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ORIGINAL ARTICLE

Clinical Characteristics and Follow-up of South Indian Children with Autoimmune Encephalopathy

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Abstract
Objective To describe the clinical characteristics of a cohort of south Indian children with probable autoimmune encephalopathy from a tertiary care academic hospital and to compare this data with the existing literature.
Methods Patients with encephalopathy plus one or more of neuropsychiatric symptoms, seizures, movement disorder or cognitive dysfunction were identified. Common infectious causes were excluded. Clinical characteristics, investigations, management and outcome were analyzed.
Results Thirteen patients were included in the study; 12 were females (92.3 %) and mean age was 9.6 y. Most common presentation was behavior change (13 patients) followed by seizures (11 patients). Three patients showed lymphocytic pleocytosis in CSF and one patient had oligoclonal bands. Initial MRI was normal in all patients except in one. Most common EEG abnormality was mild background slowing. Only one child had ovarian tumor. S.NMDA receptor antibody was positive in 10 patients (83 %), and all of them received immunotherapy. Six out of 13 children were followed up for more than 1 y (mean – 21 mo). Recurrence was noted in 4 out of 6 patients (66 %). On last follow-up, good recovery was seen in 2 children (33 %), moderate disability in 3 (50 %) and severe disability in 1 (16 %).
Conclusions The clinical characteristics and outcome of one of the largest single center cohort of Indian children with autoimmune encephalopathy is reported. Autoimmune encephalopathy should be considered as a differential diagnosis in the acute and subacute encephalopathies of childhood and treating pediatrician should be aware of this entity.

Keywords Encephalopathy · Autoimmune · NMDAR · Seizures

Abbreviations

NMDAR	N-methyl-D-aspartate receptor
VGKC	Voltage-gated potassium channel antibodies
EEG	Electroencephalography

Introduction

Autoimmune encephalopathy is increasingly being recognized in children. Even though initially described as a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation in four young women with ovarian teratomas [1], subsequent reports have clearly expanded this phenotype [2, 3].

Several types of autoimmune encephalopathies are described based on the detection of specific antibodies like antibodies against N-methyl-D-aspartate receptor (NMDAR), anti-voltage-gated potassium channel (VGKC) and other central nervous system (CNS) antigens such as glutamic acid decarboxylase (GAD) [2], the AMPA receptor (AMPAR) [4] and the γ-amino-butyric acid-B receptor (GABAB-R). Based on the available reports, most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and

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language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic and breathing instability. The disorder predominantly affects children and young adults, occurs with or without tumor association, and may respond partially to treatment with relapses during follow-up [5]. It has been recognized that some patients presenting with encephalitis show full recovery after treatment with steroids or immune modulatory therapy, even in the absence of confirmatory serology, indicating an autoimmune cause [4, 6].

The aim of the index study was to characterize the clinical features and outcome of a cohort of children with clinical and laboratory features of probable autoimmune encephalopathy.

Material and Methods

All children under 18 y with clinical features of probable autoimmune encephalitis who presented to the tertiary care pediatric neurology department from January 2011 through June 2014 were included in this study. The inclusion criteria were features of encephalopathy plus one or more of neuropsychiatric symptoms and abnormal behavior like temper tantrums, irritability, seizures, movement disorder or cognitive dysfunction. Children with cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) and/or blood tests suggestive of infective or metabolic etiology were excluded from the study.

The baseline demographic data and clinical characteristics of all the patients were analyzed. All of them had underwent extensive diagnostic studies including complete blood count, renal function test, liver function test, thyroid function test, S. ammonia, S. lactate, peripheral smear, cerebrospinal fluid analysis (cell count, biochemistry, gram staining, culture, HSV type1 PCR, Tb PCR, oligoclonal bands, CSF NMDAR), MRI brain, MRI/CT abdomen, CT chest, antithyroid antibodies and vasculitic workup (antithyroid peroxidase, antithyroglobulin, antinuclear antibody, anti dsDNA, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies) during the first admission. The Leucine-rich Glioma Inactivated 1 Protein (LGI1) antibodies, Contactin Associated Protein 2 (CASPR2) antibodies and NR1 subunit of NMDA receptor antibodies were tested in the serum by indirect immunofluorescence on human embryonic kidney cell 293 transfected with corresponding antigens (Euroimmun AG, Lubeck, Germany). Immunofluorescence at a dilution of 1:10 was taken as positive as instructed by the manufacturer. CSF NMDA receptor antibody was done in 4 patients. All the tests were done before initiating immunotherapy. Glasgow outcome scale was used to denote the outcome for patients who had completed one year of follow-up [7].

Results

Thirteen children were identified with suspected autoimmune encephalopathy during the study period. All except one were female. Mean age at the disease onset was 9.6 y (range 3 y - 17 y). Most common presenting symptom was change in behavior and personality, which was seen in all the patients. Behavior changes most commonly noted were irritability, decreased speech output and anger outbursts. Two children presented with visual and auditory hallucinations. One patient had severe encephalopathy with poor Glasgow coma scale (GCS) (6/15).

Seizures were seen in 11 out of 13 children (84 %); generalized seizures were seen in 7 out of 11 children (63 %); focal seizures were seen in 4 (36 %). Two children had generalized refractory seizures including status epilepticus during the hospital stay, requiring multiple antiepileptic drugs. One child had continuous left sided focal seizures lasting for more than 48 h. Ten out of 13 (76 %) developed dyskinesia, most common being orofacial dyskinetic movements and all were noted during the hospital stay. None of the patients had autonomic disturbances. Six out of 13 patients (46 %) required ventilation either due to poor GCS or multiple seizures.

All patients were extensively investigated during the hospital stay as described in the methodology. Baseline hematological and biochemistry workup were within normal limits in all the children. CSF was abnormal in 3 out of 13(23 %) children mainly with lymphocytic pleocytosis along with positive oligoclonal bands in one patient. In two cases, CSF was traumatic and further analysis was not performed. Brain imaging studies with MRI were performed in all the children. Only one patient had abnormal initial MRI in which T2 hyper intense lesions in right hippocampus and temporal lobe were seen along with cerebral atrophy. EEG was done in all the patients and showed mild to moderate background slowing in 11 (84 %) children. One child had significant focal delta slow waves over the right hemisphere, suggesting a focal encephalopathy which has been reported earlier as a case report [8]. Two children had additional epileptiform abnormalities; occipital spike in one and right centrotemporal spike in the other. One patient (7 %) had ovarian teratoma which was subsequently removed. Polycystic ovaries were detected in another one. Antithyroid antibodies and vasculitic workup were negative in all patients. S.NMDAR antibody levels were done in 12 out of 13 children by indirect immunofluorescence assay. Ten children (83 %) were positive for S.NMDAR antibodies. CSF NMDA antibody levels were done in 4 patients which were all positive. S.VGKC antibody level was assayed in 7 children and all were found to be negative.

All the children received both pulse dose methyl prednisolone (30 mg/kg/d for 5 d) and IVIG (0.4 g/kg/d for 5 d) during the hospital course. Seizures and behavior problems were managed symptomatically with antiepileptic drugs and

antipsychotic medications. Mean period of initial hospitalization in the authors' center was 25.2 d (range 5 d - 3 mo).

Six out of 13 children completed one year follow-up during the last review. Mean period of follow-up was 21 mo. The authors were able to follow-up two children for more than 2.5 y. During follow-up, recurrence of symptoms was noted in 4 out of 6 patients (66 %) requiring hospitalization. Out of these 6 children, three had one relapse each during follow-up. One child had several relapses requiring multiple admissions. Most of the relapses were in the form of seizures and worsening of behavior. At the time of last follow-up, Glasgow outcome scale [20] showed good recovery in 2 children (33 %), moderate disability in 3 (50 %) and severe disability in 1 (16 %). Table 1 summarizes the clinical presentations, investigations and follow-up data.

Discussion

Autoimmune forms of encephalopathy are now well recognized entities in children but there are very few studies on clinical features, outcome and follow-up to assess the natural history of this disease in Indian children. There may be many children with strong clinical suspicion of autoimmune encephalopathies but are negative for presently available antibodies. Recent studies have shown that antibody negative autoimmune encephalitis behaves similarly in initial clinical presentation, response to immunotherapy and the long term outcome, suggesting the possibility of a shared autoimmune mechanism [2, 9]. The authors have included seronegative cases of autoimmune encephalopathy in this cohort due to similarity in clinical presentation and outcome to the antibody positive cases.

The most common and well described entity among autoimmune encephalopathies in children is anti-NMDAR encephalitis; however, exact incidence of anti-NMDAR encephalitis is unknown. A multicentric study on encephalitis in UK showed anti-NMDAR encephalitis as second most common immune-mediated entity after acute disseminated encephalomyelitis [10]. Dalmau et al. had 400 patients with anti-NMDAR encephalitis in 3 y suggesting that this disorder might have a relatively high prevalence [5]. The sex ratio of this disease is highly skewed towards females as seen in several case series [2, 5, 11]. The trend seems to be similar in children as evidenced by the index study. In the index series, mean age was found to be 9.6 y (range 3y -17y) and the youngest one was 3-y-old.

The clinical picture is more or less similar compared to both adults and older children although there are some important clinical differences between these two groups. Younger patients are less likely to have tumors. Behavioral and speech problems, seizures, and abnormal movements are common early symptoms in children. Dysautonomia and hypoventilation are less frequent or less severe in children, according to some earlier studies [11]. There is a recent article from India [12] showing similar demographic data of female predominance with youngest patient of 5 y of age. The most common symptom was cognitive impairment with seizures. This cohort conforms to these earlier reports.

Children with anti-NMDAR encephalitis may have non-specific initial symptoms of headache, fever, nausea, vomiting, diarrhea, or upper respiratory-tract symptoms. Within several days, behavioral changes were noted in the form of temper tantrums, hyperactivity, or irritability. In the index series, the most common presenting symptoms were changes in behavior, in the form of irritability, decreased speech output and anger outbursts. These behavior changes may be missed during the initial days. In some children, the initial manifestations are often non-behavioral like seizures and status epilepticus, dystonia, reduction in verbal output and mutism. Both generalized and focal seizures may present at early stages of the disease and sometimes may be the initial presentation. Usually the frequency and intensity of the seizures decrease as the disease evolves. However, seizures and status epilepticus may resurface at any time during the illness [5]. In the present series, 30 % of children had seizures at the onset of the disease. Generalized seizures were seen more common than focal seizures. Current series shows that seizures may sometimes become refractory requiring multiple antiepileptic drugs.

Next phase of the illness is characterized by abnormal movements. Oro-lingual-facial dyskinesias are the most characteristic movements, but other movement disorders like choreoathetosis, oculogyric crisis, dystonia, rigidity, and opisthotonic postures are also well described [5]. Most of the children in the index series developed abnormal movements during the late phase of illness. All had characteristic orofacial and limb dyskinetic movements. Other movements noted in these children include opisthotonic posturing, pelvic thrusting, abnormal limb movements, tongue protrusion and tongue biting. In the index series, one child had severe tongue mutilation requiring removal of teeth and multiple dental procedures.

Children may also have autonomic manifestations including hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, but these are less common compared to the adult population. In the present cohort, none of the patients had autonomic disturbances. Almost all children had prolonged hospital stay (mean stay was 25.2 d) indicating the chronicity of the disease and need for continued long term support.

Brain MRI may be normal in most of the cases especially in the initial period of illness. T2 hyper intensity might be seen in the hippocampus, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, in the spinal cord [12, 13]. The findings are usually mild or

Table 1 Summary of clinical presentations, investigations and follow-up data of the patients

Cases	Sex/age	Behavior/Dyskinesia/Seizures	CSF	MRI brain/abdomen	EEG	S.NMDA/ CSF.NMDA	Follow-up period/no. of recurrences	Glasgow outcome scale disability
1	F/13y	(+)/(+)/GTCS	Cells −18, All mononuclear	N/Mature cystic teratoma	N	(+)	18 mo/One	4
2	F/10y	(+)/(+)/GTCS	N	N	N	Not sent	36 mo/One	4
3	F/17y	(+; Hallucinations)/(+)/GTCS	N	N/Polycystic disease	Mild dysfunction	(−)	24 mo/One	5
4	F/5y	(+)/(+)/Recurrent focal seizures	N	N	Mild dysfunction	(+)	21 mo/Nil	5
5	F/9y	(+)/(−)/Focal seizures	N(OCB+)	N	Right occipital spikes	(+)	19 mo/Nil	4
6	F/15y	(+)/(+)/Recurrent GTCS	Cells - 45, mononuclear, Protein - 62	T2 HT in right hippocampus, cortical atrophy/hepatomegaly	Right centro-temporal spikes	(−)	38 mo/Five	3
7	M/3y	(+)/(+)/Focal seizures	N	N	Mild dysfunction	(+)	6 mo/Nil	N/A
8	F/13y	(+)/(+)/(−)	Cells – 70, All mononuclear	N	Moderate dysfunction; slowing	(+)	7 mo/Nil	N/A
9	F/6y	(+)/(+)/GTCS	Traumatic	N	Mild dysfunction	(+)	9 mo/Nil	N/A
10	F/12y	(+)/(−)/GTCS	Traumatic	N	Right focal spikes	(+) CSF/serum	5 mo/Nil	N/A
11	F/5y	(+)/(−)/GTCS	N		Mild dysfunction	(+) CSF/Serum	3 mo/Nil	N/A
12	F/5y	(+)/(+)/(−)	Cells - 7/mm^3, rest normal	N	Moderate dysfunction	(+) CSF/serum	Nil	N/A
13	F/12y	(+; hallucinations)/(+)/focal seizures.	N	N	Moderate degree dysfunction; right focal spike	(+) CSF/serum	2 mo/Nil	N/A

F Female; *M* Male; *GTCS* Generalized tonic clonic seizures; (+) Positive; (−) Negative; *N/A* Not applicable; *N* Normal; *NMDAR* N-methyl-D-aspartate receptor; *CSF* Cerebrospinal fluid; *MRI* Magnetic resonance imaging; *OCB* Oligoclonal bands; *EEG* Electroencephalogram

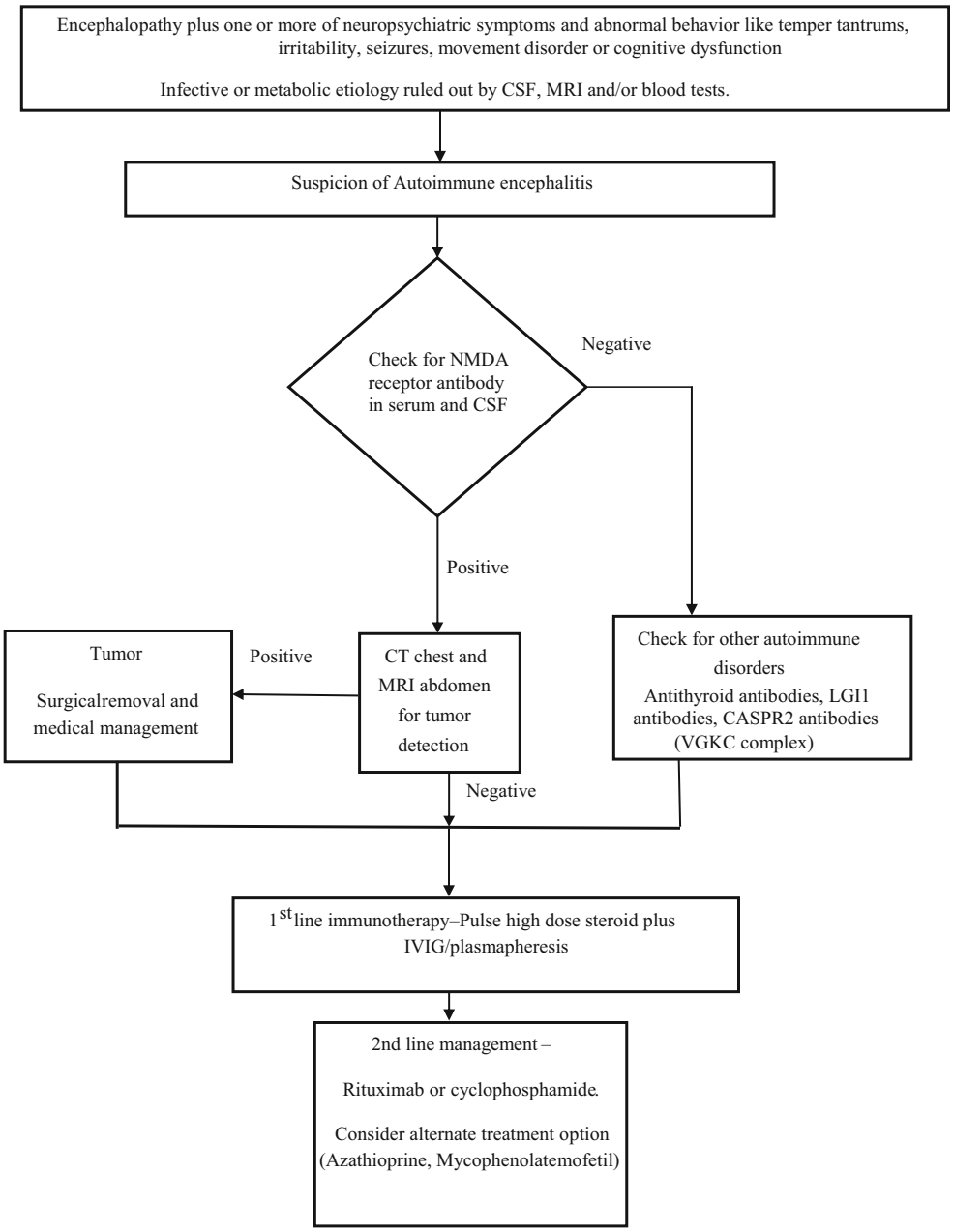

Fig. 1 Flow diagram for management of autoimmune encephalitis. *CSF* Cerebrospinal fluid; *CT* Computed tomography; *MRI* Magnetic resonance imaging; *NMDAR* N-methyl-D-aspartate receptor; *LGI1* Leucine-rich Glioma Inactivated 1 Protein; *CASPR2* Contactin associated protein 2; *VGKC* Voltage gated potassium channel complex

transient and can be accompanied by subtle contrast enhancement [14]. In severe cases, diffuse brain atrophy may be seen on follow-up [15]. In the index study, only one child showed MRI abnormality in right hippocampus and temporal lobe along with cerebral atrophy. This study emphasizes that initial imaging modalities may be normal or nonspecific in most of the cases.

Even in the initial phase of the illness, electroencephalogram (EEG) usually shows non-specific back ground slowing, sometimes with electrographic seizures [12, 14]. In the index study, most common EEG abnormality was mild to moderate diffuse slowing, though focal specific epileptiform abnormalities were also seen in two children. The cerebrospinal fluid (CSF) studies are usually normal in NMDAR encephalitis [12, 14]. During the course of disease CSF may become abnormal and show moderate lymphocytic pleocytosis, normal or mildly increased protein concentration and CSF-specific oligoclonal bands [16].

Dalmau et al. in their series of 400 patients showed that the association of ovarian tumor in children with anti NMDAR encephalitis is relatively rare compared to the adult population [5]. In the present cohort, authors found mature cystic ovarian tumor in only one child which was subsequently removed.

Treatment of autoimmune encephalopathy is mainly immunomodulation. Current treatment regimen is to initiate high dose steroid (IV methyl prednisolone) followed immediately by IVIG or plasma exchange as the first line therapy. Prognosis is better if ovarian tumor is detected and removed

early [11, 14]. In case of poor response, delayed diagnosis, severe disease or recurrent relapses, second line therapy is usually indicated. Drugs commonly used are rituximab or cyclophosphamide or both [11, 17, 18]. Some patients may have spontaneous recovery without treatment or tumor removal although this response may be delayed [19]. Second line therapy was offered to one child with frequent relapses but was declined by parents due to financial reasons. The institutional protocol for the management of suspected autoimmune encephalitis is given in Fig. 1.

Recovery is a gradual process and may take weeks to months [9], while serum titers diminish with time; CSF titers decline at much slower rate [14]. Patients with tumors tend to have higher antibody titers than those without tumors. Milder symptoms also tend to correlate with lower titers. Older children and young adults with no identifiable tumor should undergo yearly screening by pelvic MRI [5, 11].

There are very few clinical series of autoimmune encephalopathy reported from India. A cohort of 11 children with anti NMDA receptor encephalitis from a tertiary center in north India has been reported recently [20]. The mean age at presentation was 9 y with a slight female predominance (1.2:1). The commonest mode of presentation was progressive extrapyramidal syndrome with global neuroregression. CSF, EEG and imaging studies were similar to the present cohort. Fifty-eight percent showed significant response to steroids and intravenous immunoglobulins. However, the long term course was much better compared to the index series. No relapse was seen even after 2 y of follow-up and none of the children showed any evidence of malignancy.

There are very few studies in children to assess the natural history of autoimmune encephalitis. Relapses in children are usually less compared to adults [2, 11]. In the index study, two-third of the children, who completed follow-up for more than one year, had re-admissions with recurrence of symptoms like seizures and changes in behavior. Majority of these children were admitted only once during the follow-up period. Only one child had multiple relapses. It is very difficult to differentiate the symptoms of neurological sequelae of brain damage from ongoing active disease, especially in children with severe disability. However, there is a real chance that some of these children may have a chronic/relapsing immune response. The estimation of quantitative antibody titres may be one way of identifying them.

In a large series by Dalmau et al. [5], about 75 % of patients with NMDAR antibodies recovered or had mild sequelae, all other patients remained severely disabled or died [14]. The present study with limited follow-up data showed mild to moderate disability in the majority. Despite on similar treatment protocol, both the short term and long term outcome varied significantly. This may be attributed to a differing spectrum of severity. There is also be a possibility that some other unidentified pathological processes might be affecting the outcome.

Conclusions

Autoimmune encephalitis is increasingly being recognized as a cause for sub-acute encephalopathy in children. This clinical series reports the characteristics of one of the largest single center cohorts from India on this clinical entity and adds to the current body of literature on the subject. This disease may have a relapsing/chronic clinical course with a variable response to immunotherapy. Pediatricians should be aware of this entity for proper initial care of the affected children.

Contributions YS: Data collection, analyzing and preparation of the manuscript; VKP: Conceptualized, supervised the data and will act as guarantor for the paper; AW and SP: Data collection; AG and SK: Critically reviewed the literature.

Compliance with Ethical Standards

Conflict of Interest None.

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