Autoimmune encephalitis: Epidemiology, pathophysiology and clinical spectrum (part 1)

J Hiesgen, Dr Med; C M Schutte, MB ChB, MMed, MD

Department of Neurology, Faculty of Health Sciences, University of Pretoria, South Africa

Corresponding author: J Hiesgen (juliane.hiesgen@up.ac.za)

Since the identification of anti-N-methyl-D-aspartate (NMDA) receptor antibodies about 15 years ago, many patients with rapidly progressing psychiatric symptoms, abnormal movements, seizures or unexplained coma have been diagnosed with autoimmune encephalitis (AE). The symptom onset is often unspecific, and might mimic psychiatric disease, but the later course is frequently characterised by severe disease, often requiring intensive care. Clinical and immunological criteria are helpful in identifying the patients, but no biomarkers exist to guide the clinician in therapy or predict outcome. While persons of all ages can be affected by AE, some types of AE affect more children and young adults and are more prevalent in women. This review focuses on encephalitides associated with neuronal cell-surface or synaptic antibodies, which can result in characteristic syndromes, and are often recognisable on clinical grounds. AE subtypes associated with antibodies against extracellular epitopes can occur with or without tumours. Because the antibodies bind and alter the function of the antigen, the effects are often reversible if immunotherapy is initiated, and the prognosis is favourable in most instances. The first part of this series introduces the topic, provides an overview of currently known neuronal surface antibodies and how they present, describes the most common subtype anti-NMDA receptor encephalitis, and discusses the difficulties in recognising patients with underlying AE among patients with new-onset psychiatric disorders.


During the last decade, research and knowledge regarding brain inflammation precipitated by an autoimmune process has progressed rapidly, but awareness of these conditions is often still limited. On the one hand, encephalitis, defined as an inflammatory condition of the brain, is traditionally seen as an infective process secondary to bacteria, viruses, parasites and prions. On the other hand, diseases known to be associated with autoantibodies predominantly affect the peripheral nervous system such as the neuromuscular junction in myasthenia gravis, or they are clearly paraneoplastic in nature, and therefore associated with a poor prognosis.

In recent years, however, a variety of neuronal surface antibodies associated with autoimmune encephalitis (AE) has been discovered, and clinical patterns of specific antibodies linked to characteristic clinical presentations have emerged. Importantly, management guidelines are available, and with early identification and treatment, patients with AE, despite severe illness, have a good prognosis.

In our neurology units at Steve Biko Academic Hospital and Kalafong Provincial Tertiary Hospital, we have identified several patients with AE over the past years. Although the condition is well recognised among neurologists, a greater awareness in our partner disciplines, such as internal medicine, intensive care, psychiatry and paediatrics, is essential.

In part 1 of this CME review, we briefly discuss the epidemiology and pathophysiology of AE, and the antibodies associated with the disease. We describe the clinical syndromes, illustrated by two typical clinical cases. The most commonly occurring type of AE, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, is reviewed in more detail, and we discuss the importance of consideration of AE in psychiatric patients.

In part 2, we will focus on the diagnosis, differential diagnosis, special investigations, management and prognosis of AE in general.

Definition

AE comprises a heterogeneous group of inflammatory autoimmune-mediated conditions of the brain, affecting the brain parenchyma (cortical or deep grey matter and white matter). It may also involve the meninges and the spinal cord.

Epidemiology

A recent epidemiological study from the USA suggests that AE may occur much more commonly than previously thought. In this population-based study, a prevalence of 13.7/100 000 was found, which was not significantly different from the prevalence of infectious causes of encephalitis. In addition, the detection of AE has also increased over the years.

In contrast to this, an older hospital-based study from the UK in 2010 showed infective causes of encephalitis to be twice as common as autoimmune causes, likely reflecting the rising awareness and diagnostic advances of the last decade and possibly predicting a trend of autoimmune causes overtaking infectious aetiologies in frequency in the future. Whereas AE cases have been described in South Africa (SA), the epidemiology currently remains unreported.

Pathophysiology

At present, depending on the cellular localisation of the target antigen in the central nervous system (CNS), three main groups of autoantibodies that can cause AE are distinguished.

Firstly, antibodies against intracellular somato-dendritic neuronal antigens, some known for more than 30 years, cause well-characterised paraneoplastic syndromes. These antibodies are highly specific for paraneoplastic syndromes and often suggest the site of the underlying malignancy. Anti-Yo antibodies, in women with cerebellar symptoms, for instance, indicate a paraneoplastic cerebellar degeneration, usually associated with gynaecological cancers, and anti-Hu
antibodies are strongly related to lung cancer.\textsuperscript{2,6} Unfortunately, these conditions have a poor prognosis, as cytotoxic T-cells are predominantly involved, causing often irreversible neuronal damage, and the cancers tend to be difficult to manage.\textsuperscript{21}

The second group comprises antibodies directed against intracellular synaptic neuronal antigens (such as glutamic acid decarboxylase or amphiphysin). These antibodies are associated with neurological presentations such as stiff person syndrome or cerebellar ataxia, which are not in the focus of our review.

The third group, and for this review the most relevant, are antibodies against neuronal surface antigens. These antibodies target extracellular regions, such as synaptic receptors, e.g. NMDA receptor, α-aminoo-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, γ-aminobutyric acid receptor (GABA), ion channels and other cell-surface proteins, e.g. leucin-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). These autoantibodies have direct access to their epitopes, causing a more reversible neuronal dysfunction, and, although some of these also have cancer associations, the overall prognosis is favourable.\textsuperscript{22}

Case 1
A 41-year-old woman presented with a 1-week history of headaches and confusion. Collateral history revealed personality changes, nonspecific sensory symptoms and a fall before admission. There was no previous psychiatric or medical history of note. She was awake but confused, without localising neurological signs. Blood parameters and cerebrospinal fluid (CSF) investigations were normal, but a computed tomography (CT) scan of the brain showed multiple bilateral white matter hypodensities. In the ward, the patient became progressively psychotic and aggressive, necessitating sedation and antipsychotic medication. In addition, occasional abnormal movements were observed. After 1 week, her level of consciousness deteriorated, progressing to coma, and continuous, irregular perioral movements occurred. She was admitted to the intensive care unit (ICU) and intubated for suspected status epilepticus. Treatment with intravenous propofol, sodium valproate and levetiracetam was initiated. An urgent sonography revealed a large cystic pelvic mass, which was confirmed on CT. Antibody testing for neuronal cell surface antibodies, specifically NMDA receptor antibodies, was requested in the serum and CSF. Magnetic resonance imaging (MRI) of the brain (Fig. 1A and B) and serial electroencephalograms (EEG) showing a severe generalised cerebral dysfunction (Fig. 1C) were performed. The patient received high-dose intravenous steroids and five cycles of plasmapheresis. A mature ovarian teratoma was surgically removed after 1 week in ICU. Coma persisted for another 3 weeks, followed by slow regaining of consciousness. Abnormal movements, mostly peri-orally, and left-sided ataxia continued for another month. The course in ICU was complicated, with nosocomial infections and prolonged wound sepsis from necrotising fasciitis, but after 4 months, she was transferred to a rehabilitation hospital. During follow-up visits over 1 year, the anticonvulsants were weaned, and we discharged her without any residual neurological deficit.

Anti-NMDA receptor encephalitis
This form of AE has a classic, almost syndromic presentation, occurring predominantly in young females. The female-to-male ratio is 4:1, with the median age reported at 21 years, although the condition has been described from infancy well into old age.\textsuperscript{24}

Symptoms
After an unspecific prodromal phase, the disease usually manifests over a few days starting with prominent psychiatric symptoms. Patients therefore often first present to a psychiatric facility with clinical features such as irritability, aggression, emotional lability, hallucinations, catatonia and marked disturbances of the sleep-wake cycle. These symptoms are complex and can span different classic psychiatric diagnostic categories. In addition, speech abnormalities and memory deficits are frequently observed.\textsuperscript{25}

The clinical picture then commonly evolves, and after 1 month, most patients develop a combination of additional symptoms. Movement disorders are prevalent, often polymorph, and include
tremor, orofacial dyskinesia, and trunk and limb hyperkinesia. Choreiform and stereotypical movements during this phase can be difficult to distinguish from seizures. Epileptic seizures can occur at any time during the disease course, and seem to present earlier in males. Seizures are generalised or focal, and may result in status epilepticus. Autonomic symptoms frequently occur in association with this form of AE, often complicating the management of the patient. Tachy- and brady-arrhythmias, as well as marked blood pressure fluctuations, hyperthermia and eventually central hypoventilation are common. The dysautonomia is typically progressive throughout the course of the disease and may be life threatening. Up to 70% of patients with anti-NMDA receptor encephalitis need admission to ICU for management of hyperventilation, dysautonomia or status epilepticus, and a prolonged admission for several weeks is not uncommon.\(^\text{[11,12]}\)

**Investigations**

Brain imaging with CT or MRI is urgently indicated for patients with this constellation of symptoms. However, despite the dramatic clinical presentation, these investigations frequently are normal or non-contributory. Multifocal subcortical white matter lesions, as seen in our first case, have been reported,\(^\text{[13]}\) and occasionally a radiological picture of limbic encephalitis with mesio-temporal lesions is found. The CSF is generally abnormal, showing a lymphocytic pleocytosis and CSF-specific oligoclonal bands.\(^\text{[14]}\) The diagnosis of anti-NMDA receptor encephalitis is made by detecting IgG antibodies against the NMDA receptors in the CSF. Interestingly, the EEG is helpful in the diagnosis: up to 90% of patients have EEG abnormalities, which include general or focal slowing, as well as epileptiform dysfunctions in 20%. The widely described and characteristic ‘delta brush’ pattern is rare, but almost pathognomonic when present.\(^\text{[15]}\)

**Associated findings**

The likelihood of an underlying tumour depends on age, sex and ethnicity. There is a strong association with ovarian teratomas in adult female patients (up to 60%).\(^\text{[16]}\) Only ~15% of females <14 years and ~5% of affected males have an underlying tumour. Interestingly, African females are more likely to harbour an ovarian teratoma than other ethnicities.\(^\text{[16]}\) It is therefore essential to screen patients with anti-NMDA receptor encephalitis with pelvic ultrasound and imaging for teratomas, as early tumour removal is associated with a very good prognosis. While in male patients a testicular germ cell tumour might be found, other tumours are only incidentally reported.

Recently, another interesting association has emerged: after a successfully treated episode of *Herpes simplex* encephalitis, some patients may develop anti-NMDA receptor encephalitis. These patients return within days to several months after the infectious encephalitis with new neurological symptoms, often movement disorders, and anti-NMDA receptor antibodies can be detected.\(^\text{[17]}\)

**Special considerations in children**

Anti-NMDA receptor encephalitis is the most common antibody-associated AE in childhood.\(^\text{[18]}\) Children are less likely to present with a well-defined syndrome, and the sequence of symptoms often differs from adult-onset AE. It can be challenging to evaluate memory in younger children, and behavioural changes or speech abnormalities also occur in specific paediatric conditions, such as autism spectrum disorder. Children with anti-NMDA receptor encephalitis may have atypical motor symptoms (ataxia, hemiparesis) and experience seizures more often than adults. While psychosis such as in adults is rare, behavioural regression is commonly reported. Fortunately, AE in childhood is rarely associated with tumours, and dysautonomia and hyperventilation are seldom seen.\(^\text{[19,20]}\)

**Case 2**

This 23-year-old woman presented with a series of generalised tonic-clonic seizures in the week prior to admission. At the emergency unit, she had marked dyspnoea, and generalised seizures continued. Previous medical history included gestational hypertension, but her blood pressure was normal on admission. Blood gas analysis revealed a metabolic acidosis (pH 7.13, lactate 10.6 mmol/L), and a chest X-ray showed neurogenic pulmonary oedema. She was sedated, intubated and admitted to our ICU. The brain CT was normal. Acyclovir was given empirically to treat a possible *H. simplex* encephalitis, and intravenous propofol, sodium valproate and levetiracetam were administered. All blood investigations were normal, and the CSF showed 16 lymphocytes with normal biochemistry. The EEG showed a diffuse epileptiform dysfunction with prominent background slowing, and an MRI of the brain revealed bilateral mesio-temporal hyperintensities, shown in Fig. 2A and B. Abdominal ultrasound was normal, and the CSF herpes virus PCR was negative. After 1 week without clinical improvement, the patient received high-dose intravenous immunoglobulins (IVIG) for a possible AE. Over the next days, she slowly regained consciousness, but nosocomial infections complicated and prolonged her ICU stay. The autoimmune encephalopathy antibody panel came back positive for GABA-B receptor antibodies. Despite an extensive search, no underlying tumour was found. The patient followed up at the neurology outpatient department and regained independent functioning of activities of daily living. Sadly, a disabling amnestic syndrome, attributed to the mesio-temporal pathology, persisted.

**Anti-GABA-B receptor encephalitis**

This form of AE, occurring from infancy up to old age, affects males slightly more than females.\(^\text{[21]}\) As observed in our patient, the presentation with new-onset seizures progressing into status epilepticus is common, and may lead to severe complications and high mortality. Up to 90% experience seizures that may be difficult...
to treat, resulting in refractory status epilepticus.[21] Many patients show abnormalities on brain MRI, with increased signal changes in the temporal lobes in almost half.[24] An association with tumours, often small-cell lung carcinomas, is found in >50% of patients.[22,23] Overall, initial response to immunotherapy is good, but the long-term prognosis is often limited and mortality tends to be high in patients with associated cancers.[24]

**Anti-LGI1 encephalitis**

Historically, anti-LGI1 encephalitis and CASPR2 antibody encephalitis were grouped under conditions with antibodies against voltage-gated potassium channels.

After anti-NMDA receptor encephalitis, this is the most frequently encountered type of AE and the most common cause of a typical limbic encephalitis. It is predominantly seen in middle-aged and older patients, with most patients >60 years old.[23] It also occurs more commonly in men than in women and the onset may be more insidious (sometimes over months) than in anti-NMDA receptor encephalitis; tumours are rare and occur in <20% of cases.

The most striking clinical features of anti-LGI1 encephalitis are specific focal seizures known as faciobrachial dystonic seizures, which are almost pathognomonic of the condition. These are high-frequency, very brief (<3 seconds), myoclonic-like jerks, with unilateral face contraction and arm posturing, occurring hundreds of times a day and often not improving with anti-seizure treatment. Involvement of the leg may also occur, often leading to falls and injuries, and other seizure types, including subclinical seizures, may also be seen.[26]

Additional features of anti-LGI1 encephalitis include amnesia that is both anterograde as well as retrograde for autobiographical epochs, and hyponatremia, likely due to inappropriate antiuretic hormone (ADH) secretion. On MRI, features of limbic encephalitis are often visible.[25] Immunotherapy is very effective, but in the long term, cognitive problems may remain. After 2 years, up to one-third of patients may be severely disabled or do not survive, and one-third may also eventually experience a relapse.

**CASPR2 antibody encephalitis**

CASPR2 antibody encephalitis predominantly affects older males (male to female ratio 9:1) and may have a chronic presentation. Behavioural and cognitive disturbances often develop over more than 3 months, giving the impression of a neurodegenerative condition, rather than a more florid encephalitis picture. This may lead to a delay in making the diagnosis and hence delayed treatment onset. Clues to the possibility of CASPR2 antibody encephalitis are frequent seizures, which are predominantly focal in nature; generalised seizures are rare. In addition, gait and sleep disturbances commonly occur in CASPR2 antibody encephalitis, and patients may show

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**Table 1. Neuronal surface antibodies causing autoimmune encephalitis and associated clinical features**

<table>
<thead>
<tr>
<th>Neuronal surface auto-antibody</th>
<th>Age</th>
<th>Sex ratio</th>
<th>Clinical findings</th>
<th>Investigations</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR (IgG1)</td>
<td>Children and adults &lt;40 years (median 21 years)</td>
<td>1:4</td>
<td>Psychiatric symptoms, movement disorders, depressed level of consciousness, seizures, autonomic dysfunction</td>
<td>MRI In 50% - 70% normal, non-specific, CSF 80% abnormal (pleocytosis, OCB), EEG &gt;90% abnormal (delta brush)</td>
<td>55% ovarian teratomas in adult females, can occur after HSV1 encephalitis, relapses in 20% - 25% small-cell lung cancer (SCLC)</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;r&lt;/sub&gt; (IgG1)</td>
<td>Older adults (median 62 years)</td>
<td>1:5:1</td>
<td>Seizures (status epilepticus), limbic encephalitis with memory loss</td>
<td>MRI meso-temporal hyperintensities, CSF in 80% abnormal</td>
<td>&lt;10% tumours (thymus, thyroid, breast)</td>
</tr>
<tr>
<td>LGI1 (IgG4)</td>
<td>Older adults (median 64 years)</td>
<td>2:1</td>
<td>Facio-brachial dystonic seizures, amnesia, hyponatremia</td>
<td>MRI meso-temporal hyperintensities (can be unilateral), CSF often normal</td>
<td>70% associated with tumours (thymus, SCLC, breast, ovary)</td>
</tr>
<tr>
<td>AMPAR (IgG1)</td>
<td>Older adults (median 52 years)</td>
<td>2:1</td>
<td>Limbic encephalitis, with prominent confusion, psychiatric symptoms</td>
<td>MRI in 80% - 90% with abnormal, MRI in 70% and 45% abnormal</td>
<td>Limited information (thymoma, often plus LGI1 antibodies), electromyography can be abnormal</td>
</tr>
<tr>
<td>CASPR2 (IgG4)</td>
<td>Older adults (median 66 years)</td>
<td>9:1</td>
<td>Limbic encephalitis, sleep disorders, ataxia, peripheral nerve hyperexcitability</td>
<td>40% abnormal MRI, 30% CSF and 70% EEG abnormalities</td>
<td></td>
</tr>
<tr>
<td>GABA&lt;sub&gt;r&lt;/sub&gt; (IgG1)</td>
<td>Children and adults (median 40 years)</td>
<td>1:1</td>
<td>Frequent status epilepticus</td>
<td>MRI in 80% abnormal, CSF in 25-50% and EEG in &gt;80% abnormal</td>
<td>30% have a thymoma</td>
</tr>
<tr>
<td>DPPX (IgG4)</td>
<td>Adults (median 53 years)</td>
<td>2:1</td>
<td>Encephalitis with myoclonus, tremor, diaphragm, weight loss</td>
<td>MRI 100% normal, CSF in 30% and EEG in 70% abnormal</td>
<td>&lt;10% (B cell neoplasms)</td>
</tr>
<tr>
<td>IgLON5 (IgG1/4)</td>
<td>Older adults (median 64 years)</td>
<td>1:1</td>
<td>Sleep disorders, bulbar syndrome, cognitive symptoms, chorea</td>
<td>MRI in 80% normal, possible brainstem atrophy, CSF in 30% - 50% abnormal</td>
<td>Tumour association not reported</td>
</tr>
<tr>
<td>MOG (IgG1)</td>
<td>Adults (median 37 years)</td>
<td>1:1</td>
<td>Optic neuritis, transverse myelitis, encephalitis</td>
<td>MRI in 50% - 75% abnormal, CSF in 60% abnormal</td>
<td>Visual evoked potentials often abnormal</td>
</tr>
</tbody>
</table>

NMDAR = N-methyl-D-aspartate receptor; MRI = magnetic resonance imaging; OCB = oligoclonal bands; HSV = herpes simplex virus; GABA<sub>r</sub> = γ-aminobutyric acid receptor; CSF = cerebrospinal fluid; LGI1 = leucin-rich glioma inactivated protein 1; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; EEG = electroencephalogram; CASPR2 = contactin-associated protein like 2; DPPX = dipeptidyl-peptidase-like protein 6; IgLON5 = immunoglobulin-like cell adhesion molecule 5; MOG = myelin-oligodendrocyte glycoprotein.
episodic or persistent ataxia. Lastly, pain is often a feature in this form of AE, occurring with or without a peripheral nerve hyperexcitability syndrome with cramps and fasciculations.[21]

### Rare forms of autoimmune encephalitis

The rare forms of AE include anti-myelin-oligodendrocyte glycoprotein (MOG), glycine receptor, AMPA receptor, dipeptidyl peptidase-like protein 6 (DPXP) and immunoglobulin-like cell-adhesion molecule 5 (IgLON5) encephalitis.

Of these, it is noteworthy that anti-MOG causes optic neuritis, transverse myelitis and brainstem encephalitis, and often shows MRI abnormalities in the subcortical areas, brainstem and spinal cord; anti-glycine receptor encephalitis is associated with stiff-person syndrome, and progressive encephalopathy with rigidity and myoclonus (PERM); anti-AMPA receptor encephalitis is associated with a limbic encephalitis picture and associated with a variety of tumours; DPXP shows prominent symptoms of hyperexcitability with myoclonus, hyperreflexia and tremors and is associated with severe diarrhoea and weight loss; and IgLON5 can cause marked sleep disorders that include parasomnias and sleep apnoea, as well as a bulbar syndrome, a progressive supranuclear palsy-like syndrome, cognitive symptoms and chorea.

Table 1 shows a summary of different AE subtypes, antibodies, common presentations and tumour associations.

### Special considerations for AE in psychiatric patients

Because the earliest symptoms in patients with AE are often psychiatric, and between 4% and 5% of patients with AE have a monosymptomatic psychiatric course, concerns have been raised that autoimmune inflammatory processes could be the underlying cause in patients presenting with what look like primary psychiatric disorders.[20,22]

A recent study identified 145 patients with antibody-associated psychiatric syndromes. Of these, 64% were female and the mean age was 43.9 years; most patients had antibodies against the anti-NMDA receptor, and 94% of patients who received immunomodulatory treatment responded.[20] The most common presenting symptoms in primarily psychiatric AE were agitation (59%) and psychotic symptoms (54%). Visible and auditory hallucinations as well as persecutory delusions occurred frequently, and catatonia was found in 42% of adults and in 35% of children.[22] Another study from 2022 reported paranoid hallucinatory symptoms as the most common, but about 27% of patients presented with affective disorders.[22]

Patients with new onset psychosis and/or patients who do not respond to antipsychotic treatment should raise suspicion for AE,[23] but it should be noted that almost half of all patients presenting with ‘autoimmune psychoses’ may have a positive history of previous psychiatric disorders, most frequently depressive disorders.[32,34] Interestingly, patients with autoimmune psychoses appear more prone to develop side-effects to antipsychotic medication than those with pure primary psychiatric disorders; neuroleptic malignant syndrome is particularly prevalent.[31]

Other ‘red flags’ to alert clinicians to the possibility of AE in hospitalised psychiatric patients include CSF lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection, epileptic seizures and MRI or EEG abnormalities. Less strong warning signs are hyponatraemia, other autoimmune diseases, headache, catatonia and autonomic instability.[35] By taking these signs into consideration, the time between onset of the symptoms and diagnosis of AE could be reduced from 74 days to 31 days.[34]

With heightened awareness and timely diagnosis, immunotherapy can be initiated early, and close co-operation between psychiatrists and neurologists is crucial for optimal management of patients with AE for a favourable prognosis.

While some psychiatry associations have included CSF analysis, EEG and neuroimaging in their recommendation for the work-up of first manifestation of psychosis, international guidelines are lacking. The SA Society of Psychiatrists has published guidelines for the treatment of psychiatric disorders and suggests serological and drug screening in all patients with psychosis. In the SA context, HIV and syphilis screening are advocated, and additional imaging studies and EEG are suggested in atypical cases.[37]


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