Indian Academy of Pediatrics (IAP)

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Autoimmune Encephalitis

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Autoimmune Encephalitis

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Introduction

- ☑ Autoimmune encephalitis (AE) is increasingly recognized cause of encephalopathy in children.
- ☑ These are proven syndrome based on clinical semiology and antibodies associated.
- ☑ Plethora of antibodies against central nervous system (CNS) is responsible for the clinical manifestations. However, many children do not have detectable antibodies.
- ☑ The pediatricians and intensivists should be aware of this entity as early diagnosis and treatment is associated with better neurocognitive outcomes.
- ☑ The incidence is poorly reported and it may be up to the tune of 2.2/million children per year. Females are affected more.
- ☑ It may be responsible for the large number of children with encephalitis.
- ☑ Anti-NMDA receptor (NMDAR) AE is most common type in children.

Pathogenesis

☑ There is development of antibodies against neuronal antigens in response to several triggers **(Table 1)**.

TABLE 1: Causative factors.

Triggers	***Agents***	***Comments***
Infections: Postviral immune encephalitis	☑ HSV, VZV, EBV, HHV-6, CMV, HIV, and adenovirus ☑ Rickettsial ☑ Mycoplasma	☑ Triggers cause the release of brain-specific neoantigens and trigger development of pathogenic antibodies ☑ Nonspecific stimulation of range of antibodies *HSV and AE:* ☑ 30% of cases with HSV encephalitis had anti-NMDAR antibodies in CSF ☑ Anti-NMDAR antibodies lead to relapse of HSV encephalitis (20%) ☑ Improve with immunotherapy
Postvaccinal: Anti-NMDAR	☑ Influenza ☑ Polio ☑ DPT ☑ Japanese B encephalitis	
Paraneoplastic: Tumor antigens shared by neuronal cell antigens	☑ Ovarian teratoma ☑ Testicular carcinoma ☑ Hodgkin disease ☑ Neuroblastoma	☑ Antibody-mediated neuronal cell destruction ☑ Less common in children ☑ *Between 12 and 45 years:* 40% associated with tumor (97% females) ☑ *<18 years:* 31% paraneoplastic ☑ *<14 years:* 9% paraneoplastic ☑ 94% ovarian teratoma, 2% extraovarian teratoma ☑ *4%:* Small cell carcinoma lung, testicular teratoma, and breast

(AE: autoimmune encephalitis; CMV: cytomegalovirus; CSF: cerebrospinal fluid; DPT: diphtheria, pertussis, tetanus; EBV: Epstein–Barr virus; HHV-6: human herpesvirus 6; HIV: human immunodeficiency virus; HSV: herpes simplex virus; VZV: varicella-zoster virus)

☑ AE is categorized as per the antigen location (cell surface or intracellular antigen) **(Table 2)**:

TABLE 2: Categories of autoimmune encephalitis.

Antigen location	***Type of antibodies***	***Comments***
Cell surface	☑ Anti-NMDAR (most common) ☑ VGKC ☑ LGI1 ☑ CASPR2 ☑ Anti-GABA-A receptors ☑ Anti-GABA-B receptors ☑ Anti-Glycine ☑ Anti-D2 receptors ☑ Anti-AMPA receptors ☑ Anti-mGlu5 ☑ Anti-neurexin3 alpha ☑ Anti-glutamate receptors	☑ Common in children ☑ Lower association with malignancy ☑ Mediated by humoral immune system ☑ Better response to immunotherapy ☑ Favorable outcome

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Pathogenesis

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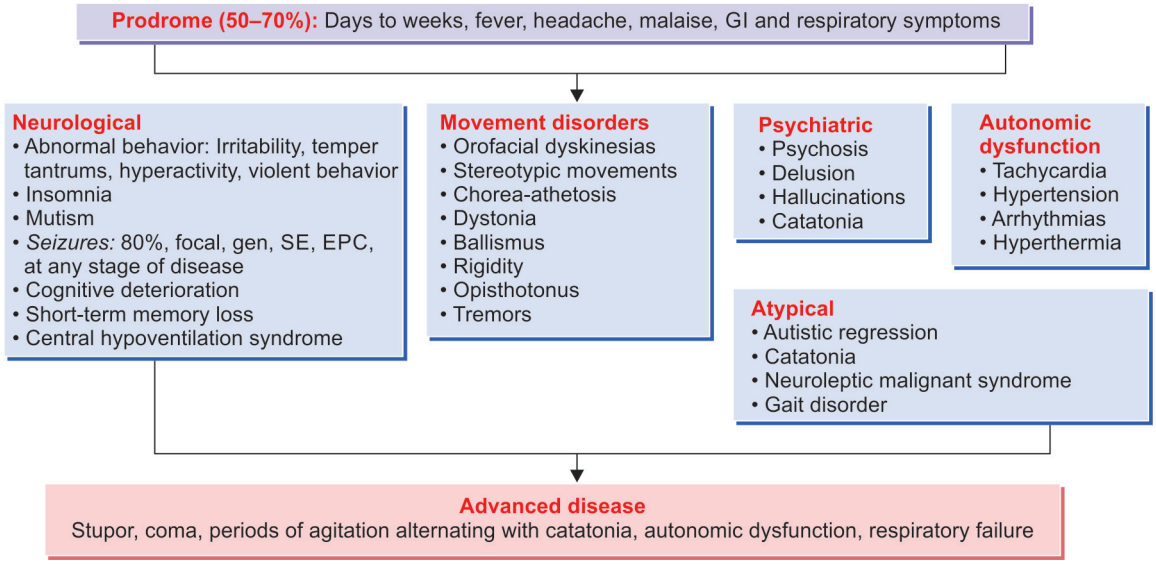
Antigen location	*Type of antibodies*	*Comments*
Intracellular	☑ Anti-Hu ☑ Anti-Ma2 ☑ Anti-GAD	☑ Less relevant in pediatric ☑ Usually, paraneoplastic ☑ Mediated by cytotoxic T-cells ☑ Respond poorly to immunomodulatory therapy ☑ Poorer outcomes

Clinical Features

- ☑ Anti-NMDAR encephalitis is prototype of AE and this will be discussed here.
- ☑ It accounts for 4% of encephalitis in children.
- ☑ It is most common cause of seropositive AE in children.
- ☑ 40% of all reported cases are below 18 years of age.
- ☑ It may also contribute to recurrence of encephalitis after herpes simplex virus (HSV) encephalitis. It was first described as a paraneoplastic syndrome in adult females in association with ovarian teratomas. However, it is being increasingly recognized in men, women, and children, with and without teratomas.
- ☑ *Pathogenesis***:** It is mostly postinfective. Immunoglobulin G1 (IgG1) NMDA antibodies bind to NR1 subunits of NMDA receptors leading to their internalization. This lead to inhibition of glutaminergic excitation to inhibitory neurons and in turn intense excitotoxicity.
- ☑ The clinical course follows triphasic pattern: Prodrome, varied neurological manifestations, and advanced disease **(Flowchart 1)**.
- ☑ Children have more pronounced seizures, movement disorders, speech abnormalities, sleep problems, and behavioral issues.

Flowchart 1: Clinical course pattern.



(EPC: epilepsia partialis continua; GI: gastrointestinal; SE: status epilepticus)

Seronegative Autoimmune Encephalitis

- ☑ Only 40–50% cases with AE have positive antibodies.
- ☑ Definition of seronegative AE include:
  - Rapid clinical progression of symptoms
  - Exclusion of well-defined AE syndromes (e.g., typical limbic encephalitis)
  - Absence of antibodies in CSF and serum antibody positivity
- ☑ And two of the following:
  - CSF pleocytosis
  - CSF-specific oligoclonal bands or elevated CSF IgG index
  - MRI findings suggestive of AE
  - Brain biopsy showing inflammation
- ☑ And exclusion of other causes

When to Suspect Autoimmune Encephalitis?

Autoimmune encephalitis should be suspected when a child present with varied combination of following features:

- ☑ Unusual manifestations in a child with acute encephalitis syndrome
- ☑ Adolescent girls
- ☑ Subacute to chronic course
- ☑ Polysymptomatic syndrome
- ☑ Encephalopathy
- ☑ *Seizures*: Focal, generalized, status epilepticus, multifocal, and super-refractory status epilepticus
- ☑ Movement, gait, and balance disorders
- ☑ Psychiatric features
- ☑ Autonomic disturbances
- ☑ Delirium and catatonia
- ☑ Cognitive slowing
- ☑ Relapse after treatment for viral encephalitis
- ☑ Involvement of multiple domains, e.g., cognition and extrapyramidal system, etc.
- ☑ *CSF*: Features of inflammation in absence of infection

Diagnosis

- ☑ Diagnosis relies on the clinical phenotype, CSF inflammation, MRI and electroencephalogram (EEG) findings, antibody positivity, response to immunotherapy, and exclusion of other causes **(Table 3)**.
- ☑ Adolescent females must be screened for tumors (association with ovarian teratomas).

TABLE 3: Diagnostic tests for autoimmune encephalitis (AE).

Diagnostic tests	***Comments***
CSF examination	It is suggestive of CNS inflammation. About 80% cases may have abnormal CSF in form of CSF pleocytosis (lymphocytic), normal/mild elevation in proteins, normal glucose, and elevated IgG index, oligoclonal bands, or CSF neopterin.
MRI brain (anti-NMDAR)	☑ Unilateral or bilateral T2/FLAIR signal hyperintensities involving mesial temporal lobe, hippocampal, cerebellar, and cerebral cortex. ☑ Hyperintensities may be seen throughout brain. ☑ Cortical enhancement in absence of restricted diffusion. ☑ MRI may be normal in 50–60% cases. ☑ PET scan can highlight involvement of mesial temporal lobes.

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Diagnosis

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Diagnostic tests	*Comments*
EEG	☑ EEG is abnormal in most patients. The findings are usually nonspecific including extreme or diffuse slowing, epileptiform discharges, and disorganized activity. ☑ Extreme delta brushes are seen in 30% of anti-NMDAR cases.
Antibody testing	☑ Detection of pathogenic antibody is basis for diagnosis of AE. ☑ *Positive:* Definite cases; *Negative:* Suspected case. ☑ *Methods:* Cell-based assays with live or fixed eukaryotic cells or IgG-based assays. ☑ Testing both serum and CSF is preferred. ☑ However, in resource limited setup, only CSF can be done as it is more sensitive. ☑ In anti-NMDAR, CSF testing is more sensitive (100% vs. 86%). ☑ In protracted disease, delayed diagnosis, and after IVIG/PE, antibodies may be present only in CSF. ☑ Only 40–50% cases with AE have antibody positivity. ☑ It has limited utility of follow-up evaluation.

(CNS: central nervous system; CSF: cerebrospinal fluid; EEG: electroencephalogram; FLAIR: fluid-attenuated inversion recovery; IgG: immunoglobulin G; IVIG: intravenous immunoglobulin; PE: plasma exchange; PET: positron emission tomography)

Differential Diagnosis

☑ It includes CNS infections [HSV and Japanese encephalitis (JE)], toxins, CNS vasculitis, inborn errors of metabolism [osteoarthritis (OA) and mitochondrial], neoplasms, primary psychiatric disorder, and subacute sclerosing panencephalitis (SSPE).
Differentiation between AE and acute infectious encephalitis is presented in **Table 4**.

TABLE 4: Differentiation between autoimmune encephalitis (AE) and acute infectious encephalitis.

Salient features	*Autoimmune encephalitis*	*Infectious encephalitis*
Clinical manifestations	☑ Seizures, movement disorders, speech abnormalities, sleep problems, and behavioral issues ☑ Fever in 50% ☑ Autonomic dysfunction ☑ Rash is rare	☑ Fever, seizures, and altered sensorium. ☑ Most cases have fever. ☑ Rash may be present in VZV and HSV encephalitis.
CSF	Mild CSF pleocytosis	More CSF pleocytosis

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Differential Diagnosis

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Salient features	*Autoimmune encephalitis*	*Infectious encephalitis*
MRI brain	☑ It is recommended in children with suspected AE during initial evaluation and to rule out alternate causes. ☑ MRI abnormalities seen in AE are commonly subtle and may be discordant from dramatic clinical features. ☑ MRI may be normal (50–66%), especially early in the course. ☑ Basal ganglia often involved. ☑ Lateral temporal lobes and insula less commonly involved. ☑ There can be T2-weighted fluid-attenuated inversion recovery abnormalities throughout the brain and in cortical and subcortical areas, including temporal, frontal, and parietal lobes; hippocampi and amygdalae, cerebellum; thalamus; and basal ganglia. ☑ There may be contrast enhancement and abnormal diffusion-weighted images.	☑ Mesial temporal lobe involvement in characteristic (HSV) ☑ Lateral temporal lobe and insula may be involved ☑ Basal ganglia spared
Treatment	☑ Immunotherapy (±surgical removal of tumor)	Antiviral (acyclovir)

(CSF: cerebrospinal fluid; HSV: herpes simplex virus; VZV: varicella-zoster virus)

Treatment

- ☑ Prognosis is better with early diagnosis and early initiation of immunotherapy.
- ☑ Second-line agent also improves prognosis in cases with poor response to first-line therapy, severe disease, and relapsing disease.
- ☑ Therefore, if AE is suspected, start empirical therapy immediately without waiting for antibody results. However, if antibody testing is not affordable or not available, start empirical therapy after excluding alternate causes.
- ☑ The tiered approach to treatment of AE is shown in **Figure 1**.

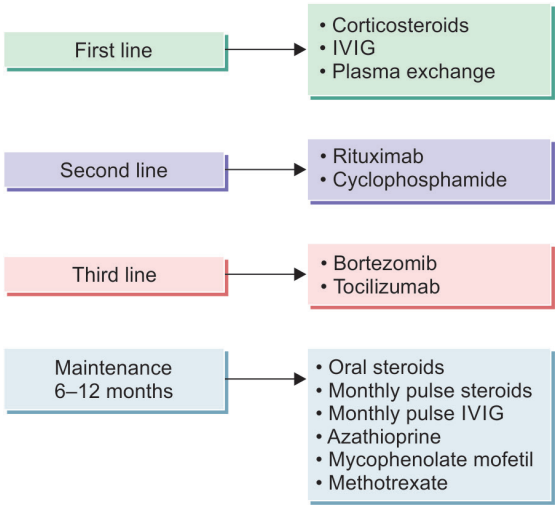

Fig. 1: Approach to treatment of AE.
(IVIG: intravenous immunoglobulin)

- ☑ A significant proportion of patients respond to first-line therapy.
- ☑ They show response to treatment within first 1–2 weeks of treatment initiation **(Table 5)**.

TABLE 5: Agents and their recommended dosages.

Agents	***Dose and comments***
First line	
Corticosteroids	☑ Corticosteroids are the cornerstone of treatment with broad spectrum of anti-inflammatory activity and good penetration across blood–brain barrier. ☑ *Methylprednisolone:* 30 mg/kg/day (maximum 1 g/day) for 3–5 days, followed by sustained oral steroids (prednisolone 1–2 mg kg/day) and slow taper over 6–12 months.
IVIG or PE	☑ It is commonly used as alternatives and occasionally, concomitantly. ☑ IVIG (2 g/kg given over 5 days) or PE (5–7 exchanges of 50 mL/kg every alternate day). ☑ Early PE along with corticosteroids have better outcomes than either alone. ☑ No evidence exists regarding superiority of PE versus IVIG. ☑ However, considering that cases with AE are often sick, IVIG might be easier. ☑ *Common regimens used:* Methylprednisolone ± IVIG or IVIG/PE during acute stage in cases with inadequate response to methylprednisolone.
Second line	
Rituximab	☑ It is chimeric monoclonal antibody against CD20. ☑ *Dose:* 375 mg/m^2 weekly for 4 weeks or 750 mg/m^2 (maximum 1 g) IV twice separated by 2 weeks. ☑ Resulting in B-cell depletion and reduced proinflammatory CD4+ and CD8+ T cells. ☑ B-cell count after 2–4 weeks and 3–6 months. ☑ To consider redosing if symptoms persist or relapse. ☑ Well tolerated and serious adverse events are rare. ☑ Infusion reactions 12%.
Cyclophosphamide	☑ It has broad cellular immune suppression effects. ☑ *Dose:* Monthly IV infusions 500–1,000 mg/m^2 BSA for 6–9 months. ☑ *Limitations:* Risks of infertility and secondary malignancies which depend on cumulative dose received. ☑ Doses <7.5 g/m^2 are justified in sick patients. ☑ Concomitant rituximab and cyclophosphamide have been tried without any increase in adverse effect profile.
Third line	☑ When both first- and second-line agents fail ☑ Bortezomib (protease inhibitor-inhibits proinflammatory signaling cascade) ☑ Tocilizumab (anti-IL-6) ☑ Intrathecal steroids and methotrexate

(BSA: body surface area; IL-6: interleukin-6; IVIG: intravenous immunoglobulin; PE: plasma exchange)

Maintenance Therapy

The options for maintenance therapy include:

- ☑ Prednisolone for 6–12 months.
- ☑ Monthly pulses of methylprednisolone (MP) or intravenous immunoglobulin (IVIG).
- ☑ Mycophenolate mofetil (MMF), methotrexate, and azathioprine:
  - Steroid-sparing agents (pediatric anti-NMDAR)
  - They are used individually or in varying combinations
  - Associated with a reduced risk of relapse if started after first event rather than after subsequent ones
  - Reasonably safe

Management of Relapse

- ☑ Relapses are not uncommon in AE.
- ☑ 10–25% of patients with anti-NMDAR relapse
- ☑ Can be reduced by use of second-line therapies and chronic immunosuppression.
- ☑ When they occur, they are managed with repeat dosing of the first-line agents.
- ☑ Considering the concern of ongoing inflammatory activity, chronic immunosuppressive therapy should be considered.
- ☑ Azathioprine, MMF, or repeated dose of rituximab

Pediatric Intensive Care Unit Needs

- ☑ 40–60% children with AE need pediatric intensive care unit (PICU) care.
- ☑ They may need mechanical ventilation due to encephalopathy, status epilepticus, and use of multiple antiepileptic drugs (AEDs). The principles of lung protective ventilation should be followed.
- ☑ For seizures and refractory status epilepticus, follow usual protocol.
- ☑ To induce and maintain sleep, relieve agitation and emotional imbalance, one can use benzodiazepines, clonidine, or chloral hydrate. Avoid neuroleptics as they are associated with high incidence of rigidity and neuroleptic malignant syndrome.
- ☑ Monitor for autonomic dysfunction.
- ☑ Dystonia can be treated with benzodiazepines, pacitane, clonidine, or baclofen.
- ☑ Maintain strict fluid balance and infection control practices.
- ☑ Early liberation from the mechanical ventilation and PICU.

Prognosis

- ☑ Majority (90%) respond to first-line therapy within 4 weeks.
- ☑ Those failed first-line therapy, 57% responded to second-line therapy.
- ☑ At 2-year follow-up:
  - 80% patients had a good outcome
  - Mortality in 4–6%
- ☑ *Predictors of poor outcome:*
  - Delayed diagnosis and treatment (immunomodulation)
  - PICU admission, altered sensorium, and dysautonomia
  - Polysymptomatic presentation.

Further Reading

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