AUTOIMMUNE ENCEPHALITIS (AIE) – DIAGNOSIS

EXCLUSION CRITERIA

- Age <3 years
- History of behavioral/psychiatric symptoms >12 weeks
- Alternate diagnosis likely

INCLUSION CRITERIA

- ≥ 3 years of age
- Symptoms present/onset <12 weeks

***MAJOR PRESENTING FEATURES**

1) Seizures (temporal lobe)
2) Movement Disorder
3) Behavioral change/Psychosis

****MINOR PRESENTING FEATURES**

1) Dysautonomia
2) Speech changes or focal neurologic deficit
3) Memory disturbance
4) Decreased level of consciousness

*Major: Most common presenting features

**Minor: Features that children will *ultimately* develop over time as disease progresses

Patient Presents with:

- 1 of 3 major features (ex-Psychosis) OR
- 2 minor features

LOW CLINICAL SUSPICION

Psych-Neuro-PCRS Huddle

Perform the following:

- Serum Workup and Urine Drug Screen
- +/- MRI of the brain
- +/- EEG as clinically indicated
- Consider Differential Diagnosis
- Rheumatology, and/or ID consult

Observe and Monitor:

- Wait for serum autoantibodies
- Observe and monitor for development of new clinical symptoms suggestive of AIE
- Based on development of new clinical symptoms consider CSF testing
- Consider other diagnosis/rule out alternate diagnosis

Development of new symptoms consistent with AIE OR Antibody + in serum or CSF AND Alternate diagnosis ruled out

Patient Presents with:

- 2 of the 3 major features OR
- 1 major and 2 minor features

MODERATE CLINICAL SUSPICION

Psych-Neuro-PCRS/PICU Huddle

Perform the following:

- Serum Workup and Urine Drug Screen
- +/- MRI of the brain
- Consider CSF analysis/Lumbar Puncture (to support evidence of neural inflammation)
- +/- EEG as clinically indicated
- Rheumatology, and/or ID consult

Evidence supporting neuroinflammation AND alternate diagnosis ruled out?

No

Yes

Patient Presents with:

- ALL 3 of the major features **OR**
- 1 major and 3-4 minor **OR**
- All 4 minor features

HIGH CLINICAL SUSPICION

Psych-Neuro-PCRS/PICU Huddle

Perform the following:

- Serum Workup and Urine Drug Screen
- MRI of the brain
- Consider CSF analysis/Lumbar Puncture
- +/- EEG as clinically indicated
- Rheumatology, and/or ID consult

Start Empiric immunotherapy:

- Consider steroids and/or IVIG for mild to moderate presentations
- Consider Plasmapheresis and steroids for severe presentations
- Rituximab or cyclophosphamide for refractory or relapsing cases

TOOLKIT: SIGNS OF NEUROINFLAMMATION RELATED TO AIE

1) CSF pleocytosis
2) Delta Brush finding on EEG
3) MRI with cortical T2 hyper-intensities suggestive of encephalitis

Maintain NPO if patient will require imaging or workup

COMMUNICATION BETWEEN THE DIFFERENT DISCIPLINES IS KEY TO AVOID UNESESSARY LP'S.

dell children's Ascension

Rev. Hardy, D.
09/2022

Addendum 1: Diagnostic Evaluation

For the patients falling into the Moderate to High suspicion category of autoimmune encephalitis, consider ordering the ***primary*** **serum evaluation AND the *primary* CSF analysis.** For patients falling into low clinical suspicion consider ordering the ***primary*** **serum evaluation.**

Please refer to the Ascension Seton intranet Lab Specimen Requirements page for specimen collection instructions, volumes, and handling requirements. (link: https://www.testmenu.com/seton)

Serum Evaluation:

Primary serologic labs

- CBC with differential, CMP, ESR, CRP, and procalcitonin (if not previously completed)
- Thyroid studies (anti-tPO antibodies, anti-thyroglobulin antibodies, TSH/T4)
- Serum drug screen
- Encephalopathy, Autoimmune/paraneoplastic evaluation (Mayo Laboratories)
- Serum Myelin Oligodendrocyte glycoprotein (MOG) antibodies (Mayo Laboratories)
- Serum Aquaporin-4 antibodies (Mayo Laboratories)
- Oligoclonal bands (only if performing LP, requires concomitant CSF sample)
- Vitamin B12, Vitamin B1, copper, ceruloplasmin

Additional Primary labs: urine drug screen (if not completed), Respiratory pathogen panel

Secondary serologic labs

Consider if history, physical exam, or initial imaging studies warrant further investigation

- Metabolic testing: plasma amino acids, urine organic acids, acylcarnitine profile, lactate/pyruvate, ammonia, MMA
- Infectious disease testing: Differential is broad based on exposure, travel history and initial lab and imaging finds. Testing could include viral, bacterial, fungal, atypical, and parasitic infections. Please discuss with Infectious Disease for appropriate laboratory evaluation.
- Rheumatology testing: Please discuss with Rheumatology for appropriate laboratory evaluation

If biologic therapy is being considered: hepatitis panel and T spot results are required prior to therapy.

CSF Analysis:

Primary CSF studies

- Routine studies: cell count, glucose, protein, routine culture
- Meningitis Encephalitis panel PCR (DSMCUT)
- West Nile antibody panel CSF (ARUP)
- Encephalopathy evaluation, CSF (Mayo)
- Oligoclonal bands (ARUP)
- Hold additional CSF (5-10 mL, if available for future testing)

Secondary CSF Studies

- CSF cytology and flow cytometry
- CSF ACE
- Paraneoplastic panel: please note testing panel is very similar to Encephalopathy CSF test to Mayo; please confirm that testing will provide additional information before ordering

Diagnostic Evaluation - <u>other tests to consider on a case-by-case basis</u>

Ocular exam

- Dilated eye examination - optic neuritis, optic edema, chorioretinitis, vasculitis, NAI, TBI (Rh or ID, recommend eye exam)

Tumor evaluation (In patients with confirmed AIE)

- Abdominal and pelvic ultrasound/ testicular ultrasound
- If negative but still high suspicion for tumor MRI or CT chest, abdomen, pelvis

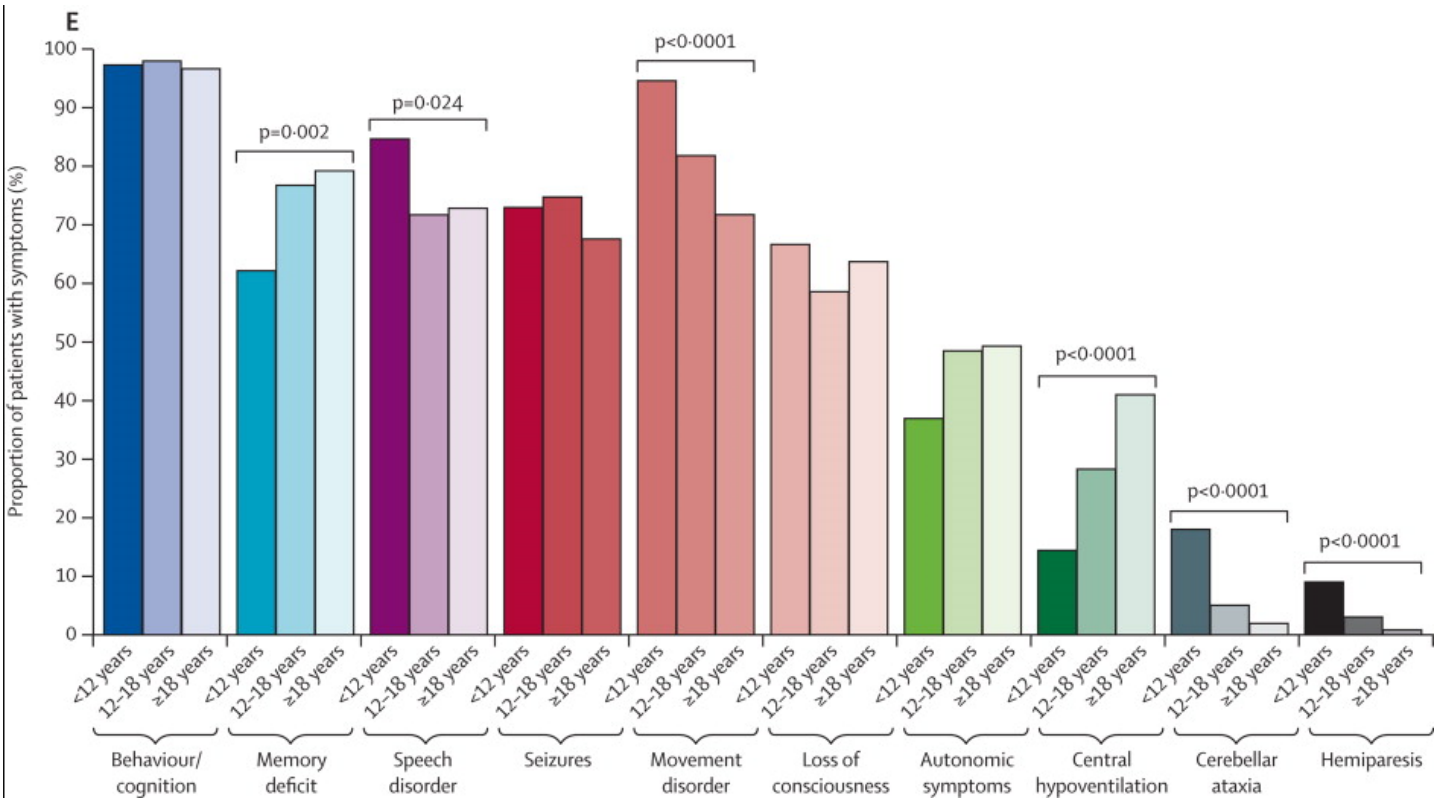
Addendum 2: Differential Diagnosis

Because the symptoms can be so varied, diagnosis can be challenging and is often delayed. Early diagnosis and treatment are critical to minimize the short-term and long-term impacts of these disorders.

Autoimmune/ Neuroinflammatory	**Infectious etiologies**	**Endocrine**
ADEM MS NMO MOG Associated disorders Opsoclonus-myoclonus ataxia Syndrome Neuropsychiatric Lupus Rasmussen encephalitis	Viral: EBV, HHV-6, VZV, HSV, HIV, Enterovirus, Arbovirus, Parechovirus, Rabies, SARS-CoV-2 Atypical: Bartonella, Mycoplasma, Rickettsia (typhi, rickettsii), TB, Coxiella burnetii (Q fever), Tropheryma whipplei Spirochetal: Lyme, Syphilis Fungal: Histoplasma, Blastomyces, Coccidioides, Cryptococcus, Toxoplasma Parasite: Entamoeba histolytica	Hashimoto's encephalopathy (steroid- responsive encephalopathy associated w/ autoimmune thyroiditis)
Epileptic Disorders	**Neurodegenerative**	**Other**
FIRES Status epilepticus NOS	Fronto-temporal dementia Creutzfeldt-Jakob disease Neuroacanthocytosis	Seizure disorder Traumatic brain injury (TBI) Intussusception
Psychiatric disorders	**Structural Disorders**	**Toxic / Metabolic**
Acute psychosis/psychotic episode Schizophrenia Conversion disorder	Neoplasm Hydrocephalus	Drug Ingestion Wilson’s disease Lesch-Nyhan syndrome Mitochondrial disorders Urea cycle disorders Inborn errors of metabolism Electrolyte changes (glucose, sodium, calcium) Thiamine deficiency
Vascular Disorders Vasculitis Bechet’s Hypertensive encephalopathy/ PRES Migraine (acute confusional) Stroke Cerebral vasculitis		

Addendum 3: Signs and Symptoms

Diagnosis of AIE in a developing child is challenging because of overlapping clinical presentation with other diseases, complexity of normal behavior changes, and limited capacity of very young children to describe symptoms. It is only once the disease has progressed that patients typically develop additional neurological symptoms, such as movement disorders, epileptic seizures, autonomic dysfunction, and cognitive deficits[11]. Each patient may experience symptoms differently and clinical features may be varied. Typically, children with AIE are previously healthy and present with rapid onset (less than 3 months) of neuropsychiatric symptoms. Viral prodrome is also very common.



Titulaer, et. al., 2013

Behavior/cognition: Behavioral changes, such as repetitive or stereotypical behaviors, irritability, hyperactivity, temper tantrums, acute developmental regression, insomnia, and anger outbursts, are common in pediatric AIE. New-onset psychosis in children younger than 13 years is uncommon and considered a red flag for an underlying medical, rather than primary psychiatric, condition[7].

Psychosis – It is a severe mental disorder where children interpret reality abnormally. Children with the disorder show impaired thinking and emotions that cause them to lose contact with reality. This could mean hearing or seeing things that aren't there (hallucinations) or believing things that aren't true (delusions). Visual hallucinations are often not related to primary Psychosis.

Movement Disorder(1) – Presentations are listed as most to least common: oro facio lingual dyskinesia (OFLD), tremor, choreoathetosis, paroxysmal dyskinesia, stereotypies, bradykinesia, followed by dystonia, catatonia, neuromyotonia, ballism, ataxia, and stiff person phenotype. The hyperkinetic movement disorders were more commonly seen compared to hypokinetic disorders.

Autonomic symptoms: Tachycardia, fever (prodromal symptoms including fever occur in over 50% of patients[7].

Memory deficit: Deficits in working memory are challenging to identify in younger children however, developmental regression, language loss or speech impairments may be presenting features of pediatric AIE.

Seizures: Seizures not explained by a previously known seizure disorder.

Pearls:

- Although recognition of autoimmune encephalitis is increasing, it still remains a diagnosis of exclusion.
- It is very uncommon for a child to present solely with a psychiatric manifestation/behavioral change or just acute psychosis; this is very rare. It is more common for a child to present with a behavioral change AND a neurological deficit (seizure or movement disorder).
- Diagnostic Toolkit: CSF pleocytosis, Delta Brush finding on EEG, MRI with cortical T2 hyper-intensities suggestive of encephalitis – used to help with AIE diagnosis.
- If patient comes in at night, make them NPO until the morning when the whole medical team has had a chance to evaluate for suspicion of AIE and what tests should be indicated. This will prevent patient from having to wait an additional day before testing can begin.
- Ensure proper communication with families/caregivers about patient symptoms and medical plan/approach for diagnosis.
- If indicated, patients should have a lumbar puncture as well as extensive blood work to evaluate for evidence of inflammation, infection and other systemic diseases. Although basic testing for infectious processes, metabolic, hematologic and oncologic diseases may be performed, the extent of testing will vary on the basis of the clinical features and initial diagnostic testing.
- Lumbar Puncture should always be done in agreement with and after consulting with Psych.
- Neuroimaging
  - The majority of children will have normal MRI
    - Exceptions: GABA -A, MOG, and limbic encephalitis
  - Normal MRI does not exclude a diagnosis of AIE

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