Autoimmune encephalitis: a case series and comprehensive review of the literature

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Summary

Encephalitic syndromes are a common medical emergency. The importance of early diagnosis and appropriate treatment is paramount. If initial investigations for infectious agents prove negative, other diagnoses must be considered promptly. Autoimmune encephalitides are being increasingly recognized as important (and potentially reversible) non-infectious causes of an encephalitic syndrome. We describe four patients with autoimmune encephalitis—3 auto-antibody positive, 1 auto-antibody negative—treated during the last 18 months. A comprehensive review of the literature in this expanding area will be of interest to the infectious diseases, general medical and neurology community.

Introduction

Encephalitis (inflammation of the brain parenchyma) is a common medical emergency. Failure to appropriately diagnose the correct aetiology of an encephalitic syndrome can lead to significant morbidity and mortality.

Of infectious agents, viruses cause a significant proportion of encephalitis. Herpes simplex encephalitis (HSE) is the most common viral encephalitis with 2000 cases per year in the USA, the majority of cases being HSV-1 infection in the young and elderly.1

However, non-infectious aetiologies and, more specifically, autoimmune phenomena are being increasingly recognized as causes of encephalitis.2 A variety of autoimmune causes have now been described including anti-LGI1 encephalitis (previously termed anti-voltage-gated potassium channel “anti-VGKC” antibody encephalitis) and anti-N-methyl-D-aspartic acid receptor (anti-NMDAR) encephalitis.3,4 It has been recognized that some patients presenting with encephalitis show full recovery after treatment with steroids or immunomodulatory therapy indicating an autoimmune cause even in the absence of confirmatory serology.5,6

Despite a growing knowledge of autoimmune encephalitis (AE), this area remains poorly understood. Diagnosis is often considered late or not at all, resulting in poor outcomes. Moreover, recent clinical review articles giving an overview of viral encephalitis omit recognized autoimmune causes such as anti-NMDAR encephalitis in an otherwise comprehensive list of non-infective differential diagnoses.7
The intention of this article is to raise awareness of AE, a potentially reversible cause of a common medical emergency. We present four illustrative cases of AE to compare and contrast the variability of presentations, aetiology, management and outcome.

Case 1

In June 2009, a 16-year-old student was admitted with change in personality after an episode of loss of consciousness (LOC). Three days prior to admission she had had an episode of depersonalization and derealization with disorientation to place. It was followed the same evening by a tonic–clonic seizure at a graduation ball. She was seen in the emergency department and discharged later that night. Over the next 2 days, she exhibited bizarre behaviour with inappropriate smiling, disinhibition, poor self-care, altered sleep pattern and an episode of faecal incontinence. There was no other relevant recent medical history. Past medical history revealed anosmia since birth of unknown origin. Family, medication, gynaecological and social history were unremarkable. A full neurological examination was normal. MR brain was normal. Cerebrospinal fluid (CSF) examination showed 360 red cells/μl in a non-traumatic tap, absent leucocytes, isolated oligoclonal bands with normal protein and CSF:serum glucose ratio. She was commenced on IV acyclovir and phenytoin.

Two days into her in-patient stay, she became very agitated. Her behaviour fluctuated and at times she was disoriented to place. An electroencephalogram (EEG) showed excess of beta and pronounced delta waves compatible with a diffuse encephalopathy. Lamotrigine was added to the antiepileptic medication and clonazepam to cover possible mycoplasma encephalitis. Auto-antibodies, tumour markers and toxicoology screen were negative, as was CSF virology. Repeat MR brain was normal. Cerebrospinal fluid (CSF) examination showed 360 red cells/μl in a non-traumatic tap, absent leucocytes, isolated oligoclonal bands with normal protein and CSF:serum glucose ratio. She was commenced on IV acyclovir and phenytoin.

The patient went on to develop episodes of hyperarousal over the next week with breath-holding attacks, oro-facial movements (manifesting as repetitive fish movements of the mouth) and pelvic thrusting. She remained disoriented with intermittent anxiety and poor memory. A repeat lumbar puncture (LP) showed 20 white cells/μl. She had a 5-day course of intravenous immunoglobulin (IVIG) at 0.4 mg/kg/day and methylprednisolone (MP) at 500 mg/day; followed by 60 mg/day of oral prednisolone. A pelvic USS and subsequent pelvic MRI were normal apart from physiological ovarian cysts. Further follow-up USS and MRI has shown resolution of the cysts with no further abnormalities.

By December 2009, 6 months post-admission there had been complete resolution of her symptoms and quetiapine and fluoxetine were also tapered off.

Case 2

A 26-year-old recruitment consultant was admitted in May 2009 with confusion and altered behaviour. His family described a single episode of LOC 3 weeks prior to admission with no recollection of the event and a Computed Tomography (CT) head at this time was normal. Since then, he had become more withdrawn and appeared paranoid. He complained of transient inability to feel his legs and his family noted episodes of shaking of limbs without LOC or other features of seizure activity. These symptoms progressed with further emotional lability, change in personality, hallucinations and one other episode of LOC.

On admission in May, he was disoriented, agitated and confused. He had neither focal neurology nor meningism at this time but a raised temperature of 38°C. CT brain scan was normal. An LP revealed 2 polymorphs/μl, 48 lymphocytes/μl, protein 0.58 g/l with a normal serum–CSF glucose ratio. Antibacterial and antiviral treatments were initiated and haloperidol and diazepam were escalated to control agitation. It was noted that the patient had a raised creatine kinase with mild renal impairment. A subsequent MR brain scan and EEG were normal. HIV antibody test was negative. Five days after admission he was transferred to the Regional Infectious Diseases unit.
Neurological review revealed catatonic posturing, globally increased tone with ankle clonus, unilateral tremulousness and shaking, cogwheel rigidity and no response to painful stimuli. A repeat LP yielded similar results to the first. He was continued on antivirals and clarithromycin was added to treat the possibility of mycoplasma encephalitis. He was commenced on MP and immunoglobulin intravenously. Anti-basal ganglia and anti-NMDA antibodies were requested. An ultrasound of the testes was normal as were tumour markers.

He continued with orofacial dyskinesias, insomnia, bland facies, catatonia and worsening visual and auditory hallucinations. All CSF virological tests returned negative including Mycobacterium tuberculosis PCR. However, after a month as an inpatient, the patient continued to be extremely unwell with severe ongoing symptomatology and lymphocytosis in the CSF. Therefore, due to these concerning features, he was commenced on empirical TB treatment, doxycycline and ceftriaxone for borreliaosis, and transferred to ITU for plasma exchange and sedation. Two further LPs did not yield any new information and were negative for M. tuberculosis PCR. The patient also received a further course of IVIG and MP shortly after starting TB therapy.

Eleven days after commencing TB treatment, the anti-NMDA antibodies result came back as strongly positive and therefore TB treatment was stopped and therapy with cyclophosphamide and rituximab was started. He also started electroconvulsive therapy (ECT) for catatonia. Over the next couple of weeks, he improved and had more lucid episodes. Then, 7 weeks after admission, mycobacterial culture on the initial CSF sample returned positive for fully sensitive M. tuberculosis and anti-tuberculous treatment was reinstated with the addition of steroids. On revisiting history, no travel, exposure or preceding clinical history (no headache, meningism, cough, weight loss, night sweats or fever) suggested either pulmonary or extra-pulmonary TB infection. Over the next couple of months, his mental state and catatonia improved and he was discharged on anti-TB therapy after an inpatient stay of 18 weeks. And 5 months after discharge he had returned fully back to normal and was able to return to work.

Case 3

In April 2010, a 76-year-old lady with a past history of diet-controlled type 2 diabetes was admitted to her local hospital with a 2-week history of fluctuating confusion. She was uniformly afebrile. Routine haematological and biochemical parameters were normal, aside from mild hyponatraemia at Na 130 mmol/l. While in hospital she suffered a short lived generalized tonic–clonic seizure. She was not orientated to time or place and her Glasgow Coma Scale (GCS) varied between 7 and 14. She had a CT head which was normal but an EEG showed slow wave activity indicative of an encephalopathic process. She was started on sodium valproate, clobazam and prednisolone.

Over the next few days her GCS deteriorated to 3–4/15 and she was started on a phenytoin infusion for suspected non-convulsive status epilepticus (NCSE). Due to profound bradycardia and hypotension this was stopped. Levetiracetam was added to her anti-epileptic regimen and the dose of sodium valproate increased. She was transferred to the neurology high dependency unit. While there she was noted to be persistently hypothermic with temperatures down to 33°C but endocrinological investigations were normal. An MRI head showed high signal changes in the hippocampal areas consistent with the clinical diagnosis of limbic encephalitis (Figure 2). She was given 3 days of MP 1 g per day before continuing on oral prednisolone at 50 mg per day. A further EEG showed NCSE and she was anaesthetized. IVIG was given for a total of 5 days and phenytoin was added to the anti-epileptic regimen.

One week into her admission, a repeat EEG showed no epileptiform activity but diffuse slow waves intermixed with small sharp waves seen over the left frontotemporal region interrupted by periods of attenuation of activity for 20–30 s. Over the next week, her GCS remained 3–4, EEG continued to show encephalopathic features and she was transferred to the ward. By day 20, there were signs of some improvement. She was given a second cycle of MP and IVIG. On day 26, anti-VGKC antibodies were reported as strongly positive (herein to be referred to as anti-LGI1 [Leucine-rich glioma inactivating 1] antibodies, see discussion). GCS improved to 8 and prednisolone was continued orally. She remained stable but was treated with antibiotics and physiotherapy for ventilator-associated pneumonia. Prednisolone began to be tapered 7 weeks into admission. She remained in a state of low arousal, was transferred to a specialist nursing home but died 10 months after her initial presentation.

Case 4

In October 2009, a previously fit and well 30-year-old male, presented with a 3-week history of headaches, confusion, sleep disturbance, personality change and a partial complex seizure. He had had a flu-like illness 4 weeks earlier treated with oseltamivir (Tamiflu®). Initial CT and MR brain scans
were normal but 2 LPs revealed CSF lymphocytosis (400/µl and 63/µl, respectively) with normal protein, glucose, virological screen and negative culture. Early therapeutic management included sedation with haloperidol, lorazepam and olanzapine; intravenous cefotaxime, aciclovir and clarithromycin; and sodium valproate.

After 4 days, he was transferred to the Regional Infectious Diseases unit. He remained confused and agitated requiring high amounts of sedation. Medication was rationalized to diazepam and quetiapine after a psychiatric review. He suffered a tonic–clonic seizure and temporarily dropped his GCS score to 3/15. He was soon noted to be catatonic. His GCS spontaneously improved to 13/15 and a neurology review revealed rigidity and the pillow sign consistent with catatopy (the “psychological pillow” describes a postural state in which the patient maintains—sometimes for long periods—a posture with head a few inches off the bed if the pillow is removed). He continued on antimicrobial therapy and an auto-immune screen and paraneoplastic (Anti-Hu, Anti-Yo, Anti-Ri, Anti-Ma 1/2, Anti-CRMP-5 and Anti-Ampiphysin) screen were requested.

A 3rd LP was performed which showed a persistently raised but improving lymphocyte count at 18/µl. EEG and MR brain were also normal. A bilateral ptosis was noted on day 8 and he was started on MP (1 g per day for 3 days). He improved dramatically over the next couple of days with reduced catatonia and increased communication. His reaction time continued to be delayed and his parkinsonian tremor remained. He was continued on oral prednisolone at 60 mg per day. All blood and CSF viral polymerase chain reaction (PCR) tests were negative as were an HIV antibody test, Hepatitis B and C screen, atypical pneumonia serology, serum ACE, autoimmune screen, treponemal and borrelia serology, anti-NMDA, anti-basal ganglia, anti-LGI1 and paraneoplastic antibodies.

Over the next 2 weeks, he was weaned off sedatives and his sleep-cycle, agitation and communication all improved. A neurological exam at this time showed a mild bilateral ptosis and intention tremor. He was discharged after a month’s inpatient stay weaning off oral prednisolone. When seen in outpatient clinic, he was well with complete resolution of symptoms apart from mild short-term memory loss.

**Discussion**

Patients presenting with an encephalitic syndrome represent a diagnostic challenge. Estimated incidence of viral encephalitis in the UK, based on hospitalized patients from 1989 to 1998, was approximately 1.5 per 100,000 overall. More recent estimates (from the northwest of England) of admission rates with encephalitic syndrome were higher at approximately 2.9 per 100,000. Incidence is higher in specific patient groups such as the young and elderly. It is of note that a large review of over 1500 patients presenting with encephalitis to healthcare facilities in California, USA, showed that only 16% had a confirmed aetiological agent (the majority of these viral followed by bacterial); 13% had a suspected aetiological agent; and 8% had a non-infectious cause identified (autoimmune disease and vasculitis being the most common). Aetiology was not found in nearly two-thirds of cases referred to specialist units. This highlights the importance of considering AE early in situations where no clear infectious aetiology has been identified.

Autoimmune conditions are not a common cause of encephalitis. However, with recognition of newer antibodies, diagnostic serology is becoming increasingly available. The above cases, encountered within an 18-month period, illustrate the spectrum of presentations of varying types of AE. Cases 1 and 2 describe two young patients with anti-NMDAR encephalitis, Case 3 describes an elderly lady with anti-LGI1 encephalitis. Case 4 describes a patient with non-infectious, presumed AE that responded well to immunomodulatory therapies (the patient was left with only mild short-term memory loss) although no autoimmune antibody was identified.

It is important to note the relevant signs, symptoms and investigations that may guide the clinician to a positive diagnosis of AE. These features are highlighted in Table 1. In addition to augmenting our understanding of the presentations of these illnesses, these cases also highlight the need for aggressive, early and appropriate treatment of patients with AE to achieve good outcomes. It is a disease process that if considered early, diagnosed promptly and treated appropriately (including aggressive treatment with therapies such as high-dose steroids, IVIG, plasma exchange, rituximab and cyclophosphamide) can be reversed and the patient restored to their premorbid state.

Initial investigation in an encephalitic patient would commonly include CT of the brain with contrast, LP with cell count, protein, glucose (and serum glucose), viral screen, acid-alcohol fast bacilli (AAFB) smear, bacterial and mycobacterial culture. An MR brain is mandatory and an EEG may also be performed depending on the clinical situation. Some of the results from these investigations in both the case of infection and AE may overlap. However, it is imperative that a diagnosis of AE be considered by treating physicians when other more common
Table 1  Characteristic features, associations and response to treatment of auto-immune encephalitides

<table>
<thead>
<tr>
<th>Antigen or antibody associated with encephalitis</th>
<th>Anti-LGI1</th>
<th>Anti-NMDA</th>
<th>CASPR2</th>
<th>GABA-B</th>
<th>AMPA</th>
<th>Paraneoplastic (Anti-Hu/Ma2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Association</strong></td>
<td>Low associated tumour rate (11%)⁴¹</td>
<td>If female, associated ovarian teratomas (70% benign)</td>
<td>Morvan’s syndrome Neuromyotonia⁴¹,⁴⁵</td>
<td>Small cell lung Ca (47%)⁴⁴</td>
<td>Tumours in female patients⁵²⁹,⁴¹</td>
<td>Testicular tumour (Anti-Ma2) Lung tumour (Anti-Hu)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Limbic encephalitis: short-term memory loss personality change, seizures (especially facio-brachial tonic seizures), depression, anxiety, hallucinations. REM sleep disorder</td>
<td>Prodromal syndrome (70%)⁴⁵,⁴⁴</td>
<td>Cognitive impairment memory loss hallucinations delusions seizures, peripheral nerve hyperexcitability Axonal sensorimotor neuropathy (symptoms can mimic MND)</td>
<td>Prominent seizures early in presentation</td>
<td>Short-term memory loss</td>
<td>Memory disturbance Amnesia psychiatric symptoms and psychosis Seizures</td>
</tr>
<tr>
<td><strong>Autonomic instability</strong></td>
<td>Hyponatraemia (60%)⁴¹,⁴⁵</td>
<td>Myotonia (40%)⁴¹</td>
<td></td>
<td></td>
<td></td>
<td>Limbic encephalitis Signs of underlying tumour (i.e. on clinical examination or imaging) Paraneoplastic skin disorder Variable presentations</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Good response</td>
<td>Good response (75% substantial recovery)⁵⁵ Relapse if associated tumour not removed</td>
<td>7 of 8²⁹ responded to immunotherapy</td>
<td>Neurological improvement in 60%⁴⁴</td>
<td>Good response⁴²</td>
<td>Treatment of underlying carcinoma</td>
</tr>
</tbody>
</table>

Ca, carcinoma; MND, Motor neurone disease; REM, rapid eye movement.
causes have been excluded or when there are certain diagnostic indicators for AE, as described below. Figure 1 shows a clinical algorithm for the diagnosis of AE.

Anti-NMDAR encephalitis has only recently been described, often occurring in female patients with associated ovarian teratomas, however, men are affected in 30% of cases. Of note, a significant (40%) proportion of anti-NMDAR encephalitis is found in children. A recent study from the US found the rates of anti-NMDAR antibodies in encephalitic patients admitted to ITU to be 1%; in the UK a prospective multicentre study showed 4% of all encephalitic patients had anti-NMDAR encephalitis. The NR1 subunit is the target antigen for NMDA receptor antibodies (NMDAR). NR1 is down-regulated by selective and reversible decrease in NMDAR surface density and synaptic localization that correlates with patients’ antibody titres. This causes reduction in GABA release from pre-synaptic neurons that subsequently results in increased glutamate release, dopamine dysregulation and excitotoxicity leading to classical anti-NMDAR encephalitis features.

A prodromal syndrome involving headache, low grade fever and non-specific viral illness (nausea, vomiting, upper respiratory tract symptoms) up to 2 weeks prior to presentation—commonly with psychiatric symptoms—is found in about 70%. Due to the prominence of psychotic symptoms, patients

![Clinical Algorithm for Diagnosis of AE](image-url)

**Encephalitic Presentation**

(history and clinical examination)

**Initial Investigations:**

- MRI Brain, CSF (inc HSV / EnV) +/- EEG
- Consider (depending on history & examination): Full Infection Screen and cytology

**Features suggestive of AE:**

- Prodromal syndrome
- Orofacial dyskinesiae
- Faciobrachial dystonic seizures
- Catatonia
- Extra-pyramidal Signs

If strong clinical suspicion & patient deteriorating consider AE treatment early

**Neoplasm screen:**

- Especially if positive anti-NMDAR or paraneoplastic screen
- USS testes
- USS / MRI abdo / pelvis
- CXR +/- CT chest / abdo

**Blood Screen:**

- Auto-immune AB (Anti-NMDA, Anti-LGI1, CASPR2, AMPA, GABA)
- Paraneoplastic AB
- Vasculitic Screen

**Poor Response:**

- Consider methotrexate
- Annual tumour screen

**Treat as AE:**

- First Line: MP + IVIG / PE
- Second Line if no improvement: Rituximab Cyclophosphamide
- Plus Tumour removal if found

**Good Response:**

- Annual tumour screen
- Supportive care
- Longterm immunosuppression with azathioprine / MMF

Figure 1. Clinical algorithm for diagnosis of AE.
may initially be admitted under psychiatric care. Early features of anti-NMDAR encephalitis include psychosis (frequently involving anxiety, paranoia, sleep disturbance, grandiose delusions and mania), speech and language problems on a varying spectrum of echolalia (see Patient 1) to mutism, and memory problems which are often under-estimated amidst the psychiatric and language problems.\textsuperscript{2,12} After this initial phase there is rapidly progressive neurological disturbance. This can include motor or complex seizures, decreasing responsiveness, dyskinesias and autonomic instability. Among the varied dyskinesiae that can occur there is a prominence of oro-lingual-facial movements (see ‘fish-mouthing’ Patient 1). Other dyskinesias noted in Dalmau et al.’s\textsuperscript{2,12} cohort include limb and trunk choreaathetosis, elaborate leg and arm motions, dystonia, rigidity, opisthotonus and oculogyric crises; these may be simultaneous or alter through the illness. Autonomic instability may be prominent causing haemodynamic and respiratory instability, in rare cases causing bradycardia requiring temporary pacemaker insertion.\textsuperscript{17} In addition centrally-originated hypoventilation may require ITU admission as occurred in Case 3.\textsuperscript{2,4} Reports of rarer neurological presentations including opsoclonus–myoclonus syndrome at presentation are also documented.\textsuperscript{18}

Case 1 had no specific prodromal period but presented with a variety of relevant neurological features including seizures, disinhibition and psychosis. Case 2, in contrast, had an episode of LOC—possibly a seizure—1 month preceding presentation, with personality changes and emotional lability in the interim. Both patients had distinct signs compatible with anti-NMDA encephalitis including sleep disturbance, seizures, behavioural disturbances and movement disorders. Our patients had prominent movement disorders including orofacial dyskinesia in both cases and catatonia in Case 2; and visual and auditory hallucinations. Case 2 had initial hyperthermia during admission: a series of female children with AE in Japan described hyperthermia as a presenting feature in 90%;\textsuperscript{19} consequently, hyperthermia does not exclude AE. A further differing feature between the presentation of adults and children is a lower frequency and severity of hypoventilation (as seen in Case 1 who also exhibited breath-holding attacks) and more autonomic instability in children.\textsuperscript{4}

A patient with anti-NMDAR encephalitis may have abnormalities of both CSF and MRI. 80% of patients with confirmed anti-NMDAR encephalitis have abnormal CSF with the majority of these exhibiting a lymphocytic pleocytosis but over half also showing raised protein; there may also be the presence of isolated oligoclonal bands in the CSF of patients with AE (around 60%\textsuperscript{12}) as found in Case 1’s initial sample. Most patients have intrathecal production of anti-NMDAR antibody and in a recent article relating to over 400 patients with anti-NMDAR encephalitis, none were shown to have anti-NMDAR antibodies in serum alone.\textsuperscript{20} Anti-NMDA antibodies can be detected in both the serum and CSF; levels may be monitored.\textsuperscript{17} Patients who respond to treatment (discussed below) have lower levels of anti-NMDA antibodies post- than pre-treatment whereas those with poor or no response to treatment may have persistently high antibody levels.\textsuperscript{2,12,15}

With regards to brain MRI, this is unremarkable in 50%. In the remaining 50%, T2 or FLAIR signal hyperintensity might be seen in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia and brainstem.\textsuperscript{12} These signal changes may only be transient however and were not seen to significantly correlate with the patients’ clinical neurological features. Over three quarters of patients had abnormal EEGs, predominantly with generalized or frontotemporal slow or disorganized (delta–theta) activity in the absence of epileptic discharges.\textsuperscript{4} In Case 1, the patient had a normal MRI brain but EEG showed an excess of beta and pronounced generalized delta waves compatible with a diffuse encephalopathy and LP revealed a CSF lymphocytosis with elevated protein. Case 2 had similar CSF abnormalities but a normal EEG and MR brain scan. Both patients had high levels of anti-NMDA antibodies. As described, the CSF of Case 2 did later grow \textit{M. tuberculosis} in the sample obtained prior to institution of any immunosuppressive intervention (including steroids). This suggests that coexistent TB infection may have been a trigger to autoimmune anti-NMDA encephalitis. The illness and clinical syndrome were predominantly due to anti-NMDA encephalitis, which responded appropriately to steroids, cyclophosphamide, rituximab and plasma exchange. The growth of \textit{M. tuberculosis} in an encephalitic patient of course necessitated anti-TB treatment. However, the clinical presentation and response to treatment in this case clearly highlights the need to analyse the clinical syndrome astutely and not be wholly reliant on investigative results in isolation.

Recent papers have described the histopathology of brain and neuronal tissue in relation to autoimmune encephalitides.\textsuperscript{20} The authors review studies of the cellular and synaptic effects of these antibodies in hippocampal neurons in vitro and preliminary work in rodent models. Moscato et al.\textsuperscript{20} found that in the anti-NMDAR brain biopsies there was a rarity of T cell infiltrates as opposed to that
found in paraneoplastic syndromes in which T cells are predominant.\textsuperscript{21} What also remains to be understood, is why the disease preferentially affects hippocampal NR1 subunits, when these can be found throughout the brain. Overall histological examination of brain biopsy have not shown any changes specific to anti-NMDAR encephalitis with the majority of the few samples taken in this setting showing mainly perivascular lymphocytic cuffing.

Around 70\% of the teratomas found in females with anti-NMDA encephalitis may be benign. If such a tumour is found, immunotherapy and removal have been associated with a better outcome than without removal or treatment.\textsuperscript{22–24} It must be remembered however, that about 40\% of patients in other patient series reported had no associated tumour found.\textsuperscript{2,12}

Immunotherapy with IVIG and high-dose steroids—intravenously initially—has been shown to improve outcome but may be associated with relapse especially without tumour removal.\textsuperscript{2,17} Case 1 was slow to respond to these treatments, thus a second course was prescribed. Imaging did not reveal an associated tumour. Both Cases 1 and 2 needed repeated courses of MP and IVIG because of poor responses to the initial treatment cycle. Of note, both responded well to the second course of IVIG and MP but, in addition, Case 2 also received cyclophosphamide and rituximab with adjunctive ECT and plasma exchange. Both patients made a full recovery.

Although previously termed ‘anti-VGKC encephalitis’, recent evidence suggests that it is actually another autoantigen—LGI1—that is associated with limbic encephalitis and this terminology will be used throughout.\textsuperscript{25} In addition, other studies suggest that another auto-antigen contactin-associated protein-like 2 ‘CASPR2’ (expressed in hippocampal neurons) is associated with illnesses previously attributed to anti-VGKC antibodies such as drug-refractory epilepsy, encephalitis, peripheral nerve dysfunction or a combination of both: Morvan syndrome or neuromyotonia.\textsuperscript{26–29} LGI1 is a secreted neuronal protein that functions as a ligand for two epilepsy-related proteins ADAM22 and ADAM23.\textsuperscript{30} As opposed to the previous supposed anti-VGKC mechanism of action, anti-LGI1 does not encode structural components of ion channels. It is speculated that antibody-mediated disruption of LGI1 function causes increased excitability, which may result in seizures or encephalopathy. Case 3 describes an elderly female with anti-LGI1 limbic encephalitis that responded poorly to immunotherapy with IVIG and MP. It must be noted that at the time of investigation the LGI1 antibodies were not being characterized in our reference laboratory’s studies. Therefore, the results only specified VGKC antibodies and the sample was since discarded. The clinical profile of this patient, however, best fits anti-LGI1 encephalitis and will be discussed as such below.

The limbic system encompasses the amygdala, hippocampus and hypothalamus and—among other functions—is responsible for memory and emotion. Limbic encephalitis was first described in patients with severe short-term memory impairment or dementia in association with bronchial carcinoma.\textsuperscript{31} There has been increasing clinical and neuro-imaging recognition of this condition in the past decade. Cardinal symptoms of LE—and therefore LGI1 encephalitis—are severe short-term memory impairment with psychiatric symptoms such as personality change, depression, anxiety, hallucinations, confusion and complex partial—often temporal or classically in LGI1 encephalitis facio-brachial tonic seizures\textsuperscript{32}—and generalized seizures.\textsuperscript{33,34} Another prominent symptom, found in 40\% of patients is myoclonus—also strongly exhibited in mice lacking LGI1.\textsuperscript{25} Of note, symptoms are similar for CASPR2 syndromes but additionally may include peripheral nerve hyperexcitability and axonal sensorimotor neuropathy.\textsuperscript{28} Our patient exhibited confusion, change in conscious level and seizures. In addition, as has previously been described in patients with anti-LGI1 encephalitis, she had autonomic instability with labile temperature and blood pressure.

Neuroimaging by MRI shows unilateral or bilateral, asymmetrical, high-signal changes in mesial temporal lobes (Figure 2) that enhance on T2-weighted scans (up to 84\% of patients).\textsuperscript{5,25} High-signal changes in the hippocampal area were seen in our patient. CSF, as for anti-NMDA encephalitis, may show a pleocytosis with a lymphocytic predominance, raised protein and oligoclonal bands.\textsuperscript{35} Hyponatraemia, as in our patient, is common, occurring in over half of patients both those with underlying carcinoma and those without; this is thought to be mediated by LGI1 expression in the hypothalamus and kidney and averaged Na 128 mmol/l in Lai’s review.\textsuperscript{25,36} EEG is often abnormal showing focal or generalized epileptic discharges or—as in Case 3—slow wave activity.\textsuperscript{37}

In contrast to Anti-NMDAR encephalitis, associated underlying tumours are only found in 11\% of patients in Anti-LGI1 encephalitis;\textsuperscript{25} in those who do have a tumour, the encephalitis can precede the identification of the neoplasm in up to three quarters of patients.\textsuperscript{34,38,39}

A thorough search, initially for an infectious aetiology and then for exclusion of underlying malignancy (tumour should be removed if found) should
be undertaken. For anti-NMDA encephalitis, the treatment is immunotherapy with high-dose steroids and IVIG with other agents such as cyclophosphamide, rituximab or plasma exchange being used as a second line. When found in the CSF or serum, anti-LGI1 antibodies are associated with a better response to treatment than those treated for presumed auto-immune encephalitis without presence of auto-antibodies. After treatment, a quarter of patients will have full recovery and one half will be left with only mild disability. The neurological deficits may be subtle and difficult to elicit, however, and in some cases are sufficient to preclude a return to work.

Our patient (Case 3) had poor response to two courses of immunotherapy despite anti-LGI1 antibodies being present and no underlying tumour being found. Her advanced age, prolonged stay on ITU and ventilator-associated pneumonia (VAP), may have negatively influenced her response to treatment. It may also be postulated that treatment was not started until approximately 3 weeks after admission and 5 weeks into her illness. Moreover, despite the poor response to the above treatments, due to the patient’s poor general condition, plasma exchange or other immunotherapy could not be initiated.

Case 4 describes a case in which the young male patient presented with features of AE with diffuse brain involvement following a prodromal influenza-like illness a few weeks previously. He had a CSF lymphocytic pleocytosis but his EEG and MRI head were normal. He had profound catatonia and parkinsonism. No infectious, auto-immune or paraneoplastic aetiology was identified on testing of serum and CSF. There are further cases in the literature reporting patients presenting with features of LE, negative anti-LGI1 and anti-NMDA antibodies but full response to immunotherapy with IVIG and steroids. These cases did note, however, EEG and MRI changes—EEG showed bitemporal slowing and paroxysmal slow wave bursts; MRI showed bilateral swelling in the medial temporal lobes. Our patient responded profoundly to immunotherapy—a response which was maintained—indicating a likely autoimmune cause for the encephalitis. It must be noted that there are other conditions which can cause AE in addition to anti-NMDAR, anti-LGI1 or CASPR2; our patient may have had one of these but this was not identified. Such disorders included Anti-AMPA, Anti-GABA and the intracellular antigens anti-Hu and anti-Ma2.

AMPA receptor antibodies (Glutamate Receptors—GluR1/2) is one of the autoimmune causes of limbic encephalitis. Glutamate is one of the main excitatory neurotransmitters with GluR1/2 being the predominant AMPA subtype in the hippocampus (GluR3 is associated with the distinct disorder, ‘Rasmussen’s syndrome’). Like Anti-NMDAR encephalitis, Anti-AMPA receptor encephalitis is associated with tumours in females and good response to immunotherapy.

Anti-GABA AE is caused by disruption of the metabotropic Anti-GABA beta receptor. When disrupted, this receptor causes limbic encephalitis with prominent seizures and memory dysfunction. The patients in Lancaster et al’s case series (average age 62 and roughly equal sex distribution) all presented with early and prominent seizures; EEG and MRI findings were consistent with predominant limbic dysfunction. Around 47% of patients had small cell lung cancer. Neurological improvement occurred in 60% of the patients and was correlated with prompt immunotherapy and tumour control. Paraneoplastic limbic encephalitides (PLE) are predominantly related to Anti-Hu and anti-Ma2 antibodies. Diagnosis is either by neuropathological examination or the presence of following 4 criteria: compatible clinical picture; interval of <4 years between neuro- symptoms and tumour identification; exclusion of other neuro-oncological complications; at least one of following—CSF with inflammatory changes but negative cytology, MRI showing temporal lobe abnormalities; EEG showing temporal activity in the temporal lobes. Around 60% of patients in a series had antineuronal antibodies. Only 57% had limbic changes on the MRI. Patients with Anti-Ma 2 encephalitis were generally young men with testicular tumours (as opposed to
l lung cancer as most common associated malignancy in anti-Hu), hypothalamic involvement and poor neurological outcome. Tumour treatment has generally been shown to have a superior outcome than immunomodulatory therapy in these cases. It is postulated that in the case of neoplastic-associated AE, the presence of a tumour expressing the specific autoimmune receptors breaks through immune control and, essentially, produces the specific symptomatic syndromes. Another mechanism may well cause this breakthrough however, in much the same way as Guillain–Barre Syndrome occurs post-Campylobacter infection and Sydenham’s Chorea post—Streptococcal infection. Overall, a combination of history, clinical, EEG and CSF findings can point to a diagnosis of AE even in the absence of positive auto-antibodies (see Figure 1).

Conclusion

Although AE can present in a similar way to other encephalitic processes—such as those of an infectious aetiology—the cases described illustrate that diseases such as anti-NMDAR, anti-LGI1 and other AE may exhibit some distinct characteristic features. The physician treating encephalitic patients, in whom aetiology has not been confirmed, be their speciality neurology, infectious diseases or general medicine, must be vigilant to the possible diagnoses of AE. The excellent response to treatment in three out of four of our patients also reiterates the need for prompt consideration, investigation and recognition of AE. Treatment should be early and aggressive, initially with steroids but also with addition of IVIG, plasma exchange and—in refractory cases—other immunotherapy such as cyclophosphamide and rituximab. This appropriate and timely management is likely to improve the outcome of AE, a condition that—in many cases—may be wholly reversible.

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