Original Research Article

Clinico-Laboratory Profile of Autoimmune Encephalitis Amongst Children at Tertiary Care Hospital

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Abstract

Introduction: The causes of encephalitis in children are numerous and is often thought to be mediated by infections, commonly viral. Children with acute encephalitis often undergo extensive testing for infectious etiologies without discovery of a causative agent. In the past 10 years growing number of non-infectious causes like autoimmune encephalitis have been identified making them one of the important causes of encephalitis in children. Hence, we planned this study.**Aims and objectives of The Study:** To study the clinical and laboratory profile of children with autoimmune encephalitis.**Material and methods:** This prospective observational study on clinical and laboratory profiles of children with autoimmune encephalitis was conducted from October 2018 to April 2020 at Indira Gandhi Institute of child health, Bengaluru. Children 1year to 18years of age attending a tertiary care super specialty children hospital who fulfil the diagnostic criteria of possible autoimmune encephalitis were considered. History clinical examination and laboratory investigations were carried out with a pre-designed proforma after obtaining the consent from the care givers. Study population were treated with the first, second- and third-line immunotherapy and followed up for 6 months.
Results: Out of 30 cases of suspected autoimmune encephalitis, 9 (30%) were serologically confirmed anti-NMDAR encephalitis and 21(70%) are seronegative. 15(50%) were males and 15 (50%) were females. Clinical symptoms were insidious in onset in 23(76%) children. Mean age of onset of symptoms was 6 y. various clinical features seen were seizures 24 (80%), movement disorders 15(50%), speech disturbances 19(63%) and psychiatric symptoms 10 (33%). sleep disturbances 7(23%) and autonomic dysfunction 3(10%). One child had preceding herpes simplex viral (HSV) encephalitis. MRI Brain was abnormal in 14(46%), cerebral atrophy in 2(14%), cystic lesion in temporal horn in 1(7%), diffusion restriction in bilateral frontal lobe in 1(7%), hyperintense signal changes in thalamus in 2(14%) and periventricular white matter signal changes in 8(57%). EEG was abnormal in 16(53%). 13 (43%) had CSF lymphocytic pleocytosis. out of 30 cases of autoimmune encephalitis 12 cases responded to iv methylprednisolone,8 cases each to IVIG and rituximab. Out of 30 cases 4 required mechanical ventilation among which 2cases were seropositive and 2 cases were seronegative AIE. Among 30 cases, 25 cases (83%) improved among which 17 cases were seronegative, and 8cases were seropositive. 3 cases left against medical advice and two children expired due to ventilator associated pneumonia each being seropositive and seronegative. Cases were followed up for 6 months. Mean duration of hospital stay was found to be 15 days. Screening for tumors was done in all and was found to be negative. Early diagnosis and initiation of immunosuppressive therapy has shown that 16(53%) cases had partial improvement, 9(30%) cases had full improvement. Hence timely initiation of immunosuppressive therapy has shown reduction in severity of the disease and improves the overall outcome of the disease. **Conclusion:** Clinical history and examination play an important role in diagnosis of autoimmune encephalitis. laboratory evidence of CSF analysis, autoantibody panel in serum and CSF, MRI brain as imaging modality further strengthens the diagnosis of autoimmune encephalitis. Early diagnosis and timely intervention is essential for long term outcome. However, it is never too late for diagnosing and treating this entity.

Keywords: seronegative autoimmune encephalitis, anti-NMDAR, methyl prednisolone, IVIG, rituximab.

Introduction

Autoimmune encephalitis is a newly recognized and treatable cause of encephalitis in children. The causes of encephalitis in children are numerous and is often thought to be mediated by infections, commonly viral[1,2].Children with acute encephalitis often undergo extensive testing for infectious etiologies without discovery of a causative agent[3].A Multicenter study on epidemiology and etiology of encephalitis found out that 63% of patients remained without an etiology even after a battery of tests for 16 potential infectious agents[4].In the past 10 years growing number of non-infectious causes like autoimmune encephalitis have been identified making them one of the important causes of encephalitis in children. Autoimmune encephalitis results from antibodies against neuronal proteins[5]. Clinically it can be defined as a clinical syndrome comprising a complex of encephalopathy, cognitive disturbance, mood/personality changes, seizures and movement disorders[6]. A multicenter study in the United Kingdom demonstrated that 4 % of patients with encephalitis had NMDA receptor antibodies[7]and it is the leading cause of autoimmune encephalitis in children. The recent

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discovery and availability of immune markers has led to a definite diagnosis in many of these children and it makes the spectrum of autoimmune encephalitis an exciting and a potential area of research to the clinician as it is a treatable cause amenable to immunosuppressive therapy. There are only retrospective case series of autoimmune encephalitis in children are available in literature from India which also predominantly included only NMDAR positive cases.There is no Indian data on antibody negative autoimmune encephalitis children. No single prospective pediatric study to the best of our knowledge has been done in India considering autoimmune encephalitis spectrum as a whole. So, it is evident that there is paucity of literature regarding the spectrum of autoimmune encephalitis in children and there is an urgent need to bridge this knowledge gap. Early recognition and prompt management leads to promising outcomes; Hence, this study has planned with objectives of describing the clinical and laboratory profile of autoimmune encephalitis.

Aims and Objectives

To study the clinical and laboratory profile of children with autoimmune encephalitis.

Materials and Methods

Children with autoimmune encephalitis admitted to Indira Gandhi Institute Child Hospital, Bengaluru were taken for the study.

Study Design: Hospital based prospective observational study

Study Period: From October 2018 to April 2020

Place of Study: Indira Gandhi Institute of Child Health, A Tertiary Care superspeciality children Hospital, Bengaluru.

Sources of data: Children 1year to 18years of age attending Indira Gandhi institute of child health, a tertiary care super speciality children hospital who fulfil the diagnostic criteria of possible autoimmune encephalitis.

Methodology

All children who fulfil the inclusion criteria of possible autoimmune encephalitis who are both autoantibody positive as well as negative were enrolled into the study.

Autoantibody negative cases who fulfilled the criteria of autoantibody negative autoimmune encephalitis only were enrolled into the study. Written, informed consent was taken from parents of children before enrolment into the study.

The cases under the above-mentioned duration was admitted and the details of the case was filled in the proforma.

Following investigations were carried out if and when required with prior consent of the patient as a part of routine care in diagnosis and management of autoimmune encephalitis.

1. Complete hemogram
2. ESR
3. Arterial blood gas analysis
4. Ammonia/lactate
5. Tandem mass spectroscopy
6. RFT/LFT/serum electrolytes
7. Quantitative CRP
8. LP-CSF
9. CECT
10. EEG
11. MRI BRAIN
12. USG ABDOMEN
13. CHEST X-RAY
14. CSF – AUTOANTIBODIES
15. SERUM AUTOANTIBODIES

Management of these children was done based on first line therapy being iv methyl-prednisolone 30mg/kg/dose for 5days and second line therapy being IVIG 2gm/kg, third line therapy being rituximab dose 375mg/m2. Followed by oral steroids for 2months.

The data will be collected at the time of admission and the proforma were completed at the time of discharge. The follow up data were collected at 1 month, 3 months and 6 months after discharge

Inclusion Criteria

Children with sub acute onset (<3 months) of working memory deficits, altered mental status or psychiatric symptoms.

Children having at least one of the following features

a. New focal CNS findings
b. Seizures (new onset)
c. CSF pleocytosis (more than 5 cells permm3 in white cell count)
d. MRI features suggestive of autoimmune encephalitis (involvement of medial temporal lobes and hippocampus)

Exclusion Criteria

Central nervous system Infection
Septic Encephalopathy
Metabolic Encephalopathy
Inborn Errors of Metabolism

Results

Table 1: Case Distribution of Anti-NMDA Receptor Positive and Negative Autoimmune Encephalitis In The Study Population

Anti-N-methyl-D-aspartate receptor		
	Frequency	**Percent**
Neg.	21	70.0
Pos.	9	30.0
Total	30	100.0

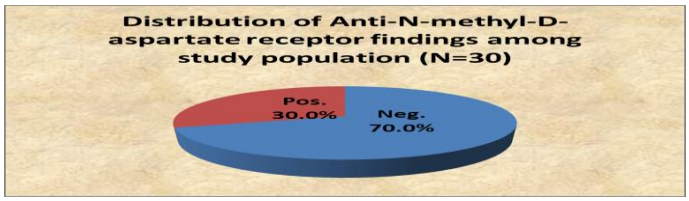

Fig 1: Case Distribution of Anti-NMDA Receptor Positive And Negative Autoimmune Encephalitis In The Study Population

Among 30 diagnosed cases of AIE, it was found that seronegative AIE was found in 21(70%) and seropositive AIE was found in 9(30%)

Table 2: Age distribution and mean age of the study population

Age	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	n	%	n	%	n	%	
1-5 yrs	13	61.9%	5	55.6%	18	60.0%	0.866
6-10 yrs	5	23.8%	2	22.2%	7	23.3%	
11-16 yrs	3	14.3%	2	22.2%	5	16.7%	
Mean ± SD	6.1 ± 4.588		5.8 ± 3.854		6.0 ± 4.316		0.886

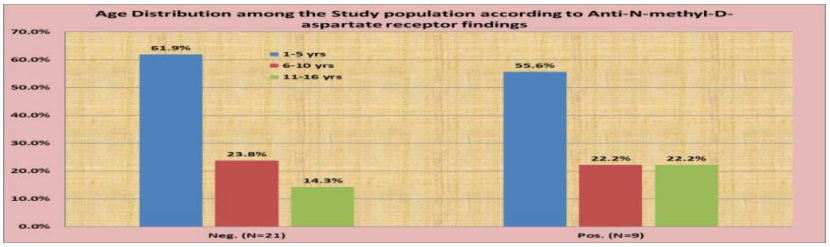

Fig 2: Age Distribution and Mean Age of the Study Population

Among 30 children from 1-16 years formed the study group. 18 (60%) were in the age group of 1-5 years,7(23%) in 6-10year age group,5(16%) were between 11-16year age group. The mean age was 6 years.

Table 3: Sex Distribution of the Study Population

Gender	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	n	%	n	%	N	%	
Male	12	57.1%	3	33.3%	15	50.0%	0.213
Female	9	42.9%	6	66.7%	15	50.0%	

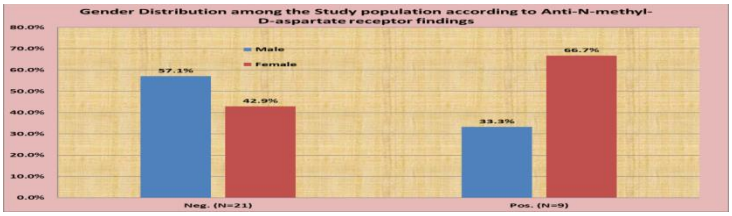

Fig 3: Sex Distribution of the Study Population

Out of 30 children, 15(50%) were males and 15(50%) were females. Male: Female ratio was found to be 1:1.

Table 4: Onset of Symptoms in the Study Population

Day of Presentation From Onset of Symptoms	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	N	%	N	%	n	%	
Acute (<=6 Days)	5	23.8%	2	22.2%	7	23.3%	0.913
Sub acute (7-14 Days)	6	28.6%	2	22.2%	8	26.7%	
Chronic (>=15 Days)	10	47.6%	5	55.6%	15	50.0%	

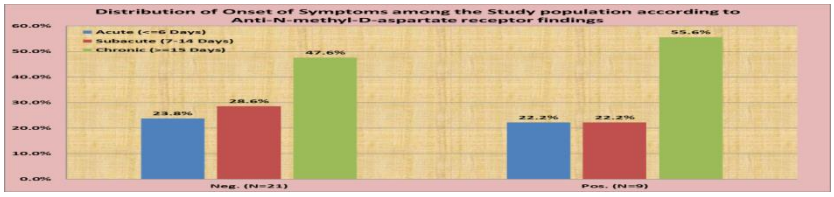

Fig 4: Onset of Symptoms in the Study Population

Out of 30 cases, 15(50%) children presented above 15 days to the hospital from the onset of symptoms, 8(26%) cases between 7 – 14 days and 7(23%) cases less than 6 days.

Table 5: Clinical Spectrum of the Disease in the Study Population

	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	n	%	N	%	n	%	
Cognitive Impairment	10	47.6%	5	55.6%	15	50.0%	0.690
Seizure	17	81.0%	7	77.8%	24	80.0%	0.842
Psychiatric Symptoms	6	28.6%	4	44.4%	10	33.3%	0.398
Movement Disorders	8	38.1%	7	77.8%	15	50.0%	***0.046***
Speech Dysfunction	11	52.4%	8	88.9%	19	63.3%	0.057
Sleep Disturbance	4	19.0%	3	33.3%	7	23.3%	0.397
Autonomic Dysfunction	2	9.5%	1	11.1%	3	10.0%	0.894

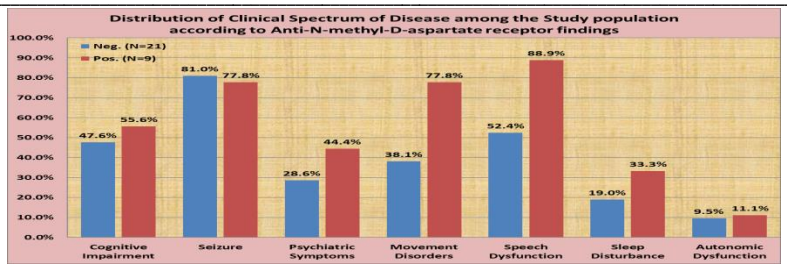

Fig 5: Clinical Spectrum of the Disease in the Study Population

Among 30 cases of AIE, the most common complaint was found to be seizures 24(80%) followed by speech dysfunction 19(63%). but the significant P-valve was found in movement disorder which showed 15 out of 30 (50%).

Table 6: Laboratory Investigations in the Study Population

		Anti-N-methyl-D-aspartate receptor						P value*
		Neg. (N=21)		Pos. (N=9)		Total (N=30)		
		n	%	n	%	n	%	
TC	High	3	14.3%	0	0.0%	3	10.0%	0.232
CRP	<6	21	100.0%	8	88.9%	29	96.7%	0.120
LP-CSF	Oligoclonal Bands	5	23.8%	5	55.6%	10	33.3%	0.091
CSF –CC	>5	8	38.1%	5	55.6%	13	43.3%	0.376
CT	Neut	5	23.8%	4	44.4%	9	30.0%	0.392
	Lym	14	66.7%	5	55.6%	19	63.3%	
	No Cell	2	9.5%	0	0.0%	2	6.7%	
CSF-PROT	Increased	6	28.6%	4	44.4%	10	33.3%	0.398
CSF GLU	<2/3	16	76.2%	7	77.8%	23	76.7%	0.925
	>2/3	5	23.8%	2	22.2%	7	23.3%	
EEG	Abnormal	13	61.9%	3	33.3%	16	53.3%	0.151
MRI	Abnormal	10	47.6%	4	44.4%	14	46.7%	0.596

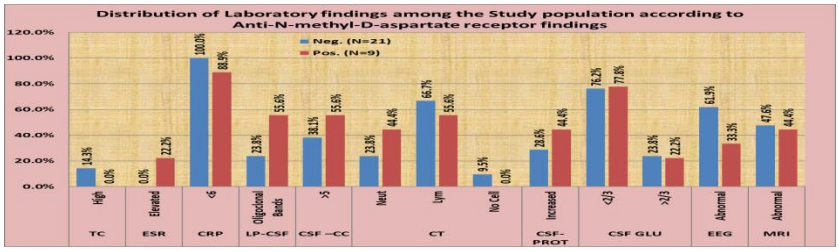

Fig 6: Laboratory Investigations in the Study Population

Among 30 cases of AIE: CSF cell count >5 was found in 13(43%) EEG was found to be abnormal in 16(53%) MRI brain was found to be abnormal in 14(46%).

Table 7: Treatment Response to the Study Population

Treatment	Admission				Total
	Neg. (N=21)		Pos. (N=9)		
	n	%	n	%	
IV Methylpred	10	83.3	2	16	12
Iv methylpred +IVIG	7	87.5	1	12.5	8
Iv methylpred + IVIG +Rituximab	3	14.3	5	55.5	8

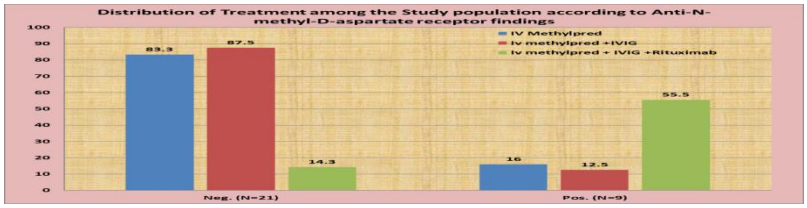

Fig 7: Treatment Response to the Study Population

Among 30 cases of AIE, 12 cases responded to only IV methyl prednisolone, 8 cases responded to methyl prednisolone and IVIG8cases responded to methylprednisolone, IVIG and rituximab.

Table 8: Number of Rituximab Doses Given to the Study Population

No of Rituximab Dose @ Admission	Anti-N-methyl-D-aspartate receptor			
	Neg. (N=21)		Pos. (N=9)	
	N	%	n	%
1	3	14.3%	2	22.2%
2	0	0.0%	2	22.2%
4	0	0.0%	1	11.1%

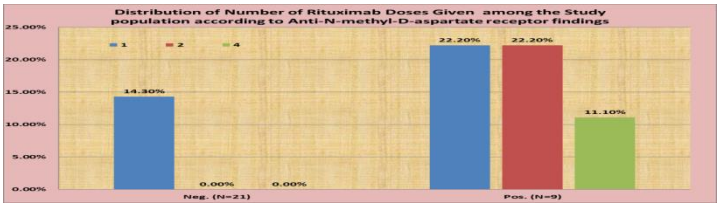

Fig 8: Number of Rituximab Doses Given to the Study Population

Out of 30 cases of AIE, 8 cases were treated with rituximab. 3 cases were seronegative and all responded to single dose of rituximab. 5 cases were seropositive, 2 cases required single doses, 2 cases required 2doses and one case required 4 doses.

Table 9: Need for Ventilation in the Study Population

Need For Ventilation	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	N	%	N	%	n	%	
No	19	90.5%	7	77.8%	26	86.7%	0.348
Yes	2	9.5%	2	22.2%	4	13.3%	

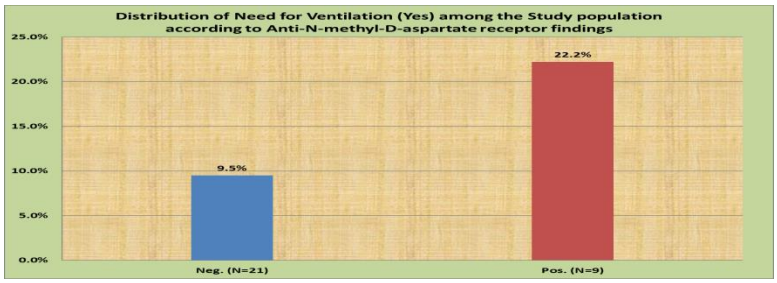

Fig 9: Need for Ventilation in the Study Population

Out of 30 cases of AIE, only 4cases (13%) were mechanically ventilated

Table 10: Day of Start of Improvement in Anti-NMDA Receptor Positive and Negative Subjects In the Study Population

Anti-N-methyl-D-aspartate receptor	N	Mean	SD	Median	Min.	Max.	P value*
Neg.	20	28.2	39.262	17.0	5	185	0.862
Pos.	8	32.6	30.514	31.5	4	95	
Total	28	29.5	36.474	17.0	4	185	

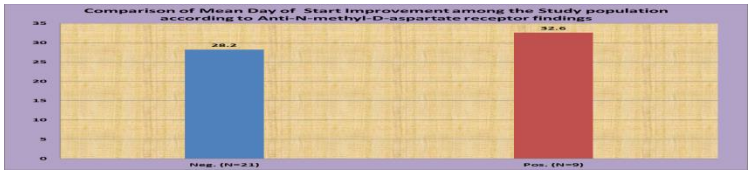

Fig 10: Day of Start of Improvement in Anti-NMDA Receptor Positive and Negative Subjects In the Study Population

Among 30 cases AIE, the mean duration of improvement was found to be 28days in seronegative AIE and 32days in seropositive AIE.

Table 11: Duration of Hospital Stay in Anti-NMDA Receptor Positive and Negative Subjects In the Study Population

ANTI-NMDAR	N	Mean	SD	Median	Min.	Max.	P value
Neg.	20	13.3	6.180	12.5	3	26	***0.008***
Pos.	8	21.1	6.446	22.0	9	28	
Total	28	15.5	7.126	14.5	3	28	

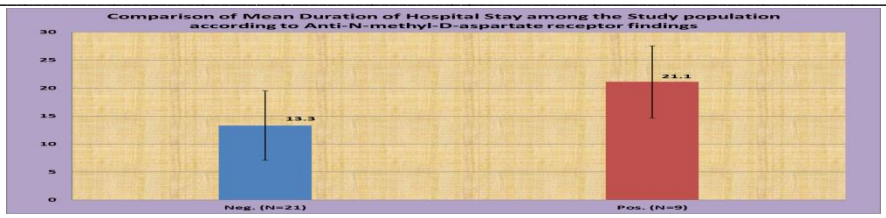

Fig 11: Duration of Hospital Stay in Anti-NMDA Receptor Positive and Negative Subjects In the Study Population

Among 30 cases AIE, the mean duration of hospital stay was found to be 13 days in seronegative AIE, and 21days in seropositive AIE

Table 12: Disease Outcome in the Study Population

Outcome	Anti-N-methyl-D-aspartate receptor						P value*
	Neg. (N=21)		Pos. (N=9)		Total (N=30)		
	N	%	N	%	N	%	
LAMA	3	14.3%	0	0.0%	3	10.0%	0.200
Death	1	4.8%	1	11.1%	2	6.7%	
Partial Improved.	9	42.9%	7	77.8%	16	53.3%	
Full Improved	8	38.1%	1	11.1%	9	30.0%	

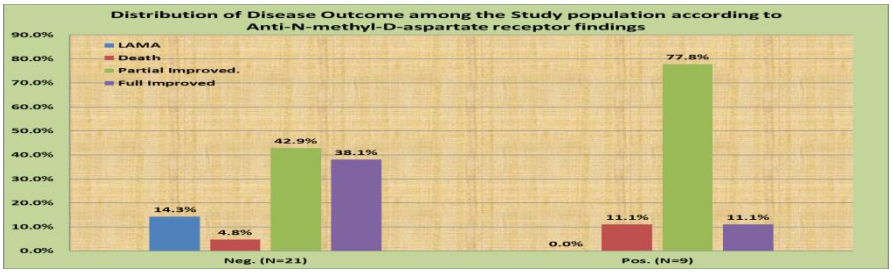

Fig 12: Disease Outcome in the Study Population

Among 30 cases of AIE: 16(53%) cases had partial improvement, 9(30%) cases had full improvement, 3(10%) cases went LAMA, 2(6.7%) cases had death.

Discussion

Table 12: Comparison of Baseline Characteristics, Clinical Features, Investigations and Treatment

Study	Awadhi Kishor et al	Asha et al	Biswaroop et al	Madhu et al	Vykuntaraju et al	Current study
Place	New Delhi AIIMS	Trivandrum	New Delhi AIIMS	NIMHANS	Bangalore,India IGICH	Bangalore,India ICIGH
Sample size	15	39	11	13	55	30
Duration of study	Dec 2011-june2013	Dec2009-jun2013	Jan2010-dec2012	July2012-aug:2015	Jan2014-aug2019	Oct2018-april2020
Type of study	Observational prospective case series	Observational prospective case series	Observational retrospective study	Observational retrospective study	Observational retrospective study	Observational prospective case series
Age group Mean age	2-64years 24years	2-55years 15years	2.5-18years 9years	3-18years 10.8+/- 4.8years	1m-18years 5years	6m-18years 6years
M:F	10:5	14:25	6:5	11:2	-	15:15
Clinical features	Seizures being most common	Seizures being most common followed by behavioural problems	Extrapyramidal symptoms	Abnormal behaviour and movement disorders	Seizures being most common followed by involuntary movements and speech disturbances	Seizures being most common followed by speech dysfunction and abnormal movement
Investigations	MRI brain was normal in 6, abnormal 9	NIL	MRI brain normal in all except in 2	EEG abnormal in all , MRI brain was normal in all except 2	MRI brain was normal in 7, abnormal in 48	EEG was abnormal in 16, and normal in 14. MRI brain was abnormal in 14, normal in 16

Treatment	MP=4 IVIG=6 MP+RITUXIMAB=1 IVIG+MP+PE=2 IVIG+MP=1 SURGERY=1	MP=15 MP+IVIG=14 MP+PE=6 SYMP=2	MP+IVIG=7 MP+IVIG+PE=3 RITUXIMAB+ CYCLOPHOSPHAMIDE=1	MP=5 MP+IVIG=2 MP+PE=6		MP=12 MP+IVIG=8 MP+IVIG+ RITUXIMAB=8

This prospective observational study was conducted from October 2018 to April 2020 at Indira Gandhi Institute of child health, Bangalore,India. A total of 30 cases with autoimmune encephalitis meeting the inclusion criteria were enrolled in the study.

Of the 30children, 15(50%)were males and 15(50%) were females, as compared to the male preponderance in all other studies except the study done by asha et al in which Females were more than males.[8]

The mean age was 6years with minimum and maximum age of 1y and 16 years respectively. The age of onset in the present study was 1years comparable to other studies wherein it was between 1m to 3 years.Among the above studies, all are paediatric studies except awadkishor et al and asha et al are adult studies.Among the above studies, the only paediatric prospective observational study is the current studyAmong all the above studies, seizures was the most common clinical manifestation among all studies except biswaroop et al and madhu nagappa et al which had extra pyramidal symptoms and abnormal behaviour and movement disorders respectively[9].On comparison with above studies, majority of the cases showed normal MRI brain, which also corresponds with our current study with 16cases out of 30 had normal MRI brain[10].In all the above studies, iv methyl prednisolone was the first line therapy except for awadhkishor et al study in which IVIG was also given as first line therapy.Surgical management was considered only in one study ieawadkishor et all study.Rituximab response was studied in only 3studies, among which current study response being 26%, biswaroop et al study response being 9% and renu Suthar et al study response being 20%.

Conclusion

In conclusion, the results of present study indicate that the clinical features like movement disorders (p=0.046) and speech (p=0.020) are good predictors of autoimmune encephalitis. seizures are the most common clinical feature.Seronegative autoimmune encephalitis responded to single dose of rituximab after treating with methylprednisolone and IVIG. But seropositive autoimmune encephalitis responded after multiple doses of rituximab after initial treatment with methylprednisolone and IVIG.Early diagnosis and initiation of immunosuppressive therapy in autoimmune encephalitis, has shown overall improvement of clinical features in 83.3% and mortality of only 6.7%.

Conflict of Interest: Nil
Source of support:Nil

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