REVIEW ARTICLE

Autoimmune Encephalitis in Children: An Update

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Context: Autoimmune encephalitis has acquired immense significance as a treatable cause of encephalopathy, epilepsy and movement disorders in children. In this review, we discuss the various clinical syndromes, diagnosis, treatment and prognosis in children.

Evidence acquisition: A MEDLINE search strategy using the following terms (1998-2019) was adopted for this review. Limits of 'Human' and 'English' were applied. Search terms included: "autoimmune encephalitis", "autoimmune encephalitis AND epidemiology", "pathophysiology", "diagnosis" and "treatment" for studies in children. Review articles, practice parameters, guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case series and case reports were included.

Conclusions: Autoimmune encephalitis is being increasingly recognized in children. Anti-NMDAR encephalitis is the most common form. Children present with a polysymptomatic presentation including behavioral changes, psychosis, sleep disturbances, mutism, seizures, movement disorders, memory impairment as well as other neurocognitive deficits. Diagnosis is based on suggestive history and ancillary investigations including magnetic resonance imaging, cerebrospinal fluid analysis, and serology for autoantibodies. Treatment is based on immunomodulation of the acute episode followed by maintenance therapy, with earlier initiation being associated with better outcomes. Prognosis depends on the type of clinical syndrome.

Keywords: *Anti-NMDAR encephalitis, Autoimmune epilepsy, Limbic encephalitis, Movement disorders.*

Autoimmune encephalitis (AIE) is being increasingly recognized as a significant as well as frequent cause of encephalopathy in the pediatric age group. Despite a plethora of antibodies being described against the central nervous system, a significant proportion of childhood autoimmune encephalitis do not exhibit detectable known antibodies, spawning a diagnostic challenge [1]. These children may have as yet unidentified antibodies or other immune mechanisms. AIE incorporates proven syndromes based on clinical phenomenology and based on autoantibody associations. Of these, syndromes with antibodies to cell surface antigens have evidence to suggest pathogenicity. Rarely, antibodies to intracellular antigens can be a biomarker but their role is unproven.

The most common antibody associated with AIE in children is anti-NMDA receptor (NMDAR) antibody. Unlike adult AIE, association with cancer is less frequent in children [2]. Early diagnosis and treatment leads to better neurocognitive outcomes. Pediatricians and intensivists need to be aware of this entity so that they can ensure timely and appropriate diagnosis and treatment. This review will provide readers with an updated account of clinical presentation, diagnosis and treatment options in autoimmune encephalitis in children, with discussion of future priorities and challenges.

METHODS

A MEDLINE search strategy using the following terms (1998-2019) was adopted for this review. Limits of 'Human' and 'English' were applied. Search terms included: "autoimmune encephalitis", "autoimmune encephalitis AND epidemiology", "pathophysiology", "diagnosis" and "treatment" for studies in children. Review articles, practice parameters, guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case series and case reports were included.

EPIDEMIOLOGY

Data on the epidemiology of pediatric AIE is limited. A retrospective study of anti-NMDAR encephalitis conducted over seven years in Hong Kong estimated an incidence of 2.2/ million children per year [3]. This disorder likely accounts for a large number of cases of encephalitis in children. Anti-NMDAR encephalitis may also contribute to recurrence of encephalitis following herpes simplex virus encephalitis in both children and

adults [4]. Other non-herpes viruses may also act as triggers for anti-NMDAR encephalitis [5]. Anti-NMDAR encephalitis accounts for 4% of all encephalitis and is the most common cause of seropositive AIE in children. Almost 40% of all reported cases are below 18 years of age [6]. Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's encephalopathy has a prevalence of 2/100,000 in adults but its frequency in children is much less [7]. Anti-thyroid antibodies may be detected in up to 10% of normal children, entailing caution while interpreting these in the presence of neurological impairment in children [8].

PATHOGENESIS

Autoimmune encephalitis can be categorized as per antigen location into two groups. In one group, antibodies target intracellular antigens, and in the second, antibodies target cell surface antigens. This categorization has clinical relevance as well. Intracellular antigen-based diseases are usually paraneoplastic and are mediated by cytotoxic T-cells [9]. These syndromes respond poorly to immunomodulatory therapy with poorer outcomes [10]. Cell surface antigen-based diseases have a lower association with malignancy and are mediated by the humoral immune system [11]. These have a better response to immunotherapy and a more favourable outcome [12]. AIE may also be paraneoplastic or non-paraneoplastic, based on the presence or absence of an underlying neoplasm, respectively - although, this is less relevant in pediatric AIE.

Paraneoplastic syndromes: These result when tumor antigens are shared by neuronal cell antigens, leading to antibody-mediated immunological destruction of neural tissue [13,14].

Infections: Another mechanism is post-viral autoimmune encephalitis. This was first highlighted in a study that reported the development of anti-NMDAR antibodies in 30% of patients with HSV encephalitis based on CSF PCR studies [15]. It is now known that relapsing symptoms following HSV encephalitis that lack viral antigen positivity may be attributable to anti-NMDAR antibodies in 20% of the cases, with a higher frequency in children [16]. These relapses improve dramatically with immune therapy. A putative mechanism involves the release of brain-specific neo-antigens caused by viral toxicity that trigger development of pathogenic antibodies. Another mechanism may be the non-specific stimulation of a range of antibodies following viral inflammation. In children, these relapses frequently take the form of choreo-athetosis and diminished consciousness. Even the viral phase of herpes virus encephalitis may have immunological basis, supported by the occurrence of less severe disease in immunocompromised individuals [17], as well as the beneficial role of steroid therapy in this condition [18]. Although less frequently documented, other viral infections such as varicella zoster, Epstein Barr virus (EBV), Human herpes virus-6 (HHV-6), Cytomegalo-virus (CMV), adenovirus, rickettsial infection as well as HIV are also known to predate AIE [19]. Non-NMDAR antibodies have also been reported after viral encephalitis, including anti-D2 receptor, anti-GABA-A/B, anti-AMPAR antibodies [20].

Post-vaccinal: Several cases of anti-NMDAR encephalitis have been reported following vaccination with influenza (H1N1), diphtheria, tetanus, pertussis, polio and Japanese B encephalitis vaccination [21].

CLINICAL FEATURES

Pediatric autoimmune encephalitis clinically manifests as various clinical syndromes dictated by the type of antibody. Both paraneoplastic and non-paraneoplastic syndromes are associated with the following broad type of antibodies: (*i*) antibodies directed against cell-surface antigens, (*ii*) antibodies directed against intracellular antigens, and (*iii*) antibodies directed towards synaptic antigens present on the extracellular surface. The clinical syndromes are summarized in ***Web Table* I**.

Anti-NMDAR Encephalitis

Anti-NMDAR encephalitis accounts for 4% of all encephalitis and is the most common cause of seropositive AIE in children. This entity was first described in 2007 as a paraneoplastic syndrome in adult females in association with ovarian teratomas [22]. Since then, it has been described in men, women and children of all age groups, with and without teratomas. Almost 40% of all reported cases are below 18 years of age [6]. Pathogenic IgG1 antibodies bind to the GluN1 subunits of the N-Methyl-D-aspartic acid receptor leading to their internalization. Clinical features include a prodrome in 50% of cases lasting weeks to months comprising fever, malaise, headache, gastrointestinal or respiratory complaints followed by neurological (abnormal behavior, cognitive deterioration, short-term memory loss, seizures, movement disorders, central hypoventilation syndrome), psychiatric (delusions, hallucinations, catatonia) and autonomic dysfunction [23,24]. Younger patients tend to present with seizures and movement disorders compared to adults who present with psychiatric abnormalities [22]. Children with anti-NMDAR encephalitis have multiple symptoms, and monosymptomatic cases are present in only 1% of patients which is why, anti-NMDAR encephalitis is unlikely to be a cause of isolated psychosis and is usually

accompanied by seizures [23]. Seizures, seen in up to 80% of patients, may be focal or generalized, including status epilepticus, and may occur in any stage of the disease [23]. In a study from New Delhi of 15 patients with AIE (age range 2-64 years), seizures were reported in 100% patients [24]. Movement disorders include orofacial dyskinesias, chorea-athetosis, ballismus, rigidity, opisthotonus and tremors [25]. Advanced disease is characterized by stupor, coma, periods of agitation alternating with catatonia as well as autonomic dysfunction. In younger children, behavioral changes may be difficult to discern as they present with temper tantrums, irritability and hyperactivity as opposed to frank psychosis. Unlike adults, the first symptoms are non-psychiatric, ranging from dystonia and seizures to mutism. In a study from Chandigarh that studied patients below 12 years of age with anti-NMDAR encephalitis, the presence of extreme irritability, insomnia and mutism were reported in all the children [26]. Three clinical phenotypes have been described *viz*., the classic form and the psychiatric form (associated with good outcomes) and the catatonia-predominant form (associated with poor outcome) [27].

Atypical forms have also been described with children presenting with dominant autistic regression [28], catatonia and neuroleptic malignant syndrome [29] and gait disorder [30]. The presentation of pediatric anti-NMDAR encephalitis differs from adult AIE in several respects and these are summarized in ***Table* I**.

Overlapping Encephalitis

A recent study showed that some patients with anti-NMDAR encephalitis had an overlap in terms of clinical features or magnetic resonance imaging (MRI) findings with neuromyelitis optica (NMO) [31]. Syndromes with dual-positive antibodies have also started to be recognized, for *e.g.* anti-NMDAR and anti-MOG or anti-AQP4 or anti-D2 receptor positivity, anti-GAD and anti-GABA-A etc [32]. The proportion of anti-GABA-B antibodies with overlap seem to be more. Among 20 patients with anti-GABA-B receptor encephalitis, seven showed overlap with other antibodies [33]. Anti-NDMAR encephalitis may also overlap with opsoclonus syndrome [34].

Seronegative Autoimmune Encephalitis

Only up to 44% of patients with AIE have an antibody-positive status [1]. 'Seronegative but suspected autoimmune encephalitis' has received a consensus definition [1]. The definition includes rapid progression of symptoms, along with exclusion of well-defined AIE syndromes such as typical limbic encephalitis, absence of serum and CSF antibodies along with two of: MRI abnormalities suggestive of autoimmune encephalitis, CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index or brain biopsy showing inflammatory infiltrates, along with exclusion of other causes [35].

When to Suspect Autoimmune Encephalitis?

The diagnosis of AIE should be suspected in all children who develop a polysymptomatic syndrome encompassing encephalopathy, seizures, movement disorders, psychiatric features, gait disturbances and autonomic disturbances. The clinical features suggestive of autoimmune encephalitis include:

- Abrupt onset / rapid decline
- Autonomic instability
- Delirium slipping into catatonia and vice versa
- Urinary/ faecal incontinence
- Cognitive slowing
- Gait and balance disorder
- Relapse after treatment for viral encephalitis
- Seizures that may be in the form of status epilepticus or multifocal drug resistant epilepsy or seizure clusters
- Involvement of multiple domains *eg*. Cognition and

Table I Clinical Features of Anti-NMDAR Encephalitis in Children and Adults

Clinical features	*Adults*	*Children*
Initial feature	Change in mood and behavior, psychosis	Seizures, movement disorders, speech abnormalities, sleep problems
Features at nadir of	Seizures, impaired memory, movement disorders, impaired consciousness	Seizures, movement disorders, change of behavior
Autonomic dysfunction	Arrhythmia, central hypoventilation	Tachycardia, hyperthermia, hypertension
Association	Tumors, post-infective	Post-infective

NMDAR: *N-methyl D-aspartate receptor.*

extrapyramidal system etc.

- CSF may also reveal features of inflammation in the absence of infection.

Features that point away from the diagnosis of AIE include:

- A very chronic or indolent course
- Plateauing of symptoms
- No impairment in activities of daily living
- Cognition remaining intact
- Purely psychiatric symptoms

***Table* II** depicts some differentiating features between autoimmune and infective (viral) encephalitis.

DIAGNOSIS

The diagnosis of AIE is based on the presence of an appropriate clinical syndrome supported by various ancillary investigations. All other possible etiologies should be ruled out along with confirmatory antibody testing. The common differentials include CNS infections, toxins, CNS vasculitis, inborn errors of metabolism, neoplasms and a primary psychiatric disorder. The features supportive of an autoimmune etiology include evidence of CNS inflammation (CSF pleocytosis, elevated IgG index or oligoclonal bands, elevated CSF neopterin), MRI abnormalities and a response to immunosuppressive treatment. Criteria for the diagnosis of anti-NMDAR encephalitis have been proposed by Graus, *et al*. [35]. As per this criteria, probable anti-NMDAR encephalitis can be made if all three of the following criteria have been met: (*i*) Rapid onset (less than three months) of at least four symptoms among psychiatric/behavioral dysfunction, speech abnormalities, seizures, movement disorders, decreased consciousness or autonomic dysfunction; (*ii*) Abnormal EEG/CSF; and (*iii*) Exclusion of other causes. A study evaluating the reliability of these criteria found them to be 90% sensitive and 96% specific for the diagnosis of anti-NMDAR encephalitis in children [36]. Diagnostic evaluation includes the following:

Magnetic Resonance Imaging of Brain

Classic neuroimaging abnormalities in AIE include unilateral or bilateral T2/ FLAIR signal hyperintensities involving the mesial temporal lobe. The large majority of patients (66%) with anti-NMDAR encephalitis do not exhibit neuroimaging abnormalities [37]. Abnormalities in the form of signal hyperintensities may be seen throughout the brain. Transitory cortical enhancement in the absence of restricted diffusion or hemorrhage may also be seen [37]. In patients with normal MRI and typical clinical and EEG picture, positron emission tomography may be useful to highlight involvement of the mesial temporal lobes [38]. In contrast to NMDAR encephalitis, the large majority of patients with limbic encephalitis such as anti-Lgi1 antibodies exhibit mesial temporal hyperintensities and may go on to develop mesial temporal sclerosis on follow-up imaging [39]. The presence of restricted diffusion and contrast enhancement correlated with the development of mesial temporal sclerosis [39]. MRI is mostly abnormal in anti-GABA-A receptor and anti-D2 receptor encephalitis. Most patients with anti-GABA-A receptor encephalitis show MRI abnormality in the form of extensive, multifocal or diffuse cortical and subcortical T2/FLAIR signal alterations. Rapid progression from frontal and temporal T2/FLAIR abnormalities to atrophy and extensive bilateral lesions has been reported in some patients. Majority of patients with anti-D2 receptor encephalitis exhibit bilateral basal ganglia T2/FLAIR signal abnormalities.

Electroencephalography

EEG may show focal or diffuse slowing as well as epileptiform discharges. 30% of anti-NMDAR encephalitis patients may exhibit a typical pattern called 'extreme delta brush' [40].

Table II Differentiating Features Between Autoimmune Encephalitis and Infective Encephalitis

Feature	*Autoimmune encephalitis*	*Infectious encephalitis*
Clinical presentation	Psychosis, language dysfunction, autonomic instability, movement disorder; around 50% may have fever. Rash is not seen	Fever, altered sensorium, seizures; most patients have fever. Rash may appear in HSV/ VZV encephalitis
CSF findings	CSF lymphocytic pleocytosis milder	More severe lymphocytic pleocytosis
MRI findings	MRI may be normal in anti-NMDAR encephalitis.The lateral temporal lobes and insula are less commonly involved; basal ganglia often involved.	Characteristic mesial temporal involvement; Lateral temporal lobe and insula may also be involved, basal ganglia spared.
Treatment	Immunotherapy (+/- tumor removal)	Antiviral agents (acyclovir)

Antibody Testing

Confirmation of the pathogenic antibody forms the basis for diagnosis of autoimmune encephalitis. Those testing positive are deemed 'definite' cases, while those who do not are labelled 'suspected'. These antibodies bind to conformational extracellular epitopes of proteins on the cell surface like receptors, synaptic proteins or ion channels. Their shape and conformation determine antibody binding. Therefore, cell-based assays with live or fixed eukaryotic cells should be used. The importance of the same was highlighted in the false positivity associated with voltage gated potassium channel (VGKC) complex radioimmunoassay because it not only precipitates the target antigens: leucine rich glioma inactivated (LGI1) and contact in associated protein 2 (CASPR2) but also other intracellular antigens [41]. Serum testing for these antibodies is non-inferior to CSF testing, except in the case of anti-NMDAR encephalitis, where CSF testing is more sensitive [42] with CSF sensitivity being 100% (versus 85.6% in serum). In addition, commercial anti-NMDAR testing should be done using assays that test IgG antibodies to the extracellular domain of the NR1 subunit of the receptor. Antibodies such as serum IgA or other antibody types other than IgG, or antibodies to the NR2 subunit, do not necessitate treatment as these are not clinically relevant.

Testing both serum and CSF should be done whenever possible. The utility of follow up evaluation of these antibodies has not yet been ascertained and is therefore not indicated as of now. If diagnosis is delayed or patients have received treatment with plasma exchange or IV immunoglobulin, antibodies might be detected only in CSF. Patients with a protracted clinical course or persistent symptoms might be sero-negative and have persistently raised CSF titres until symptoms improve [43]. Less frequently, long-term follow-up reveals patients who, after recovery, still have high serum titers and absent or barely detectable titers in the CSF. Findings are consistent with a disease in which the immune response is initially triggered systemically by a tumor or other unknown causes and is reactivated and expanded in the CNS.

TREATMENT

Basic tenets that guide the treatment of autoimmune encephalitis are that patients treated with immunotherapy fare better than those not given immunotherapy. Earlier initiation of immune therapy is associated with better prognosis. Lastly, if the patient does not respond to first line therapy, or if the disease is severe or relapsing, treat-ment with a second-line agent improves prognosis [44].

The primary immunomodulation options include steroids, intravenous immunoglobulins or plasma exchange. This may be followed by maintenance therapy in the form of oral steroid taper, monthly pulse steroids or pulse IVIG therapy. Azathioprine and mycophenolate mofetil are often used in maintenance therapy as steroid-sparing agents. Usual duration of maintenance therapy ranges from 6 to 12 months but is individualized. Second line therapy in case of non-response to first line agents includes rituximab. Cyclophosphamide is another second line agent. Third line agents include bortezomib and tocilizumab. Another important tenet is to screen for tumours, especially in adolescent females, due to the association with ovarian teratomas. Additionally, clinicians must consider Subacute sclerosing panencephalitis (SSPE) in the differential as it is a close mimic of AIE, presenting as cognitive decline, seizures, myoclonic jerks, ataxia and extrapyramidal disorders.

First-line Therapy

Corticosteroids form the cornerstone of treatment. They have good penetration across the blood brain barrier and have a broad spectrum of anti-inflammatory activity. They are usually given as a pulse therapy with methylprednisolone (30 mg/kg/d for 3-5 days, maximum 1g/d), followed by sustained oral steroids according to bodyweight (prednisolone 1-2 mg kg/day) followed by slow taper over 6-12 months (in severe syndromes like anti-NMDAR encephalitis), determined by case-based scenario. Intravenous immunoglobulin (IVIG) (2 g/kg given over 5 days) or plasma exchange (PLEX) (5 to 7 exchanges of 50 mL/kg every alternate day) are commonly used as alternatives and occasionally, concomitantly. Evidence, although scarce, has found early PLEX along with corticosteroids to have better outcomes than either alone [45]. No evidence exists regarding the superiority of PLEX *versus* IVIG. However, considering that patients with autoimmune encephalitis are commonly agitated, IVIG might be easier to administer. In a study from Bangalore, 13 children with anti-NMDAR encephalitis were followed up for a mean duration of 10.3 (6.7) months [46]. All patients were administered intravenous methylprednisolone followed by monthly pulses of methyl prednisolone. IVIG and PLEX were administered during the acute phase for inadequate response to methyl prednisolone. The study concluded that Anti-NMDAR encephalitis required prolonged immunomodulatory therapy and methylprednisolone was effective for this purpose [46].

If AIE is suspected, empirical therapy has to be initiated immediately. Waiting for the results of antibody tests is not an essential pre-requisite. If resources are a

constraint, CSF is the preferred sample for antibody testing because it is more sensitive than serum, especially for anti-NMDAR encephalitis [42]. If the patient is unable to afford antibody testing altogether, empirical therapy should be initiated after reasonably excluding alternate causes. ***Fig.* 1** depicts a diagnostic and therapeutic algorithm in children with suspected AIE.

Second-line Therapy

A significant proportion of patients respond to first line therapy, showing benefit of treatment within the first 1-2 weeks of treatment initiation. Non-responders are treated with 2nd line agents *viz*, rituximab or Cyclophosphamide. Rituximab is a chimeric monoclonal antibody against CD20 resulting in B-cell depletion, which leads to reduced pro-inflammatory CD4+ and CD8+ T cell responses [47].

B-cell measurement should be done 2-4 weeks after dosing to check for B-cell depletion (some children may be resistant which entails a substitute treatment) and 3-6 monthly thereafter to look for B-cell repopulation, that may assist redosing, if clinical symptoms persist or a relapse is suspected [48]. Although well tolerated, infusion reactions occur in approximately 12% individuals, and serious adverse events are rare. Dale, *et al*. reported serious adverse events in 4 children out of the 144 treated with it, including two deaths [49].

Cyclophosphamide is the other alternative and has broad cellular immune suppression effects. Monthly intravenous infusions of 500-1000 mg/m^2 body surface area for 6-9 months is the usual course of treatment. The risks of infertility and secondary malignancies are the major limitations to its use. However, these are dependent on the cumulative dose received and doses <7.5 g/m^2 are justified in sick patients. In the case series of Dale et al [49], 58 of the 144 patients received concomitant rituximab and cyclophosphamide without any increase in the adverse effect profile. This provides re-assurance for using both together, if the need arises.

Third-line Agents

Third line agents are needed when both 1st and 2nd line agents fail. Literature regarding their use is limited to general recommendations. Behrendt, *et al*. [50] showed benefit of Bortezomib (protease inhibitor which inhibits the pro-inflammatory signalling cascade) in two adults with severe refractory anti-NMDAR encephalitis. Tocilizumab, an anti-IL6, has also been tried [51] based on the observation of elevated levels of IL6 in the CSF of patients with anti-NMDAR and anti-MOG associated disease [52]. Tatencloux, *et al*. have used intrathecal steroids and methotrexate in pediatric patients with refractory anti-NMDAR encephalitis.

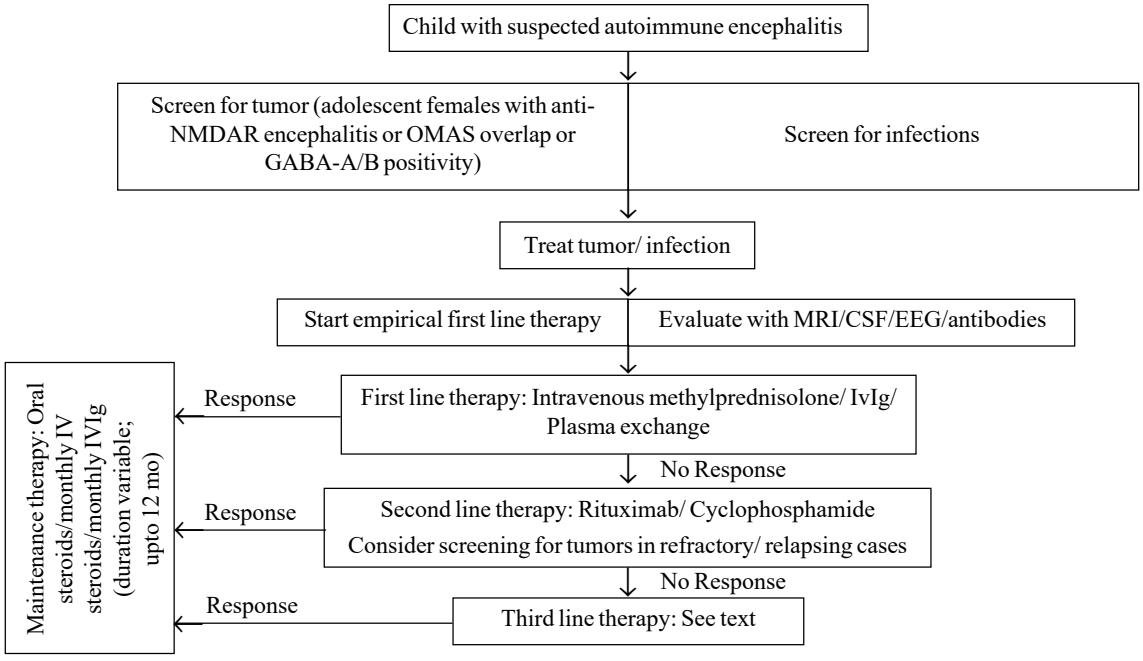

Fig. 1 *Suggested management algorithm for a child with suspected autoimmune encephalitis.*

KEY MESSAGES

- Pediatric autoimmune encephalitis forms a group of acquired disorders with antibodies targeting cell-surface antigens or intracellular antigens that are treatable.
- Pediatric disease manifests differently from adults, with less frequent association with neoplasms and predominance of movement disorders, behavioral abnormalities and seizures.
- Anti-NMDAR encephalitis is the most common pediatric autoimmune encephalitis. It exhibits typical clinical features (limbic encephalitis) as well as imaging abnormalities (mesial temporal signal change) although these may be seen in only 30-40% of patients. Hence, clinical recognition is the key. It responds well to early therapy.
- Treatment involves immunomodulation which should be initiated empirically as soon as the diagnosis of autoimmune encephalitis is suspected, even prior to the availability of antibody test results.

Maintenance Therapy

Mycophenolate mofetil (MMF), methotrexate and azathioprine have been used as steroid-sparing agents in paediatric anti-NMDAR encephalitis. In a systematic review of retrospective cohort data, MMF/ methotrexate/ azathioprine used individually or in varying combinations were associated with a reduced risk of relapse if started after the first event rather than after subsequent ones, and were reasonably safe [54].

Other Measures

Symptomatic therapy: Symptomatic management should be given along with immunosuppressive treatment. Sedating agents are used to induce and maintain sleep, relieve agitation and emotional imbalance. Benzodiazepines, anti-epileptics, clonidine and chloral hydrate are commonly used for this purpose. Neuroleptics are best avoided due to the high incidence of adverse effects like rigidity and neuroleptic malignant syndrome.

Management of relapses: Relapses tend to be uncommon in AIE. However, when they do occur, they are managed with repeat dosing of the first line agents. In these cases, there is concern of ongoing inflammatory activity, and hence, chronic immunosuppressive therapy such as azathioprine, mycophenolate or repeated dose of rituximab may be considered.

PROGNOSIS

Most patients with anti-NMDAR encephalitis respond to immune therapy. A study with a median follow up of 24 months showed that 94% patients responded within four weeks to first line immunotherapy/ tumour removal [23]. Of the patients who failed first line therapy, 57% underwent second line therapy and had better outcomes. At 24 months follow up, 81% patients had a good outcome, with mortality in 6%. Outcomes continued to improve up to 18 months following treatment. Predictors of good outcome included early treatment and lack of intensive care unit admission.

Relapses in AIE tend to be uncommon and the approximate percentage varies according to the subtype being dealt with. Approximately 12% of patients with anti-NMDAR encephalitis were found to relapse in initial descriptions [42]. However, this has reduced, probably due to the use of second line therapies and chronic immunosuppression, which lead to the alteration in the natural history of disease. The patients that do relapse tend to be mono-symptomatic, presenting with seizures or movement disorders commonly, unlike the initial presentation which almost always tends to be polysymptomatic. Chronic immunosuppression with mycophenolate, azathioprine or re-dosing with rituximab is done in this scenario.

FUTURE DIRECTIONS

Pediatric autoimmune encephalitis is a challenging condition to diagnose and treat and these are suffers from several lacunae in evidence. More literature is required on the diagnosis of suspected autoimmune encephalitis in children with seronegativity as well as on overlap syndromes. Duration of optimal therapy in children is also not clear. Another challenging aspect of therapy that demands research is the management of refractory autoimmune encephalitis. However, it is heartening that with the current status of knowledge, appropriate and timely management can ensure satisfactory outcomes in the majority.

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Web Table I Features of Autoimmune Encephalitis in Children

Antibody syndrome	*Antigen*	*Clinical features*	*Evaluation*	*Additional findings*	*Tumor-association*
Antibodies to cell surface antigens					
Anti-NMDAR	Amino terminus of NR1 subunit of NMDA receptor	Seizures, encephalopathy, dyskinesias, autonomic dysfunction, mutism.	Mesial temporal hyperintensity on MRI; Extreme delta brush on EEG	May follow herpes simplex encephalitis	Present Ovarian teratoma
Limbic encephalitis	Component proteins of the VGKC complex, leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (Caspr2)	Limbic encephalitis, fever-related epileptic encephalopathy, status epilepticus and drug-refractory epilepsy.Caspr2-encephalitis includes features of peripheral nerve hyperexcitability including neuromyotonia and Morvon syndrome.	Mesial temporal/ basal ganglia hyperintensity, white matter signal changes on MRI.	Typical faciobrachial dystonic seizures in anti-LGI1.Antibodies to VGKC complex may be positive in the absence of antibody positivity or LGI1 or CASPR2	Rare- thymus, lung
Anti-GABA-A receptor	Anti-gamma -amino butyric acid type A (GABA-A) receptor	Seizures and status epilepticus, movement disorders and memory impairment.	Mesial temporal hyperintensities on MRI.	A few cases described in children	Rare- thymus, Hodgkin lymphoma
Anti-GABA-B receptor	Anti-gamma -amino butyric acid type B (GABA-B) receptor	Limbic encephalitis or seizures.	Mesial temporal hyperintensity, cortical-subcortical hyperintensities on MRI.	Few reports in adolescent females	Lung, thymus
Anti-Glycine	Alpha-1 subunit of the receptor	Progressive encephalomyelitis with rigidity and myoclonus, as well as optic neuritis.	MRI usually normal	Reported in only a few cases of pediatric AIE.	None
Anti-D2 receptor	Amino terminus of dopamine D2 receptor	Parkinsonism, dystonia, lethargy, psychiatric intensities symptoms.	Bilateral basal ganglia hyper- may be seen.	Rare	–
Anti-AMPA receptor	Target the glutamate receptor (GluR1) or (GluR2) subunit of the AMPA receptor	Limbic encephalitis		Extremely rare in children	–
Anti-mGluR5	Anti-metabotropic glutamate (mGluR5) receptor	Limbic encephalitis	May exhibit hippocampal hyperintensity on MRI.		Hodgkin lymphoma (Ophelia syndrome)
Anti-Neurexin-3 alpha	Neurexin-3 alpha	Anti-NMDAR like syndrome, orofacial dyskinesias, seizures, encephalopathy		After the initial report, findings not replicated	
Anti-DPPX	Dipeptidyl peptidase-like protein	Stiff-person syndrome, myoclonus, ataxia, tremor,		Diarrheal symptoms may be present	–

Cont....

From pre page

Antibody syndrome	*Antigen*	*Clinical features*	*Evaluation*	*Additional findings*	*Tumor-association*
		parkinsonism, opsoclonus myoclonus			
Anti-glutamate receptor	Glutamate receptor delta 2	Opsoclonus-myoclonus-ataxia syndrome (OMAS)	–	–	–
Antibodies to intracellular antigens					
Anti-Hu	Anti-neuronal nuclear antigen 1	Limbic encephalitis, drug refractory epilepsy	–	–	Paraneoplastic (neuroblastoma) and non-paraneoplastic
Anti-Ma2	Intracellular onconeural protein	Limbic encephalitis/ brainstem or diencephalic dysfunction	–	Infrequent in children	Testicular tumors in males (young adults)
Anti-GAD	Glutamic acid decarboxylase (responsible for GABA synthesis)	Neuropsychiatric and memory impairment, focal seizures, pediatric stiff-person syndrome	MRI usually normal. May have hyperintensities in hippocampus, cerebellum.	Infrequent in children	Not described