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AUTOIMMUNE ENCEPHALITIS: LABORATORY DIAGNOSIS, PROGNOSIS AND MANAGEMENT STRATEGIES IN CHILDREN

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ABSTRACT

Autoimmune(antibody mediated)encephalitis (AE) is emerging as a more common cause of pediatric encephalopathy than previously thought. The autoimmune process may be triggered by an infection, vaccine or occult neoplasm. Affected children may initially present to psychiatrists, as neurological features are most commonly occurring symptoms,viz., movement disorders, seizures, altered consciousness level, and cognitive regression.Hypoventilation and autoimmune features may be an additional aspect. Inflammatory findings in the cerebrospinal fluid may be present but are relatively non specific. Magnetic Resonance Imaging (MRI) may also demonstrate abnormalities that provide clues for diagnosis, particularly on fluid- attenuated inversion recovery or T2- weighted images. AE is well responsive to immunotherapy, with prompt diagnosis and treatment strongly beneficial.

KEYWORDS: Autoimmune Encephalitis, N- Methyl –D- Aspartic acid, Immunotherapy

INTRODUCTION

In pediatric age, AE usually occurs in females and a history of other antibody mediated condition is frequent. Several antibodies have been demonstrated to be associated with paraneoplastic and non-paraneoplastic neurological syndromes. Various antibodies can be divided in to following groups.

a) Antibodies to intracellular antigens
b) Antibodies to cell surface antigens
c) Antibodies to extracellular synaptic antigens[1]

a).Pediatric AE with antibodies targeting neuronal cell surface antigens

- Anti- N- Methyl –D-Aspartic acid encephalitis
- AE with leucine – rich glioma – inactivated protein-1 IgG
- Anti-glycine receptor encephalitis
- Anti- GABA type A receptor encephalitis
- Anti- GABA type B receptor encephalitis
- Antibodies targeting the glutamate receptor 1 or 2
- Ophelia syndrome
- Anti- dopamine D2 receptor encephalitis

b).Pediatric AE with antibodies targeting intracellular antigens

These AE typically show a poor response to immunotherapy and a poor outcome, with refractory epilepsy and for cognitive mediated cytotoxicity, in conjuntion with the intracellular antigenic location. These are:

- Anti- Hu encephalitis
- Anti- Ma 2 encephalitis
- Anti- glutamic acid decarboxylase encephalitis.

Clinical Approach to the Diagnosis

Diagnosis of AE in a developing child is challenging because of overlap in clinical presentation with other diseases and complexity of normal behavior changes. Existing diagnostic criteria for adult AE require modification to be applied to children, who differ from adults, in their clinical presentations, paraclinical findings, autoimmune profiles, treatment response and long term outcomes.[2]

Existing Diagnostic Criteria for AE

The International Encephalitis consortium 2013 diagnostic criteria for encephalitis of presumed infections or autoimmune etiology require patients to have altered mental status lasting more than 24 hours with no alternative cause identified. Confirmation of this diagnosis requires at least 3 minor criteria, including fever within 72 hours of presentation; new onset focal focal neurologic findings; CSF leukocytosis; acute new neuro imaging abnormality suggestive of encephalitis; or EEG abnormalities consistent with encephalitis.

Behavioral changes such as repetitive or stereo typical behaviors, irritability, hyperactivity, hypersexuality, insomnia and anger outburst are common in pediatric AE.[3] Children with AE are more likely to present with

multifocal neuropsychiatric symptoms. Pediatric AE is less associated with tumors compared with adults.

Diagnostic Evaluation of Children and Teenagers with suspected AE

Although no single investigation is diagnostic of pediatric AE, the presence of a suggestive clinical phenotype and supportive para-clinical testing is essential to diagnose an underlying inflammatory process and to exclude alternative diagnosis. A detailed list of investigations is as under.

I).Recommended investigations for children with suspected AE.

- Diagnosis imaging- Brain MRI with gadolinium
- Blood tests- Complete blood cell count and differential, ESR, C-reactive protein, Ferritin, Vitamin B12, Vitamin- D level, Serum lactate, Thyroid function tests, Specific antinuclear antibodies.
- Urine tests- Testing for recreational drugs (eg.- marijuana, Cocaine and Opioids).
- Lumber puncture, respiratory tests, EEG etc.

II).More specific investigations for patients with possible AE:

- Blood tests- Serum testing for antibodies associated with AE.
- Lumber puncture- CSF testing for antibodies associated with AE.
- Neurocognitive tests- Assess for cognitive deficits affecting memory, attention, problem solving, language and cognitive functions.
- Other tests- Consider if available and / or if required based on initial investigations: PET and SPECT.

AE: Clinical Phenomenology

Auto-antibodies that bind to conformational extracellular epitopes of neuronal receptors or synaptic proteins have provided clinicians with essential biomarkers in acute neurology. In recent findings, in children, anti –N-Methyl-D-aspartate receptor encephalitis remains the most identifiable autoimmune AE, although many patients have a clinical syndrome of brain and inflammation in which no antibodies are identified. Anti-myelin oligodendrocyte glycoprotein antibody associated demyelination is now recognized as a major cause of monophasic and relapsing demyelination, after presenting with encephalopathy.[4]

Treatment and Management Strategies

Patients with definite AE may benefit from continued or advanced immunosuppressive therapy, although specific protocols are not yet validated, also timing of clinical responses to immunotherapy in children with AE may vary from immediate to months after starting therapy.[5]

Treatment options for AE range from broadly immune suppressing agents to those targeting processes in anti body mediated disease pathogenesis.

Therapeutic agents used in AE

I).Immunotherapy	***Regimen***
(a) First -line immunotherapy	
Methylprednisolone	1 gm daily, for 3-5 days
Intravenous immunoglobin (IVIg)	2gm/kg over 5 days(400mg/kg/d)
Plasma exchange (PLEX) and immunoadsorption	1 session every other day for 5-7 cycles
(b) Second- line immunotherapy-	
Rituximab	375mg/m2 weekly, IV infusion for 4 weeks
Cyclophosphamide	750mg/m2 monthly for 3-6 months
II).Alternative therapy	
Tocilizumab(IL-6,receptor inhibitor)	Initially 4 mg/kg, followed by an increase to 8mg/kg monthly based on clinical response.
Low dose interlukin-2 (therapy and Treg modulation)	1.5 million IU/day, 4 subcutaneous injections,with 3-week interval.
Bortezomib	
III).Steroid – sparing agents used for maintenance therapy	
Azathiopurine	Initially 1-1.5 mg/kg once daily or divided twice daily target 2-3 mg/kg/ once daily or divided twice daily, target 2-3 mg/kg/d.
Mycophenolate mofetil	Initially 500mg twice daily, target 1000mg twice daily.
Plasmapheresis	-
Tumor removal	-

Evaluation as per Mayo Clinical Laboratory Testing[6-7]

Encephalopathy autoimmune evalution (serum and CSF)

1. **Radio immunoprecipitation Assay(RIA)**

- P/Q – type calcium channel antibody
- N-type calcium channel antibody

- Ganglionic acetylcholine receptor
- Glutamic acid decarboxylase antibody assay

2. Immunoflouroscence Assay(IFA)

- Antineuronal nuclear antibody type-1
- Antineuronal nuclear antibody type-2
- Antineuronal nuclear antibody type-3
- Purkinje cell cytoplasmic antibody type 1 and 2
- Purkinje cell cytoplasmic antibody type Tr(PCR-Tr)
- Amphiphysin antibody assay
- Collapsin response mediator protein-5 neuronal
- Antiglial /neuronal nuclear antibody-type-1
- Dipeptidyl peptidase like protein -6
- Metabotropic glutamate receptor 1 antibody
- Glial fibrillary acidic protein alpha subunit antibody

3. Immunofluroescence Assay Cell Binding/(CBA)

- NMDA- receptor antibody
- AMPA- receptor antibody
- GABA-B receptor antibody
- Contactin associated protein like -2-IgG
- Leucine rich glioma inactivated protein -1 IgG

CONCLUSION

Although AE responds to immunotherapy and the majority of patients recover from the self destructive auto immune process, many patients fail to regain base line cognitive and functional status. Early aggressive therapy is recommended in AE but steroid abuse should be avoided to prevent potential cognitive and other adverse effects. Further, there have been significant developments, future priorities include : the need for paediatric specific consensus definitions for sero negative suspected autoimmune encephalitis ; novel tools for monitoring patients with AE ; consensus treatment recommendations, and neuroprotective strategies.

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