

Diagnosing autoimmune limbic encephalitis

Adrian Budhram MD, Andrew Leung MD, Michael W. Nicolle MD DPhil, Jorge G. Burneo MD MSPH

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Autoimmune limbic encephalitis (ALE) is an inflammatory disease involving the medial temporal lobes; it classically presents with rapid neuropsychiatric decline. Patients with ALE have, and may present with, a diverse array of neuropsychiatric symptoms, which means that they may initially be assessed by any one of a range of medical practitioners. The condition was first described as a paraneoplastic phenomenon, but subsequently, with the discovery of disease-causing antibodies, was shown to be nonparaneoplastic in many cases.^{1,2} Although ALE is uncommon (an epidemiologic study of encephalitis found the prevalence of ALE without antibody positivity to be only 2 cases per 100 000 people), the incidence of autoimmune encephalitides has risen over the last decade, driven largely by improved antibody detection.³ Autoimmune limbic encephalitis is commonly misdiagnosed, yet early diagnosis and treatment can improve outcomes.

We review the approach to diagnosis of ALE, drawing on findings of large cohort and case-control studies, which represent the highest level of evidence in this field (Box 1). We discuss diagnostic criteria for ALE presented in a 2016 position paper by Graus and colleagues (hereafter referred to as the Graus criteria; Box 2),⁴ which aim to prevent overdiagnosis of ALE and are highly specific.⁵ These criteria serve as an excellent resource for both specialists and generalists. The treatment of ALE is best coordinated by a specialist in autoimmune neurologic diseases and is beyond the scope of this review.

What are the clinical features of autoimmune limbic encephalitis?

Typical symptoms of ALE reflect dysfunction of the limbic structures of the brain and include short-term memory deficits, behavioural changes, anxiety, depression, psychosis and seizures.^{1,6,7} Autoimmune limbic encephalitis most often occurs in middle-aged adults, but it can affect people of all ages, ranging from children to older people.^{1,6-8}

Pace of disease progression

In retrospective studies of patients with ALE, the median time from symptom onset to clinical assessment was usually several weeks;^{6,9} this subacute presentation of the disease is highlighted in the Graus criteria and is a hallmark of the disorder.⁴ Although ALE should be considered in any patient who presents with rapidly progressive memory difficulties, behavioural changes, psychiatric symptoms or seizures of unclear cause, an individual

KEY POINTS

- Autoimmune limbic encephalitis is an inflammatory disease involving the medial temporal lobes; it classically presents with the subacute onset of short-term memory deficits, seizures or psychiatric symptoms.
- Brain magnetic resonance imaging can show medial temporal lobe abnormalities typical of autoimmune limbic encephalitis in suspected cases, but clinicians should be aware of other diseases that may have a similar imaging appearance.
- Analysis of both electroencephalogram (EEG) and cerebrospinal fluid can provide supportive evidence of neuro-inflammation in patients with suspected autoimmune limbic encephalitis, but a normal EEG or cerebrospinal fluid profile does not exclude the diagnosis.
- Testing for antibodies to onconeural, cell-surface and synaptic proteins represents a major advancement in the diagnosis of autoimmune limbic encephalitis, although false-positives are possible.

who presents with sudden-onset neurologic symptoms is more likely to have suffered an acute neurologic or systemic insult such as a stroke or toxic ingestion.

However, it is important not to classify a patient's illness as acute before questioning family, friends or caregivers about subtle memory problems or behavioural changes in the preceding days or weeks. Conversely, an individual may seem to have a precipitous deterioration concerning for ALE, but after further history-taking, it becomes apparent that there has been milder cognitive impairment over many months, or even years. Although certain antibodies have been associated with a more insidious presentation of ALE,¹⁰ a protracted disease course should alert the physician to the possibility of an alternative diagnosis such as a neurodegenerative disease.

Involuntary movements

Clinicians should ask caregivers about any hemi-body jerking leading up to presentation, which may represent faciobrachial dystonic seizures. These involuntary movements consist of brief contractions that affect the ipsilateral face, arm and sometimes leg; last a few seconds; can occur up to hundreds of times a day; and are often refractory to treatment with anti-epileptic drugs.¹¹ They are seen with anti-leucine-rich glioma inactivated 1 (LG1) antibodies, the most common antibody causing ALE.⁹ Other symptoms likely resulting from focal seizure activity may occur in anti-LG1 encephalitis, including thermal sensations, piloerection and

Box 1: Search strategy for this review

We screened titles of all publications via PubMed pertaining to the diagnosis of autoimmune limbic encephalitis and/or exclusion of its mimics, dating back to 1964, and reviewed those that were relevant to the subject. We also reviewed the references of all relevant publications for potential inclusion. We emphasized larger cohort and case-control studies over case reports, as well as publications within the last 10 years, given the recent advancements in antibody testing.

Box 2: Diagnostic criteria for definite autoimmune limbic encephalitis⁴

Diagnosis can be made when all 4* of the following criteria have been met:

- Subacute onset (rapid progression of less than 3 mo) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system.
- Bilateral brain abnormalities on T₂-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
- At least one of the following:
 - CSF pleocytosis (white blood cell count of more than 5 cells per mm³)
 - EEG with epileptic or slow-wave activity involving the temporal lobes
- Reasonable exclusion of alternative causes

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Note: CSF = cerebrospinal fluid, EEG = electroencephalogram, MRI = magnetic resonance imaging.
 *If one of the first 3 criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins.
 †18 Fluorodeoxyglucose (18 F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that 18 F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.

paroxysmal dizziness spells, but faciobrachial dystonic seizures are especially helpful diagnostically as they are nearly pathognomonic of this disease.^{11–14} Importantly, a normal electroencephalogram (EEG) during faciobrachial dystonic seizures should not dissuade practitioners, as coincident epileptiform discharges are seen only in the minority.¹¹ A retrospective study of 26 patients with such seizures found that they preceded cognitive impairment typical of ALE in 20 patients (77%);¹¹ thus, faciobrachial dystonic seizures may be a clue to prodromal autoimmune neurologic disease in a patient who appears to present acutely.

Why is prompt, correct diagnosis essential?

A retrospective study examining admission diagnoses of 50 patients with autoimmune encephalitis such as ALE found that two-thirds were initially thought to have conditions other than encephalitis, including primary psychiatric disorders, idiopathic epilepsy, cerebral ischemia or neurodegeneration.¹⁵ Even

Table 1: Antibodies that may be found in autoimmune limbic encephalitis, and their tumour associations

Antibodies*	Main tumour association	Approximate tumour frequency, %
Antibodies to extracellular cell surface or synaptic proteins		
LG11 ^{12,14}	Various (thymoma, breast, thyroid, colon, pancreatic and other cancers)	10
CASPR2 ^{10,14}	Thymoma	20†
GABA_BR ^{6,17}	SCLC	50
AMPA ^{18,19}	SCLC, thymoma	60
NMDAR ²⁰	Ovarian teratoma	40‡
mGluR5 ²¹	Hodgkin's lymphoma	50
Neurexin-3-α ²²	None identified	NA
Antibodies to intracellular proteins		
Hu ^{9,23}	SCLC	> 90§
Ma2 ²⁴	Testicular tumour	> 90¶
GAD ²⁵	SCLC, thymoma	25**
Amphiphysin ²⁶	SCLC, breast cancer	> 90
CV2/CRMP5 ²⁷	SCLC, thymoma	> 90
AK5 ²⁸	None identified	NA

Note: AK5 = adenylate kinase 5, ALE = autoimmune limbic encephalitis, AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CASPR2 = contactin-associated protein-like 2, CRMP5 = collapsin response mediator protein 5, GABA_BR = γ-aminobutyric acid B receptor, GAD = glutamic acid decarboxylase, LG1-1 = leucine-rich glioma inactivated 1, mGluR5 = metabotropic glutamate receptor 5, NA = not applicable, NMDAR = N-methyl-D-aspartate receptor, SCLC = small-cell lung cancer.
 *Antibodies in bold are major diagnostic considerations in patients with ALE.
 †Thymoma is more likely in patients with anti-CASPR2 antibodies and concomitant peripheral nervous system hyperexcitability, or dual anti-LG11/CASPR2 antibody positivity.
 ‡Ovarian teratoma is most likely in female patients with anti-NMDAR antibodies, who are between the ages of 12 and 45 years. Tumours are less common in older patients with anti-NMDAR antibodies and are more likely to be carcinomas.
 §SCLC is most likely in adults with anti-Hu antibodies. Tumours are less common in children with anti-Hu antibodies and more likely to be neuroblastomas.
 ¶Testicular tumour is most likely in young (< 45 yr) male patients with anti-Ma2 antibodies. In older patients with co-existent anti-Ma1 antibodies, a variety of other tumours have been identified, most commonly non-SCLC.
 **Likelihood of tumour is higher in older (median age 60 yr) patients with anti-GAD antibodies or who have co-existent neuronal cell-surface antibodies (e.g., anti-GABA_BR antibodies).

among the one-third of patients in whom encephalitis was considered, an infectious rather than autoimmune cause was more commonly assumed.¹⁵ The potential symptom overlap between these 2 disease processes was highlighted in a prospective study of 203 patients with encephalitis, which found that many traditionally infectious symptoms such as fever did not readily distinguish between an infectious and immune-mediated cause.¹⁶

Identification of ALE is important because it facilitates prompt use of immunotherapy which, in observational studies, has been associated with reduced seizure frequency, recovery of cognition and likely even improved survival.^{12,17} Recognition of ALE also triggers malignancy screening, especially among patients with antibodies that strongly predict the presence of a tumour (discussed later; Table 1). Detection of any occult neoplasm is critical as the malignancy may ultimately determine clinical outcome.¹

What tests aid in the diagnosis of ALE?

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the brain can show medial temporal lobe changes typical of the disease (Figure 1) and is recommended by expert consensus in suspected cases.⁴ 18-Fluorodeoxyglucose positron emission tomography (18-FDG PET) of the brain may be even more sensitive for temporal lobe abnormalities;²⁹ because this modality is not as accessible to many Canadian practitioners, MRI remains a first-line neuroimaging technique. Bilateral imaging abnormalities restricted to the medial temporal lobes are required for a definitive diagnosis of ALE in the absence of antibody positivity. It is important to bear in mind that other diseases — such as other infectious and inflammatory encephalitides, as well as vascular or neoplastic conditions — may involve these structures (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181548/-/DC1).

Differential diagnosis of temporal lobe changes on MRI

In a retrospective review of 251 suspected cases of encephalitis with temporal lobe abnormalities on MRI, nearly 25% were due to herpes simplex virus encephalitis; it is therefore important to rule out this potentially devastating infection in patients with suspected ALE.³⁰ Unilateral rather than bilateral temporal lobe changes, insular involvement and absence of basal ganglia involvement are neuroimaging clues that suggest herpes simplex virus encephalitis rather than ALE (Figure 2A, 2B).^{30,31} Other major infectious considerations are varicella zoster virus, tuberculosis and neurosyphilis; appropriate testing for these entities should be considered early in the disease course.^{30,32}

Several noninfectious diseases may involve the temporal lobes and be mistaken for ALE. Gliomas may cause diffuse temporal lobe changes on MRI, while imaging features of high-grade neoplasm such as necrosis, irregular enhancement and vasogenic

edema are absent early on. Although classically thought to present unilaterally, in one retrospective series, bilateral medial temporal lobe involvement was seen in 54% cases of patients with suspected ALE who later developed glioblastoma.³³ Follow-up with magnetic resonance imaging is therefore recommended in any patient with possible ALE who progresses atypically, as malignant transformation indicative of high-grade neoplasm may occur (Figure 2C, 2D).

Seizures can also cause temporal lobe imaging abnormalities³⁴ (Figure 2E), but early control of seizures with anti-epileptic drugs alone, lack of prodromal neuropsychiatric symptoms and the resolution of temporal lobe changes after cessation of seizure activity are all supportive of seizure-related MRI changes rather than ALE. Ischemic stroke involving the medial temporal lobe usually presents acutely but sometimes causes only mild neurocognitive deficits; patients may delay seeking medical attention. Careful history-taking is needed to differentiate a subacute progression of symptoms over days from a static neurologic insult that occurred days earlier. On MRI, signal abnormality restricted to a vascular territory helps distinguish ischemic stroke from ALE³⁵ (Figure 2F).

Electroencephalography

Patients with ALE may occasionally have a normal EEG, which does not rule out the diagnosis.^{9,36} Usually, however, EEG shows slow-wave activity or epileptiform discharges from the temporal lobes of patients with ALE — a clue to brain inflammation. In a retrospective analysis of 19 patients with autoimmune encephalitis and seizures, 10 of 16 patients with ictal EEGs (63%) had seizure onset over the temporal lobe region, which closely mirrored the medial temporal lobe abnormalities seen on MRI in three-quarters of those studied.³⁷ Importantly, EEG abnormalities of the temporal lobes without any observed changes on imaging are not sufficient to make a diagnosis of ALE in the absence of a

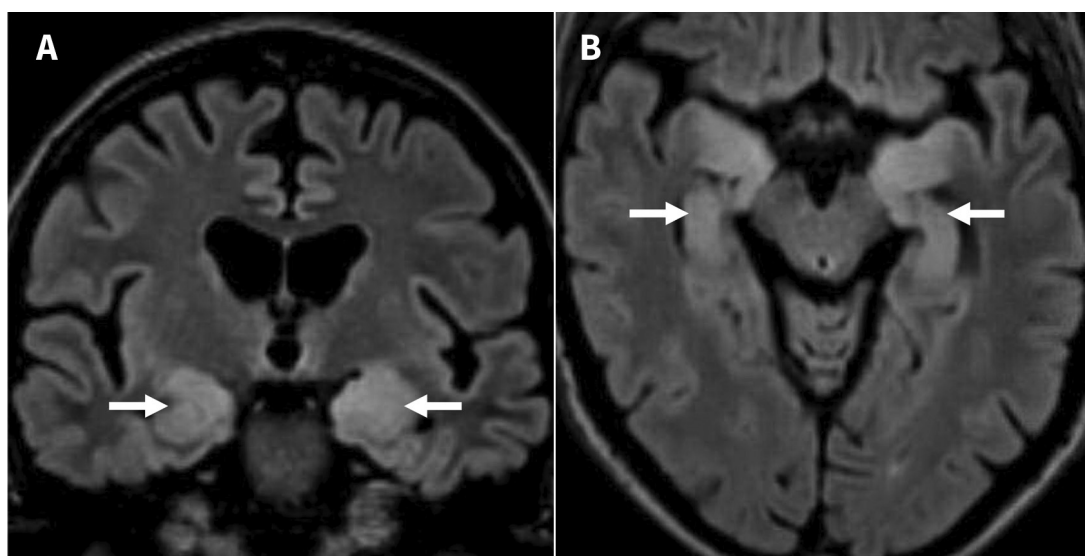


Figure 1: Brain magnetic resonance imaging in autoimmune limbic encephalitis. On coronal fluid-attenuated inversion recovery (FLAIR) image, bilateral T_2 -hyperintensity of the medial temporal lobes is seen (A, arrows). (B) Bilateral T_2 -hyperintensity of the medial temporal lobes is also shown on an axial FLAIR image (arrows). Antibodies targeting contactin-associated protein-like 2 were identified in serum by cell-based assay.

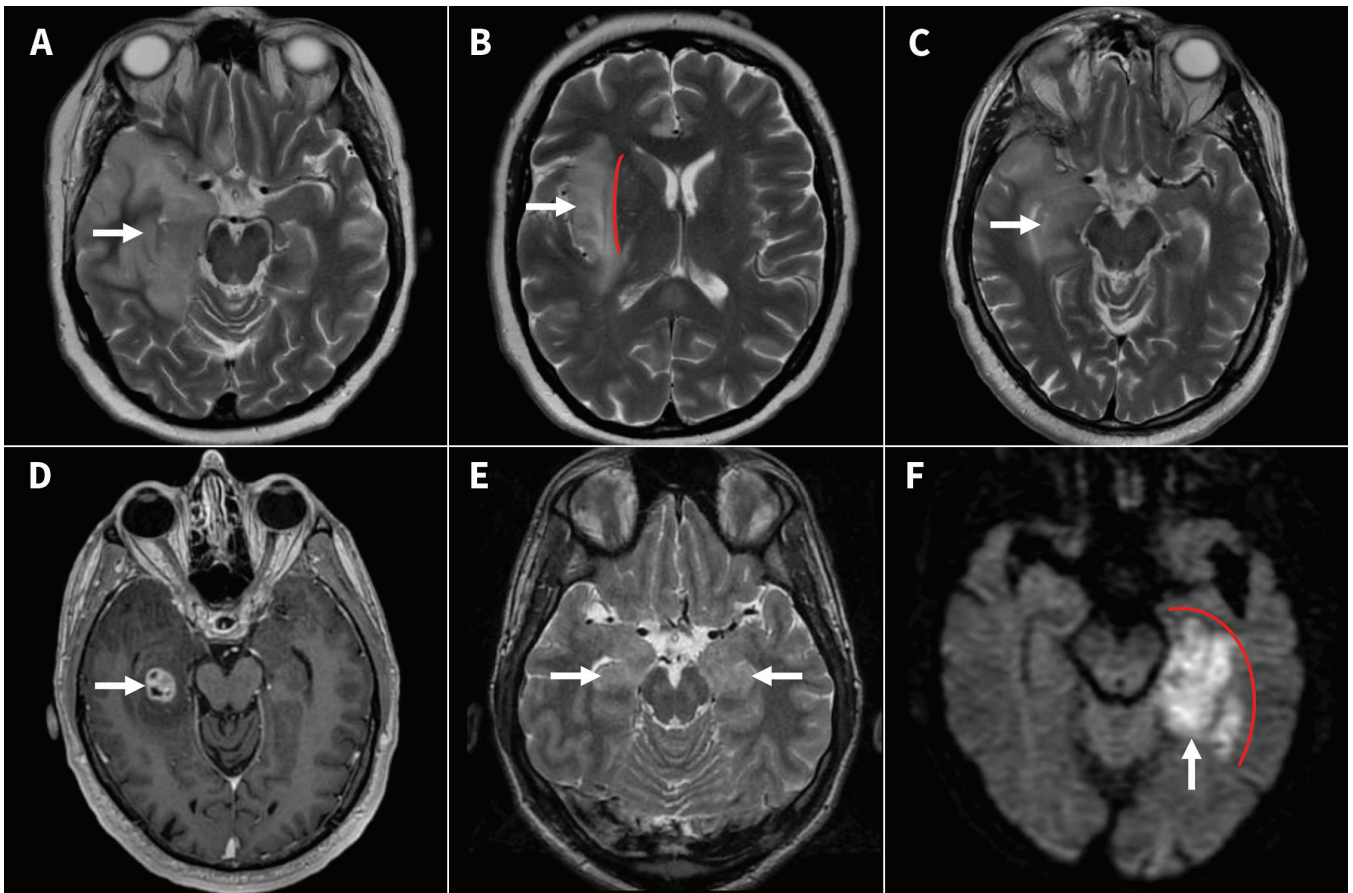


Figure 2: Magnetic resonance imaging (MRI) mimics of autoimmune limbic encephalitis. (A, B) Herpes simplex virus encephalitis: On axial T_2 -weighted image, diffuse T_2 -hyperintensity of the right anteromedial temporal lobe with swelling is seen (A, arrow). There is also T_2 -hyperintensity of the right insula (B, arrow) that spares the adjacent basal ganglia (red line demarcating separation). (C, D) Temporal lobe glioma: On axial T_2 -weighted image, diffuse T_2 -hyperintensity of the right anteromedial temporal lobe is seen (C, arrow). On follow-up MRI 6 months later, there is heterogeneous enhancement with local edema on axial T_1 -weighted post-gadolinium image, concerning for transformation into high-grade glioma (D, arrow). (E) Status epilepticus: On axial T_2 -weighted image, there is focal T_2 -hyperintensity of the medial temporal lobes bilaterally (arrows). (F) Acute ischemic stroke: On axial diffusion-weighted image, there is a diffusion-bright lesion of the left medial temporal lobe within the territory of the left posterior cerebral artery (arrow). There is no extension of the lesion into the more anterior or lateral temporal lobe supplied by the left middle cerebral artery (red line demarcating separation), in keeping with acute infarction restricted to a vascular territory.

positive antibody, according to the Graus criteria⁴ outlined in Box 2. In clinical practice, an EEG that shows slow-wave activity or epileptiform discharges from the temporal lobes in a patient with possible ALE should raise suspicion of the condition even if the initial MRI is normal; in such cases, repeat MRI may be considered, to look for the interval development of medial temporal lobe abnormalities.³⁸

Cerebrospinal fluid analysis

Analysis of cerebrospinal fluid can provide evidence of neuro-inflammation in patients with possible ALE. In a retrospective study of 50 patients with paraneoplastic ALE, about 50% had a modest leukocyte pleocytosis in cerebrospinal fluid (< 100 cells/ μL), while three-quarters of samples tested for oligoclonal bands were positive.¹ In a larger retrospective pooled-data analysis of 205 patients with ALE, however, leukocyte pleocytosis and oligoclonal bands were each noted in only about 25% of tested cerebrospinal fluid samples.³⁹ These findings suggest that although the presence of leukocyte pleocytosis and oligoclonal bands in

cerebrospinal fluid supports a diagnosis of ALE in the appropriate clinical context, their diagnostic sensitivity is low. This is reflected in the Graus criteria, which do not require leukocyte pleocytosis or oligoclonal bands in cerebrospinal fluid for a diagnosis of definite ALE even in the absence of antibody positivity.

Testing of the cerebrospinal fluid is also helpful to exclude mimics of ALE, in particular herpes simplex virus encephalitis. A retrospective study found that the cerebrospinal fluid profile alone (leukocyte count, erythrocyte count, protein and glucose) could not reliably differentiate between herpes simplex virus encephalitis and autoimmune encephalitis with temporal lobe abnormalities.³⁰ Polymerase chain reaction (PCR) testing for herpes simplex virus in the cerebrospinal fluid has high diagnostic sensitivity and specificity, but clinicians should be aware that it may be negative early in the disease course.⁴⁰ If a patient has a negative PCR result but herpes simplex virus encephalitis remains a concern clinically or on neuroimaging, continuing antiviral treatment while awaiting a second lumbar puncture for repeat PCR testing is wise.⁴⁰

Antibody testing

Testing for antibodies to onconeural, cell-surface or synaptic proteins is very helpful in suspected ALE, as a positive disease-specific antibody can make the diagnosis in patients who would not otherwise satisfy Graus criteria.⁴

The recognition that ALE may be associated with malignancy was followed by the discovery of antineuronal antibodies that supported an immune-mediated disease mechanism.^{1,41} In a retrospective study of paraneoplastic ALE, antibodies to neural antigens expressed by a tumour (referred to as onconeural antibodies) were identified in 30 of 50 (60%) of patients.¹ These were most often anti-Hu or Ma2 antibodies, which are classically found with small-cell lung cancer and testicular tumour, respectively.¹

Onconeural antibodies bind intracellular antigens and are therefore of unclear pathogenic significance in ALE; they may simply be an epiphenomenon of a primarily cytotoxic T-cell-mediated process that can lead to irreversible neuronal damage and poor clinical outcomes.^{42,43} Antibodies to the intracellular antigen glutamic acid decarboxylase may also be associated with ALE, but at much higher titres than are typically seen in type 1 diabetes mellitus.⁴⁴

More recently, antibodies targeting neuronal cell-surface or synaptic proteins have been discovered in patients with ALE; they bind extracellular antigens and are thus more likely to be pathogenic.^{6,7,45} These antibodies are variably associated with malignancy, and patients often improve with immunotherapy, owing to reversal of antibody-mediated neuronal dysfunction.² In a retrospective study of 163 patients with ALE, antibodies were found in 93%, the majority of which targeted neuronal cell-surface or synaptic proteins: LGI1 in 44%, γ -aminobutyric acid B receptor (GABA_BR) in 16%, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) in 7%, and contactin-associated protein-like 2 (CASPR2) in 6%.⁹

Of note, antibodies to the voltage-gated potassium channel were initially reported in ALE but later found to target the associated proteins LGI1 and CASPR2, rather than the voltage-gated potassium channel itself.⁴⁶ Antibodies to the *N*-methyl-D-aspartate receptor (NMDAR) may be identified in ALE, but more often are found in patients with a normal MRI and a characteristic clinical syndrome (anti-NMDAR encephalitis), consisting of abnormal behaviour, speech dysfunction, seizures, dyskinesias or dysautonomia.^{20,47}

Approach to antibody testing

Both serum and cerebrospinal fluid testing for the most commonly identified antibodies in ALE (anti-LGI1, GABA_BR, AMPAR, CASPR2, Hu, Ma2 and GAD) should be considered, to maximize diagnostic yield, as some antibodies (e.g., anti-LGI1) are more sensitive in serum and others (e.g., anti-GABA_BR) may be identified only in cerebrospinal fluid.^{14,17} Antibody testing is also worthwhile even in a patient who already meets Graus criteria for definite ALE, as a positive antibody may indicate the likelihood of a specific tumour (Table 1) and inform malignancy screening.

The presence of an antibody with a strong tumour association should prompt repeated screening for malignancy if an initial screen is negative, to ensure an occult neoplasm is not missed.⁴⁸

Box 3: Unanswered questions

- Should 18-fluorodeoxyglucose positron emission tomography routinely be performed in patients with suspected autoimmune limbic encephalitis who have a normal magnetic resonance imaging scan?
- Should more extensive antibody testing be performed in patients who already meet criteria for definite autoimmune limbic encephalitis, but are negative for the most common antibodies associated with this disease?
- What is the threshold of suspicion for autoimmune limbic encephalitis above which antibody testing should be sent, so as to avoid indiscriminate ordering and minimize the risk of false-positive results?
- Should methods of antibody testing be standardized across Canadian institutions?

Even if a patient is ultimately determined to have a diagnosis other than ALE, a positive antibody still requires investigation if it strongly associates with an underlying tumour (e.g., anti-Hu).⁴⁹ Further detail regarding screening for tumours in paraneoplastic neurologic syndromes such as ALE is beyond the scope of this review, but a comprehensive guideline has been published.⁴⁸ If a positive antibody is reported in a patient deemed unlikely to have ALE, inquiry should be made into whether the testing laboratory can perform a confirmatory assay to exclude false-positives.^{10,50}

Conclusion

Accurate diagnosis of ALE is critical to ensure appropriate management of the disease and to maximize the likelihood of a good patient outcome. Although recently published criteria provide a valuable diagnostic framework for ALE, it is important to understand the rationale behind using conventional diagnostic tools (MRI, EEG and analysis of cerebrospinal fluid), as well as their limitations. While questions remain (Box 3), the ongoing discovery of antibodies to onconeural, cell-surface and synaptic proteins represents a major advancement in the refined diagnosis of ALE, and, as such testing becomes more accessible, a thoughtful diagnostic approach will help to balance patient care with resource management in Canada.

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Affiliations: Departments of Clinical Neurological Sciences (Budhram, Nicolle, Burneo), and Medical Imaging (Leung), and the Neuroepidemiology Research Unit (Burneo), Western University, London, Ont.

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Correspondence to: Adrian Budhram, adrian.budhram@medportal.ca