Autoimmune encephalitis

The term encephalitis is often used in the emergency department or acute medical setting to describe a syndrome of abrupt mental status change, often with fever, seizures, psychosis and abnormal movements. This article focuses on autoimmune encephalitis which is increasingly diagnosed, from infants to the elderly, yet remains an overlooked differential diagnosis compared to viral encephalitis or other causes of encephalopathy. Autoimmune encephalitis may be as common as infective encephalitis and therefore each time the diagnosis of infective meningo-encephalitis is considered clinicians should consider the diagnosis of autoimmune encephalitis.

Patients with autoimmune encephalitis may have a frank encephalitis syndrome or more subtle symptoms that lead many to have an initial review with psychiatry services. The common syndromes are described, with red flag features to aid recognition and a framework for handling the possibility of autoimmune encephalitis on the acute medical take. Infections and cancer can mimic autoimmune encephalitis, which remains a difficult diagnosis to make. Patients with autoimmune encephalitis generally require treatment cover for common infections from the outset, with onward referral to neurology, infectious diseases and psychiatry teams.

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Epidemiology

While relatively rare, autoimmune encephalitis is under-diagnosed and accurate epidemiological data are lacking. The UK encephalitis public health study (Granerod et al, 2010) discussed the difficulty of ascertaining incident case numbers (probably around 1–2/100 000 patient years) as a result of diagnostic difficulties, with many cases having no definite infective or autoimmune cause found. A recent Olmsted County study found autoimmune encephalitis to have a prevalence (13.7/100 000) no different to infective encephalitides, and increased prevalence over time reflecting new diagnostic tests (Dubey et al, 2018). An important clinical pearl from the UK data is that fever did not distinguish between infective or autoimmune causes of encephalitis, and so fever should not put clinicians off from considering autoimmune disease.

Limbic encephalitis associated with antibodies to proteins complexed to potassium channels

Before 2001, antibody-associated autoimmune encephalitis was considered a difficult to treat syndrome associated with underlying cancer (e.g. small cell lung cancer). Angela Vincent and colleagues in 2001 described patients with an autoimmune encephalitis associated with serum antibodies directed to voltage-gated potassium channels in complex with associated proteins (measured by radio-immunoassay, which is no longer recommended because it produces non-specific results) (Buckley et al, 2001). The encephalitis frequently caused seizures (including brief contractions of face and limb – 'faciobrachial dystonic seizures'), and dense anterograde memory loss.

The antibody associations have been better characterized over the last 7 years and it is now known that patients with antibodies to LGI1 (leucine-rich glioma inactivated 1 protein) have the most common autoimmune encephalitis of this group (Irani et al, 2011).

N-methyl D-aspartate receptor antibody-associated encephalitis: the game changer

First identified as a discrete entity in 2007, patients with this form of autoimmune encephalitis make up most cases. Children to the elderly can be affected, although the typical case is of a young woman with prodromal psychosis (indistinguishable from first episode schizophrenia), developing hyperkinetic movements, seizures, coma and autonomic dysfunction. Ovarian teratomas are a common tumour association in up to 40% of young women, sometimes challenging to find.

Patients with this form of encephalitis frequently present to psychiatrists and the diagnosis should be considered in any individual with mental status change and psychosis attending the emergency department (Titulaer et al, 2013). N-methyl D-aspartate receptor (NMDAR) antibodies, measured by cell-based assays, also occur as secondary irrelevant antibodies, or false positives in up to a quarter of cases (Zandi et al, 2015), so the presence of an antibody in patients without the full NMDAR antibody syndrome needs to be interpreted with caution. This is primarily a focus of research studies and clinical trials (Zandi et al, 2014).

Clinical presentations

Clinical features to look for include fever, movement disorders, dysautonomia and cognitive dysfunction (that can be tested rapidly at the bedside, e.g. rapid forgetting of an address or inability to negotiate a map or describe how to reach a local landmark familiar to the patient). Movements can be subtle and include chorea (systemic lupus erythematosus and post-streptococcal autoimmunity are possible differential diagnoses here) or parkinsonism, rigidity and exaggerated startle responses and myoclonus (glycine receptor antibody patients exhibit these movements commonly), slow contractions of face and ipsilateral arm or leg (faciobrachial dystonic seizures, associated with LGI1 antibodies),

opsoclonus (rapid darting eye movements). Vertical nystagmus is a clue to cerebellar or brainstem involvement. A screening neurological examination, to look for papilloedema, meningism, abnormal reflexes or focal weakness, abnormal movements, blood pressure and labile blood pressure, anterograde memory deficits, can be done rapidly at the bedside. Urgent investigation is then required (Dalmau and Graus, 2018). *Table 1* lists core syndromes and features to be aware of.

Investigations and mimics

If the diagnosis of encephalitis is considered then brain imaging followed by CSF examination and electroencephalogram are the core investigations, with a broad range of blood tests.

Urgent brain imaging with computed tomography acutely and then magnetic resonance imaging is an essential first step. The imaging can identify changes associated with autoimmune encephalitis, but also the differential diagnoses, particularly herpes encephalitis, acute infarcts and space-occupying lesions. Magnetic resonance imaging in patients with autoimmune encephalitis may be normal (up to 50% in patients with NMDAR encephalitis) or may reveal increased signal in the medial aspect of the temporal lobes bilaterally on T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging. Some magnetic resonance imaging patterns seen in patients with prion disease are also seen in patients with autoimmune encephalitis.

CSF analysis is important and should be done promptly after brain imaging (the imaging is required to ensure that lumbar puncture is safe), to exclude infective and malignant mimics. Treatment with intravenous aciclovir (watch renal function) can commence as soon as the patient reaches the emergency department and CSF analysis done after brain imaging but ideally within 6–12 hours of admission. Routine investigations such as opening pressure, glucose, protein, cell count, oligoclonal bands, viral polymerase chain reaction and serology including herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus, enterovirus, parechovirus, mumps, Gram stain and bacterial culture are all useful, particularly at ruling out other significant differential diagnoses. Herpes simplex virus polymerase chain reaction may be falsely negative within the first 72 hours – this is not a reason to delay CSF analysis, but a reason to carry out a second CSF if the first polymerase chain reaction is negative and herpes encephalitis remains a possible diagnosis (Puchhammer-Stöckl et al, 2001). CSF may be slightly cellular (up to 50 or so white cells per microlitre), or reveal oligoclonal bands, or be normal in patients with autoimmune encephalitis. CSF NMDAR antibodies are likely to be more specific than serum NMDAR antibodies, as a result of the presence of non-specific binding of serum when reading assays (Graus et al, 2016).

Other infections should be considered and patients should be assessed and tested for HIV, hepatitis B, C and E, syphilis, mumps, measles, and immunoglobulin levels to look for immune deficiency. Patients with primary CNS infection can have NMDAR or related antibodies positive as a secondary phenomenon (Hacohen et al, 2013), and infections can be missed.

Table 1. Clinical features of the core autoimmune encephalitis syndromes

Subtype	Psychiatric associations	Other associated symptoms	Typical demographic	Associated tumour
N-methyl D-aspartate receptor encephalitis	Behavioural change (agitation, personality change) may follow 'prodromal' period Psychosis (paranoia, hallucinations, delusions) Catatonia and movement disorders may follow 'psychiatric' phase Autonomic features may worsen with antipsychotic treatment	'Viral symptoms' prodromal period (1–2 weeks) Altered conscious level Memory deficits New seizures Autonomic instability Dyskinesias Speech disturbance (including mutism) Delta brush sign on electroencephalogram	Young women, although infants to elderly of both sexes can be affected	Ovarian teratoma
LGI1 antibody-associated	Mood and affective symptoms	Memory deficits Faciobrachial dystonic seizures Myoclonus Confusion Hyponatraemia	Middle aged or elderly	Thymoma
Caspr2 antibody-associated (van Sonderen et al, 2016)	Hallucinations	Limbic encephalitis Morvan syndrome (peripheral nerve hyperexcitability), neuromyotonia Muscle spasms or fasciculations Insomnia, amnesia Confusion	Middle aged or elderly	Thymoma
Antibody negative cases or other (GABA(A)R, GABA(B)R, glycine receptor, neurexin 3 alpha, dipeptidyl peptidase 6 (DPPX), AMPAR, IgLON5, and emerging antigens) – present with a range of features of autoimmune encephalitis	Behavioural change, hallucinations or delusions, opsoclonus	Confabulation, short-term memory loss, disorientation, seizures, movement disorders, sleep disturbance	Middle aged or elderly	Thymoma, breast, small cell lung carcinoma

> Good 'high-dose' rehabilitation with physiotherapy, occupational therapy, psychological therapy and cognitive rehabilitation is vital.

Clinically systemic lupus erythematosus should be considered (arthralgia, rash, nephritis – urine dip for protein, positive anti-nuclear antibody), as should sarcoid, tuberculosis, Sjögren's syndrome, lymphoma (often requiring 2–3 large volume CSF examinations for flow cytometric analysis and bone marrow examination), hepatic and toxic encephalopathies, non-convulsive status epilepticus and cerebrovascular disease.

Gliomas can mimic autoimmune or viral encephalitis on magnetic resonance imaging, and often empirical aciclovir while awaiting brain biopsy is the only way forward, but with close discussion with neurology and neurosurgery colleagues.

RNA sequencing is playing more of a clinical role in identifying rare viruses, and close involvement of infectious diseases and microbiology teams can help here (Brown et al, 2018). Autoantibodies to the common antigens can be measured (see section on pathophysiology and subtypes) in most teaching hospitals and couriered from smaller hospitals, although antibody-negative cases are encountered, requiring careful diagnosis.

Electroencephalogram is often non-specific in autoimmune encephalitis, although may reveal slow activity, a delta brush pattern or subclinical seizure activity. Triphasic sharp waves in the electroencephalogram can point to hepatic encephalopathy or prion disease as differential diagnoses.

It is important to tailor investigations for any associated underlying tumour, and this would be typically done by the admitting medical or neurology team over the following days. Magnetic resonance imaging of the pelvis allows non-invasive imaging of the ovaries, minimizing radiation exposure. Investigation for other tumours may include positron emission tomography computed tomography scanning, mammography, testicular ultrasound and bone marrow examination.

Psychiatric features in autoimmune encephalitis

Adults with autoimmune encephalitis commonly present with psychiatric disturbance. For example, approximately 77% of cases of later confirmed cases of NMDAR encephalitis are initially seen by a psychiatrist as their first contact with the health-care system (Titulaer et al, 2013). Under current National Institute for Health and Care Excellence guidelines (2016) there are no standard investigations for patients who present with first episode psychosis with tests being left to the treating physician's discretion. There are many causes of psychosis (Keshavan and Kaneko, 2013). Undoubtedly a proportion of patients with NMDAR encephalitis are initially admitted to psychiatric units. Thus, the differential of NMDAR encephalitis should be kept in mind when 'neuroleptic malignant syndrome' has been identified as such cases can be misdiagnosed (Herken and Prüss, 2017).

Pathophysiology and subtypes

The autoantibodies in autoimmune encephalitis may be directly disease causing by binding to brain cell receptors or associated proteins, akin to antibodies to the acetylcholine receptor in myasthenia gravis, but other immune processes are likely to be important too. Autoimmune encephalitis can occur in the context of the remote effects of cancer (paraneoplasia), in which the immune system becomes immunised to an occult cancer and through friendly fire engages in autoimmunity towards nervous system tissue (Höftberger et al, 2015). The reversible antibody binding to receptors means it is possible for patients to make a full recovery to normal functioning, e.g. particularly in NMDAR encephalitis, even after months in the intensive care unit.

Novel antibody associations include antibodies to AMPAR, GABA(A)R, GABA(B)R, glycine receptor, IgLON5, DPPX, but the general principles of management are the same. Laboratories in all hospitals will have links to a regional neuroimmunology laboratory to allow rapid diagnostics, and most tests are becoming available within 48–72 hours given the availability of rapid commercial assays. However, in many centres antibody test results can still take a few weeks to come back, and therefore a clinical diagnosis and careful management, after excluding mimics, followed by expectant treatment is advisable.

Management

In the individual with suspected encephalitis, mimics should be sought, and conventionally viral encephalitis is actively covered and treated with aciclovir until proven otherwise, given the devastating effects of a missed diagnosis of herpes simplex virus or related encephalitis. Intensive care support is often required and many individuals recover after months in the intensive care unit (usually requiring transfer to a regional neuroscience centre). Cardiac monitoring is recommended in the acute and convalescent phase as arrhythmias and sudden cardiac death can occur, sometimes through autonomic or insula involvement.

No randomized clinical trials for immune therapies exist, but retrospective data allow some general recommendations after secure diagnosis with first-line corticosteroids, plasmapheresis or intravenous immunoglobulins, and early consideration of second line therapies including rituximab and cyclophosphamide. In parallel a search should be performed with the aim of removing or treating any underlying tumour (Titulaer et al, 2013).

Rehabilitation and support for patients and their families

Good 'high-dose' rehabilitation with physiotherapy, occupational therapy, psychological therapy and cognitive rehabilitation is vital, and while hard to obtain in many parts of the country is available. Charities including the Encephalitis Society and Headway can help support patients, and for commissioners encephalitis can be considered among any cause of brain injury. Epilepsy and psychosis charities can provide support too if needed. Individuals who drive must inform the Driver and Vehicle Licensing Agency and will often require driving assessments as part of their occupational rehabilitation. **BJHM**

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KEY POINTS

- Autoimmune encephalitis is common and underdiagnosed – the clinical suspicion for this should be high for any patient attending the emergency department with altered mental status.
- Infectious encephalitis can mimic autoimmune encephalitis, and brain imaging followed by lumbar puncture, with immediate initiation of antiviral therapy (intravenous aciclovir) should be considered in all patients in whom the diagnosis of autoimmune encephalitis is considered.
- N-methyl D-aspartate receptor antibody encephalitis can present to psychiatrists with a psychosis indistinguishable from first episode schizophrenia.
- Autoimmune encephalitis is highly treatable with an excellent outcome if diagnosed accurately and treated early – involve neurology and infectious diseases colleagues early.
- Patients with autoimmune encephalitis are at risk of psychosis, seizures, dysautonomia, including sudden cardiac death – close monitoring with involvement of the intensive care unit early is recommended, and cardiac monitoring.