MELLEN CENTER APPROACH: Diagnosis and Management of Autoimmune Encephalitis

What is Autoimmune Encephalitis (AE)?

Autoimmune encephalitis (AE) is a heterogeneous group of non-infectious, immune-mediated inflammatory disorders that primarily affect the brain but can also have multifocal involvement of the spinal cord, peripheral nervous system and/or systemic manifestations.[1] AE is a common cause of encephalitis that can present in all age groups with several studies showing it to be as common as infectious etiologies.[2] An increasing number of neuroglial autoantibodies (NAAs) targeting glial, extracellular/synaptic or intracellular neuronal antigens have been identified with characteristic clinical presentations and epidemiological features.[3–5] Autoantibodies targeting extracellular antigens have been shown to be pathogenic in disease models whereas intracellular antigens, often paraneoplastic, seem to reflect T-cell mediated inflammation and, with few exceptions, do not seem to be directly pathogenic.

What are clinical features that warrant consideration of autoimmune encephalitis as a diagnosis?

Patients with AE can present with a host of different symptoms. Although some NAA are associated with well-characterized clinical features (i.e., facial brachial dystonic seizures with anti-LGI1 encephalitis), there is considerable overlap across the different disorders and even patients with the same NAA can present in a myriad of ways.

A diagnosis of AE should be considered in patients presenting with progressive neurocognitive symptoms evolving over the course of weeks to months. Typical features include cognitive dysfunction (poor short-term memory, attention deficits), and seizures which are often refractory to antiseizure medication.

Additional features include dysautonomia (labile blood pressure, tachycardia), extrapyramidal manifestations (cerebellar ataxia, dyskinesias, dystonia, choreiform movements), sleep disorders (insomnia, hypersomnolence, sleep disordered breathing and narcolepsy) and neuropsychiatric symptoms (mania, psychosis, agitation, catatonia - predominantly seen in anti-NMDA-R encephalitis).[1,3,6]

Certain patient characteristics should raise the suspicion for AE. Patients with malignancy are at higher risk for AE, particularly small cell lung cancer. Paraneoplastic AE can present prior to or after cancer diagnosis. A personal or family history of systemic autoimmunity can indicate an increased susceptibility to these disorders as well. More recently, treatment with immune checkpoint inhibitors has been associated with AE. [1,3]

What is the diagnostic work-up for patients suspected to have autoimmune encephalitis?

The most recent diagnostic criteria (published in 2016) reflect the consensus opinion of international experts to expedite the diagnosis and facilitate early treatment. These criteria focus

on serological, cerebrospinal fluid (CSF), electroencephalogram (EEG), and radiographic evidence to support the diagnosis.[6] Although is possible to make the diagnosis with negative NAA testing, so called 'seronegative AE', it is important to anchor the diagnosis of AE on objective findings. [6]

In all patients with suspected AE, serum and CSF studies should be performed to rule out metabolic, infectious, and nutritional causes of encephalopathy while testing both samples for NAA (Table 1). It may be appropriate to test for mitochondrial, genetic, and neurodegenerative etiologies in certain situations.

To optimize sensitivity and specificity of NAA testing, both serum and CSF samples need to be analyzed in patients with suspected AE. Both false positive and false negative test results can occur therefore it is important to send testing to a reference laboratory. Our current practice is to send for neural antibody testing in both serum (ENS2) and CSF (ENC2) to Mayo Labs which incorporates testing for the majority of currently recognized NAAs.

What oncological evaluation should be pursued for patients with AE?

When deciding upon who should be screened for malignancy there are several factors to consider: age, smoking history, personal or family history of cancer, specific NAA and its known association with cancer.

If a patient is diagnosed with a high-risk paraneoplastic disorder syndrome, we typically order surveillance testing every 6-12 months for at least 3-5 years. If the patient has an antibody with a low likelihood of an underlying neoplasm, we typically recommend routine age-appropriate cancer screening. Table 2 lists neoplasms most strongly associated with NAA that can present with AE. If the identified antibody is associated with specific tumors, there may be targeted testing (e.g., pelvic ultrasound with NMDA-R-IgG).[16]

For patients with high-risk NAAs we utilize a CT of the chest, abdomen, and pelvis as a screening measure initially. In addition, sex-specific tests such as pelvic US, mammogram/ breast MRI, and testicular ultrasound are pursued if the initial evaluation is unrevealing as CT can fail to detect some types of malignancy. Whole body FDG PET-CT is sometimes employed if suspicion for malignancy is high as it has better sensitivity for the detection of cancers. [13]

What is the initial treatment for AE?

Treatment guidelines for AE are based on a combination of expert opinion, case series and case reports.[9–11] Treatment initiation and escalation depends on the certainty of diagnosis of AE along with the clinical severity.

An important caveat for all clinicians to consider is that corticosteroid responsiveness does not secure the diagnosis of AE as other disorders can respond dramatically to steroids such as lymphoma or sarcoidosis. Additionally, some AE patients do not respond to corticosteroids but require prolonged treatment with various other immunotherapies to successfully manage their disease.[6]

First-line therapies we employ include high dose intravenous corticosteroids, intravenous immunoglobulin, or plasmapheresis. These can be used sequentially or in combination with little evidence favoring one modality over the other. Once infectious etiologies are reasonably excluded, empiric treatment may be appropriate especially in severe cases (e.g., status epilepticus, patients requiring ICU level care) prior to the availability of results of NAA testing. However, it is important to consider all available clinical data carefully in terms of diagnosis, in particular before commencing second line therapies.

Second-line agents commonly used include rituximab (a monoclonal antibody targeting CD20 positive lymphocytes) and cyclophosphamide (an alkylating agent that targets rapidly dividing cells).[12] Although these agents are classified as second-line therapies, they can be used in the acute phase of the disease either due to the disease severity of the presentation or to reduce the risk of relapse. Theses treatment decisions can be complicated and depend on individual patient characteristics (age, clinical condition, concurrent cancer treatment, side effects, patient preference), the specific neural antibody, the hypothesized pathogenic mechanism and risk of relapse. Additional considerations need to be considered in pediatric patients in whom long term consequences of disease and treatments have a greater impact.

Treatment beyond first-line acute therapies may warrant consultation with a subspecialist experienced in treating neuroinflammatory disorders to decide on the appropriate agent and length of treatment.

It is also important to consider carefully what objective measures will be used to determine clinical response to immunotherapy. These may include, but are not limited to: clinical examination, neuroimaging, EEG, neurocognitive testing.

First-line Therapies:

-- Intravenous Methylprednisolone (IVMP): 1g daily x 5 days followed by oral prednisone 1mg/kg (maximum dose 60-80mg daily with a prolonged taper)
-- Intravenous immunoglobulin (IVIg): 400mg/kg/day x 5 days
-- Plasmapheresis (PLEX): 5-7 exchanges over 10-14 days

Second-line Therapies/Long term immunosuppressive agents:

Can be given as monotherapy or in combination for refractory disease activity 1-2 weeks from the completion of first-line treatment acutely.

-- Rituximab (Rituxan/Ruxience):
1000 mg IV repeat dose in 2 weeks (Preferred agent given safety profile)
-- Cyclophosphamide:
750 mg mg/m^2 (maximum 1000 mg) IV once with pre-hydration initially

Adjuvant therapies for long-term immunosuppression and steroid sparing.

-- Rituximab 1000 mg every 6 months
-- IV cyclophosphamide 750 mg/m^2 IV monthly or oral cyclophosphamide 1-2 mg/kg/day
-- IVIg 2g/kg dose over 2-5 days repeated every 3 weeks
-- Mycophenolate mofetil (Cellcept)
-- Azathioprine (Imuran)

How do I monitor response to treatment in a patient with AE?

There are no validated biological markers or clinical measures to assess treatment response or clinical disease activity in AE. Serum or CSF antibody titers do not adequately reflect response to treatment in AE. It can be difficult to discern new/ongoing inflammatory activity versus neurological sequalae from the sentinel event. For example, longitudinal imaging can illustrate improvement following the appropriate treatment but it can also show irreversible changes (i.e., generalized or focal atrophy).

Disease monitoring is therefore primarily based on the clinical history and examination in combination with objective measures such as validated bedside cognitive tests should be performed regularly (i.e. Montreal Cognitive Assessment [MoCA]), formal neuropsychological testing, EEG monitoring and in some cases serial neuroimaging.

What is the long-term outlook for patients with autoimmune encephalitis and how do I care for these patients after resolution of the acute phase of the disease?

Broadly speaking, AE associated with intracellular antigens portends a poor outcome and are less responsive to immune therapies.[2] Conversely, patients with NAA targeting cell surface or synaptic antigens have a better response to immune therapy and if treated in a timely fashion show good long-term functional outcome. [10,14]

There are several important clinical long-term sequelae arising from AE which impact quality of life. Neurocognitive symptoms (e.g. impaired concentration, memory problems, processing speed), mood disorders, sleeping difficulties, seizures, and fatigue are commonly seen.[15–18] A multidisciplinary approach is recommended to best help patients in managing these complications and may include consultations with occupational therapy, speech therapy, neuropsychology, social work and psychology.[19]

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Table 1. Suggested serum and CSF first-line diagnostic testing in patients with suspected autoimmune encephalitis.

Serum	CBC, CMP, ESR, CRP, ANA +/- ENA B12, MMA, Thiamine, TSH Neural antibody testing: (Mayo ENS2) or AQP4-IgG and MOG-IgG (Mayo CDS1)*
Cerebrospinal fluid	Routine analysis (WBC, RBC, protein, glucose), IgG index CSF oligoclonal bands Gram stain and culture, HSV1/2 PCR, VZV PCR** Neural antibody testing (Mayo ENC2)

*For patients with concurrent clinical features of these disorders.

** Additional fungal, mycobacterial, and viral testing as clinically indicated.

Table 2. Findings supportive of a diagnosis of AE. [6]

Cerebrospinal fluid	Mild to moderate pleocytosis (5-100/uL) Elevated IgG index and oligoclonal bands*
MRI Brain with/without contrast	Bilateral or unilateral temporal lobe T2/FLAIR hyperintensities Multifocal grey/white matter changes** add superscript (can be normal)
EEG (routine initially, though long term monitoring may be warranted)	Focal epileptiform discharges, seizures or slowing over the temporal lobes Extreme delta-brush (NMDA-R-IgG) Multifocal epileptiform discharges or seizures Subclinical seizures, non-convulsive status epilepticus

* Can be normal

** Can be normal

Table 3. Neoplasms associated with NAA that NAA status and associated malignancies for commonly encountered AE

Tumor	Associated NAAs
Small Cell Lung Cancer	ANNA-1/2/3, CRMP-5, PCA-2, AMPAR, GABA-B
Breast Cancer	ANNA-2 (Ri), PCA-1 (Yo), AMPAR,
Ovarian Cancer	PCA-1 (Yo)
Ovarian Teratoma	NMDAR, GFAP
Thymoma	CRMP-5, CASPR2, LGI1, GABA-A
Testicular Cancer	Ma2, KLHL11