Published in final edited form as:
Curr Opin Neurol. 2014 June ; 27(3): 361–368. doi:10.1097/WCO.0000000000000087.

Auto-immune encephalitis as differential diagnosis of infectious encephalitis

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Abstract

Purpose of review—To describe the main types of autoimmune encephalitis with special emphasis on those associated with antibodies against neuronal cell surface or synaptic proteins, and the differential diagnosis with infectious encephalitis.

Recent findings—There is a continuous expansion of the number of cell surface or synaptic proteins that are targets of autoimmunity. The most recently identified include the mGluR5, DPPX, and the $GABA_AR$. In these and previously known autoimmune encephalitis (NMDAR, AMPAR, $GABA_BR$, LGI1, CASPR2), the prodromal symptoms or types of presentations often suggest a viral encephalitis. We review here clues that help in the differential diagnosis with infectious encephalitis. Moreover, recent investigations indicate that viral encephalitis (e.g., herpes simplex) can trigger synaptic autoimmunity. In all these disorders immunotherapy is usually effective.

Summary—Autoimmune encephalitis comprises an expanding group of potentially treatable disorders that should be included in the differential diagnosis of any type of encephalitis.

Keywords

autoimmune encephalitis; immunotherapy; herpes simplex encephalitis; viral encephalitis; neuronal surface antibodies

Introduction

Encephalitis is a significant cause of morbidity and mortality worldwide. In order to find the etiology of the disorder patients frequently undergo extensive testing but despite this, the cause remains unknown in about 60% of the cases.[1–3] The discovery that several forms of

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Conflict of interest:

Dr. Dalmau hold patents for the use of Ma2 and NMDAR as autoantibody tests, and has filed patents for the use of $GABA_AR$ and $GABA_BR$ as diagnostic tests.

encephalitis result from antibodies against neuronal cell surface or synaptic proteins, and that they are potentially treatable[4] has led to a paradigm shift in the diagnostic approach of encephalitis.[5–10] A recent multicenter population-based prospective study found that in 42 of 203 patients (21%) the etiology was immune-mediated and 38% of them occurred with neuronal antibodies.[6] Another study by the California Encephalitis Project, a center focused in the epidemiology of encephalitis found that the frequency of anti-N-methyl-D-Aspartate receptor (NMDAR) encephalitis surpassed that of any individual viral etiology in young individuals.[7] Moreover, recent studies show that some forms of autoimmune encephalitis can be triggered by herpes simplex encephalitis (HSE).[11,12] This review focuses on the diagnosis and treatment of autoimmune encephalitis, mainly those associated with antibodies to cell surface or synaptic proteins (Table 1), with emphasis on the differential diagnosis with infectious etiologies.

Comparison between autoimmune and infectious encephalitis

Autoimmune encephalitis occurs more frequently in immunocompetent than immunocompromised patients (22% versus 3%).[6] Most patients with antibody-associated encephalitis and HSE have seizures.[6] In contrast, patients with encephalitis associated to varicella zoster virus (VZV) or *Mycobacterium tuberculosis* infrequently develop seizures.[6] Psychosis, language dysfunction, autonomic instability and abnormal movements are a hallmark of anti-NMDAR encephalitis.[5,7,13] Most patients with infectious encephalitis have fever, but approximately 50% of cases with autoimmune encephalitis present or develop fever during the course of the disease.[6,7] Prodromal symptoms such as headache or flu-like symptoms occur frequently in autoimmune encephalitis and may lead to the suspicion of an infectious etiology.[5] Skin lesions can assist in the recognition of VZV, however, CNS VZV reactivation may occur in the absence of rash.[14]

Most autoimmune encephalitis associate with cerebrospinal fluid (CSF) lymphocytic pleocytosis that is usually milder than that found in viral etiologies.[5,7] Patients with viral and autoimmune encephalitis have normal glucose levels and normal or mildly increased protein concentration[5,7], while patients with bacterial infections or *Mycobacterium tuberculosis* have a decrease of CSF glucose concentration.[6]

Magnetic resonance imaging (MRI) of the brain can be useful in the differential diagnosis of encephalitis, particularly in patients with limbic encephalitis. Most patients with autoimmune or paraneoplastic limbic encephalitis have uni- or bilateral increased T2/FLAIR signal in the medial temporal lobes without contrast enhancement or abnormal diffusion-weighted images; an exception is the paraneoplastic encephalitis with antibodies against the intracellular protein Ma2, in which MRI often shows contrast enhancement.[15] The syndromes with classical findings of limbic encephalitis include those associated with antibodies against the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the gamma-aminobutyric acid-B receptor ($GABA_BR$), leucine-rich glioma inactivated protein 1 (LGI1), and less frequently the metabotropic glutamate receptor 5 (mGluR5).[16–19] In patients with anti-NMDAR encephalitis the brain MRI is normal in approximately 60% of the patients and shows nonspecific findings in the rest including, cortical-subcortical FLAIR changes in brain or posterior fossa, transient meningeal

enhancement, or areas of demyelination.[20] The brain MRI in other autoimmune encephalitis, such as those associated with antibodies against contactin-associated protein-like 2 (CASPR2) or dipeptidyl-peptidase-like protein-6 (DPPX) is frequently abnormal but rarely suggestive of focal limbic encephalitis.[21,22] Patients with high titer serum and CSF $GABA_AR$ antibodies may develop extensive cortical and subcortical T2-FLAIR changes during the course of the disease.[23]

Only a few infectious encephalitis associate with MRI findings similar to those occurring in autoimmune limbic encephalitis; they include, post-transplant acute limbic encephalitis related to human herpesvirus 6 (HHV6), exceptional cases of neuro-syphilis, and HSE. Of note, HSE typically shows asymmetric medial temporal lobe necrosis along with involvement of cingulate and insular regions. Some patients, usually children, may develop more extensive MRI abnormalities in frontal, occipital or parietal lobes.[24] The polymerase chain reaction (PCR) for herpes simplex virus (HSV) can be false-negative during the first 48 hours of HSE.[24]

Autoimmune encephalitis with antibodies against intracellular antigens

Most of the antibodies to intracellular proteins considered here are paraneoplastic and therefore, they occur in middle aged or elder patients who sometimes have a previous history of cancer. They include antibodies to Hu, Ma2, Ri, CRMP5, and amphypisin.[25] In approximately 70% of the cases the development of neurological symptoms precedes the cancer diagnosis.[25,26] Patients with any of these antibodies can develop limbic encephalitis, usually in the context of encephalomyelitis. Some patients with Hu antibodies develop focal cortical encephalitis and *epilepsia partialis continua* suggesting a focal infectious process.[27] Patients with Ma2 antibodies may develop prominent brainstem dysfunction with abnormal gaze and facial movements which frequently suggest Whipple's disease. In a series of 38 patients with anti-Ma2 encephalitis, 16% underwent duodenal biopsy for suspected Whipple's disease before the final diagnosis was made.[28]

A subset of patients with limbic or non-focal encephalitis with or without seizures has antibodies against GAD65.[29] These antibodies rarely associate with cancer, and also occur in patients with cerebellar degeneration, stiff-person syndrome, and non-neurological disorders such as type I diabetes mellitus, vitiligo, or pernicious anemia. Moreover, GAD65 antibodies may associate with encephalitis related to other more relevant antibodies, such as AMPAR, $GABA_BR$ or $GABA_AR$.[18,23] All patients with encephalitis or seizures with GAD65 antibodies should be assessed for the co-occurrence of other antibodies against cell surface proteins.

Autoimmune encephalitis with antibodies to cell surface or synaptic proteins

Anti-NMDAR encephalitis

This disorder predominates in young women and children although it can affect males and people of all ages (the youngest and the oldest patient described were 2 month and 85 year-old).[12,20] The presence of a tumor (mostly an ovarian teratoma) is age dependent, and rarely

encountered in patients younger than 12 years.[20] The antibodies target the GluN1 subunit of the NMDAR receptor.[30] The neuropsychiatric symptoms are often preceded by prodromal headache, fever or other features that may suggest an infection. In teenagers and young women, the onset is characterized by prominent psychiatric manifestations (delusional thoughts, bizarre behavior, psychosis, catatonia), followed by a decrease of consciousness, seizures, orofacial or limb dyskinesias, and autonomic instability.[30] In children and adult male patients, the first symptom can be seizures or movement disorders.[31–34] The differential diagnosis often includes a primary psychiatric disorder, drug abuse, neuroleptic malignant syndrome, or infectious encephalitis.[5] In some instances the diagnosis of rabies has been considered due to the presence of extreme agitation, prominent sialorrhea, and abnormal movements.[5] In contrast to anti-NMDAR encephalitis in which the brain MRI is frequently normal,[30] the MRI of patients with rabies often shows symmetric involvement of the grey matter of dorsal brainstem, thalamus, basal ganglia, or central region of the spinal cord.[35]

Due to the frequent presence of prodromal symptoms (hyperthermia, headache, and other), most patients with anti-NMDAR encephalitis are investigated for an infectious etiology. In a few cases (overall less than 5% of the cases) positive serologies for *Mycoplasma pneumoniae*, HHV6, or enterovirus have been described; the significance of these findings is currently unclear.[30,32] Detection of HHV6 or 7 in the CSF by PCR may represent detection of a latent rather than an active viral infection.[36] A link between HSE and anti-NMDAR encephalitis (and other types of synaptic autoimmunity) was recently identified (discussed later).

The antibodies of patients with anti-NMDAR encephalitis cause a specific internalization of these receptors, and alter the NMDAR synaptic currents.[30] A similar antibody mediated internalization of receptors was observed after infusing patients' antibodies into the hippocampus of rats. Autopsies of patients with these antibodies show a decrease of NMDAR in areas of deposits of antibodies along with absence of cytotoxic T-cell infiltrates or deposits of complement.[37]

Encephalitis with predominant limbic involvement—The term limbic encephalitis refers to an inflammatory process of the limbic system including, the medial temporal lobes, amygdala, and cingulate gyri, resulting in severe memory deficits, behavioral changes, psychiatric symptoms and temporal lobe seizures.[38] The most frequent cell surface target antigen of limbic encephalitis is LGI1. The median age of patients with these antibodies is 60 years, and the neurological symptoms are often accompanied by hyponatremia.[17,39] Patients rarely have an underlying tumor, and if so, it is usually a thymoma. Some patients develop myoclonic-like movements, also described as facio-brachial dystonic seizures, but with EEG features of tonic seizures.[40,41] These seizures can precede or occur simultaneously with symptoms of limbic dysfunction and may lead to an early recognition of the disorder. Approximately 70% of the patients with LGI1 antibodies improve with immunotherapy although residual memory deficits are frequent (unpublished observation). There is evidence that LGI1 antibodies may disrupt the normal interaction of LGI1 with the synaptic proteins ADAM22 and ADAM23, resulting in a decrease of post-synaptic AMPAR.[42]

Other cell surface antigens related to limbic encephalitis include AMPA and $GABA_B$ receptors.[16,18] More than half of the patients with these antibodies have cancer; the type of tumor varies with the antibodies (small cell lung carcinoma, SCLC, predominantly with $GABA_B$ receptor, and breast cancer and thymomas with AMPAR). Patients with SCLC may have other antibodies suggesting the presence of this tumor, such as SOX1 or N-type voltage-gated calcium channel (VGCC). Patients' antibodies against AMPAR cause internalization of receptors and decrease of AMPAR mediated currents strongly suggesting a pathogenic role of these antibodies.[16]

Other autoimmune encephalitis—A subset of patients with autoimmune encephalitis harbor antibodies to DPPX,[22] a critical regulatory subunit of the Kv4.2 potassium channel. These patients develop agitation, confusion, psychiatric symptoms, seizures, tremor, myoclonus, and less frequently hyperekplexia.[22,43] Characteristically, most of these patients have diarrhea or other gastrointestinal symptoms leading to profound weight loss. The etiology of these gastrointestinal symptoms is unclear, but may be related to the expression of DPPX in the myenteric plexus.[22] This clinical presentation often leads to extensive gastrointestinal studies for a malignancy or infectious etiology, which in all cases has been negative.

A form of non-focal encephalitis (although often referred as limbic encephalitis) associates with Hodgkin's lymphoma, and is known as Ophelia syndrome.[44] These patients usually have antibodies to mGluR5.[19] Identification of this disorder is important because it is highly responsive to treatment of the tumor and immunotherapy.[19,45] Autoantibodies to mGluR5 can also occur in patients with autoimmune encephalitis without Hodgkin's lymphoma.

CASPR2 is the target antigen of antibodies of some patients with Morvan's syndrome, encephalitis (sometimes focal limbic encephalitis), or a subset of cases with neuromyotonia. Autoantibodies against CASPR2, and those directed against LGI1 were previously reported as voltage-gated potassium channels (VGKC) antibodies. About 30% of patients with CASPR2 antibodies have an underlying thymoma.[21,39,46]

The most recently identified autoimmune encephalitis occurs with antibodies against the $GABA_A$ receptors.[23] High titers of these antibodies in serum and CSF usually result in refractory seizures and status epilepticus, along with extensive MRI cortical/subcortical FLAIR changes. Approximately, 40% of the patients are children. Low titers of serum antibodies associate with encephalitis and seizures, but also opsoclonus and stiff-person syndrome (with or without GAD65 antibodies). Patients with $GABA_AR$ receptor antibodies are often misdiagnosed as having anti-GAD65 associated encephalitis or Hashimoto's encephalitis due to the frequent co-occurrence of GAD65 or thyroid-peroxidase (TPO) antibodies. Patient's $GABA_AR$ antibodies cause a specific decrease of these receptors at synapses.[23]

Several studies have indicated the presence of antibodies to dopamine receptor 2 (DR2) in some patients with basal ganglia encephalitis or Sydenham chorea.[47,48] At this time, the frequency and pathogenic significance of these antibodies are unclear.

HSE triggers synaptic autoimmunity

There is recent evidence that HSE triggers synaptic autoimmunity.[11,12] This finding likely explains cases with prolonged or atypical neurological symptoms after successful control of the viral infection, or patients who develop a syndrome described as “relapsing post-HSE” or “choreoathetosis post-HSE”.[12,32,49–51] These disorders are important to recognize because the outcome without immunotherapy is usually poor.[52] In contrast, aggressive immunotherapy appears to be beneficial, sometimes with substantial recoveries.[32,49,53] Choreoathetosis post-HSE, usually develops a few weeks after patients have recovered from HSE;[52,54] the main differences between true viral relapses and autoimmune encephalitis post-HSE are shown in Table 2. The clinical features of autoimmune encephalitis post-HSE are similar to those of anti-NMDAR encephalitis, although some patients develop fragments of this syndrome. A recent study showed that the novel synthesis of NMDAR antibodies occurred after the viral encephalitis.[12] Some patients may develop antibodies to DR2[51] and other yet unknown cell surface neuronal proteins.[12]

Diagnosis and treatment of encephalitis with antibodies to cell surface antigens

Current experience suggests that any rapidly progressive encephalopathy of unclear etiology, particularly if accompanied by lymphocytic CSF pleocytosis (although routine CSF studies can be normal), and multifocal symptoms with or without MRI changes should raise concern for an immune mediated process. FLAIR-T2 MRI abnormalities (without substantial enhancement) involving medial temporal lobes occur frequently in patients with typical limbic encephalitis, and should increase the suspicion of an immune mediated process, keeping in mind that the MRI findings could be the result of seizures or a viral infection.

Antibody testing cannot replace the clinical evaluation. Determination of antibodies should be considered as a supportive test to confirm the etiology of a disorder clinically suspected to be immune mediated. In our experience the association of some syndromes with one or a restricted number of antibodies is so high that in many patients the type of syndrome directs the antibody testing. This high syndrome-antibody specificity is obtained when comprehensive testing for one or a specific subset of antibodies is applied, including immunohistochemistry with brain tissue and cell-based assays with patient’s serum and CSF. If studies are less comprehensive (e.g., serum only with cell-based assays only) the specificity decreases and the number of false positive or negative cases increases.[55] The importance of a comprehensive evaluation including CSF and serum was recently demonstrated in a study on anti-NMDAR encephalitis.[55]

Comprehensive testing identifies also cases that might erroneously be considered variants of a syndrome or “widening” of the spectrum of symptoms, while in fact represent the overlap of two different syndromes with independent immune responses (e.g., myelitis or optic neuritis with aquaporin4 or myelin oligodendrocyte glycoprotein [MOG] in patients with anti-NMDAR encephalitis).[56] Therefore, it is important to store aliquots of CSF when spinal taps for viral studies are done. Depending on the syndrome and degree of clinical suspicion,

the study for autoantibodies can be initiated at the same time that viral studies are conducted or wait until PCR or serological studies for the most common viruses are completed. However, it is important to keep in mind that some tests (eg. HSV or *Mycoplasma pneumoniae*) can be positive and the patient still have an immune mediated process.

If studies for an infectious or autoimmune etiology are negative, but there is concern for an underlying autoimmune process, one should consider examining the CSF and serum in a research laboratory. The rate of novel autoantibodies described (approximately 1–2 per year) and the fact that for many of them the initial assessment of patient's CSF was critical, emphasize the importance of banking or keeping aliquots of CSF.

The extent of tumor search depends on the type of antibody, age, and sex of the patient (as discussed above).[26] Immunotherapy (steroids, IVIg or plasma exchange) can be effective, but patients often require more aggressive therapies (rituximab, cyclophosphamide).[20] Although the follow-up of CSF and serum antibody titers may assist in some assessments (e.g., relapses or effects of treatment), clinical decisions about changing or discontinuing treatments should rely more on clinical assessment (e.g., antibody titers may remain detectable after neurological recovery).[55]

Conclusion

Autoimmune encephalitis comprises an expanding group of potentially treatable disorders that should be in the differential diagnosis of any type of encephalitis. They can resemble infectious encephalitis, and sometimes are triggered by infectious disorders (e.g., HSE). Aggressive immunotherapy is often effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study support: Instituto Carlos III, FI12/00366 (TA), FIS PI11/01780 (JD), and the National Institutes of Health RO1NS077851 (JD), MH094741 (JD) and Fundació la Marató TV3 (101530 JD).

Funding:

The National Institute of Health, the McKnight Neuroscience of Brain Disorders award, the Fondo de Investigaciones Sanitarias, and Fundació la Marató de TV3.

Dr. Dalmau receives research grant support from Euroimmun.

Abbreviations

ADC	apparent diffusion coefficient
ADEM	acute disseminated encephalomyelitis
AQP4	aquaporin 4
AMPAR	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

CASPR2	contactin-associated protein-like 2
CNS	central nervous system
DPPX	dipeptidyl-peptidase-like protein-6
DR2	dopamine receptor 2
CSF	cerebrospinal fluid
CT	computed tomography
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
$GABA_{B\ or\ A}R$	gamma-aminobutyric acid-B or A receptor
GAD65	65 kDa isotype of glutamic acid decarboxylase
HHV	human herpesvirus
HSE	herpes simplex encephalitis
HSV	herpes simplex virus
LGI1	leucine-rich glioma inactivated protein 1
mGluR5	metabotropic glutamate receptor 5
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
NMDAR	N-methyl-D-apartate receptor
NMO	neuromyelitis optica
PCR	polymerase chain reaction
SCLC	small cell lung carcinoma
TPO	thyroid peroxidase
VGKC	voltage-gated potassium channels
VGCC	voltage-gated calcium channels
VZV	varicella zoster virus
WBC	white blood count

References

1. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006; 43:1565–1577. [PubMed: 17109290]
2. Mailles A, Stahl JP. Infectious encephalitis in france in 2007: a national prospective study. Clin Infect Dis. 2009; 49:1838–1847. [PubMed: 19929384]
3. Koskiniemi M, Rantalaiho T, Piiparinen H, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. J Neurovirol. 2001; 7:400–408. [PubMed: 11582512]
4. Lancaster E, Dalmau J. Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012; 8:380–390. [PubMed: 22710628] * Comphrensive review on

autoimmune encephalitis and the main differences between those associated with antibodies to intracellular and cell surface antigens. It provides guideliness about the interpretation of antibody findings.

5. Gable MS, Gavali S, Radner A, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis. 2009; 28:1421–1429. [PubMed: 19718525]
6. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010; 10:835–844. [PubMed: 20952256]
7. Gable MS, Sheriff H, Dalmau J, et al. The Frequency of Autoimmune N-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project. Clin Infect Dis. 2012; 54:899–904. [PubMed: 22281844]
8. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. J Infect. 2012; 64:449–477. [PubMed: 22120594]
9. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013; 57:1114–1128. [PubMed: 23861361] ** Study providing definitions and classification of encephalitis by an international study group on these disorders. It provides guidelines about evaluating patients with suspected encephalitis according to patient's age
10. Panzer JA, Gleichman AJ, Lynch DR. Glutamatergic autoencephalitides: an emerging field. J Neural Transm. 2014 (in press). ** Comphrensive review on autoimmune encephalitis due to glutamatergic autoantibodies. It provides guideliness about the interpretation of antibody findings.
11. Pruss H, Finke C, Holtje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol. 2012; 72:902–911. [PubMed: 23280840] *Initial report showing that patients with Herpes virus encephalitis develop NMDAR antibodies.
12. Armangue T, Leypoldt F, Malaga I, et al. Herpes Simplex Virus Encephalitis is a Trigger of Brain Autoimmunity. Ann Neurol. 2013 *Study showing that herpes simplex encephalitis (HSE) can trigger synaptic autoimmunity, leading to the syndrome "choreoathetosis post-HSE".
13. Thomas L, Mailles A, Desestret V, et al. Autoimmune N-methyl-D-aspartate receptor encephalitis is a differential diagnosis of infectious encephalitis. J Infect. 2013
14. Gregoire SM, van Pesch V, Goffette S, et al. Polymerase chain reaction analysis and oligoclonal antibody in the cerebrospinal fluid from 34 patients with varicella-zoster virus infection of the nervous system. J Neurol Neurosurg Psychiatry. 2006; 77:938–942. [PubMed: 16844949]
15. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004; 127:1831–1844. [PubMed: 15215214]
16. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009; 65:424–434. [PubMed: 19338055]
17. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010; 9:776–785. [PubMed: 20580615]
18. Hoftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013; 81:1500–1506. [PubMed: 24068784]
19. Lancaster E, Martinez-Hernandez E, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology. 2011; 77:1698–1701. [PubMed: 22013185]
20. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12:157–165. [PubMed: 23290630] *Series of 577 patients examining the effects of first and second line immunotherapies, prognostic factors, and the long-term clinical outcome.
21. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011; 69:303–311. [PubMed: 21387375]
22. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. Ann Neurol. 2012; 73:120–128.

[PubMed: 23225603] *This article describes the identification of the disorder associated to DPPX antibodies.

23. Petit-Pedrol M, Armangue T, Xiaoyu P, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014; 13:276–286. [PubMed: 24462240] *Description of the disorder associated with $GABA_AR$ antibodies and characterization of the antigen.
24. Elbers JM, Bitnun A, Richardson SE, et al. A 12-year prospective study of childhood herpes simplex encephalitis: is there a broader spectrum of disease? Pediatrics. 2007; 119:e399–e407. [PubMed: 17272602]
25. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004; 75:1135–1140. [PubMed: 15258215]
26. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol. 2011; 18 19-e3.
27. Shavit YB, Graus F, Probst A, et al. Epilepsia partialis continua: a new manifestation of anti-Hu-associated paraneoplastic encephalomyelitis. Ann Neurol. 1999; 45:255–258. [PubMed: 9989630]
28. Castle J, Sakonju A, Dalmau J, Newman-Toker DE. Anti-Ma2-associated encephalitis with normal FDG-PET: a case of pseudo-Whipple's disease. Nat Clin Pract Neurol. 2006; 2:566–572. [PubMed: 16990830]
29. Peltola J, Kulmala P, Isojarvi J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology. 2000; 55:46–50. [PubMed: 10891904]
30. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008; 7:1091–1098. [PubMed: 18851928]
31. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009; 66:11–18. [PubMed: 19670433]
32. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013; 162:850–856. [PubMed: 23164315]
33. Viaccoz A, Desestret V, Ducray F, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. Neurology. 2014 (in press). *Description of seizures as a first symptom of anti-NMDAR encephalitis in adult male patients.
34. Titulaer MJ, Dalmau J. Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men. Neurology. 2014 (in press).
35. Laothamatas J, Sungkarat W, Hemachudha T. Neuroimaging in rabies. Adv Virus Res. 2011; 79:309–327. [PubMed: 21601052]
36. Ward KN, Leong HN, Thiruchelvam AD, et al. Human herpesvirus 6 DNA levels in cerebrospinal fluid due to primary infection differ from those due to chromosomal viral integration and have implications for diagnosis of encephalitis. J Clin Microbiol. 2007; 45:1298–1304. [PubMed: 17229866]
37. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007; 61:25–36. [PubMed: 17262855]
38. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain. 2000; 123:1481–1494. [PubMed: 10869059]
39. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010; 133:2734–2748. [PubMed: 20663977]
40. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011; 69:892–900. [PubMed: 21416487]
41. Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? Neurology. 2011; 76:1355–1357. [PubMed: 21482953]

42. Ohkawa T, Fukata Y, Yamasaki M, et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptors. J Neurosci. 2013; 33:18161–18174. [PubMed: 24227725] **Description of the epitope region of LGI1, effects of LGI1 antibodies altering the interaction of LGI1 with ADAM, and analysis of the effects of LGI1 antibodies on AMPA receptors in cultured neurons.
43. Balint B, Jarius S, Nagel S, et al. Progressive Encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology. 2014 (in press).
44. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. Lancet. 1982; 1:844–845. [PubMed: 6122069]
45. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology. 2013; 80:1349–1350. [PubMed: 23486886]
46. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol. 2012; 72:241–255. [PubMed: 22473710]
47. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012; 135:3453–3468. [PubMed: 23065479] *Description of a subset of patients with basal ganglia encephalitis and Sydenham chorea who had antibodies to DR2.
48. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS One. 2013; 8:e73516. [PubMed: 24073196]
49. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes Simplex Virus-1 Encephalitis can trigger anti-NMDA receptor encephalitis : a case report. Neurology. 2013; 81:1637–1639. [PubMed: 24089390]
50. Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord. 2013; 29:90–96. [PubMed: 24014096]
51. Mohammad SS, Sinclair K, Pillai S, Merheb V, Aumann TD, Gill D, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. Mov Disord. 2013; 29:117–122. [PubMed: 24115338]
52. Hargrave DR, Webb DW. Movement disorders in association with herpes simplex virus encephalitis in children: a review. Dev Med Child Neurol. 1998; 40:640–642. [PubMed: 9766743]
53. Titulaer MJ, Leypoldt F, Dalmau J. Antibodies to N-methyl-D-aspartate and other synaptic receptors in choreoathetosis and relapsing symptoms post-herpes virus encephalitis. Mov Disord. 2014; 29:3–6. [PubMed: 24458319]
54. De Tiège X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. Neurology. 2003; 61:241–243. [PubMed: 12874408]
55. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2013; 13:167–177. [PubMed: 24360484] * Study that emphasizes the importance of comprehensive antibody testing (serum and CSF) and assesses the significance of NMDAR antibody titers at diagnosis and follow-up of anti-NMDAR encephalitis.
56. Titulaer MJ, Höftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-NMDA receptor encephalitis. Ann Neurol. 2014

Key points

1. A rapidly expanding subset of autoimmune encephalitis occurs in association with antibodies to neuronal cell surface or synaptic proteins
2. Symptoms of autoimmune encephalitis are diverse and include psychiatric manifestations (psychosis, catatonia, abnormal behavior), seizures, abnormal movements, decrease of level of consciousness, or autonomic dysfunction.
3. Detection of antibodies to cell surface or synaptic proteins often associates with response to immunotherapy.
4. Autoimmune encephalitis can mimic infectious encephalitis. Comprehensive testing for autoantibodies should include CSF and serum.

Table 1

Clinical features of encephalitis associated with well characterized antibodies to intracellular and neuronal cell surface antigens

Antigen	Neurological symptoms	Age, sex, presence of tumor, response to immunotherapy
Intracellular antigens		
Hu (ANNA I)	Encephalomyelitis, PCD, Brainstem encephalitis, focal cortical encephalitis, limbic encephalitis	Mostly adults, 96–98% associated with cancer. Mostly SCLC (Hu, CV2, amphiphysin, Ri), thymoma (CRMP5), breast (amphiphysin, Ri, Yo), ovary (Yo, Ri), testes (Ma2) Limited response to immunotherapy, and treatment of the tumor
CRMP5	Encephalomyelitis, chorea, PCD, limbic encephalitis	
Amphiphysin	Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis	
Ri (ANNA 2)	Brainstem encephalitis, opsoclonus myoclonus	
Ma2	Diencephalitic, limbic encephalitis, brainstem encephalitis	
GAD65	Ataxia, stiff person syndrome, epilepsy	Adults, <10% tumors, limited response to immunotherapy
Neuronal surface antigens		
NMDAR receptor (NR1 subunit)	Psychiatric symptoms, language dysfunction, abnormal movements, seizures, decreased level of consciousness, autonomic instability	Children (40%) and young adults (median 19 y), 80% female. Presence of a tumor varies with age, sex, and race (9–55%), mostly ovarian teratomas 80% good recovery with immunotherapy
$GABA_AR$	High titers in serum and CSF: refractory seizures, or status epilepticus. Low titers in serum: more broad spectrum of symptoms including seizures, stiff person syndrome, opsoclonus myoclonus syndrome	Limited experience, 39% in children; no clear cancer association (some patients may have thymoma). Severe disorder (2/6 patients with high titres died, but the other 4 had substantial response to immunotherapy.
$GABA_BR$ (B1 subunit)	Classic limbic encephalitis. Early and prominent seizures ($GABA_BR$), isolated psychiatric symptoms (AMPAR), hyponatremia and brief tonic-myoclonic seizures (LGI1)	Adults (median 62y, 50% female) 60% small-cell lung cancer Good response to immunotherapy
AMPAR (Glu R1/2 subunit)		Adults (median 80y, 90% female) 70% tumors (lung, breast, thymus) Good response to immunotherapy
LGI1		Adults (median 60y, 65% male) <10% tumors (thymoma)
CASPR2	Morvan's syndrome, encephalitis, peripheral nerve hyperexcitability	Adults (median 60y, male predominance) Limited experience, ~30% thymoma
DPPX	Diffuse encephalitis, prodromal severe diarrhea. Psychiatric symptoms, tremor, myoclonus, ataxia, nystagmus, hyperekplexia	Adults Limited experience, no association with cancer, response to immunotherapy

Abbreviations: AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2: contactin-associated protein-like 2; CNS: central nervous system; CSF: cerebrospinal fluid; DPPX: dipeptidyl-peptidase-like protein-6; $GABA_{B or A}R$: gamma-aminobutyric acid-B or A receptor; GAD65: 65 kDa glutamic acid decarboxylase; LGI1: leucine-rich glioma inactivated protein 1; mGluR5: metabotropic glutamate receptor 5; NMDAR: N-methyl-D-apartate receptor; PCD: Paraneoplastic cerebellar degeneration; SCLC: small cell lung carcinoma; y: years

Table 2

Relapsing symptoms post-HSE

	VIRAL-RELATED POST-HSE ENCEPHALITIS	NON VIRAL RELATED POST-HSE OR "CHOREATHETOSIS POST-HSE"
TIME HSE TO RELAPSE	Variable	4 – 6 weeks (also described so early as 7 days after onset of HSE)
NEUROLOGICAL SYMPTOMS	focal neurological signs, seizures, behavioral abnormalities, low frequency of abnormal movements	In children frequent abnormal movements (choreoathetosis, ballism), adults and adolescents (abnormal behavior)
HSV PCR IN CSF	Positive	Negative
NEW NECROTIC LESIONS ON MRI	Yes	No
RESPONSE TO ANTI-VIRAL THERAPY	Yes	No
ETIOLOGY	Infectious	Suspected autoimmune. A substantial number of patients have NMDAR antibodies. Some patients may have antibodies to DR2 and against unknown cell surface antigens

Abbreviations: CSF: cerebrospinal fluid; D2R: dopamine 2 receptor; HSE: herpes virus encephalitis; HSV: herpes simplex virus; MRI: magnetic resonance imaging; NMDAR: N-methyl-D-aspartate receptor; PCR: polymerase chain reaction. (adapted from Höftberger R, Armangue T, Leypoldt F, Graus F, Dalmau J. Clinical Neuropathology practice guide 4–2013: post-herpes simplex encephalitis: N-methyl-Daspartate receptor antibodies are part of the problem. Clin Neuropathol. 2013 Jul–Aug;32(4):251–4.)