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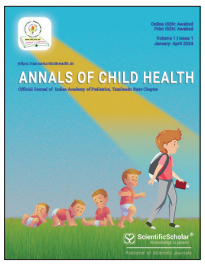

Original Article

Paradigm Shift in the Etiology of Encephalopathy in Children from Infectious to Non-infectious Causes – A Single-Center Experience

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ABSTRACT

Objectives: Among children admitted with acute non-traumatic encephalopathies, non-infectious etiologies are emerging as important causes. The objective of this study was to analyze the clinical features, etiologies, and outcome of children presenting with acute non traumatic encephalopathies.

Material and Methods: This was a hospital-based descriptive study. Children aged 1 month to 18 years admitted during the period from 2019 to 2023 with altered sensorium for >12 hours were included in the study. Data on clinical, laboratory findings, management, diagnosis, outcomes at discharge, and follow-up were retrieved from the case records of children selected based on preset criteria. Children with a history of trauma and seizure disorder/epileptic encephalopathy were excluded from the study. Data was analyzed and projected as descriptive statistics and comparison of groups done with tests of significance, as applicable.

Results: Seventy children were included in the study. Immune etiologies contributed to 20 (28.58%) cases and central nervous system infections for 16 (22.86%) cases. Seventy (100%) children had altered sensorium, 51 (72.8%) children had fever and 46 (65.7%) children had seizures. Two (2.8%) children expired (one in each of tuberculous meningitis and autoimmune encephalitis). Among those who survived, 2 (2.9%) children had moderately severe disability, 8 (11.7%) had slight disability and 7 (10.2%) were symptomatic but without significant disability at discharge. On follow-up, the majority of patients had a Gross Motor Function Classification/Manual Ability Classification System score of 1 and a favorable epilepsy score on the Early Childhood Epilepsy Severity Scale. The average social quotient was found to be 95.60.

Conclusion: Autoimmune encephalitis and acute disseminated encephalomyelitis are emerging as important causes of acute non-traumatic encephalopathies. Awareness among health care providers will help in early diagnosis, management, and better outcomes in such children.

Keywords: Acute disseminated encephalomyelitis, Acute encephalopathy, Autoimmune encephalitis, Etiology, Outcome

INTRODUCTION

In recent years, acute non-traumatic encephalopathies are important causes of pediatric intensive care admission. "Encephalopathy" is a broad term for any disease that alters brain function or structure, characterized by altered mental status. It may be caused by infectious or non-infectious causes such as toxins, metabolic problems, or inflammatory conditions[1] "Encephalitis" is characterized by acute onset of fever and altered mental state (with or without seizures or other neurological signs) due to central nervous system (CNS) inflammation.[2]

They pose a great challenge to the physician due to the acute presentation in a well-child, propensity for rapid deterioration, diagnostic difficulties amidst limited resources, and need for intensive care. Prompt identification of the etiology by judicious use of cerebrospinal fluid (CSF) analysis and neuroimaging is the need of the hour, as the initial presentation may be similar in all cases, making it difficult to arrive at a diagnosis with clinical suspicion alone. The treating physician needs to be aware of the varied etiologies to plan ideal evaluation and appropriate therapy, as specific therapeutic agents like immunomodulators may be lifesaving in certain circumstances. Most of the studies available to date have shown that infections are the common cause of acute encephalopathy.[3] The emergence of autoimmune encephalitis as a distinct and prevalent entity has led to a paradigm shift in the management of these children.[3] There is a paucity of data on the clinical profile and the outcome of non-infectious etiologies such as autoimmune encephalitis and acute disseminated encephalomyelitis (ADEM). Different geographical regions also have the emergence of newer organisms from time to time, further aggravating the problem.[4] Hence, this study was done with an aim to identify the spectrum and outcome of children with acute non-traumatic encephalopathies in our region.

MATERIAL AND METHODS

This is a hospital-based descriptive study done at an urban referral center in South India with the Institutional Ethical Committee clearance. Children aged 1 month–18 years presenting with altered sensorium for more than 12 hours were included in the study. Children with a history of trauma and seizure disorder/epileptic encephalopathies were excluded from the study.

Case records of such cases admitted from January 2019 to May 2023 were retrieved and analyzed with ethical clearance. History, examination findings at admission, reports of relevant blood investigations (complete blood count, serum ammonia, serum lactate, blood culture, blood gas, renal, liver function tests, coagulation profile, C-reactive protein, procalcitonin, toxicology screen, metabolic panel, and serum autoimmune panel) CSF analysis, magnetic resonance imaging (MRI)/computed tomography (CT) brain, and electroencephalogram (EEG) were collected. A final diagnosis of the cases as per predefined criteria and outcome at follow-up with a duration ranging from 2 months to 4 years was noted. Following are the definitions used for the categorization of the cases:

Pyogenic meningitis

Acute febrile encephalopathy (AFE) ± meningeal signs + culture of compatible micro-organisms from CSF or presence of ≥2 of the following CSF abnormalities (i) polymorphonuclear leukocytosis, (ii) glucose <40 mg/dL or 50% of blood sugar, and (iii) bacteria seen by Gram staining or polymerase chain reaction (PCR).[5]

Viral meningoencephalitis

AFE ± positive CSF PCR ± CSF pleocytosis with lymphocyte predominance (>5 cells/mm^3) and absence of bacteria on Gram stain and culture with no other alternative diagnosis identifiable.[5]

Tubercular meningitis

Based on criteria by Doerr *et al*. or CSF GeneXpert positive.[6]

Enteric encephalopathy

AFE + evidence of Salmonellosis (positive blood culture and / or positive serology).[5]

H1N1 encephalopathy

AFE + H1N1 PCR positive respiratory tract infection within 5 days of influenza lile illness (ILI) symptom onset with no other alternative diagnosis identifiable.[5]

Dengue encephalopathy

AFE + positive NS1 antigen or dengue IgM with no other alternative diagnosis identifiable.[5]

Acute disseminated encephalomyelitis (ADEM)

Diagnosis is made when all five of the following criteria have been met:

a. The first multifocal clinical CNS event of the presumed inflammatory demyelinating cause
b. Encephalopathy that cannot be explained by fever
c. Abnormal brain MRI: Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter, T1-hypointense lesions in the white matter in rare cases, and deep grey matter abnormalities (e.g., thalamus or basal ganglia)
d. No new clinical or MRI findings after 3 months of symptom onset
e. Reasonable exclusion of alternative causes.[3]

Anti N-methyl-D-aspartate (NMDA) receptor encephalitis

Diagnosis made in the presence of one or more of the six major groups of symptoms and immunoglobulin G (IgG) anti-NMDA receptor antibodies, after reasonable exclusion of other disorders. Rapid onset (<3 months) of at least four of the six following major groups of symptoms:

a. Abnormal (psychiatric) behavior or cognitive dysfunction

b. Speech dysfunction (pressured speech, verbal reduction, and mutism)
c. Seizures
d. Movement disorder, dyskinesias or rigidity/abnormal posture
e. Decreased level of consciousness
f. Autonomic dysfunction or central hypoventilation.[3]

Probable autoimmune encephalitis was made when all the four following criteria have been met

a. Rapid progression (<3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
b. Exclusion of well-defined syndromes of autoimmune encephalitis (e.g., typical limbic encephalitis, Bickerstaff's brainstem encephalitis, and ADEM)
c. Absence of well-characterized autoantibodies in serum and CSF and at least two of the following criteria:
   - Magnetic resonance imaging abnormalities suggestive of autoimmune encephalitis
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (e.g., tumor).
d. Reasonable exclusion of alternative causes.[3]

Seventy children admitted during the study period were included. Clinical presentation, course in the hospital, treatment, and outcome of all the cases were entered in a predesigned case recording form and analyzed. The neurological outcome at the time of discharge was assessed by modified Rankin Scale (mRS), which has scores ranging from 0 to 6.[7]. All cases were followed up by in-person/telephonic assessment for functional status: gross motor by Gross Motor Function Classification System (GMFCS), hand function by Manual Ability Classification System (MACS), epilepsy severity using Early Childhood Epilepsy Severity Scale (E-CHESS), and social quotient (SQ) by Vineland Social Maturity Scale.[8,9]

Statistical analysis

Analysis was done using Statistical Package for the Social Sciences software version 21. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages. The chi-square test was used to determine the significance of association between two categorical variables. Fisher's exact test was used when more than 20% of the cell values had expected cell value <5. Analysis of variance was used to compare three or more groups. $P < 0.05$ was considered statistically significant.

RESULTS

Seventy-seven children satisfied the definition of acute encephalopathy. Seven cases were discharged against medical advice and, hence, were excluded from the study. Seventy cases were taken for analysis.

Demographic features

The mean [standard deviation (SD)] age was 5.25 (4.95) years, ranging from 1 month to 18 years, and 46 (65.71%) children were males, and 24 (34.29%) children were females.

Etiology

Immune etiologies contributed to 20 (28.58%) cases [10 (14.29%) cases of autoimmune encephalitis and 10 (14.29%) cases of ADEM], while CNS infections to 16 (22.86%) cases. Other causes were toxic/metabolic in 13 (18.57%) cases, infection-related encephalopathies (influenza, dengue, and enteric) in 7 (10.00%) cases, Acute Necrotizing Encephalopathy of Childhood (ANEC) in 1 (1.43%) case, Acute Encephalopathy with Biphasic Seizures and late reduced diffusion (AESD) in 1 (1.43%) case, Reversible Splenial Lesion Syndrome in 2 (2.86%) cases, tumor in 2 (2.86%) cases, aseptic meningitis in 1 (1.43%) case, adverse event following immunization (AEFI) in 1 (1.43%) case, and unclassified causes in 6 (8.57%) cases [Figure 1].

Clinical features

Altered sensorium and fever were observed in all cases with infective etiology. Nineteen children were afebrile during the course of illness. Among them, 7 (36.8%) children had toxin exposure, 5 (26.3%) had autoimmune encephalitis, 4 (21%) had unclassified causes, 2 (10.5%) had tumors, and 1 (5.2%) had ADEM. The next frequent symptom seen, irrespective of etiology, was seizures. Prodrome constituting upper respiratory symptoms was noted in 50% of cases of autoimmune encephalitis and 40% of cases of viral encephalitis. Other relatively common findings were

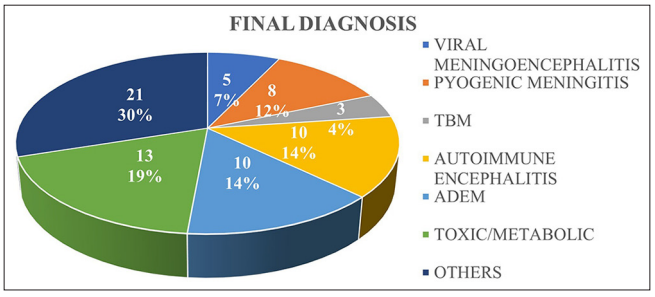

Figure 1: Final diagnosis of children with acute non traumatic encephalopathy. TBM: Tubercular meningitis, ADEM: Acute disseminated encephalomyelitis

Table 1: Clinical features of children with various encephalopathies (N=70).

Clinical features	Viral meningoencephalitis (*n*-5) (%)	Pyogenic meningitis (*n*-8) (%)	TBM (*n*-3) (%)	Autoimmune encephalitis (*n*-10) (%)	ADEM (*n*-10) (%)	Toxic/ Metabolic (*n*-13) (%)	Others (*n*-21) (%)
Fever	5 (100)	8 (100)	3 (100)	5 (50)	9 (9)	6 (46.15)	15 (71.42)
Viral prodrome	2 (40)	1 (12.5)	0 (0)	2 (50)	2 (20)	0 (0)	5 (23.8)
ALOC	5 (100)	8 (100)	3 (100)	10 (100)	10 (100)	13 (100)	21 (100)
Seizures	5 (100)	4 (50)	2 (66.66)	9 (90)	4 (40)	10 (76.92)	12 (57.14)
Headache	1 (20)	2 (25)	2 (66.66)	3 (30)	6 (60)	3 (23.07)	3 (14.28)
Photophobia	1 (20)	0 (0)	1 (33.3)	0 (0)	1 (10)	0 (0)	0 (0)
Sleep disturbances	1 (20)	0 (0)	1 (33.33)	4 (40)	0 (0)	0 (0)	5 (23.8)
Cranial nerve palsy	0 (0)	0 (0)	2 (66.66)	3 (30)	2 (20)	0 (0)	2 (9.52)
Focal deficits	0 (0)	3 (37.5)	1 (33.33)	2 (20)	3 (30)	1 (7.69)	3 (14.28)
Abnormal behavior	1 (20)	0 (0)	2 (66.66)	6 (60)	0 (0)	2 (15.38)	8 (38.09)
Involuntary movements	1 (20)	0 (0)	0 (0)	5 (50)	2 (20)	2 (15.38)	0 (0)
Past similar illness	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (10)	0 (0)	1 (4.76)
AVPU							
V	3 (60)	4 (50)	1 (33.3)	7 (70)	8 (80)	10 (76.92)	13 (61.9)
P	2 (40)	4 (50)	2 (66.66)	3 (30)	1 (10)	3 (23.07)	7 (33.3)
U	0 (0)	0 (60)	0 (0)	0 (0)	1 (10)	0 (0)	1 (4.7)
Tachycardia	2 (40)	7 (87.5)	2 (66.66)	4 (40)	4 (40)	4 (30.7)	10 (47.6)
Bradycardia	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	2 (9.5)
Bradypnea	1 (20)	1 (12.5)	0 (0)	2 (20)	0 (0)	1 (7.69)	3 (14.2)
Hypertension	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (10)	2 (15.38)	2 (9.52)
Hypotension	1 (20)	1 (12.5)	1 (33.3)	2 (20)	0 (0)	1 (7.69)	0 (0)
Meningeal signs	0 (0)	2 (25)	3 (100)	1 (10)	2 (20)	0 (0)	0 (0)
Cranial nerve deficit	1 (20)	0 (0)	1 (33.3)	2 (20)	3 (30)	0 (0)	2 (9.52)
Motor deficit	0 (0)	3 (37.5)	1 (33.3)	2 (20)	1 (10)	1 (7.69)	2 (9.52)
Sensory deficit	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebellar signs	0 (0)	1 (12.5)	1 (33.3)	0 (0)	5 (50)	2 (15.38)	2 (9.52)
Extra pyramidal signs	0 (0)	0 (0)	0 (0)	4 (40)	2 (20)	1 (7.69)	0 (0)
Signs of raised ICT	0 (0)	2 (25)	3 (100)	2 (20)	1 (10)	1 (7.69)	2 (9.52)
MODS	0 (60)	2 (25)	1 (33.3)	2 (20)	2 (20)	1 (7.69)	2 (9.52)

TBM: Tuberculous meningitis, ADEM: Acute disseminated encephalomyelitis, ALOC: Altered level of consciousness, AVPU: Alert, Verbally responsive, Pain responsive, Unresponsive, V: Verbally responsive, P: Pain responsive, U: Unresponsive, ICT: Intracranial tension, MODS: Multiorgan dysfunction syndrome

headaches, abnormal behavior, focal neurologic deficits, and cranial nerve palsies [Table 1].

Laboratory findings

Among 16 children admitted with infective etiology, the CSF meningoencephalitis panel detected organisms in 8 (50%) cases (Human herpes virus 7 – 1, Herpes simplex virus – 1, *Streptococcus agalactiae* – 1, *Haemophilus* spp. – 1, *Group B Streptococci* – 1, *Escherichia coli* – 1, and *Streptococcus pneumoniae* – 2).

Among eight children admitted with pyogenic meningitis, organisms were isolated from blood in 4 (50%) cases [*Streptococcus pneumoniae* in 2 (50%) and *Streptococcus agalactiae* in 2 (50%)] and CSF in 2 (25%) cases (*Acinetobacter baumannii*).

Serum autoimmune panel was done in 27 children, out of which 6 (22.2%) cases were positive for myelin oligodendrocyte glycoprotein (MOG) antibodies. CSF autoimmune panel was done for 18 children out of whom 3 (16.6%) cases were positive for NMDA antibodies.

Out of the five cases with viral encephalitis, 1 child had normal MRI, whereas the rest showed features of meningoencephalitis, leptomeningeal enhancement, microbleeds, and post-encephalitic sequelae. Out of the eight cases with pyogenic meningitis, three children had normal

MRI, and the rest showed features of meningoencephalitis, leptomeningeal enhancement, subdural empyema, subdural effusion, and hydrocephalus. Nine out of the ten children with ADEM showed features of demyelination on MRI. Six out of the ten children with autoimmune encephalitis showed features of encephalitis, leptomeningeal enhancement, and post ictal cerebral edema on MRI.

Management

Six (8.5%) children required surgical interventions (two cases of tumor, three cases of subdural effusion/empyema, and one case of sphenoid meningocele).

Six (8.8%) cases required plasma exchange, including four cases of autoimmune encephalitis, one case of ADEM, and one case of atypical hemolytic uremic syndrome/posterior reversible encephalopathy syndrome (HUS/PRES).

Forty (57.1%) children needed intravenous steroids and 31 (44.2%) children needed intravenous immunoglobulin.

Among 11 children needing immunomodulation, 8 (72%) received rituximab, 3 (27.2%) received cyclophosphamide, 1(9%) received mycophenolate mofetil (MMF), 1(9%) received tacrolimus, and 1(9%) received tocilizumab [Figure 2].

Outcome at discharge

The mean duration of hospital stay was significantly higher in autoimmune encephalitis (28.1 days; SD-24.7), followed by ADEM (19.7 days; SD-14) and pyogenic meningitis (19.5 days) compared to 10.4 days in viral encephalitis, 12.3 days in TB meningitis, and 9 days in toxic/metabolic cases ($P < 0.05$; which is statistically significant) [Table 2].

One child each with tuberculous (TB) meningitis and autoimmune encephalitis expired. Among the 68 children who survived, 51 (75%) recovered without any symptom or disability while 2 (2.9%) children had moderately severe disability, 8 (11.7%) had slight disability, and 7 (10.2%) were symptomatic but without significant disability at discharge [Table 3].

Outcome at follow-up

Sixty-eight children who survived were followed up by either telephonic interview/in person visit for gross motor, hand function, epilepsy severity, and SQ. Five cases were lost to follow-up. Motor outcomes were assessed in 63 children. Gross motor status revealed GMFCS-I in 57 (90.4 %) children, GMFCS-II in 3 (4.7 %) children and GMFCS-III in 3 (4.7%) children.

Hand functioning assessment in 28 children showed ability to handle objects easily (MACS I) in 26 (92.8%) children and ability to handle most objects but with reduced speed and accuracy (MACS II) in 2 (7.1%)children.

Forty-five (64.28%) children required anti-convulsants for seizures during the course of illness. On assessment with Early Childhood Epilepsy Severity Scale (E-CHESS) on follow-up, one child had score > 9, indicating an unfavorable prognosis. Four children had score > 6, and 40 children had score ≤6 [Table 4].

Fifty-two (82.5%) children had a normal Social Quotient (SQ) of 100, 1 (1.5%) case had SQ of 92.5, 3 (4.7%) cases had SQ of 90, 2 (3.1%) cases had SQ of 80, 1 (1.5%) case had SQ of 63, 3 (4.7%) cases had SQ of 60, and 1 (1.5%) case had SQ of 57.14.

DISCUSSION

Various etiological factors have been identified in children presenting with acute encephalopathy; however, considerable regional diversity exists in these etiological factors.

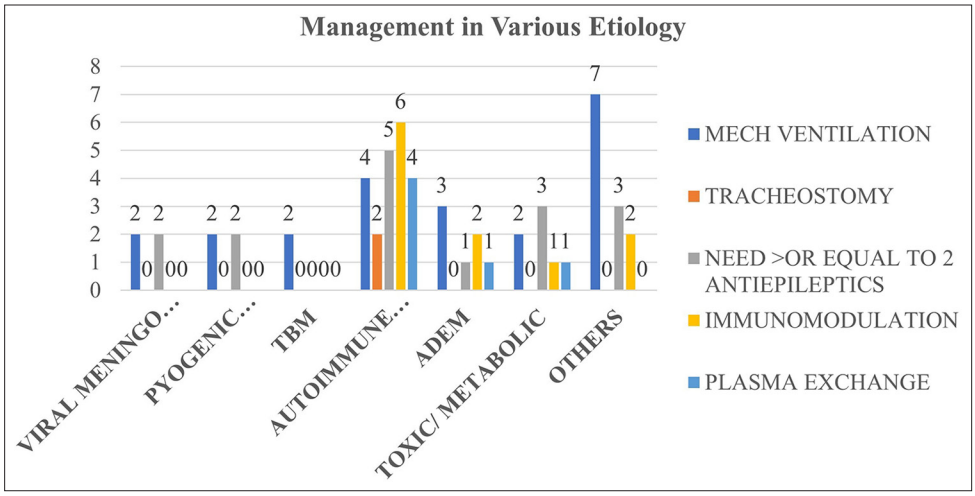

Figure 2: Management in different etiological categories. TBM: Tuberculous meningitis, ADEM: Acute disseminated encephalomyelitis

Table 2: Duration of hospital stay in different etiological categories.

Final diagnosis	Duration of hospital stay				Statistical Significance*
	Mean	Standard deviation	Minimum	Maximum	
Viral meningoencephalitis	10.4	5.5	4	17	*P*-0.008
Pyogenic meningitis	19.5	12.5	10	46	
TBM	12.3	9	2	18	
Autoimmune encephalitis	28.1	24.7	7	75	
ADEM	19.7	14.2	7	46	
Toxic/metabolic	9	11	1	40	
Others	9.4	5.7	3	23	

*Test of significance: Analysis of Variance (ANOVA).TBM: Tuberculous meningitis, ADEM: Acute disseminated encephalomyelitis

Table 3: Outcome at discharge among different etiological categories

Outcome at discharge	Final diagnosis													
	Viral meningoencephalitis		Pyogenic meningitis		TBM		Autoimmune encephalitis		ADEM		Toxic/ Metabolic		Others	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
No symptoms	5	100.0	6	75.0	1	33.3	4	40.0	7	70.0	12	92.3	16	76.2
No significant disability	0	0.0	2	25.0	1	33.3	3	30.0	0	0.0	0	0.0	1	4.8
Slight disability	0	0.0	0	0.0	0	0.0	3	30.0	1	10.0	1	7.7	3	14.3
Moderate disability	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Moderately severe disability	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0	0	0.0	1	4.8
Severe disability	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Dead	0	0.0	0	0.0	1	33.3	0	0.0	1	10.0	0	0.0	0	0.0
Total	5	100.0	8	100.0	3	100.0	10	100.0	10	100.0	13	100.0	21	100.0

Chi square Test - *P*-value - 0.015. TBM: Tuberculous meningitis, ADEM: Acute disseminated encephalomyelitis

There are not many studies from our region which describe the outcome of acute encephalopathies in children.

In the present study, the common etiology of non-traumatic encephalopathy was immune-related (28.58%), followed by infections (22.86%) and toxic-metabolic causes (18.57%). In a study by Mondal *et al.* from Bangalore in 2020, out of 121 cases with acute encephalitis syndrome (AES), 67.8% were due to infections, 21.5% due to immune etiology (autoimmune encephalitis – 12.4% and ADEM – 9.09%) and 10.7% were due to inflammatory/unknown etiology (ANEC – 8.26%).[3] This study highlighted that although infection is still the predominant etiology of sporadic AES, autoimmune and other inflammatory etiologies are being increasingly diagnosed in recent years. Similarly, a study by Pillai *et al.* in 2014 in Australian children showed immune-mediated/autoantibody-associated encephalitis in 34% cases, infectious encephalitis in 30% cases, infection-associated encephalopathy in 8% cases, and unknown encephalitis in 28% cases.[10] This study was conducted in a developed country. Better infection control measures in developed countries may be the cause of a lower incidence of infective encephalitis. This is in contrast with the study done by Bansal *et al.* in 2005 in northern India, which reported that 60% of cases were due to CNS infections.[11]

Our study reports three cases of NMDA positive autoimmune encephalitis, four cases of serum anti-myelin oligodendrocyte glycoprotein (MOG) IgG positive autoimmune encephalitis, and four cases of seronegative autoimmune encephalitis. Similarly, Mondal *et al.* reported 2 NMDAR antibody-positive autoimmune encephalitis, 1 anti-TPO positive Hashimoto's encephalopathy, 9 seronegative autoimmune encephalitis, 2 Bickerstaff encephalitis, and 1 limbic encephalitis.[3]

In a recent study from North India, among 20 cases of possible autoimmune encephalitis, six were found to be NMDAR antibody positive.[12]

In a large study from Australia, Pillai *et al.* found that among 21 cases of autoimmune encephalitis, five cases were positive for NMDAR antibody, seven and four cases were positive for voltage gated potassium channel complex and dopamine

Table 4: Outcome at follow-up in different etiological categories.

Outcome at follow-up	Viral meningo encephalitis (*n*=5)	Pyogenic meningitis (*n*=8)	TBM (*n*=2)	Autoimmune encephalitis (*n*=9)	ADEM (*n*=9)	Toxic/metabolic (*n*=12)	Others (*n*=18)
GMFCS (*n*=63)							
1 (*n*=57)	5	8	2	7	7	11	17
2 (*n*=3)	0	0	0	2	1	0	0
3 (*n*=3)	0	0	0	0	1	1	1
	Viral meningo encephalitis (*n*=1)	**Pyogenic meningitis (*n*=4)**	**TBM (*n*=2)**	**Autoimmune encephalitis (*n*=7)**	**ADEM (*n*=6)**	**Toxic/metabolic (*n*=3)**	**Others (*n*=5)**
MACS – I (*n*=28)							
1 (*n*=26)	1	4	2	6	5	3	5
2 (*n*=2)	0	0	0	1	1	0	0
	Viral meningo encephalitis (*n*=5)	**Pyogenic meningitis (*n*=4)**	**TBM (*n*=2)**	**Autoimmune encephalitis (*n*=8)**	**ADEM (*n*=6)**	**Toxic/metabolic (*n*=10)**	**Others (*n*=10)**
E-CHESS score (*n*=45)							
<9 (*n*=44)	4	4	2	8	6	10	10
>9 (*n*=1)	1	0	0	0	0	0	0

TBM: Tuberculous meningitis, ADEM: Acute disseminated encephalomyelitis, GMFCS: Gross motor fucntion classification system, MACS: Manual ability classification system, E-CHESS: Early childhood epilepsy severity scoring

D2 receptor antibody, respectively, and another five children had probable autoimmune encephalitis.[10]

Earlier diagnostic criteria for autoimmune encephalitis were too reliant on antibody testing and response to immunotherapy. Since antibody testing is not available everywhere and results take time, Graus *et al*. suggested that despite the absence of autoantibodies, one should not exclude the diagnosis of autoimmune encephalitis.[13]

Our study showed a mortality of 2.8%, which is similar to the mortality rate of 4.8% reported by Mondal *et al*.[3] This is in contrast to a study from Northern India, which reported a higher mortality rate of 40%.[10] The low mortality in the current series could be attributed to the earlier presentation, intensive care, and early initiation of immune modulator therapy. There was also easy access to neuroimaging, CSF meningoencephalitic panel, serum, and CSF autoimmune panel, and better culture yield which helped in prompt diagnosis.

At the time of discharge, 51 (75%) recovered without any symptom or disability, 2 (2.9%) children had moderately severe disability, 8 (11.7%) had slight disability, and 7 (10.2%) were symptomatic but without significant disability. In a study done by Mondal *et al*., 81 (66.95%) cases recovered completely, and 4 children (3.3%) died. Fifteen cases (12.39%) had mild disability, whereas 11 (9.09%) and 10 (8.26%) cases had moderate and severe disability at the time of discharge from the hospital.[3]

Follow-up of the patients over a duration ranging from 2 months to 4 years was possible in the study. This is in contrast to a study done by Pillai *et al*., where an abnormal outcome occurred in 49.5% with a mean duration of follow-up of 5.8 years.[10]

Strengths: All cases were completely evaluated to arrive at a final diagnosis. Outcomes were assessed by standardized scores such as GMFCS, MACS, E-CHESS, and Vineland Social Maturity Scale, making the outcome assessment objective.

Our study had few limitations. It is a single-center study with a relatively smaller sample size.

What is already known?

Infections are the most common cause of acute non-traumatic encephalopathies.

What this study adds?

Immune-associated encephalitis is emerging as a leading cause of non-traumatic encephalopathies in the past 10 years. They have good long-term outcomes as assessed by standardized scores such as GMFCS, MACS, E-CHESS, and Social Quotient.

CONCLUSION

Despite the stormy course of immune related encephalopathies, better outcomes and ability of the children to resume school and other routine activities suggest that it is worth the battle. Every pediatrician, as the primary care provider must have early suspicion for autoimmune encephalitis and institute early therapy with the help of a multidisciplinary team, including an intensivist and a pediatric neurologist.

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REFERENCES

1. Davies E, Connolly DJ, Mordekar SR. Encephalopathy in Children: An Approach to Assessment and management. Arch Dis Child 2012;97:452-8.
2. Banerjee B, Hafis M, Mahalingam A, Acharya U. Acute Encephalitis Syndrome: Approach to a Changing Paradigm. Pediatr Infect Dis 2019;1:86-94.
3. Mondal K, Banerjee B, Ram A, Ram G, Guruprasad HS. Changing trend in sporadic acute Encephalitis Syndrome in Indian Children-A Retrospective Cohort Study. J Pediatr Crit Care 2020;7:124-30
4. Chakrabarty B. Acute Encephalitis Syndrome: Current Trends and the Future. Indian J Pediatr 2018;85:335-6.
5. Gupta K, Purani CS, Mandal A, Singh A. Acute Febrile Encephalopathy in Children: A Prospective Study of Clinical Features, Etiology, Mortality, and Risk Factors from Western India. J Neurosci Rural Pract 2018;9:19-25.
6. Doerr CA, Starke JR, Ong LT. Clinical and Public Health Aspects of Tuberculous Meningitis in Children. J Pediatr 1995;127:27-33.
7. Nair AP, Kumar R, Mehrotra A, Srivastava AK, Sahu RN, Nair P. Clinical, Radiological Profile and Outcome in Pediatric Spetzler-Martin Grades I-III Arteriovenous Malformations. Childs Nerv Syst 2012;28:593-8.
8. Bhanudeep S, Madaan P, Sankhyan N, Saini L, Malhi P, Suthar R, *et al*. Long-Term Epilepsy Control, Motor Function, Cognition, Sleep and Quality of Life in Children with West Syndrome. Epilepsy Res. 2021;173:106629.
9. Humphrey A, Ploubidis GB, Yates JR, Steinberg T, Bolton PF. The Early Childhood Epilepsy Severity Scale (E-Chess). Epilepsy Res 2008;79:139-45.
10. Pillai SC, Hacohen Y, Tantsis E, Prelog K, Merheb V, Kesson A, *et al*. Infectious and Autoantibody-Associated Encephalitis: Clinical Features and Long-term Outcome. Pediatrics 2015;135:e974-84.
11. Bansal A, Singhi SC, Singhi PD, Khandelwal N, Ramesh S. Non Traumatic Coma. Indian J Pediatr 2005;72:467-73.
12. Suthar R, Saini AG, Sankhyan N, Sahu JK, Singhi P. Childhood Anti-NMDA Receptor Encephalitis. Indian J Pediatr 2016;83:628-33.
13. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, *et al*. A Clinical Approach to Diagnosis of Autoimmune Encephalitis. Lancet Neurol 2016;15:391-404.

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