Definition:

Encephalitis is defined as inflammation of the brain with multiple etiologies, most commonly infectious or idiopathic. Recent advances in testing and research have identified autoimmune encephalitis as an etiology in pediatrics. Autoimmune Encephalitis (AIE) represents a group of neuroinflammatory disorders associated with autoantibodies targeted against intracellular antigens, synaptic receptors, and ion-channels or cell-surface proteins. Symptoms of AIE in pediatrics include neurologic changes, including seizure and movement disorders, cognitive changes, and psychiatric symptoms. Diagnosis of AIE in pediatrics remains challenging because of the broad differential diagnosis and overlap in clinical presentations with other conditions.

Epidemiology:

In children, autoimmune encephalitis syndromes (AES) are less frequently associated with tumors as compared with adults. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and acute disseminated encephalomyelitis (ADEM) are the most frequently described forms of autoimmune encephalitis in children.[(6)] The estimated incidence of autoimmune encephalitis is 0.8/100,000/person-year and the prevalence is 13.7/100,000 in children and adults. The prevalence and incidence of autoimmune encephalitis are comparable to infectious encephalitis.

Etiology:

Autoimmune encephalitis encompasses a group of entities associated with antibodies against intracellular and neuronal cell surface antigens. The pathogenesis of AIE has not been fully described but some evidence suggests a link between infection and AIE (Li et al).

Guideline Eligibility Criteria:

Children 3 to 18 years of age with clinical signs that fulfill the criteria of possible autoimmune encephalitis (AIE). See Autoimmune Encephalitis Diagnosis Algorithm

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

Guideline Exclusion Criteria:

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

Differential Diagnosis:

The differential diagnosis for possible autoimmune encephalitis is quite broad. Many diseases of the central nervous system present similarly to autoimmune encephalitis. Through evaluations and testing, the possibilities of what disease process is occurring with the patient will be eliminated.

See the additional list of Diff-Dx.

Clinical Presentation:

The syndrome is highly predictable in adults and teenagers and usually evolves in stages, including a prodromal phase of fever, headache, or viral-like symptoms that often goes unnoticed. This is followed within a few days or weeks by the onset of psychiatric and behavioral problems including anxiety, bizarre behaviors, paranoid thoughts, grandiose delusions, and insomnia that progress to a decreased level of consciousness, seizures, dyskinesias, choreoathetoid movements or postures, and breathing or autonomic instability. [(2)]

In young children, the syndrome is similar, but the presenting symptoms may be different. In a recent cohort study of 500 patients including 180 of ages 18 years or less, showed that the most common presenting symptoms in children under the age of 12 years were abnormal behavior, seizures, and movement disorders. The behavioral changes included new-onset temper tantrums, agitation, aggression, and changes in mood or personality. Many parents report changes in speech, including reduced speech, mutism, echolalia, or perseveration. [(4)] Autonomic dysfunction that is common in adults occurs less frequently in children. Signs of autonomic dysfunction in children include urinary incontinence and episodes of tachycardia, hypertension, or hyperthermia. [(2)]

Specific to NMDAR-Ab, the characteristic polysymptomatic presentation includes early neuropsychiatric deficits with seizures, autonomic disturbance, reduced consciousness, and a movement disorder (orofacial dyskinesias, choreoathetosis, tremor, dystonia). This movement disorder, seen in around 90% of cases, can be the presenting feature, particularly in children, and is typically hyperkinetic with limb plus orofacial involvement.[(9)]

Although a viral prodrome with fever often occurs prior to neurologic changes, presence of fever in the later weeks of illness should not lead providers to exclude AIE. Case reports of NMDA-receptor encephalitis with concurrent infection and fever have been reported. Coordination with Infectious Disease can help guide testing for prodromal or acute infection.

Diagnostic Evaluation

Autoimmune encephalitis remains a diagnosis of exclusion. Diagnosing AIE is challenging because of the overlap in clinical presentations between the types of AIE. The broad spectrum of symptoms including, psychosis, catatonia, alterations of behavior and memory, seizures, abnormal movements, and autonomic dysregulation usually requires a multidisciplinary treatment approach.[(2)] Clinical diagnosis of AIE is based on the combination of a clinical history consistent with diagnostic testing. Evaluation typically includes identifying the presence of clinical symptoms, evaluating biological abnormalities in serologic testing, and assessing paraclinical abnormalities via neuroimaging, electroencephalography (EEG), and lumbar puncture.[(5)] Because the early application of immunotherapy is essential for the treatment of autoimmune encephalitis, early suspicion based on clinical findings is important. [(1)]

The differential is broad and collaboration between subspecialists in Neurology, Hospital Medicine, Infectious

Disease and Psychiatry is needed for diagnostic clarification and symptom management. Antibody testing takes several days, response to immunotherapy can be slow, and over half of suspected autoimmune encephalitis cases are seronegative. Accordingly, a clinical diagnostic approach has been developed, combining neurologic assessment, neuroimaging, and cerebrospinal fluid (CSF) testing, with levels of evidence established for possible, probable, or definite diagnosis of autoimmune encephalitis to support initiation of prompt immunotherapy where appropriate.[5] See AIE Algorithm.

Imaging and Labs[6]

See Addendum 1 for suggested serum workup and CSF studies.

Treatment

Treatment for autoimmune encephalitis is often empiric and may involve corticosteroids, plasmapheresis, and/or intravenous immunoglobulin (IVIG). Specifically, there have been no head-to-head clinical trials comparing acute treatments or long- term treatments for NMDA receptor encephalitis. A retrospective review suggests that plasmapheresis may be more effective than steroids alone. (DeSana AD et al. J Clin Apher 2015;30:212-216) Immunosuppressive therapy is the cornerstone of treatment. The use of immunosuppressive therapy should be prompt and should not wait for antibody characterization, provided an underlying infectious etiology has been excluded and there are no other contraindications. The results of antibody testing can then be used to refine or alter the treatment strategy.[6]

At DCMC, systemic steroids with or without IVIG is the first line of therapy for mild to moderate cases. For severe presentations of AIE, systemic steroids AND plasmapheresis can be used concurrently. Rituximab is more often used in children as second-line therapy due to its relatively favorable safety profile, as compared to cyclophosphamide.[5]

Critical Points of Evidence

Evidence Supports

Diagnosis/Evaluation

- The psychiatric phenotype of AIE in children is highly heterogeneous. Involving psychiatry consultation services can help differentiate features of psychosis and catatonia, which may otherwise be misidentified. Patients presenting with psychiatric symptoms along with impairments in other domains should prompt a workup for AIE, including testing for all known antineuronal antibodies.[5] ***(strong recommendation; high-quality evidence)***
- The diagnosis of AIE should be suspected in patients developing subacute cognitive impairment, psychiatric disturbances, movement disorders, or seizures. Patients with high suspicion of AIE should have neuroimaging (MRI), electroencephalogram (EEG), lumbar puncture, and antibody testing in serum and CSF at the same time that treatment is initiated based on a clinical diagnosis.[1-6] ***(strong recommendation; high-quality evidence)***

Labs, EEG and Imaging

- Patients with autoimmune encephalitis may have normal or abnormal cerebrospinal fluid (CSF) findings. Abnormalities include modest elevation of protein (<100 mg/dL), mild to moderate lymphocytic pleocytosis, elevated immunoglobulin G (IgG) index, and/or the presence of oligoclonal bands.
- Metabolic and toxic encephalopathies should also be considered and excluded.
- Paraneoplastic and autoimmune antibody testing should be performed on both serum and cerebrospinal fluid (CSF) to avoid false-positive and false-negative results.[6-8]) ***(strong recommendation; high-quality evidence)***

  - Negative results do not exclude a paraneoplastic or autoimmune disorder.
- An EEG should be performed to exclude nonconvulsive seizures in patients with AIE. [7] ***(strong recommendation; high-quality evidence)***
  - Approximately one-third of patients with anti-NMDAR encephalitis have an EEG pattern called extreme delta brush that is considered characteristic of the disorder, however, this finding is less common in children.
- Characteristic MRI findings in patients with autoimmune encephalitis include signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images in medial temporal lobes and/or brainstem; subcortical regions and the cerebellum are sometimes affected.
  - A brain magnetic resonance image (MRI) is helpful to exclude a cerebrovascular event or metastatic disease.[7] ***(strong recommendation; high-quality evidence)***

Treatment Approach

- Basic tenets that guide the treatment of autoimmune encephalitis are that patients treated with immunotherapy fare better than those not given immunotherapy.[1-6] ***(strong recommendation; high-quality evidence)***
- Immunosuppressive therapy should be started based on medical history and clinical features, laboratory and radiologic evidence of central nervous system (CNS) inflammation, exclusion of infection, ensuring other alternative etiologies have been ruled out, and no contraindications.
  - Early initiation of treatment (immunotherapy and tumor-directed therapy, if present) is associated with a better prognosis (i.e., improved outcomes, speed of recovery, and reduction in the risk of relapses). ***(strong recommendation; high-quality evidence)***
- The primary immunomodulation options include steroids, intravenous immunoglobulins, or plasma exchange (PLEX). This may be followed by maintenance therapy in the form of oral steroid taper, monthly pulse steroids, or pulse IVIG therapy.[8]
- Second-line immunotherapy in case of non-response to first-line agents includes rituximab.[6-8]

Evidence Lacking/Inconclusive

- Most children with AIE do not require brain biopsy. However, a targeted brain biopsy of MRI abnormalities may be needed when the diagnosis remains uncertain after the initial workup.[7] ***(strong recommendation; moderate-quality evidence)***
- Consensus criteria on the appropriate time to initiate second-line immunotherapy are yet to be established.[8]

Outcomes

Early and aggressive treatment for AIEs leads to better prognostic outcomes. Some patients will need immunosuppression for weeks or months as autoimmune encephalitis may relapse; therefore, follow-up is always necessary. It is not uncommon that fully recovered patients still have detectable levels of antibodies in serum or cerebrospinal fluid, suggesting a potential for reactivation of the immune response. This finding likely explains the occurrence of clinical relapses in 20% of children with anti-NMDA receptor encephalitis.[3] About half of the patients with anti-NMDAR encephalitis show improvement within four weeks of receiving treatment and 80% of these patients eventually have partial or complete recovery. Some patients can take up to 18 months to recover. While anti-NMDAR is the most studied of the antibodies, the treatment for other forms of autoimmune encephalitis is generally similar.

Early diagnosis and effective treatment might improve long-term outcomes. Outcomes may vary from full recovery to death.

Methods

Existing External Guidelines/Clinical Pathways

Existing External Guideline/Clinical	Organization and Author	Last Update
Autoimmune Encephalitis	Children's Hospital at Vanderbilt	2019
	AMERICAN ACADEMY OF PEDIATRICS	2020
	Autoimmune Encephalitis Alliance	2014

Any published clinical guidelines have been evaluated for this review using the **AGREE II criteria**. The comparisons of these guidelines are found at the end of this document. **AGREE II criteria** include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms Used:	Encephalitis, autoimmune encephalitis, lumbar puncture, abnormal psychiatric behavior, cognitive dysfunction, NMDA, neuronal surface autoantibodies, paraneoplastic syndromes
Years Searched - All Questions	2007 - 2022
Language	English
Age of Subjects	3 – 18 Years of age
Search Engines	PubMed, Cochrane, Google Scholar
Government/ State Agencies	International Encephalitis Consortium, American Academy of Neurology, International Autoimmune Encephalitis Society,

Evidence Found with Searches

Check Type of Evidence Found	Summary of Evidence – All Questions	Number of Articles Obtained
☐	Systematic Reviews	
☒	Meta-analysis articles	1
☒	Randomized Controlled Trials	2
☒	Non-randomized studies	5
☒	Review articles	6
☐	Government/State agency regulations	
☒	Professional organization guidelines, white papers,	1
☐	ect. Other:	

Evaluating the Quality of the Evidence

The **GRADE** criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation

Strong Desirable effects clearly outweigh undesirable effects or vice versa

Weak Desirable effects closely balanced with undesirable effects

Type of Evidence

High Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies

Moderate Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies

Low Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence

Very Low Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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 - other tests to consider on a case-by-case basis

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

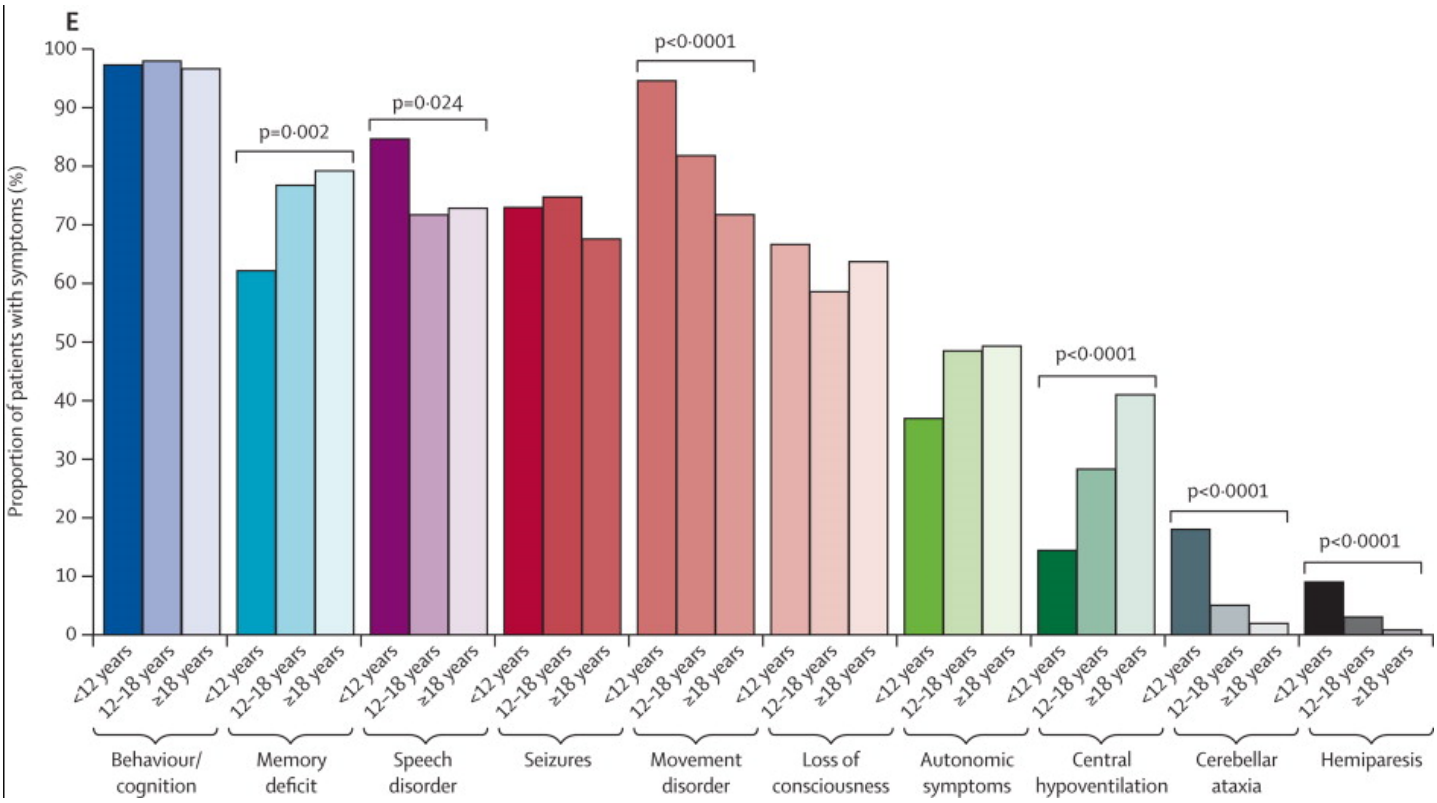
Addendum 2: Differential Diagnosis

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.

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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.

Rev. Hardy, D.
09/2022

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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