Autoimmune Encephalitis

May 29, 2021 by Josh Farkas

[Image of brain with text: International Autoimmune Encephalitis Society]

(https://emcrit.org/ibcc/ae/attachment/aetop/)

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definitions & classifications
autoimmune encephalitis

- Autoimmune encephalitis refers to a group of disorders which vary along numerous dimensions, as shown in the table below. This includes disorders associated with malignancy (paraneoplastic encephalitides), as well as postinfectious and idiopathic disorders.
- Diseases can also be subclassified based on their anatomic location, as well as the causative antibody. Both of these classifications will be explored further below, since both are useful in the process of diagnosing and treating these varied diseases.
- Our understanding of autoimmune encephalitis has advanced enormously in the past two decades. It is currently estimated that autoimmune encephalitis is as common as viral encephalitis (although historically, most cases of autoimmune encephalitis have eluded accurate diagnosis). With the increasing use of checkpoint inhibitors for treatment of malignancy, it's conceivable that autoimmune encephalitis could become the most common form of encephalitis.

### general clinical features

**time course**

- These disorders usually evolve over days to weeks.
- A nonspecific, viral-like prodromal illness is common (e.g., respiratory or gastrointestinal). Some cases may be preceded by a known viral illness (e.g., HSV encephalitis or COVID).

**epidemiological risk factors**

- Malignancy:
  - Paraneoplastic encephalitides should be considered in patients with known malignancy or who are at-risk for malignancy (especially small cell lung carcinoma).
  - Highest risk is associated with patients receiving checkpoint inhibitors.
- Autoimmune disorders:
  - 25% of patients with autoimmune encephalitis may have an underlying autoimmune disorder. (PMC7122238)
  - Family history of autoimmune disease may also increase risk.

**symptoms**

- Symptoms vary dramatically, depending on which neurological structures are involved.
- The most common symptoms include altered cognition, psychosis, or seizures. Various symptom patterns are discussed further below.

**diagnostic criteria**

- Describing a single set of diagnostic criteria for autoimmune encephalitis is largely impossible, since these disorders are so heterogeneous. Nonetheless, the criteria below may be useful to highlight some core aspects of these disorders.
CSF evaluation

CSF labs to consider

- Basic tests (e.g., cell count and differential, protein, glucose).
- Autoimmune tests:
  - (1) CSF oligoclonal bands.
  - (2) CSF albumin and IgG level (to allow for determination of the CSF IgG index).
  - (3) Autoimmune encephalitis panel.
- Broad viral studies (including at least HSV 1/2 PCR & VZV PCR).
- Bacterial and fungal studies as appropriate.
- Cytology and flow cytometry.

accompanying serum labs

- Serum albumin and IgG level.
- Serum for oligoclonal bands.
- Serum autoimmune encephalitis panel. Some antibodies are easier to find in the CSF, whereas others are easier to find in the serum.

CSF findings

- CSF abnormalities seem to be relatively uniform across different types of autoimmune encephalitis.
- Pleocytosis with lymphocyte predominance. Generally, there are ~20-200 white blood cells/mm³, but there can be up to 900. Greater than five cells/mm³ is sufficient to meet the diagnostic criteria for pleocytosis.
- Protein is generally mildly elevated.
- Oligoclonal bands may be present (which can be absent in the serum).
- Elevated immunoglobulin G index (may be calculated using an online calculator).

⚠️ Limitations of laboratory testing

- Normal CSF studies don't exclude autoimmune encephalitis. Thus, a CSF autoimmune encephalitis panel may be considered even if the routine CSF tests are normal (33649022).
- Serum testing can yield false-positive antibody results (so if an isolated antibody is found in the serum and this doesn't fit with the clinical picture, consider repeat testing).
  - As more and more antibodies are discovered, there may be an increase in the rate of false-positive antibody test results.
- Some patients with autoimmune encephalitis may have negative serologic tests, because their antibody target hasn't been discovered yet. Thus, lack of an identifiable antibody doesn't exclude autoimmune encephalitis.

MRI
• MRI can reveal abnormalities that may point towards a specific anatomic syndrome (e.g., hyperintensities on FLAIR or T2 sequences).
• Overall, the sensitivity of MRI may be on the order of 70%, but this varies depending on the specific antibody involved. MRI can be initially normal, with a repeat MRI subsequently showing abnormalities.
• Mesial temporal lobe sclerosis may be a late finding, especially among autoimmune limbic encephalitides.

**EEG**

• EEG may show focal or multifocal abnormalities when MRI is negative. Abnormal EEG findings may support a diagnosis of encephalitis (rather than metabolic encephalopathy or schizophrenia), for example:
  • Focal slowing or seizures, especially localized to the temporal lobes.
  • Periodic lateralized epileptiform discharges (PLEDs).
• Extreme delta brush, if seen, strongly suggests anti-NMDA receptor encephalitis.

**evaluation for underlying malignancy**

In patients where an autoimmune encephalitis is known or highly suspected, it may be reasonable to evaluate for an underlying malignancy. Depending on the context, the following studies may be considered:

• CT scan of the chest, abdomen, and pelvis.
• Transvaginal or testicular ultrasound.
• Whole body PET scan.

**anatomic classification**

Figure 3  Anatomical subtypes of autoimmune encephalitis. (A) Limbic encephalitis, (B) cortical/subcortical encephalitis, (C) striatal encephalitis, (D) diencephalic encephalitis, (E) brainstem encephalitis (arrow), (F)
Autoimmune encephalitides can be subclassified into groups based on which neuroanatomic structures are involved. This is an imperfect science, because many disorders can involve several anatomic regions simultaneously. Thus, for many patients, it will be impossible to neatly classify the encephalitis into a single category. Nonetheless, in some cases, anatomic subclassification can provide a useful approach to help narrow and focus the differential diagnosis. The classification below is based largely on a best practice recommendation by Abboud et al. (33649022)

**limbic encephalitis**

### clinical syndromes

- Cognitive presentation (e.g., short-term memory loss).
- Psychiatric presentation (e.g., mood changes, psychosis).
- Epileptic presentation (e.g., complex partial seizures, status epilepticus which may be treatment-refractory).
- Hypothalamic dysfunction may cause hyperthermia, endocrine abnormalities, or somnolence.

### differential diagnosis

- HSV, VZV.
- HHV-6 (human herpesvirus 6), among immunocompromised patients.
- Glioma (if unilateral or asymmetric abnormalities).

### additional evaluations

- CSF viral PCR.
- CSF VZV IgG/IgM.

### diagnosis

- EEG may show epileptiform activity in the temporal regions.
- MRI may show T2 or FLAIR hyperintensity in the **medial temporal lobes**.
  - This finding is ~80% sensitive (although sensitivity may vary between different antibodies).
  - A characteristic MRI pattern with negative viral workup may be sufficient to render the diagnosis (even in the absence of an identified antibody; see diagnostic criteria below).

![Box 2: Diagnostic criteria for definite autoimmune limbic encephalitis](image)

### associations

- Antibodies: Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65, GABABR, DPPX, mGLUR5, AK5, Neurexin-3 alpha.

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**cortical-subcortical encephalitis**

### corresponding clinical syndromes

- Cognitive presentation.
- Seizure presentation.
**differential diagnosis**

- ADEM (acute disseminated encephalomyelitis).
- Acute hemorrhagic leukoencephalitis.
- Tumefactive multiple sclerosis.
- Progressive multifocal leukoencephalopathy (PML).
- Creutzfeldt-Jakob disease (CJD).
- Lupus cerebritis.
- Behcet's disease.
- Neurosarcoïdosis.
- Neurosyphilis.
- Lymphoma.
- Anoxic injury.
- Seizure-related changes.

**possible additional tests**

- Myelin oligodendrocyte glycoprotein – IgG.
- JC virus PCR.
- CSF prior panel.
- ANA.
- HLA-B51.
- Chest imaging to evaluate for sarcoïdosis.
- Treponemal antibodies.
- CSF cytology & flow cytology.

**associated antibodies**

- PCA-2 (MAP1b), NMDAR, GABA A/B R, DPPX, MOG

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**striatal encephalitis**

**presentation**

- Movement disorder presentation.

**differential diagnosis**

- Creutzfeldt-Jakob disease.
- West Nile virus.
- Toxic encephalopathy.
- Anoxic injury.
- Hyperglycemic injury.
- Uremia.

**evaluation**

- Prion panel.
- West Nile virus IGM.
- CSF viral PCR.
- Metabolic panel.
- Toxicology screen.

**associated antibodies**

- CRMP5/CV2, DR2, NMDAR, LGI1, PD10A

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**diencephalic encephalitis**
**clinical syndromes**

- Autonomic presentation.
- Sleep disorder presentation.

**differential diagnosis**

- Neurosarcoïdosis.
- Behcet's disease.
- Wernicke's encephalopathy.
- Whipple disease.
- Autoimmune autonomic neuropathy/ganglionopathy (may associate with antibodies against Hu, CRMP5, anti-ganglionic AChR).

**evaluation**

- Chest imaging to evaluate for sarcoidosis.
- HLA-B51.
- Thiamine level.

**associated antibodies**

- MA 1-2, IgLON5, DPPX, AQP4.

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**brainstem encephalitis**

**clinical presentations**

- Cognitive presentation.
- Movement disorder presentation.
- Cranio-bulbar presentation (e.g., extraocular movement deficits, nystagmus, dysphagia, dysarthria).

**differential diagnosis**

- Rhombencephalitis (Listeria).
- Viral infection.
- CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids).
- Neurosarcoïdosis.
- Behcet's disease.
- Lymphoma.
- Progressive multifocal leukoencephalopathy.
- Central pontine myelinolysis.
- Erdheim-Chester disease.
- Whipple disease.

**evaluation**

- CSF bacterial culture.
- CSF viral PCR.
- HLA-B51.
- CSF cytology and flow cytometry.
- CSF JCV PCR.
- Bone scan.

**associated antibodies**

- Ri, Ma 1-2, KLHL11, IgLON5, DPPX, AQP4, MOG, GQ1b.
cerebellitis or cerebellar degeneration

clinical syndrome

- Ataxic presentation.

differential diagnosis

- Viral or post-viral cerebellitis.
- Celiac disease.
- Miller Fisher syndrome.
- Vitamin E deficiency.
- Cerebellar multiple system atrophy.
- Spinocerebellar ataxia.

evaluation

- Viral PCR.
- Celiac serologies.
- anti-GQ1b (for Miller Fisher syndrome).
- vitamin E level.
- Dopamine transporter scan.

associated antibodies

- Hu, Ri, Yo, Tr, CASPR2, KLHL11, NIF, mGluR1, GAD65, VGCC.

meningoencephalitis

clinical syndromes

- Abnormal cognition.
- Seizures.
- Meningeal irritation.

differential diagnosis

- Tuberculosis.
- Neurosarcoidosis.
- Behçet's disease.
- Bacterial or viral infection.
- Leptomeningeal carcinomatosis.
- Gliomatosis with polyangiitis.
- IgG4-related disease.

evaluation

- Bacterial PCR.
- Chest imaging for sarcoidosis.
- HLA-B51.
- CSF bacterial culture.
- CSF viral PCR.
- CSF cytology and flow cytometry.

associated antibody

- GFAP antibody.
- Can be seronegative (with no identifiable antibody).
encephalomyelitis

clinical syndromes

- Movement disorder presentation (including progressive encephalomyelitis with rigidity, myoclonus, and stiff person syndrome).
- Spinal presentation.
- Opticospinal presentation.

differential diagnosis

- Acute disseminated encephalomyelitis.
- West Nile virus.

evaluation

- Myelin oligodendrocyte glycoprotein-IgG.
- West Nile virus IgM.
- CSV viral PCR.

associated antibodies

- GAD65, amphiphysin, glycine receptor, PCA-2 (MAP1B), GABA A/B receptor, DPPX, CRMP5/CV2, AQP4, MOG.

classification by antibody

antibodies directed against intracellular pathogens (table below)

- These antibodies are not directly pathogenic, but rather they are merely immunological markers that correspond to autoimmune illness. The pathogenesis of these processes involves cellular damage due to a cytotoxic T-cell response.
- Since these disorders are T-cell mediated, they respond less well to immunotherapies such as plasmapheresis or IVIG.
- Overall, these disorders are often more closely linked to malignancy.
- The ability to recover function is often poor, since dysfunction reflects cellular damage (with the possible exception of anti-Ma2 encephalitis).

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Clinical features may include:</th>
<th>Association with malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQP4</td>
<td>Limbic encephalitis, progressive encephalomyelitis with rigidity and myoclonus, stiff person syndrome, cerebellar degeneration, brainstem encephalitis.</td>
<td></td>
</tr>
<tr>
<td>ANNA-1</td>
<td>Limbic encephalitis, encephalomyelitis, brainstem encephalitis, myo-epilepsia, ataxic cerebellar dysfunction, oculomotor apraxia.</td>
<td></td>
</tr>
<tr>
<td>ANNA-2</td>
<td>Limbic encephalitis, encephalomyelitis, myo-epilepsia, multiple sclerosis/myopathy.</td>
<td></td>
</tr>
<tr>
<td>ASSA</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>CRMP5</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>GAD-65</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>IGH-11</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>Anti-Ma1 &amp; Anti-Ma2</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>Only Ma2</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>PCA-2 (anti-MAP1B)</td>
<td>Brainstem and/or cerebellar encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
<tr>
<td>CFH alpha-IgG</td>
<td>Hemispheric encephalitis.</td>
<td>Diagnosis cerebellar ataxia, cerebellar degeneration, myoclonus/myopathy.</td>
</tr>
</tbody>
</table>

*Modified from Lacaille J and Pirhonen EJ JNMD 376.300. email.org/900/ece*

antibodies directed against cell surface pathogens (table below)

- Antibodies are directly pathologic in these disorders.
- Since antibodies are the culprit, patients respond better to immunotherapy and plasma exchange. However, patients can often relapse following recovery.
- Overall, these disorders are often less closely linked to malignancy. For example, some may be triggered by immunological mimicry following viral
The ability to recover function is **better**, since dysfunction often reflects **transient neuronal dysfunction** (rather than cellular destruction). Patients can make stunning recoveries, despite initially being entirely debilitated.

**Management of autoimmune encephalitis**

- There is no high-quality evidence regarding the optimal therapy.
- High-dose corticosteroid is often the initial therapy of choice (e.g., 1 gram methylprednisolone daily for 3-7 days).
- Plasma exchange combined with steroid may accelerate recovery in some situations (especially patients with autoantibodies to cell surface proteins, such as anti-NMDA receptor encephalitis).
- Intravenous immunoglobulin (IVIG) may be an alternative to steroid, among patients with contraindications to steroid.
- For patients with paraneoplastic autoimmune encephalitis, resection of the primary tumor is ideal. However, for patients with autoimmune encephalitis following checkpoint-inhibitor therapy, steroid is the front-line therapy.
supportive therapy for manifestations

- Treatment for seizures and status epilepticus may be necessary (more on this [here](#)).
- Elevated intracranial pressure can occur at rates of up to 25% of patients with anti-NMDA receptor encephalitis. ICP elevation may be diagnosed and managed as described [here](#).

management of dysautonomia

- Fever may be managed with external cooling to achieve normothermia.
- Significant hypotension may require intubation.
- Avoid overaggressive treatment of hypertension or tachycardia, as this may merely exacerbate subsequent hypotension or bradycardia (33896534).
- Bradycardia may require temporary transvenous pacing. In some cases, a permanent pacemaker may be required to support the heart rate for weeks-months, until medical therapies take effect.
- Medications typically used for paroxysmal sympathetic hyperactivity may be helpful in some patients (e.g., alpha-2 agonists and propranolol).
- Monitor carefully to avoid ileus or toxic megacolon.

management of movement disorders

- Hyperkinetic disorders: dystonia, dyskinesia, or chorea
  - Cholinergic neurotransmission seems to be an important substrate for these abnormalities, so anticholinergic agents can be rapidly effective. (31732848)
  - Hyperkinesis may be treated with dopamine (D2) antagonists. If this is ineffective, vesicular monoamine transporter type 2 inhibitors such as tetrabenazine may be considered (33896534).
- Myoclonus
  - Myoclonus results from cortical irritability, due to encephalitis.
  - Treatments may include antiepileptic therapies, such as levetiracetam or sodium valproate.
Anti-NMDA receptor encephalitis is the most common form of autoimmune encephalitis that is caused by antibodies binding to the neuronal cell surface. Particular attention is necessary to recognize this, as it may tend to be initially misdiagnosed as a psychiatric illness.

**epidemiology**

- Most commonly affects women (4:1 ratio) in their 20s-30s (although elderly people can be affected) (32675144)
- An underlying neoplasm may be present:
  - In half of affected women, the disease is triggered by an ovarian teratoma. Teratomas should be aggressively sought (e.g., via transvaginal ultrasonography +/- MRI). Teratomas may rarely be found elsewhere in the body (e.g., head, neck, thyroid, testis). (33896534)
  - Less commonly, other malignancies may be involved (e.g., lung or breast carcinoma). (PMCID:7122238)
- Infection may trigger the disorder:
  - HSV encephalitis may precede the development of anti-NMDA receptor encephalitis. This may cause diagnostic confusion, as it may appear that the HSV encephalitis has simply "relapsed."
  - Anti-NMDA receptor encephalitis may arise following COVID infection.

**clinical features**

- **Prodromal viral-like illness** (e.g., headache, fever, malaise).
- **Psychiatric symptoms** are often the first notable feature:
  - Anxiety, agitation.
  - Psychosis (hallucinations, delusions, disorganized thought, bizarre behavior).
- **Cognitive dysfunction** (apathy, short-term memory loss).
- **Sleep disruption** (initially insomnia, later on hypersomnia).
- **Speech dysfunction** (mutism, echolalia).
- **Abnormal movements**:
  - Ballismus.
  - Catatonia.
  - Choreaathetosis.
  - Dyskinesias (e.g., chewing movements). Orofacial dyskinesia with new-onset psychosis may be particularly suggestive of the diagnosis. (PMCID:7122238)
  - Dystonias, including dystonic limb posturing, rigidity, opisthotonic postures.
- **Reduced level of consciousness**, stupor with catatonic features.
- **Seizure** (generalized or partial-onset seizures, including super-refractory status epilepticus).
- **Autonomic dysfunction**:
  - Especially bradycardia/tachycardia, labile blood pressure, and hyperthermia.
  - Hypoventilation that requires intubation can occur.

**diagnosis**

- Basic CSF analysis may be normal initially. However, CSF will generally reveal a lymphocytic pleocytosis or oligoclonal bands.
- The key test is CSF evaluation for IgG against the GluN1 subunit of the NMDA receptor, which is highly sensitive and specific. However, serum testing for antibodies has a lower performance.
  - Serum testing for antibodies has lower sensitivity, so CSF must be sent.
- EEG may show an extreme delta brush pattern in 30% of patients, which is highly suggestive for the diagnosis of anti-NMDA encephalitis.
MRI is often normal, especially initially. There may be FLAIR or contrast-enhancing abnormalities in the cortex or subcortical areas (e.g., hippocampus, basal ganglia, white matter, even the spinal cord).

**Box 3**

<table>
<thead>
<tr>
<th>Diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>1. Rapid onset (&lt;3 months) of at least 4 of the 6 following major groups of symptoms:</td>
</tr>
<tr>
<td>Abnormal (psychiatric) behavior or cognitive dysfunction</td>
</tr>
<tr>
<td>Speech dysfunction ( pressured speech, verbal reduction, mutism)</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Movement disorder, dyskinesias, or rigidity/abnormal postures</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
</tr>
<tr>
<td>Autonomic dysfunction or central hypoventilation</td>
</tr>
<tr>
<td>2. At least 1 of the following:</td>
</tr>
<tr>
<td>Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)</td>
</tr>
<tr>
<td>CSF with pleocytosis or oligoclonal bands</td>
</tr>
<tr>
<td>3. Reasonable exclusion of other disorders</td>
</tr>
<tr>
<td>Diagnosis can be made in the presence of 3 of the above group symptoms accompanied by a systemic teratoma</td>
</tr>
</tbody>
</table>

**Definite**

1. Diagnosis can be made in presence of 1 or more of the 6 major group of symptoms and immunoglobulin (Ig) G anti-GLU/N1 antibodies, after reasonable exclusion of other disorders.

**treatment**

- Ovarian teratomas must be resected if present.
- Pulse-dose steroid (e.g., 1 gram/day methylprednisolone) plus IVIG or plasma exchange are often utilized in more severe cases.
- Otherwise, treatment is similar to autoimmune encephalitis in general (discussed above).

**Going further:**


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The Internet Book of Critical Care is an online textbook written by Josh Farkas [@PulmCrit], an associate professor of...