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA, Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, De Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, GE D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jonsson EG, Terenius L, Agartz I, Petursson H, Nothen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, ST Clair D, Goldstein DB, Stefansson K, Collier DA (2009) Common variants conferring risk of schizophrenia. Nature 460:744–747

Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein HG, Vielhaber S, Kastner A, Skalej M, Jordan W, Schiltz K, Klingbeil C, Wandinger KP, Bogerts B, Stoecker W (2013) Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry 70:271–278

Stone JM, Dietrich C, Edden R, Mehta MA, De Simoni S, Reed LJ, Krystal JH, Nutt D, Barker GJ (2012) Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. Mol Psychiatry 17:664–665

Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, Stephan DA, Morton DH (2006) Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med 354:1370–1377

Striano P, Busolin G, Santulli L, Leonardi E, Coppola A, Vitiello L, Rigon L, Michelucci R, Tosatto SC, Striano S, Nobile C (2011) Familial temporal lobe epilepsy with psychic auras associated with a novel LGI1 mutation. Neurology 76:1173–1176

Sun Y, Wu Z, Kong S, Jiang D, Pitre A, Wang Y, Chen G (2013) Regulation of epileptiform activity by two distinct subtypes of extrasynaptic GABAA receptors. Mol Brain 6(1):21. https://doi.org/10.1186/1756-6606-6-21

Titulaer MJ, Mccracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12:157–165

Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, Appendino JP, Lucchinetti CF, Matsumoto JY, Pittock SJ, Sandroni P, Tippmann-Peikert M, Wirrell EC, Mckeon A (2014) DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology 83:1797–1803

Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, Mori A, Hishikawa Y, Shimizu T, Nishino S (2012) Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. BMC Psychiatry 12:37

Usiello A, Baik JH, Rouge-Pont F, Picetti R, Dierich A, Lemeur M, Piazza PV, Borrelli E (2000) Distinct functions of the two isoforms of dopamine D2 receptors. Nature 408:199–203

Van Sonderen A, Arino H, Petit-Pedrol M, Leypoldt F, Kortvelyessy P, Wandinger KP, Lancaster E, Wirtz PW, Schreurs MW, Sillevis Smitt PA, Graus F, Dalmau J, Titulaer MJ (2016a) The clinical spectrum of Caspr2 antibody-associated disease. Neurology 87:521–528

Van Sonderen A, Schreurs MW, Wirtz PW, Sillevis Smitt PA, Titulaer MJ (2016b) From VGKC to LGI1 and Caspr2 encephalitis: the evolution of a disease entity over time. Autoimmun Rev 15:970–974

Van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, De Bruijn MA, Van Coevorden-Hameete MH, Wirtz PW, Schreurs MW, Sillevis Smitt PA, Titulaer MJ (2016c) Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. Neurology 87:1449–1456

Van Sonderen A, Roelen DL, Stoop JA, Verdijk RM, Haasnoot GW, Thijs RD, Wirtz PW, Schreurs MW, Claas FH, Sillevis Smitt PA, Titulaer MJ (2017) Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. Ann Neurol 81:193–198

Varley J, Vincent A, Irani SR (2015) Clinical and experimental studies of potentially pathogenic brain-directed autoantibodies: current knowledge and future directions. J Neurol 262:1081–1095

Varley J, Taylor J, Irani SR (2017) Autoantibody-mediated diseases of the CNS: structure, dysfunction and therapy. Neuropharmacology 132:71–82

Verkerk AJ, Mathews CA, Joosse M, Eussen BH, Heutink P, Oostra BA (2003) CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. Genomics 82:1–9

Vincent A, Irani SR (2010) Caspr2 antibodies in patients with thymomas. J Thorac Oncol 5:S277–S280

Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J (2005) Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 58:594–604

Wagner-Jauregg J, Bruetsch WL (1946) The history of the malaria treatment of general paralysis. Am J Psychiatry 102:577–582

Waxman EA, Lynch DR (2005) N-methyl-D-aspartate receptor subtypes: multiple roles in excitotoxicity and neurological disease. Neuroscientist 11:37–49

Whalley HC, O'connell G, Sussmann JE, Peel A, Stanfield AC, Hayiou-Thomas ME, Johnstone EC, Lawrie SM, Mcintosh AM, Hall J (2011) Genetic variation in CNTNAP2 alters brain function during linguistic processing in healthy individuals. Am J Med Genet B Neuropsychiatr Genet 156b:941–948

Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, Smith M, Lim M, Wassmer E, Vincent A (2015) N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child 100(6):521–526

Xi B, Chen J, Yang L, Wang W, Fu M, Wang C (2011) GABBR1 gene polymorphism(G1465A)is associated with temporal lobe epilepsy. Epilepsy Res 96:58–63

Zai G, Arnold P, Burroughs E, Barr CL, Richter MA, Kennedy JL (2005) Evidence for the gamma-amino-butyric acid type B receptor 1 (GABBR1) gene as a susceptibility factor in obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet 134b:25–29

Zai CC, Tiwari AK, King N, De Luca V, Mueller DJ, Shaikh S, Wong GW, Meltzer HY, Lieberman JA, Kennedy JL (2009) Association study of the gamma-aminobutyric acid type a receptor gamma2 subunit gene with schizophrenia. Schizophr Res 114:33–38

Zandi MS, Irani SR, Lang B, Waters P, Jones PB, Mckenna P, Coles AJ, Vincent A, Lennox BR (2011) Disease-relevant autoantibodies in first episode schizophrenia. J Neurol 258:686–688

Zandi MS, Deakin JB, Morris K, Buckley C, Jacobson L, Scoriels L, Cox AL, Coles AJ, Jones PB, Vincent A, Lennox BR (2014) Immunotherapy for patients with acute psychosis and serum N-methyl d-aspartate receptor (NMDAR) antibodies: a description of a treated case series. Schizophr Res 160:193–195

Zhou L, Messing A, Chiu SY (1999) Determinants of excitability at transition zones in Kv1.1-deficient myelinated nerves. J Neurosci 19:5768–5781

Zweier C, De Jong EK, Zweier M, Orrico A, Ousager LB, Collins AL, Bijlsma EK, Oortveld MA, Ekici AB, Reis A, Schenck A, Rauch A (2009) CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. Am J Hum Genet 85:655–666