A clinical approach to diagnosis of autoimmune encephalitis

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Abstract

Encephalitis is a severe inflammatory disorder of the brain with many possible causes and a complex differential diagnosis. Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. However, existing criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis. We reviewed the literature and gathered the experience of a team of experts with the aims of developing a practical, syndrome-based diagnostic approach to autoimmune encephalitis and providing guidelines to navigate through the differential diagnosis. Because autoantibody test results and response to therapy are not available at disease onset, we based the initial diagnostic approach on neurological assessment and conventional tests that are accessible to most clinicians. Through logical differential diagnosis, levels of evidence for autoimmune encephalitis (possible, probable, or definite) are achieved, which can lead to prompt immunotherapy.

Introduction

Acute encephalitis is a debilitating neurological disorder that develops as a rapidly progressive encephalopathy (usually in less than 6 weeks) caused by brain inflammation.[1] The estimated incidence of encephalitis in high-income countries is about 5–10 per 100 000 inhabitants per year; encephalitis affects patients of all ages and represents a significant burden to patients, families, and society.[2,3]

Because the most frequently recognised causes of encephalitis are infectious, existing diagnostic criteria and consensus guidelines for encephalitis assume an infectious origin.[1,4–6] However, in the past 10 years an increasing number of non-infectious, mostly autoimmune, encephalitis cases have been identified and some of them do not meet existing criteria.[7] These newly identified forms of autoimmune encephalitis might be associated with antibodies against neuronal cell-surface or synaptic proteins (table)[8–23] and can develop with core symptoms resembling infectious encephalitis, and also with neurological and psychiatric manifestations without fever or CSF pleocytosis.[7] To improve the recognition of these disorders, in this Position Paper, we aim to provide a practical clinical approach to diagnosis that should be accessible to most physicians.

General scope and objectives

These guidelines focus on autoimmune encephalitis that presents with subacute onset of memory deficits or altered mental status, accompanied or not by other symptoms and manifestations, with the goal of helping to establish a prompt diagnosis. These guidelines do not address the clinical approach to other CNS autoimmune disorders (stiff person syndrome,[24] progressive encephalomyelitis with rigidity and myoclonus,[25] or autoimmune cerebellopathies[26]) that usually present with a clinical profile clearly different from autoimmune encephalitis.

Existing diagnostic criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy.[27] In our opinion, it is not realistic to include antibody status as part of the early diagnostic criteria in view of the fact that antibody testing is not readily accessible in many institutions and results can take several weeks to obtain. Furthermore, the absence of autoantibodies does not exclude the possibility that a disorder is immune mediated, and a positive test does not always imply an accurate diagnosis. Use of the response to immunotherapy as part of the diagnostic criteria is also not practical because this information is not available at the time of symptom onset or early clinical evaluation. Some patients with autoimmune encephalitis might not respond to immunotherapy or could need intensive and prolonged therapies that are not available in most health-care systems unless a firm diagnosis has been pre-established.[28] Conversely, patients with other disorders might respond to immunotherapy (eg, primary CNS lymphoma).

The clinical facts and evidence suggesting that early immunotherapy improves outcome[29–31] have been considered in the development of the guidelines presented here, in which conventional neurological evaluation and standard diagnostic tests (eg, MRI, CSF, or EEG studies) prevail in the initial assessment. This approach should allow the initiation of

preliminary treatment while other studies and comprehensive antibody tests are processed and subsequently used to refine the diagnosis and treatment.

The above-mentioned focus of these guidelines and the initial approach based on conventional clinical assessment explain why some disorders are included in the main text and others are included in the appendix or excluded. As an example, we have included acute disseminated encephalomyelitis because the clinical presentation can be similar to that of other autoimmune encephalitis disorders.[32] Another example is Hashimoto's encephalopathy, the existence of which is under discussion, but in practice is frequently listed in the differential diagnosis of autoimmune encephalitis;[33] thus, we believed it should be discussed, while emphasising the controversies and diagnostic limitations. By contrast, Morvan's syndrome[34] and Rasmussen's encephalitis,[35] which have a solid autoimmune basis, are not included in the main text because they usually follow a more chronic course and the initial or predominant symptoms (peripheral nerve hyperexcitability, or focal seizures and unilateral deficits) are different from those mentioned above. We recognise the overlap that can occur between these disorders and autoimmune encephalitis and for this reason they are discussed in the appendix.

Because children do not develop many of the autoimmune encephalitis disorders that affect adults, and the syndrome presentation might be different or less clinically recognisable, these guidelines should be applied with caution in children, particularly in children younger than 5 years.[36,37]

Methods

An initial draft of these guidelines was developed by two authors (FG and JD) and subsequently underwent three rounds of reviews and updates by a panel of investigators who have expertise in autoimmune encephalitis. In the first stage, we reviewed previously published guidelines and diagnostic criteria for encephalitis (of any cause or idiopathic). This review along with clinical experience with forms of autoimmune encephalitis described in the past 10 years (eg, some of them not necessarily causing alteration in consciousness, but changes in memory or personality) led us to a definition of so-called possible autoimmune encephalitis, which is not dependent on neuronal autoantibody status. We next reviewed the existing criteria for specific clinical syndromes (eg, limbic encephalitis or Bickerstaff's brainstem encephalitis), identified other disorders for which criteria were unclear, and modified or developed new diagnostic criteria (eg, probable anti-NMDA receptor encephalitis), which focused on symptom assessment and standard paraclinical tests, and were not dependent on autoantibody status. This work resulted in the establishment of three levels of clinical evidence for autoimmune encephalitis: possible and probable for which the autoantibody status is not needed in most cases, and definite for which the autoantibody status is often needed. In parallel, we reviewed the literature and our experience in neuronal autoantibody studies and identified caveats for interpretation, which led to recommendations for the use and interpretation of findings of autoantibodies in autoimmune encephalitis.

Initial clinical assessment: possible autoimmune encephalitis

We regard a patient with new-onset encephalitis as having possible autoimmune encephalitis if the criteria shown in panel 1 are met. These criteria differ from those previously proposed for encephalitis (any cause or idiopathic) in which changes in the level of consciousness, fever, CSF pleocytosis, and EEG alterations are more often needed.[1,4–6] These criteria needed to be adapted for autoimmune encephalitis because patients with autoimmune encephalitis could present with memory or behavioural deficits without fever or alteration in the level of consciousness, or with normal brain MRI or CSF results.[7] In this context, memory deficits refer to the inability to form new, long-term memories owing to hippocampal dysfunction, or problems with working memory, which refers to structures and processes used for temporary storage and manipulation of information.

Panel 1

Diagnostic criteria for possible autoimmune encephalitis

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

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status[*], or psychiatric symptoms

2. At least one of the following:

    • New focal CNS findings

    • Seizures not explained by a previously known seizure disorder

    • CSF pleocytosis (white blood cell count of more than five cells per mm^3)

    • MRI features suggestive of encephalitis[†]

3. Reasonable exclusion of alternative causes (appendix)

Most patients with encephalitis undergo brain MRI at early stages of the disease. The findings could be normal or non-specific, but sometimes they might suggest an autoimmune cause (see below). By contrast, alterations in EEG are rarely specific. We acknowledge the use of some EEG patterns in the diagnosis of specific forms of encephalitis (eg, extreme delta brush in anti-NMDA receptor encephalitis),[38] in the differential diagnosis of other disorders (Creutzfeldt-Jakob disease), or to reveal subclinical seizures and non-convulsive status epilepticus.

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[*]Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change.
[†]Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

In addition to the above criteria, patients should be carefully examined for other diseases that can mimic autoimmune encephalitis and cause rapidly progressive encephalopathy (appendix). These diseases should be excluded before immunotherapy begins and in most instances a detailed clinical history, complete general and neurological examination, routine blood and CSF analysis, and brain MRI including diffusion sequences will suffice to accomplish this goal. The most frequent differential diagnoses are herpes simplex virus encephalitis and other CNS infections. Importantly, CSF herpes simplex virus PCR can be negative if done too early (eg, within 24 h), and this test should be repeated if the clinical suspicion remains high.[39] Previous reviews have addressed the differential diagnosis of infectious encephalitis.[1,40]

Approach to patients with clinically recognisable syndromes

A substantial number of patients with autoimmune encephalitis do not present with a well defined syndrome. In some of these patients, demographic information and some comorbidities (eg, diarrhoea, ovarian teratoma, faciobrachial dystonic seizures) might initially suggest the underlying disorder (anti-dipeptidyl-peptidase-like protein-6 [DPPX], anti-NMDA receptor, anti-leucine-rich, glioma-inactivated 1 [LGI1] encephalitis), but these features are not pathognomonic and might be absent in some patients.[11,41,42] In such cases, the diagnosis of definite autoimmune encephalitis greatly depends on the results of autoantibody tests. By contrast, disorders exist in which the clinical syndrome and MRI findings allow for classification as probable or definite autoimmune encephalitis before the autoantibody status is known. These include limbic encephalitis, acute disseminated encephalomyelitis and other syndromes with MRI features that predominantly involve white matter, anti-NMDA receptor encephalitis, and Bickerstaff's brainstem encephalitis (Figure 1).[43]

Autoimmune limbic encephalitis

Diagnostic criteria for autoimmune limbic encephalitis are shown in panel 2.[44,45] We have modified our previous criteria to include evidence of bilateral involvement of the medial temporal lobes on T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI studies (Figure 2; see below).[46,47] In our proposed criteria, antibody status is not needed to consider limbic encephalitis as having a definite autoimmune origin because immune-mediated limbic encephalitis can occur without detectable autoantibodies (figure 2, appendix).[48,49] Measurement of autoantibodies, however, remains important for two reasons: their presence clarifies the immunological subgroup of limbic encephalitis, with comorbidities, tumour association, and prognosis that might differ according to the autoantibody;[8,10,50–53] and, in patients who do not satisfy the indicated criteria, detection of autoantibodies establishes the diagnosis of autoimmune limbic encephalitis (panel 2).

Panel 2

Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four[*] of the following criteria have been met:

1.   Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system

2.   Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes[†]

3.   At least one of the following:

     •   CSF pleocytosis (white blood cell count of more than five cells per mm^3)

     •   EEG with epileptic or slow-wave activity involving the temporal lobes

4.   Reasonable exclusion of alternative causes (appendix)

The clinical picture of limbic encephalitis is characterised by rapid development of confusion, working memory deficit, mood changes, and often seizures. The subacute development of short-term memory loss is considered the hallmark of the disorder, but it can be overlooked because of the presence of other symptoms.[46] CSF analysis shows mild-to-moderate lymphocytic pleocytosis (usually less than 100 white blood cells per mm^3) in 60–80% of patients, and elevated IgG index or oligoclonal bands in approximately 50% of cases.[46,51,52] Among all immunological subtypes of limbic encephalitis, patients with LGI1 antibodies present with a lower frequency of CSF pleocytosis (41%) or elevated CSF protein concentrations (47%) and rarely have intrathecal IgG synthesis.[54] The absence of inflammatory changes in the CSF of these patients might initially suggest a non-inflammatory encephalopathy.

MRI often shows increased signal on T2-weighted FLAIR imaging in the medial aspect of the temporal lobes. Although limbic encephalitis can occur with MRI evidence of unilateral involvement (or be normal) we do not consider these cases as definite limbic encephalitis unless specific antibodies are subsequently detected. The reason for this is that several non-immune disorders could result in similar unilateral MRI abnormalities, including among others, seizures, herpes simplex virus encephalitis, or gliomas (appendix, figure 2).[40,55–57] MRI findings of immune-compromised patients with human herpes virus 6-associated encephalitis can mimic precisely findings from patients with autoimmune limbic encephalitis, but the clinical setting is different and directs the diagnosis.[58] By contrast, the findings in herpes simplex virus encephalitis are less confined to the limbic system, can occur with haemorrhagic features, and often show restricted diffusion abnormalities and contrast uptake.[59]

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[*]If one of the first three 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.[44,45]

Some demographic and clinical clues could suggest the underlying immune response of limbic encephalitis (appendix), but the immunological subtypes can be established only by measurement of autoantibodies.[7] Distinction among immunological subtypes is important because those associated with onconeuronal antibodies are much less responsive to immunotherapy than those associated with cell-surface antibodies. The onconeuronal antibodies that more frequently occur with limbic encephalitis are Hu and Ma2, and patients who have these antibodies almost always have an underlying cancer.[8,9] By contrast, the neuronal cell-surface antibodies that are more frequently associated with limbic encephalitis are LGI1,[18] GABA$_B$ receptor,[51,60] and AMPA receptor[52] antibodies (see appendix for less frequent antibodies). The frequency and type of tumours vary according to the antibody (table).[7]

Antibodies against the intracellular antigen glutamic acid decarboxylase (GAD) occur in a subgroup of patients with limbic encephalitis. These patients are mainly young women (median age 23 years) with predominant seizures and no evidence of cancer.[10] The risk of cancer, usually small-cell lung carcinoma or thymoma, is higher, however, among patients with GAD antibodies and limbic encephalitis who are older than 50 years or have concomitant GABA$_B$ receptor antibodies.[23]

Acute disseminated encephalomyelitis and other syndromes with MRI features of demyelination

Acute disseminated encephalomyelitis is a monophasic, inflammatory disease of the CNS that mainly occurs in children and adults younger than 40 years.[61] The disorder can be preceded by an acute systemic infection or vaccination.[62,63] It is characterised by a variable extent of encephalopathy (a mandatory criterion for a definitive diagnosis; panel 3), and other neurological signs, such as cranial nerve palsies, ataxia, hemiparesis, myelopathy, or optic neuritis. CSF analysis typically shows mild pleocytosis (less than 50 lymphocytes per mm^3), but CSF oligoclonal bands are uncommon (less than 7% of all cases).[64] Brain MRI shows multiple, large (>2 cm) abnormalities on T2-weighted FLAIR imaging that can be present in the supratentorial white matter, basal ganglia, brainstem, cerebellum, and spinal cord, with or without contrast enhancement (figure 2).[65] There are no specific biomarkers of acute disseminated encephalomyelitis, and a set of criteria has been proposed for children (panel 3).[32] According to these criteria one of the requirements for definite acute disseminated encephalomyelitis is the absence of new clinical and MRI findings 3 months after symptom onset. Except for this criterion (which cannot be predicted at onset), we believe the rest of the criteria are robust enough to establish that patients who meet them have probable acute disseminated encephalomyelitis and can be started on immunotherapy.

Panel 3

Diagnostic criteria for definite acute disseminated encephalomyelitis[32]

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

1. A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause

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> **2.** Encephalopathy that cannot be explained by fever
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> **3.** Abnormal brain MRI:
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> - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter
>
> - T1-hypointense lesions in the white matter in rare cases
>
> - Deep grey matter abnormalities (eg, thalamus or basal ganglia) can be present
>
> **4.** No new clinical or MRI findings after 3 months of symptom onset
>
> **5.** Reasonable exclusion of alternative causes

Evidence exists that myelin oligodendrocyte glycoprotein (MOG) antibodies can transiently occur in almost 50% of children with acute disseminated encephalomyelitis.[20,66,67] At present, the inclusion of MOG antibodies in the diagnostic criteria for acute disseminated encephalomyelitis is not considered for two reasons: the antibodies can be present in demyelinating disorders with encephalopathy, but without MRI features of acute disseminated encephalomyelitis, or in patients with demyelinating disorders without encephalopathy;[68] and antibody testing remains unavailable at many centres.

Susac's syndrome is a rare, but important, differential diagnosis in patients who meet criteria for possible autoimmune encephalitis and have MRI features of demyelination. The syndrome is considered an autoimmune vasculopathy resulting in microvessel thromboses at three levels: the brain, retina, and inner ear.[69] In a review of 304 cases of Susac's syndrome, 230 (76%) patients presented with encephalopathy, but simultaneous involvement of the three levels at disease onset occurred in only 31 of 247 (13%) patients.[70] The diagnosis is based on presence of branch retinal artery occlusions on fluorescein angiography, and MRI findings including snowball-like lesions or holes in the central portion of the corpus callosum and other periventricular white matter abnormalities on T2-weighted FLAIR imaging (figure 2). These MRI findings are different from those seen in acute disseminated encephalomyelitis and in the setting of encephalopathy are highly suggestive of Susac's syndrome.[70]

Anti-NMDA receptor encephalitis

Anti-NMDA receptor encephalitis is frequently recognisable on clinical grounds and is associated with CSF IgG antibodies against the GluN1 subunit of the NMDA receptor.[11] These antibodies are highly specific and their pathogenicity has been demonstrated in cultured neurons and in-vivo models.[71,72] In a multicentre, observational study of 577 patients, the disease was shown to predominantly affect young individuals (549 [95%] younger than 45 years, and 211 [37%] younger than 18 years) with a female sex predominance of 4:1. This female predominance was less evident in children younger than 12 years and adults older than 45 years.[28] The frequency of an underlying tumour varied with age and sex, ranging from 0–5% in children (male and female) younger than 12 years, to 58% in women older than 18 years (usually an ovarian teratoma).[28] Adults older than 45

years have a lower frequency of tumours (23%), and these are usually carcinomas instead of teratomas.[11]

Teenagers and adults usually present with abnormal behaviour (psychosis, delusions, hallucinations, agitation, aggression, or catatonia) with irritability and insomnia, followed by speech dysfunction, dyskinesias, memory deficits, autonomic instability, and a decrease in the level of consciousness.[11,73] Seizures can take place at any time during the disease, but tend to occur earlier in males.[74] In the above-mentioned observational cohort study,[28] compared with teenagers and adults, young children more frequently presented with abnormal movements or seizures. Regardless of the patient's age and presentation, the clinical picture at 3–4 weeks after symptom onset was similar in most cases. By the end of the first month, 498 (87%) of 571 patients had four or more of the following categories of symptoms, including (from highest-to-lowest frequency) abnormal behaviour and cognition; memory deficit; speech disorder; seizures; abnormal movements (orofacial, limb, or trunk dyskinesias); loss of consciousness or autonomic dysfunction; central hypoventilation; and cerebellar ataxia or hemiparesis.[28] Only six patients (1%) had one category of symptoms.

On the basis of these data, and while waiting for confirmatory IgG anti-GluN1 antibody results, we regard a patient with rapidly progressive encephalopathy as having probable anti-NMDA receptor encephalitis if they satisfy the criteria shown in panel 4. Memory deficit is common, but we have excluded it from the criteria because it is difficult to assess in patients with psychosis or agitation, or in young children. Hemiparesis and cerebellar ataxia are not included because these symptoms are less frequent and if they occur they predominantly affect children in combination with the other symptoms. In patients who meet these criteria, immunotherapy and the search for a neoplasm (according to sex and age) should be started. In a retrospective analysis of data from the observational cohort study,[28] 425 (80%) of 532 patients with anti-NMDA receptor encephalitis met these criteria within the first month of symptom onset, including 254 (74%) of 342 without teratoma and 171 (90%) of 189 with teratoma.

Panel 4

Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis[*]

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

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:

   - Abnormal (psychiatric) behaviour or cognitive dysfunction

   - Speech dysfunction (pressured speech, verbal reduction, mutism)

[*]Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis).

- Seizures

- Movement disorder, dyskinesias, or rigidity/abnormal postures

- Decreased level of consciousness

- Autonomic dysfunction or central hypoventilation

2. At least one of the following laboratory study results:

- Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)

- CSF with pleocytosis or oligoclonal bands

3. Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis[*]

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,[†] after reasonable exclusion of other disorders (appendix)

Patients with partial symptoms who might be missed with these initial criteria will be identified with an antibody test (figure 1). Antibody studies should include CSF analysis; a risk of false-negative or false-positive diagnoses exists if only serum is used.[75] Findings from three other studies have suggested that serum testing is less consistent, or showed antibodies in patients without anti-NMDA receptor encephalitis or immune-mediated disorders.[74,76,77]

Analysis of CSF for the presence of NMDA receptor antibodies is mandatory in patients with relapsing symptoms after herpes simplex encephalitis.[78,79] This relapsing form of herpes simplex encephalitis is an autoimmune disorder that at times is indistinguishable from the full-blown syndrome of anti-NMDA receptor encephalitis, affects 20% of patients with herpes simplex encephalitis, and manifests with new-onset choreoathetosis (predominantly in children)[79,80] or psychiatric symptoms (mainly in adults and teenagers) a few weeks or, rarely, months after the viral infection.[81] In addition to NMDA receptor antibodies, a few patients develop $GABA_A$ receptor or dopamine receptor 2 antibodies.[81,82]

Bickerstaff's brainstem encephalitis

Bickerstaff's brainstem encephalitis is characterised by subacute onset, in less than 4 weeks, of progressive impairment of consciousness along with ataxia and bilateral, mostly symmetrical, ophthalmoparesis.[83] The syndrome is usually preceded by an infectious event, runs a monophasic course, and has a good outcome. Additionally, patients frequently

[†]Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

develop pupillary abnormalities, bilateral facial palsy, Babinski's sign, and bulbar palsy. Generalised limb weakness can occur, which overlaps with features of Guillain-Barré syndrome.[84] CSF pleocytosis occurs in 45% of patients. Brain MRI is usually normal, but brainstem abnormalities on T2- weighted FLAIR imaging are present in 23% of patients.[83]

Most of the proposed criteria for Bickerstaff's brainstem encephalitis include the triad of abnormal mental status, bilateral external ophthalmoplegia, and ataxia (panel 5).[83] IgG anti-GQ1b antibodies are highly specific for this disorder and the related Miller-Fisher syndrome, leading some clinicians to group these disorders under the term GQ1b antibody syndrome.[22] We agree with the criteria proposed in 2014, which do not specify the need for GQ1b antibody testing for a definitive diagnosis of Bickerstaff's brainstem encephalitis because up to 32% of patients do not have detectable antibodies.[43] Measurement of these antibodies, however, allows confirmation of the diagnosis in patients with incomplete syndromes or atypical symptoms, or when the altered mental status prevents the assessment of ataxia. The occasional complexity in the differential diagnosis is exemplified by the third case in the original report by Bickerstaff and Cloake,[85] in which a 24-year-old woman, who was admitted for ovarian cystectomy, in addition to brainstem symptoms, developed seizures, hyperthermia, psychosis, and episodes of maniacal excitement alternating with catatonia that lasted 2 months. Measurement of GQ1b and NMDA receptor antibodies (not available at that time) would probably have clarified the diagnosis.

Panel 5

Diagnostic criteria for Bickerstaff's brainstem encephalitis

Probable Bickerstaff's brainstem encephalitis

Diagnosis can be made when both of the following criteria have been met:

1. Subacute onset (rapid progression of less than 4 weeks) of all the following symptoms:

   - Decreased level of consciousness

   - Bilateral external ophthalmoplegia

   - Ataxia

2. Reasonable exclusion of alternative causes

Definite Bickerstaff's brainstem encephalitis

Diagnosis can be made in the presence of positive IgG anti-GQ1b antibodies even if bilateral external ophthalmoplegia is not complete or ataxia cannot be assessed, or if recovery has occurred within 12 weeks after onset

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Disorders to consider in the differential diagnosis of Bickerstaff's brainstem encephalitis include *Listeria* rhombencephalitis, EV71 encephalitis in children, paraneoplastic and postinfectious brainstem encephalitis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), neurosarcoidosis, and primary CNS lymphoma.[86–88]

Antibody testing: clinical considerations and caveats

The detection of specific autoantibodies (table, figure 1) establishes a definitive diagnosis of autoimmune encephalitis, identifies immunological subtypes of limbic encephalitis, and assists in the differential diagnosis of atypical clinical cases. Therefore, measurement of antibodies is a crucial step in the definite diagnosis of many types of autoimmune encephalitis and clinicians must be aware of potential pitfalls in the interpretation of results.

Several concepts that apply to classic onconeuronal or GAD antibodies (discussed later) are not applicable to antibodies against neuronal cell-surface proteins. Onconeuronal and GAD antibodies target intracellular proteins and because they are present in the serum and CSF, and their epitopes are linear, they are detectable with many techniques including ELISA, immunoblotting, and immunohistochemistry. By contrast, antibodies against neuronal cell-surface proteins have different properties that should be considered for a better understanding of the most appropriate tests to use and interpretation of their results. Here, we discuss these issues and some more general caveats applicable to the detection of autoantibodies.

Conformational antigens

Most antibodies against neuronal cell-surface proteins recognise target epitopes only if they are expressed in their native conformation. Techniques that meet this requirement are cell-based assays (used by most clinical laboratories), immunohistochemistry of brain sections adapted to membrane proteins (commercially available; sometimes used as a confirmatory test), and immunocytochemistry of cultures of dissociated rodent live hippocampal neurons (only used in research laboratories).[12]

Molecular precision

The target antigens of autoantibodies can be composed of several subunits. Antibodies against each of the subunits can have different clinical significance and implications. For example, the NMDA receptor is a heterotetramer comprised of two GluN1 subunits and two GluN2/3 subunits. Detection of IgG antibodies against the GluN1 subunit is a signature of anti-NMDA receptor encephalitis.[89] By contrast, antibodies against linear epitopes of GluN2 or GluR ε2 have been reported in many different disorders and their clinical significance is uncertain.[90]

Molecular precision is important for the voltage-gated potassium channel complex (VGKC) antibodies. This name was adopted by some investigators after they showed that the target antigen was not the VGKC itself, but the proteins LGI1 and contactin-associated protein-like 2 (CASPR2), complexed with the VGKC.[17,18] Antibodies against LGI1 and CASPR2 have well defined syndrome associations. By contrast, radioimmunoassay studies have shown that antibodies directed against the VGKC complex that do not target LGI1 or CASPR2 are not syndrome specific and cannot be used as proof of an immune-mediated pathogenesis.[91–93]

Immunoglobulin class

The antibodies associated with autoimmune encephalitis in the table are IgG antibodies. Detection of IgA or IgM antibodies against any of these antigens has unclear significance. For example, whereas IgG antibodies against the GluN1 subunit of the NMDA receptor are specific for anti-NMDA receptor encephalitis, IgM or IgA antibodies have been reported in the serum of 10% of patients with different disorders and in a similar proportion of healthy people.[94]

CSF studies

Analysis of CSF plays a central part in all diagnostic criteria for encephalitis, including infectious encephalitis, and has a similar role in the detection of autoantibodies in suspected cases of autoimmune encephalitis. The investigation of CSF antibodies is important for four reasons: (1) most patients with autoimmune encephalitis have CSF antibodies and relevant antibodies might be found only in the CSF[51,52]—eg, in patients with anti-NMDA receptor encephalitis up to 14% have antibodies in the CSF, but not in the serum;[75] (2) the repertoire of antibodies in the CSF and serum can be different in the same patient (eg, NMDA receptor in CSF and serum, and GABA$_A$ receptor only in serum), and in this setting, the types of antibodies in the CSF usually determine the clinical picture;[14] (3) for some disorders, such as anti-NMDA receptor encephalitis, the concentration of CSF antibodies correlates better with the clinical course than antibody concentrations in the serum;[75] and (4) neuronal antibody testing using serum and cell-based assays could lead to false-positive or false-negative results; this problem rarely occurs with CSF analysis. On the basis of these data and while we await larger studies with other autoantibodies, our recommendation is to include both CSF and serum for neuronal antibody testing in patients with suspected autoimmune encephalitis.

These concepts have implications for patient management. The approach of first testing the serum and proceeding with the CSF if negative could delay diagnosis. If serum testing is positive, but the CSF is negative, or if the clinical picture does not fit with the antibody identified, the possibilities of a laboratory result unrelated to the syndrome or a false-positive result should be considered;[95] in such cases, the laboratory should be contacted regarding retesting of the samples or the use of confirmatory tests (eg, brain immunohistochemistry or cultured neurons). Finally, treatment decisions during the course of the disease should rely more on clinical assessment than on antibody titres. Although the titres might correlate with the clinical course, this correlation is imperfect, and antibodies often remain detectable after clinical recovery.[75]

Antibodies in demyelinating disorders that overlap with anti-NMDA receptor encephalitis

About 4% of patients with anti-NMDA receptor encephalitis develop two different syndromes that can occur separately or simultaneously. Each syndrome is related to a distinct pathogenic mechanism, such as anti-NMDA receptor encephalitis along with MOG-related or aquaporin 4 (AQP4)-related syndromes (figure 2).[96] In practice, physicians should be aware that a demyelinating disorder can present as an autoimmune encephalitis disorder, and that overlapping syndromes can occur. Patients with a demyelinating disorder and atypical features (eg, dyskinesias or prominent psychiatric manifestations) or patients with

anti-NMDA receptor encephalitis with atypical features (eg, optic neuritis or demyelination on MRI) should be comprehensively studied for coexisting disorders, rather than being classified as having an expansion of the spectrum of a single disease. These clinical situations imply the need for testing for AQP4 and MOG antibodies in the serum (because intrathecal production of these antibodies is rare),[20,97] and for NMDA receptor antibodies in the serum and CSF.

GAD antibodies in limbic encephalitis and other syndromes

Serum antibodies against intracellular GAD can occur at low titres in 1% of healthy people and in 80% of people with type 1 diabetes mellitus.[98] Only serum GAD antibodies at high titres are associated with autoimmune neurological disorders, such as limbic encephalitis and other syndromes.[99] The definition of high titre depends on the technique used, but neurological symptoms usually occur with titres that are 100–1000 times higher than those seen in people with diabetes. When examining a patient with limbic encephalitis, clinicians should keep in mind that, albeit rare, high titres of serum GAD antibodies could suggest the presence of diabetes or other endocrine disorders. In this setting, specific intrathecal production of GAD antibodies or CSF oligoclonal bands support an association with the neurological syndrome.[99]

Approach to patients without recognisable syndromes or autoantibodies

After excluding all well characterised syndromes of autoimmune encephalitis (with or without autoantibodies) and other syndromes accompanied by well defined auto-antibodies, a group of patients who have possible autoimmune encephalitis will remain (panel 1). Patients in this group can be regarded as having probable autoimmune encephalitis if they satisfy criteria for Hashimoto's encephalopathy (panel 6)[101] or the criteria proposed in panel 7.

Panel 6

Diagnostic criteria for Hashimoto's encephalopathy

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

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes

2. Subclinical or mild overt thyroid disease (usually hypothyroidism)

3. Brain MRI normal or with non-specific abnormalities

4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies[*]

5. Absence of well characterised neuronal antibodies in serum and CSF

6. Reasonable exclusion of alternative causes

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[*]There is no disease-specific cutoff value for these antibodies (detectable in 13% of healthy individuals).[100]

Panel 7

Criteria for autoantibody-negative but probable autoimmune encephalitis

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

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2. Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)

3. Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:

   - MRI abnormalities suggestive of autoimmune encephalitis[*]

   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both[*]

   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)

4. Reasonable exclusion of alternative causes

The definition of Hashimoto's encephalopathy has been linked to a good response to steroids, and consequently the disorder is deemed immune mediated, despite the unclear physiopathology and the absence of response to prednisone in the patient in the original report.[103] This disorder predominantly affects women in a wide age range, from the first to the eighth decade of life. Overt or subclinical thyroid disease, usually hypothyroidism, occurs in most cases (54 of 80 patients in a review of reported cases).[104] By definition, patients develop encephalopathy, which can be associated with seizures (56 of 85 reviewed patients), myoclonus (32 patients), hallucinations (31 patients), and stroke-like episodes (23 patients) with normal or non-specific CSF and brain MRI abnormalities.[33,104] Most reported patients (66 of 69 patients treated with corticosteroids with or without levothyroxine) improved;[104] however, this outcome is expected in view of the definition of the disorder, which in 2006 was renamed as steroid-responsive encephalopathy with autoimmune thyroiditis.[101]

Patients who have a non-specific encephalopathy with subclinical or overt thyroid disease, anti-thyroid antibodies, and no better explanation for the symptoms should be considered for a trial of steroids. However, thyroid antibodies are not specific for Hashimoto's encephalopathy because they are present in up to 13% of healthy individuals (27% in white women older than 60 years) and patients with other autoimmune encephalitis disorders.[100]

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[*]Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder.[102]

Similarly, α-enolase antibodies have been identified in up to 68% of patients with Hashimoto's encephalopathy,[105] but they cannot be used as biomarkers of the disease because they have been detected in healthy people and in patients with other autoimmune disorders.[33,106]

We propose use of the term Hashimoto's encephalopathy only when rigorous clinical assessment and comprehensive testing for well characterised neuronal antibodies exclude other potential causes of encephalopathy (panel 6).[100] Because the underlying pathogenic mechanism is unclear, diagnosis of Hashimoto's encephalopathy should be classified as probable autoimmune encephalitis (figure 1).

Other poorly defined syndromes with no antibodies can be regarded as probable autoimmune encephalitis if they satisfy the criteria in panel 7. When considering these criteria the following should be kept in mind: (1) the absence of pleocytosis does not rule out autoimmune encephalitis (eg, 59% of patients with LGI1 antibody-associated encephalitis do not have CSF pleocytosis),[54] normal routine CSF studies do not imply that there is no intrathecal IgG synthesis or an absence of CSF antibodies, and in fact, almost all antibody-associated autoimmune encephalitis disorders have detectable antibodies in the CSF; (2) autoimmune encephalitis can occur with normal or atypical MRI findings (figure 2); and (3) mainly applicable to children, several genetic disorders, mitochondrial diseases, or leukodystrophies can develop with MRI and CSF abnormalities (eg, symmetric brain involvement, pleocytosis) similar to those found in autoimmune encephalitis and might also respond to steroids.[102]

For patients who meet the criteria of probable autoimmune encephalitis, but do not have well characterised autoantibodies (panel 7), investigation of CSF and serum for new antibodies in reference laboratories is important. Detection of CSF antibodies that react with the cell surface of neurons (even when the antigens are unknown) strongly supports the diagnosis of autoimmune encephalitis; the clinical significance of the detection of antibodies in serum only is less clear (eg, serum $GABA_A$ receptor antibodies are associated with a wide variety of symptoms, some of unclear clinical relevance).[14,107] The importance of these studies cannot be overemphasised and surpasses the clinical significance of inflammatory infiltrates in a brain biopsy, which suggest an inflammatory process, but cannot be used to establish the autoimmune cause.

For patients who do not satisfy criteria for probable autoimmune encephalitis and do not have any autoantibody (well characterised or against unknown neuronal cell-surface antigens), or who do not satisfy criteria for any of the aforementioned diseases and syndromes, the likelihood of an autoimmune cause becomes smaller and alternative diagnoses should be reconsidered.

There are several autoimmune CNS disorders (primary CNS angiitis [appendix],[108] Rasmussen's encephalitis,[35] Morvan's syndrome[34]) and other diseases of unclear cause (eg, febrile infection-related epilepsy syndrome [FIRES][109]) that are often considered in the differential diagnosis of autoimmune encephalitis (panel 1). We have summarised these

disorders (appendix) and emphasised the clinical features that lead to the differential diagnosis with autoimmune encephalitis.

Implications and directions for future research

We have shown that it is possible to proceed through a logical differential diagnosis of autoimmune encephalitis using criteria based on conventional clinical neurological assessment and standard diagnostic tests (MRI, EEG, and CSF studies). Through this approach, levels of evidence of probable and definite autoimmune encephalitis can be achieved early and therapies implemented quickly, with the possibility of fine-tuning the diagnosis and treatment when antibody results become available. Treatment recommendations for each type of autoimmune encephalitis are outside the scope of these guidelines; moreover, the evidence is limited for many of these disorders. The stepwise escalation of immunotherapy, which includes first-line therapy (steroids; IVIg, plasma exchange, or both) followed, if there is no clinical response, by second-line therapy (rituximab, cyclo phosphamide, or other), is often used in the treatment of anti-NMDA receptor and other autoimmune types of encephalitis, but rituximab is increasingly being considered as a first-line therapy.[16] Not all autoimmune encephalitis syndromes, however, need a similar approach. For example, patients with limbic encephalitis and LGI1 antibodies appear to respond faster and better to steroids than patients with anti-NMDA receptor encephalitis, yet the long-term outcome seems to be better for those with anti-NMDA receptor encephalitis.[28,53]

We acknowledge the need for future research to drive improvements in the diagnosis of autoimmune encephalitis. The repertoire of autoimmune encephalitis in children is different from that of adults. The younger the child the more difficult it is to recognise specific autoimmune encephalitis syndromes, which suggests that guidelines for paediatric autoimmune encephalitis will be more dependent on antibody and other ancillary tests than the syndrome-based guidelines in this Position Paper. Conversely, clinical assessment of autoimmune encephalitis in elderly people (aged over 65 years) has another set of challenges imposed by the high frequency of brain changes in this group caused by systemic and non-immune-mediated disorders, or the coexistence of age-related disorders that can affect memory and cognition. Other areas of improvement will be dictated by cumulative clinical experience, better differential diagnoses with diseases that resemble autoimmune encephalitis, and increased accessibility to antibody tests with faster turnaround, while keeping in mind the caveats for interpretation of some of these tests.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Search strategy and selection criteria

Relevant papers were identified through PubMed searches of articles published in English up to Nov 23, 2015, using the search terms (alone or in combination): "autoimmune encephalitis", "limbic encephalitis", "anti-NMDA receptor encephalitis", " acute disseminated encephalomyelitis", "brainstem encephalitis", "basal ganglia encephalitis", "Hashimoto encephalopathy", "Rasmussen encephalitis", "primary CNS angiitis", "primary CNS vaculitis", "Susac syndrome", "Morvan syndrome", and "neuronal autoantibodies". Additional studies were identified from the authors' files. The final reference list was generated on the basis of relevance to the topics covered in this Position Paper.
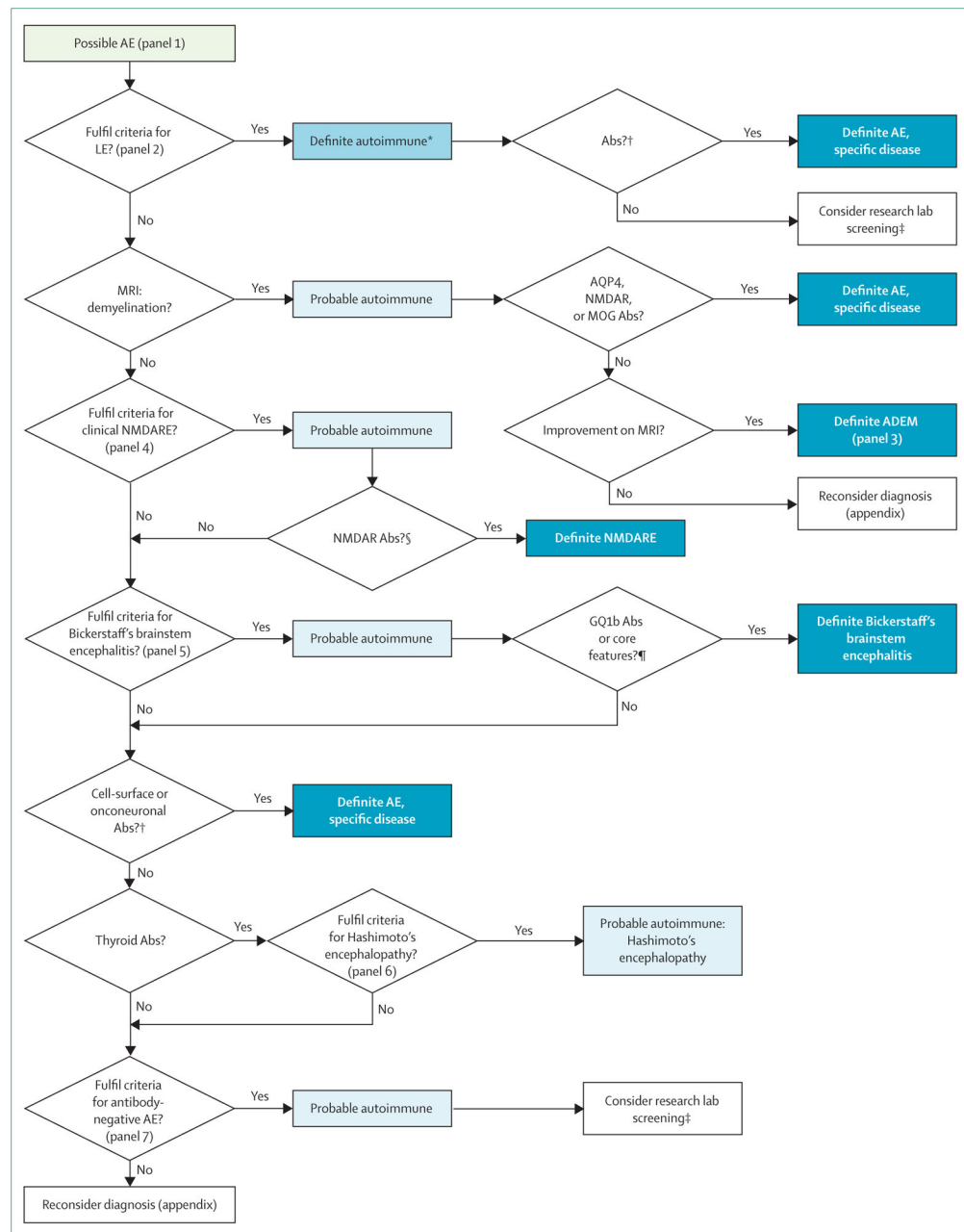
Figure 1. Algorithm for the diagnosis of autoimmune encephalitis
AE=autoimmune encephalitis. LE=limbic encephalitis. Abs=antibodies. AQP4=aquaporin 4. MOG=myelin oligodendrocyte glycoprotein. NMDARE=NMDA receptor encephalitis. ADEM=acute disseminated encephalomyelitis. *Although results of autoantibodies are not necessary for a definitive diagnosis of some types of autoimmune encephalitis, their determination is important to further characterise subtypes of limbic encephalitis that have different prognosis, type of treatment, and comorbidities. †See table. ‡Research laboratories can screen for new antibodies (eg, using live neurons). §IgG anti-GluN1 antibodies in the CSF; if only serum is used, confirmatory tests should be included (panel 4). ¶Definitive diagnosis of Bickerstaff's brainstem encephalitis can be made in the presence of core

clinical features (hypersomnolence, ophthalmoplegia, and ataxia)[43] or positive GQ1b antibodies if core symptoms are incomplete.
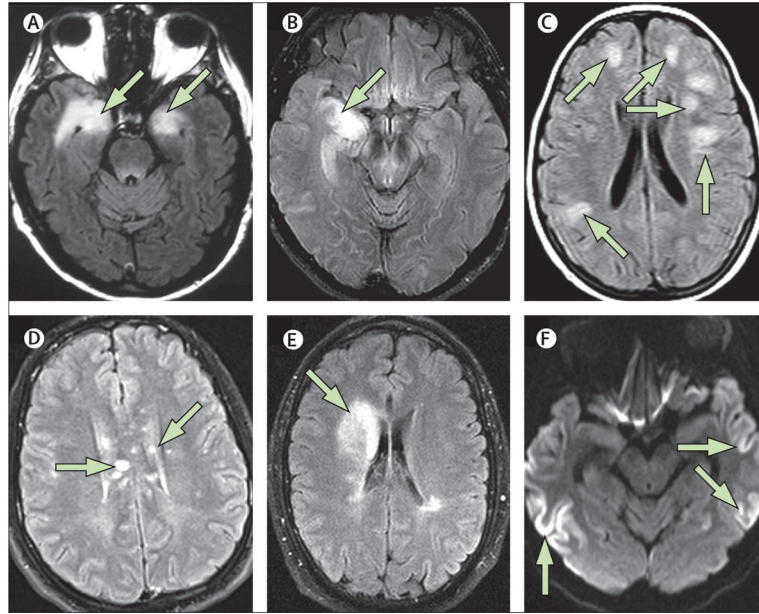
Figure 2. MRI patterns in autoimmune encephalitis and its mimics

Typical MRI of limbic encephalitis (A) with bilateral abnormalities in the medial temporal lobe on T2-weighted fluid-attenuated inversion recovery imaging; this patient with autopsy-proven limbic encephalitis did not have serum or CSF antineuronal antibodies. Patient with final diagnosis of glioma (B) who presented with unilateral right hippocampal involvement mimicking limbic encephalitis. Typical MRI of acute disseminated encephalomyelitis (C) with bilateral large lesions in the white matter. Multiple lesions involving the corpus callosum in a patient with Susac's syndrome (D). MRI of a patient with overlapping syndrome (NMDA receptor and myelin oligodendrocyte glycoprotein antibodies; E) showing a right frontal abnormality compatible with demyelination. Diffusion MRI sequence in a patient with AMPA receptor antibody-associated encephalitis (F) mimicking MRI changes seen in patients with Creutzfeldt-Jakob disease. Left side of images=right side of brain.

Table 1

Antibodies in the diagnosis of autoimmune encephalitis

	Syndrome	Diagnostic assay	Frequency of cancer	Main type of cancer
Antibodies against intracellular antigens				
Hu (ANNA1)[8] *	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2[9]	Limbic encephalitis †	Western blot	>95%	Testicular seminoma
GAD[10]	Limbic encephalitis ‡	Radioimmunoassay	25% §	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor[11]	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma ¶
AMPA receptor[12]	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
GABA_B receptor[13]	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
GABA_A receptor[14]	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5[15]	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine 2 receptor[16]	Basal ganglia encephalitis	Cell-based assay	0%	..
Antibodies against ion channels and other cell-surface proteins				
LGI1[17]	Limbic encephalitis	Cell-based assay	5–10%	Thymoma
CASPR2[18]	Morvan's syndrome ‖ or limbic encephalitis	Cell-based assay	20–50%	Thymoma **
DPPX[19]	Encephalitis ††	Cell-based assay	<10%	Lymphoma
MOG[20]‡‡	Acute disseminated encephalomyelitis	Cell-based assay	0%	..
Aquaporin 4[21]‡‡	Encephalitis	Cell-based assay	0%	..
GQ1b[22]	Bickerstaff's brainstem encephalitis	ELISA	0%	..

GAD=glutamic acid decarboxylase. LGI1=leucine-rich glioma inactivated 1. CASPR2=contactin associated protein 2. DPPX=dipeptidyl-peptidase-like protein-6. MOG=myelin oligodendrocyte glycoprotein.

* Amphiphysin or CV2 (CRMP5) antibodies instead of Hu antibodies in a few patients with limbic encephalitis and small-cell lung carcinoma.

† Limbic encephalitis frequently associated with hypothalamic and mesencephalic involvement.

‡ GAD antibodies occur more frequently in patients with stiff person syndrome and cerebellar ataxia. The association with cancer preferentially occurs in patients with limbic encephalitis.

§ Tumours found more frequently in men older than 50 years.[23]

¶ Ovarian teratoma usually found in young women aged 12–45 years.

‖ Morvan's syndrome usually has a more chronic clinical course, but might present with predominant cognitive and behavioural symptoms fulfilling criteria of possible autoimmune encephalitis.

** Thymoma associated with Morvan's syndrome rather than limbic encephalitis.

†† Encephalitis associated with diarrhoea and hyperekplexia.

‡‡ Mostly restricted to children.