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Neuroimmunological antibody-mediated encephalitis and implications for diagnosis and therapy in neuropsychiatry

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Review Article

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Abbreviations:
ADAM: A disintegrin and metalloprotease, NMDA: N-methyl-D-aspartate, MRI: magnetic resonance imaging, EPTP: epitempin, EEG: electroencephalography, FDG: fluorodeoxyglucose, NMDARE: NMDA receptor encephalitis, CSF: cerebrospinal fluid, HSV: herpes simplex virus, IVIg: intravenous immunoglobulin, BBB: blood–brain barrier, GAD: glutamic acid decarboxylase, GABA: γ-aminobutyric acid, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, LGI1: leucine-rich glioma-inactivated 1, PANDAS: pediatric autoimmune neuropsychiatric disorder associated with streptococcus, PET: positron emission tomography

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Abstract

The past decade has seen a surge of reports and investigations into cases of autoimmune-mediated encephalitis. The increasing recognition of these disorders is especially of relevance to the fields of neurology and psychiatry. Autoimmune encephalitis involves antibodies against synaptic receptors, neuronal cell surface proteins and intracellular targets. These disorders feature prominent symptoms of cognitive impairment and behavioural changes, often associated with the presence of seizures. Early in the clinical course, autoimmune encephalitis may manifest as psychiatric symptoms of psychosis and involve psychiatry as an initial point of contact. Although commonly associated with malignancy, these disorders can present in the absence of an inciting neoplasm. The identification of autoimmune encephalitis is of clinical importance as a large proportion of individuals experience a response to immunotherapy. This review focuses on the current state of knowledge on N-methyl-D-aspartate (NMDA) receptor-associated encephalitis and limbic encephalitis, the latter predominantly involving antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, the γ-aminobutyric acid $(GABA)_B$ receptor and leucine-rich glioma-inactivated 1 (LGI1) protein. In addition, we briefly describe anti-dopamine D2 receptor encephalitis. A summary of the literature will focus on common clinical presentations and course, diagnostic approaches and response to treatment. Since a substantial proportion of patients with autoimmune encephalitis exhibit symptoms of psychosis, the relevance of this disorder to theories of psychosis and schizophrenia will also be discussed.

Summations

- There are multiple types of autoimmune encephalitis mediated by antibodies against synaptic receptors, neuronal cell surface proteins and intracellular targets.
- These patients often present with predominant psychiatric symptoms and may have psychiatry as an initial point of contact.
- A substantial proportion of patients respond favourably to immunotherapy.

Considerations

- Initial diagnosis of autoimmune encephalitis remains a challenge, sometimes presenting with normal imaging, CSF and serological investigations.
- Although often associated with malignancy, autoimmune encephalitis often presents without discovery of inciting cancer.

Introduction

Autoimmune encephalitis (also known as antibody-mediated encephalitis) is an increasingly recognised group of conditions (Table 1) with neuropsychiatric presentations. Given the increasing attention to immune-mediated aetiologies of encephalitis, further study is underway to develop approaches to these conditions as well as to delineate them from infectious causes (Graus *et al.*, 2016). Current research is also investigating the link between chronic psychotic disorders and inflammation (Herken & Pruss, 2017; Riedmuller & Muller, 2017). Generally, autoimmune encephalitis involves antibodies against the neuronal cell surface proteins, synaptic proteins or intracellular targets (Lancaster & Dalmau, 2012; Dalmau & Graus, 2018). Systemic/rheumatic conditions such as systemic lupus erythematosus and vasculitis can also present with neuropsychiatric symptoms (Oldham, 2017); however, these syndromes are outside the scope of this review. The antibody-mediated encephalitis examples in this review do not usually have other systemic presentations, distinguishing them from many autoimmune disorders with

Table 1. Selected types of antibody-mediated encephalitis and their associated general classification

Antibody target	Antigen location	Syndrome classification	Known epitopes
NMDA	Cell surface	NMDA receptor encephalitis	GluN1
AMPA	Cell surface	Limbic encephalitis	GluR1, GluR2
$GABA_B$	Cell surface	Limbic encephalitis	$GABA_{B1}$
D2	Cell surface	Basal ganglia encephalitis	D2R N-terminus
Ma2	Intracellular	Limbic encephalitis	
Hu	Intracellular	Limbic encephalitis	
LGI-1	Cell surface	Limbic encephalitis	LRR and EPTP domains
GAD65	Intracellular/ synaptic	Limbic encephalitis (stiff person syndrome)	GAD65

LRR, leucine-rich repeat; EPTP, epitempin.

neuropsychiatric presentations. Although there is some overlap with other autoimmune-mediated conditions such as stiff person spectrum syndrome and neuromyelitis optica, the altered mental status, impaired cognition and psychotic symptoms usually seen in antibody-mediated encephalitis are not typical in these other conditions (Dalmau & Graus, 2018), which are also outside the scope of this review.

Immune-mediated encephalitis can be organised in multiple ways such as by neuroanatomical correlates; however, we have organised our review according to the antibodies involved and their pathological mechanisms – antibodies against intracellular antigens, synaptic receptors and cell surface proteins. Given that the neuropsychiatric symptoms of antibody-associated encephalitis may be the first presentation of neoplastic processes, these disorders have garnered interest with regard to their early identification, diagnosis and appropriate treatment.

This review focuses on anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (NMDARE) and antibodies against intracellular antigens, synaptic receptors and cell surface proteins with an emphasis on clinical presentation in adults. Limbic encephalitis mediated by antibodies against AMPA receptors, $GABA_B$ receptors and LGI-1 will also be explored.

To construct this review, we searched PubMed, Web of Science and PsycINFO databases with the following search terms: 'antibody-mediated encephalitis', 'autoimmune encephalitis', 'NMDA receptor encephalitis', 'limbic encephalitis', 'AMPA encephalitis', 'GABA encephalitis', 'dopamine D2 encephalitis' and 'leucine-rich glioma-inactivated 1 encephalitis'. We reviewed articles published between 2000 to 2018 inclusive in addition to the references cited within.

NMDARE

NMDARE was first described in a case series of 12 patients with neuropsychiatric symptoms in association with teratomas in 2007 (Dalmau *et al.*, 2007). Investigative findings revealed that these patients had antibodies to the NMDA receptor subunits in either the cerebrospinal fluid (CSF) or the serum. Cases of neurologic and cognitive dysfunction in patients with ovarian teratomas suggested an immune-related mechanism (Dalmau *et al.*, 2007). Subsequent studies have shown that the majority of cases first draw clinical attention due to psychiatric symptoms (Dalmau *et al.*, 2008). Current models of NMDARE link tumours with proposed pathophysiology, clinical presentation and response to treatment; however, this association is not always straightforward (Irani *et al.*, 2010b; Dalmau *et al.*, 2011).

Although the exact prevalence is not known, the literature suggests that NMDARE is more common than any single viral cause of encephalitis and appears to be the most common antibody-mediated encephalitis (Dalmau *et al.*, 2011; Gable *et al.*, 2012). The incidence of NMDARE is reported to be 5 in 100 000 people per year, although this is thought to be an underestimate due to the previous lack of awareness of the diagnosis (Dalmau & Graus, 2018). Furthermore, Granerod *et al.* (2010) found that antibody-related encephalitis cases tended to have more longer-lasting residual dysfunction and higher mortality rates in comparison to encephalitis of infectious aetiologies. Cases of NMDARE are most common in children and young adults, with a median age of 21 years, but have been diagnosed in patients as young as 2 months (Titulaer *et al.*, 2013; Armangue *et al.*, 2014). NMDARE affects younger women with a 4:1 preponderance, but this distribution does not apply to populations at ages <12 or >45 years of age. NMDARE is also more common in patients of African descent (Titulaer *et al.*, 2013).

NMDARE has mainly been associated with ovarian teratomas, which have been seen in up to 58% of younger female patients. Other extragonadal teratoma presentations are also seen, although much less commonly (Titulaer *et al.*, 2013). Additional malignancies and neoplasms associated with NMDARE include mediastinal and testicular teratomas, sex cord stromal tumours, small cell lung cancer, breast cancer, thymic carcinoma, pancreatic cancer, neuroblastomas and Hodgkin's lymphoma (Venkatesan & Adatia, 2017). Cases of men and children with NMDARE have a weaker association with tumours in comparison to women. The presence of neoplasms in antibody-mediated encephalitis can influence the treatment approach and prognosis; these topics are explored later in this review.

Pathophysiology

The pathophysiology of NMDARE is thought to involve the production of antibodies against the GluN1 subunit of the NMDA receptor. In tumour-positive patients, these antibodies may be synthesised in response to the presentation of tumour cells with antigens similar to the NMDA receptor (Dalmau *et al.*, 2017; Dalmau & Graus, 2018). Interestingly, ovarian teratomas associated with NMDARE appear to have differing histopathological features in comparison to sporadic teratomas, including a higher frequency of containing nervous tissue components and expression of GluN1 by glial cells, as well as demonstrating prominent infiltration of nervous tissue by immune cells (Chefdeville *et al.*, 2019). Antibodies may traverse the blood–brain barrier (BBB) and cross-link with cell surface NMDA receptors, leading to endocytosis. Of note, increased clinical severity and symptom progression correlate with increased antibody titre and decreased concentration of NMDA receptors. As antibody titres decrease with treatment, symptoms resolve in reverse sequence, often leading to the resurgence of clinical features seen earlier in presentation (Gresa-Arribas *et al.*, 2014).

Clinical presentation

The typical clinical course of NMDARE starts with a viral prodrome characterised by non-specific flu-like symptoms, such

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as fever and headache, in up to 70% of cases (Dalmau *et al.*, 2011). Within 1–2 weeks, there is development of cognitive and psychiatric symptoms, including sleep disturbance, agitation, psychosis, catatonia, impaired memory and speech difficulties. Seizures may also be seen during this period. Further deterioration is marked by the onset of dyskinetic movements, dysautonomia, respiratory failure and coma (Dalmau *et al.*, 2011). With treatment, these symptoms tend to recur in reverse sequence. As such, counselling the team and the patient's family about the expectation of return of the behavioural symptoms may be prudent.

Post-HSV anti-NMDA receptor encephalitis

A different mechanism of autoimmunity occurs in approximately 20% of patients with herpes simplex virus (HSV) encephalitis, leading to a secondary autoimmune encephalitis usually seen in adults as neuropsychiatric and cognitive dysfunction following the initial treatment of viral encephalitis (Pruss *et al.*, 2012; Armangue *et al.*, 2015; Linnoila *et al.*, 2016). The model for these cases proposes that the viral infection (such as HSV) causes cell damage leading to antigen exposure and the initiation of immune response and antibody production (Dalmau *et al.*, 2017; Baizabal-Carvallo & Jankovic, 2018; Dalmau & Graus, 2018). The presence of antibodies in the CSF, but not the serum, coupled with findings of BBB disruption in certain cases suggests the possibility of intrathecal antibody synthesis where B cells migrate past the BBB and produce antibodies rather than serum antibodies crossing the BBB (Dalmau *et al.*, 2008, 2017). In cases of NMDARE secondary to viral encephalitis, treatment with immunomodulating agents can lead to clinical improvement and does not seem to result in the re-emergence of HSV infection in children (Nosadini *et al.*, 2017). In comparison to patients without antecedent viral encephalitis, cases of secondary NMDARE show more persistent deficits (Gable *et al.*, 2009; Dalmau *et al.*, 2017). Secondary autoimmune encephalitis also occurs with antibodies to targets other than the NMDA receptor; however, this appears to be less common (Dalmau *et al.*, 2017). Compared to secondary NMDARE, HSV encephalitis usually has a faster progression of symptoms and is not frequently associated with autonomic instability (Dalmau & Graus, 2018).

Limbic encephalitis

Limbic encephalitis involves a group of autoimmune conditions with antibodies targeting the limbic structures. Historically, limbic encephalitis was thought to always have an associated neoplasm, but this relationship has not been as strong as previously thought (Tuzun & Dalmau, 2007). Limbic encephalitis is characterised by magnetic resonance imaging (MRI) findings with hyperintesities in the medial temporal areas in addition to other structures such as the brainstem and cerebellum (Dalmau *et al.*, 2004; Graus *et al.*, 2016). Common symptoms involve changes in mood, altered mental status and working memory as well as seizures. Limbic encephalitis is most known for subacute loss of short-term memory function, usually over a period of less than 3 months (Graus *et al.*, 2016).

Paraneoplastic limbic encephalitis

Limbic encephalitis can involve one of many antibodies that target epitopes at the cell surface, synaptic or intracellular level (Table 1). Determination of antibody type can help predict response to immunotherapy and which associated tumours are likely. The onconeuronal/paraneoplastic antibodies Hu and Ma2 have intracellular antigen targets and demonstrate a weaker response to immunotherapy. Anti-Hu antibodies are usually associated with small cell lung carcinoma, while anti-Ma2 antibodies are commonly associated with testicular seminoma. These onconeuronal antibodies are distinguished from other types of autoimmune encephalitis because they are much more frequently associated with neoplasms. Immunohistochemical and immunopathological findings show that anti-Hu and Ma2 antibodies do not localise to the cell surface. These findings suggest a T-cell-mediated response against intracellular antigens rather than directly pathogenic antibodies (Bernal *et al.*, 2002; Bien *et al.*, 2012; Lancaster & Dalmau, 2012; Dalmau *et al.*, 2017). This T-cell-mediated intracellular mechanism and resulting cell death may explain the relative refractoriness of these subtypes to usual immunomodulating treatment. Other intracellular antigen targets include Yo, Ri and CV2.

The pathophysiology of the onconeuronal paraneoplastic syndromes is thought to start with a loss of immune tolerance against proteins expressed by both cancer cells and intracellularly in neurons. These antigens may be detected following apoptosis with uptake by antigen-presenting cells. Cytotoxic T-cells causing cell death are thought to be the main immunologic mechanism rather than directly pathogenic antibodies. The presence of irreversible neuronal damage and/or death leads to reduced response to immunotherapy in comparison to outcomes with cell surface antibody-mediated conditions (Bernal *et al.*, 2002; Darnell & Posner, 2003; Dalmau *et al.*, 2008; Bien *et al.*, 2012).

Autoimmune limbic encephalitis

Glutamic acid decarboxylase (GAD) antibodies target intracellular GAD, an enzyme involved in the conversion of glutamate to GABA. Anti-GAD antibodies are associated with stiff person syndrome – a condition characterised by fluctuating stiffness in various muscle groups, painful spasms and increased startle response. Anti-GAD65 cases usually affect younger women, who present with seizures (Solimena *et al.*, 1990; Dalmau *et al.*, 2017). Although cancer is not always present at the time of initial diagnosis, there is an increased risk of small cell lung carcinoma and thymoma being found in patients older than 50 as well as those who test positive for concomitant anti-$GABA_B$ receptor antibodies. Anti-GAD65 antibodies may be involved with a separate pathogenic mechanism where either T-cells or antibodies disrupt synaptic vesicle fusion (Lancaster & Dalmau, 2012). These antibodies are sometimes grouped separately in the literature given the different outcomes and pathological mechanisms (Dalmau *et al.*, 2017).

Within the limbic encephalitis group, common neuronal cell surface antibody targets include AMPA receptors, $GABA_B$ receptors, LGI-1, contactin-associated protein-like 2 (Caspr2), glycine receptors and metabotropic glutamate receptors (mGluR5). Numerous other antibody targets are listed in Table 1. In the literature, reports of antibody-mediated limbic encephalitis have largely focused on antibodies against the AMPA, $GABA_B$ and LGI-1 targets. As such, we will describe these types of encephalitis in detail for this review.

Anti-AMPA receptor encephalitis

Glutamatergic AMPA receptors are ionotropic receptors mediating fast excitatory neurotransmission. They are tetrameric in structure and composed of combinations of GluR1-4 subunits.

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Activation of AMPA receptors results in the removal of the NMDA receptor channel magnesium ion block and facilitates NMDA receptor activation. As such, AMPA receptors are usually co-localised with NMDA receptors and play a role in long-term potentiation, a cellular mechanism postulated to be involved in learning and memory.

Since 2009, there have been several published case studies and series describing autoimmune encephalitis caused by antibodies to GluR1 and GluR2 AMPA receptor subunits. In two separate analyses of anti-AMPA receptor encephalitis, it appears that this disorder affects individuals of older age (median ages of 60–62 years) and has a 64%–90% female predominance (Lai *et al.*, 2009; Höftberger *et al.*, 2015). Most patients (64%–70%) had an underlying neoplasm, either of the lung, breast, thymus or ovarian teratoma. The majority of individuals present with symptoms of limbic encephalitis, including short-term memory loss, disorientation, confusion and behavioural changes such as aggression and agitation. Seizures, either focal or generalised tonic-clonic, were noted in less than half of patients on presentation. Furthermore, several cases were reported to exhibit psychotic features with or without other neurological abnormalities (Graus *et al.*, 2010; Höftberger *et al.*, 2015). Of interest, one of these patients developed neuroleptic malignant syndrome as a result of treatment with an antipsychotic medication. On CSF analysis, approximately half of patients had elevated lymphocyte counts. The majority of patients exhibited MRI findings of increased signal in the temporal lobes and EEG abnormalities, although some had unremarkable MRI and electroencephalography (EEG) results. According to Lai *et al.* (2009), response to immunotherapy approached 90%. In the Höftberger *et al.* (2015) investigation, 24% of patients had a good response to immunotherapy, whereas 48% had a partial response and 29% did not improve. It appears that anti-AMPA encephalitis is also prone to relapses, as 5%–50% of individuals in the aforementioned studies experienced up to several relapses following initial treatment.

In cultures of live rat hippocampal neurons, GluR2 antibodies isolated from patients reduced the number of AMPA receptor clusters and decreased the co-localisation of GluR2 with presynaptic and postsynaptic markers (Lai *et al.*, 2009). Furthermore, patient antibodies against GluR1 and GluR2 were shown to decrease synaptic AMPA receptor cluster density through the induction of receptor internalisation (Peng *et al.*, 2015). These studies suggest that AMPA receptor antibodies are associated with a loss of function of the AMPA receptor.

Anti-GABA$_B$ receptor encephalitis

Inhibitory neurotransmission in the central nervous system is mainly mediated by GABA. This neurotransmitter interacts primarily with two types of receptors: the ionotropic GABA$_A$ and metabotropic GABA$_B$ receptors. While the GABA$_A$ receptor activation mediates fast inhibition by enabling chloride ion entry into the postsynaptic neuron, GABA$_B$ receptors are G-protein-coupled and facilitate presynaptic and postsynaptic inhibition of voltage-gated calcium channels and opening of potassium channels. The GABA$_B$ receptors are dimeric in structure and are composed of GABA$_{B1}$ and GABA$_{B2}$ subunits.

The first report of encephalitis associated with GABA$_B$ receptors was described in 15 patients by Lancaster *et al.* (2010). This appears to be a relatively rare cause of encephalitis, comprising approximately 4% of suspected paraneoplastic or immune-related encephalitis cases investigated. Individuals with anti-GABA$_B$ receptor encephalitis all presented with seizures, confusion and memory impairment. All were determined to have antibodies directed against the GABA$_{B1}$ subunit, with only one of the patients having additional reactivity with GABA$_{B2}$. Out of the 15 patients included, 10 had MRI findings in medial temporal lobes, consistent with limbic encephalitis, and 4 had normal MRI imaging. Most, but not all, exhibited abnormal EEG findings of seizure activity and CSF pleocytosis. The median age was 62 with 53% of patients being males. Nearly half were noted to have a malignancy, predominantly small cell lung cancer. Of note, five individuals were younger with a median age of 30 and did not appear to have any form of cancer. Of those who received immunotherapy and treatment of the primary malignancy, 90% demonstrated neurological improvement.

Subsequent case series by Boronat *et al.* (2011) and Höftberger *et al.* (2013) reaffirmed a strong association of anti-GABA$_B$ receptor antibodies with limbic encephalitis (91%–95%) and small cell lung cancer (50%–73%). Most patients were male (60%–82%) and presented with seizures, confusion and memory deficits. Of interest, one patient had prominent psychiatric symptoms. The median age of participants in the Boronat *et al.* (2011) study was 60 years; however, Höftberger *et al.* (2013) noted that individuals without small cell lung cancer were generally younger with a median age of 39 years. Up to a third of patients documented had normal initial MRI findings, and 42% had unremarkable EEG results. In the Höftberger *et al.* (2013) study, 79% of individuals had either complete or partial neurological recovery after immunotherapy and cancer treatment when indicated.

Since this time, additional case series of anti-GABA$_B$ receptor encephalitis were reported in Korean (Kim *et al.*, 2014), European (Dogan Onugoren *et al.*, 2015) and Chinese (Guan *et al.*, 2015; Chen *et al.*, 2017) studies. Another Chinese investigation demonstrated that nearly two-thirds of patients presented with bizarre behaviour and hallucinations (Cui *et al.*, 2018). Moreover, anti-GABA$_B$ receptor encephalitis does not appear to be limited to the adult population as it was also described in a paediatric case of a 3-year-old boy (Kruer *et al.*, 2014). Interestingly, one case report describes a patient with no abnormalities on MRI but significant medial temporal hypermetabolism with gross hypometabolism in the rest of the brain on 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computerised tomography (CT) (Su *et al.*, 2015), indicating a possible role for PET in diagnosis.

LGI1 encephalitis

LGI1 is a secreted protein that was first discovered in the study of gliomas. Furthermore, mutations in the LGI1 gene were noted to contribute to autosomal-dominant lateral temporal lobe epilepsy (Kegel *et al.*, 2013). Although the role of LGI1 is still largely unknown, this protein interacts with the ADAM (A Disintegrin and Metalloprotease) transmembrane protein family and has possible roles in synaptic maturation and function (Kegel *et al.*, 2013). An important discovery was made in 2010 when it was determined that limbic encephalitis previously attributed to antibodies against voltage-gated potassium channel complexes actually involved antibodies directed against LGI1 rather than potassium channel subunits (Irani *et al.*, 2010a; Lai *et al.*, 2010).

In a case series of 57 patients with anti-LGI1 encephalitis (Lai *et al.*, 2010), common presentation included memory loss (100%), seizures (82%), hyponatremia (60%) and myoclonus (40%). Most patients were older (median age of 60) and had a male predominance of 65%. Further investigation revealed that 84% had

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MRI findings involving medial temporal lobes, 76% had abnormal EEG studies, and 41% had CSF abnormalities. In contrast to anti-AMPA and anti-$GABA_B$ receptor encephalitis, only 11% were found to have a malignancy. Out of those who received immunotherapy, 81% had a good clinical outcome and 17% experienced residual moderate disability. Additionally, 18% of patients were noted to have relapses. The tendency of anti-LGI1 encephalitis to be weakly associated with cancer and often presenting with hyponatremia was reinforced in a subsequent case series of 14 patients (Shin *et al.*, 2013).

Prior to the onset of limbic encephalitis, patients with anti-LGI1 antibodies were noted to present with a variety of neurological and psychiatric symptoms. This included a prodrome of dystonic seizures involving the arm and face (Andrade *et al.*, 2011; Irani *et al.*, 2011), termed faciobrachial dystonic seizures and chorea (Tofaris *et al.*, 2012). Furthermore, LGI1 encephalitis was reported to present as a brief psychotic disorder in a 25-year-old patient (van Elst *et al.*, 2011). This individual developed a preoccupation with infection and delusions of reference, resulting in subsequent admission to a psychiatric unit. Of note, the neurological exam was unremarkable at the time of admission. Initial psychotic symptoms were followed by the development of aphasia, mutism, akinesia and seizures. This individual made a steady recovery following immunotherapy, eventually achieving full psychiatric and neurological remission.

Anti-dopamine D2 receptor encephalitis

Dopamine D2 receptor encephalitis is a part of the spectrum of basal ganglia encephalitis that includes Sydenham chorea and possibly paediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) and Tourette syndrome. Studies on the role of anti-D2 receptor antibodies in PANDAS have reported conflicting findings (Brimberg *et al.*, 2012; Dale *et al.*, 2012; Dalmau *et al.*, 2017). The onset of D2 receptor encephalitis usually occurs in childhood, affecting both sexes equally (Dale *et al.*, 2012). This condition is mostly seen after infection with β-hemolytic streptococcus, mycoplasma and enterovirus as well as after vaccination. MRI lesions are seen in the basal ganglia in approximately 50% of patients. Clinical presentation involves dystonia and oculogyric crises, features of parkinsonism and chorea. Neuropsychiatric manifestations include emotional lability, difficulty sustaining attention and psychosis (Baizabal-Carvallo & Jankovic, 2018). D2 receptor encephalitis is not usually associated with tumours.

Investigation and diagnosis

Autoimmune encephalitis can initially present with psychiatric symptoms, but the development and progression of cognitive symptoms, seizures, other neurologic findings, as well as medical instability usually prompt investigation for underlying organic processes (Herken & Pruss, 2017). Graus *et al.* (2016) outlined a proposed diagnostic algorithm to guide clinicians. CSF is used to investigate other encephalitic causes, obtain cell counts and confirm the presence and type of antibodies. Initial findings suggesting autoimmune encephalitis include mild pleiocytosis and oligoclonal bands. If the clinical presentation and CSF findings support an autoimmune encephalitis, it may be reasonable to start treatment before results confirm antibody subtype. In comparison, serum samples have lower sensitivity and specificity compared to CSF. Furthermore, the presence of serum antibodies does not reliably correlate with the presence or absence of antibodies in the CSF (Lancaster, 2016).

Other supportive investigations include MRI and EEG; these can be completed prior to antibody confirmation. EEG investigations of autoimmune encephalitis usually show non-specific abnormalities. The presence of an extreme delta brush pattern is not found in most cases, but is specific for NMDA receptor encephalitis (Baysal-Kirac *et al.*, 2016).

Brain imaging may help rule out other possible diagnoses, and MRI findings can vary depending on the antibody subtype. Limbic encephalitis may present with hyperintensities in the medial temporal structures, while NMDA receptor encephalitis does not consistently present with MRI abnormalities (Lancaster, 2016). Functional MRI and PET are other imaging modalities of interest; however, they are not currently employed in the routine workup of autoimmune encephalitis (Finke *et al.*, 2013; Heine *et al.*, 2015; Peer *et al.*, 2017). Autoimmune encephalitis can present as metabolic abnormalities on PET scans, and further investigation will delineate if specific patterns are associated with antibody subtypes. Given these findings, PET may become involved in the routine workup of autoimmune encephalitis (Morbelli *et al.*, 2016). Probasco *et al.* (2017) found that 52 out of 62 patients had abnormalities on FDG-PET scans, with hyper- and hypometabolism in various areas. Furthermore, FDG-PET abnormalities were also present in cases where other investigative modalities did not yield significant findings (Probasco *et al.*, 2017; Solnes *et al.*, 2017). Other investigations suggest that PET scan findings may be more sensitive than MRI in autoimmune encephalitis, and patterns may correlate with disease severity and antibody subtype (Lee *et al.*, 2014; Quartuccio *et al.*, 2015; Solnes *et al.*, 2017). Further research correlating which investigational abnormalities are likely to emerge with disease progression and antibody subtype may clarify the heterogeneity in these findings.

Investigations for tumours are often done concurrent to the autoimmune encephalitis workup given the association with malignancy. Specific investigations are tailored towards the tumours associated with the suspected or confirmed antibody subtype.

Treatment

Treatment usually commences prior to the return of confirmatory antibody results given the association of early treatment with better prognosis (Titulaer *et al.*, 2013). Limited studies have investigated psychiatric and behavioural symptom management in the context of autoimmune encephalitis. Kuppuswamy *et al.* (2014) advise using antipsychotics judiciously given the risk of neuroleptic malignant syndrome. Further, valproic acid may be useful given its role in treating seizures and manic symptoms. Electroconvulsive therapy may have a role in managing catatonic symptoms if patients do not present with any contraindications (Kuppuswamy *et al.*, 2014). Supportive measures regarding associated dysautonomia, hypoventilation and other medical considerations are also important. Immune-based therapies are more definitive treatments and first-line agents usually include steroids, intravenous immunoglobulin (IVIg) and plasmapheresis. These treatments may be used in combination depending on patient presentation and progression of symptoms. Steroids are usually started after ruling out infectious causes given the risk of clinical worsening. Plasmapheresis may present practical challenges in agitated and confused patients. Superiority between first-line

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treatments is not clear at this time (Titulaer *et al.* 2013; Lancaster, 2016; Shin *et al.*, 2018).

Second-line therapies are used when patients do not respond to first-line interventions or show clinical worsening. Rituximab is commonly used in patients with limited or suboptimal response with first-line agents, but requires monitoring of cell counts with ongoing use. Cyclophosphamide is used with caution in patients of child-bearing age given the risk of future infertility. Of note, tocilizumab and interleukin-2 use may be useful as treatments in the future (Lee *et al.*, 2016; Lim *et al.*, 2016). Patients with recurrent encephalitis may also be treated with other immunomodulatory agents such as methotrexate, mofetil mycophenolate and azathioprine (Shin *et al.*, 2018). Associated tumours and malignancies are treated concurrently in addition to immunotherapy. Patients with an identified tumour receiving appropriate combined resection and immunotherapy are more likely to respond to treatment and less likely to have relapses than tumour-negative patients (Dalmau *et al.*, 2011; Titulaer *et al.*, 2013).

Relevance to psychosis

The theory of glutamatergic dysregulation in the pathophysiology of schizophrenia has been gaining ground in the past few decades. Support was first noted in the observations that abuse of phencyclidine and ketamine, both non-competitive NMDA receptor antagonists, by healthy individuals can elicit positive, negative and cognitive symptoms similar to that of schizophrenia (Lodge & Mercier, 2015). As such, phencyclidine administration was considered as a pharmacological animal model of the disorder (Jones *et al.*, 2011). Although the mechanism of glutamate dysregulation in schizophrenia is still far from understood and outside the scope of this review, it is thought to possibly involve downstream alterations of the GABA and dopamine neurotransmitter systems. Nonetheless, the clinical presentation of NMDARE supports the notion of NMDA receptor hypofunction as a primary feature of schizophrenia (Coyle *et al.*, 2003; Moghaddam & Javitt, 2011) and lends credence to the exploration of mechanisms targeting glutamatergic pathways in the development of novel antipsychotic strategies. One such example is the investigation of D-serine, a potent co-agonist at the NMDA receptor, as a potential therapeutic agent in schizophrenia (MacKay *et al.*, 2019). Furthermore, the identification of NMDARE has also led to the consideration of whether the aetiology of psychosis has a possible autoimmune component (Al-Diwani *et al.*, 2017).

To date, there have been multiple investigations into the presence of autoimmune antibodies in schizophrenia, mostly with largely conflicting results. Dahm *et al.* (2014) and Hammer *et al.* (2014) reported a 10% prevalence for serum antibodies against the NMDA GluN1 receptor subunit in both healthy control individuals and in patients with a variety of neuropsychiatric disorders, including schizophrenia. However, other investigations were not able to find serum anti-NMDA receptor antibodies in individuals with schizophrenia spectrum disorders (Rhoads *et al.*, 2011; Masdeu *et al.*, 2012; de Witte *et al.*, 2015). Alternatively, when compared to controls, there have been reports of significant elevations in serum anti-NMDA receptor antibodies in schizophrenia (9.9% vs. 0.4%) (Steiner *et al.*, 2013) and in children presenting with first-episode psychosis (14% vs. 0%) (Pathmanandavel *et al.*, 2015). The presence of anti-NMDA antibodies in schizophrenia was also reported by several other authors (Zandi *et al.*, 2011; Tsutsui *et al.*, 2012), although no control subjects were used in these investigations. A meta-analysis of five studies and over 3300 participants demonstrated a three-fold increased likelihood of having elevated NMDA receptor serum antibodies in schizophrenia, bipolar disorder or major depressive disorder in comparison to healthy controls (Pearlman & Najjar, 2014).

In a recent study from Finland on serum from patients with first-episode psychosis, those demonstrating only prodromal syndromes and controls were investigated for a multitude of antibodies associated with encephalitis (Mantere *et al.*, 2018). Only a single patient with a high risk of psychosis demonstrated positive serum antibodies against the NMDA receptor. Of interest, this patient had not experienced an episode of psychosis after 1 year of follow-up and did not require treatment for encephalitis.

In contrast, Jezequel *et al.* (2017) found that nearly 19% of individuals with a diagnosis of schizophrenia and only 3% of controls had positive serum anti-NMDA receptor antibodies. In the article, the authors comment that the differences in methodology used to establish seropositivity may be a contributor to prior conflicting results – this particular paper used cell-based assays with a novel single-molecule tracking approach. Of specific interest is the finding that anti-NMDA receptor antibodies from schizophrenic patients and healthy controls behaved differently; only the schizophrenia patients' anti-NMDA receptor antibodies were shown to destabilise synaptic NMDA receptors, decrease NMDA receptor content and impair long-term potentiation. When compared to antibodies from patients with NMDA receptor encephalitis, those with schizophrenia had lower antibody titres, absence of NDMA receptor antibodies in the CSF and no overlap in binding to NMDA receptor targets. These findings suggest that there are some differences between the anti-NMDA receptor antibodies present in the two disorders.

At this time, there is no consensus as to the presence or role of autoimmune antibodies in schizophrenia. Many of the aforementioned studies have been limited to serological testing and have not incorporated CSF levels of antibodies, which is a much more sensitive method for detection. In addition, the finding that seropositivity of antibodies in autoimmune encephalitis can fluctuate in the disease course complicates the interpretation of results in a chronic disease such as schizophrenia. As such, further investigation of immunological factors in schizophrenia is certainly warranted.

Conclusion

The biological mechanisms underlying psychosis and other neuropsychiatric symptoms have been the subject of many investigations. With contributions of the immune system becoming increasingly recognised with autoimmune and primary psychiatric illnesses, novel treatment strategies may be possible. With all the possible antigenic targets available and to be discovered with regard to encephalitis, further research will help delineate biological correlates with behaviour.

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