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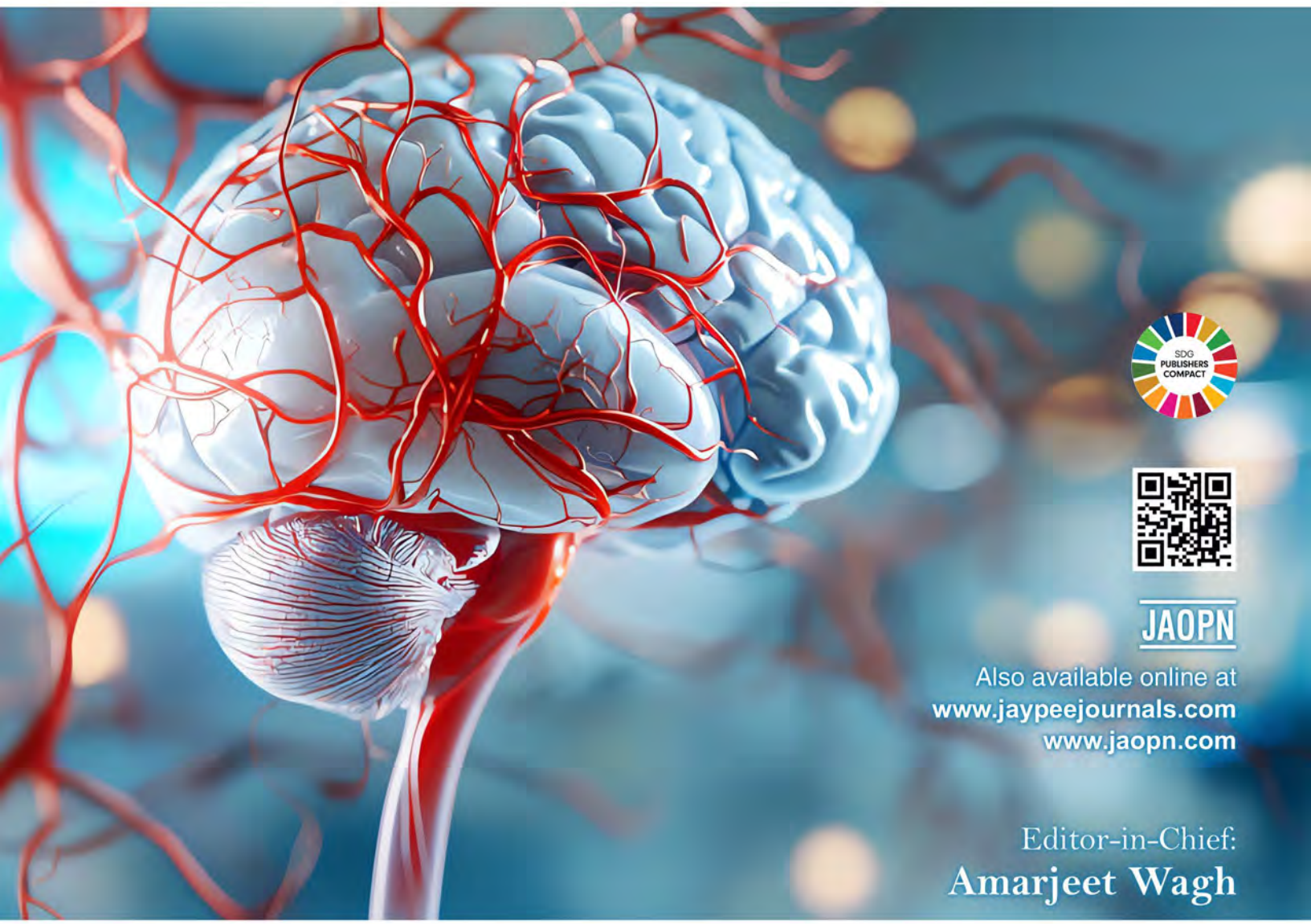

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Journal of Academy of Pediatric Neurology (JAOPN) is the official Journal of the Academy of Pediatric Neurology, India (AOPN, India). The Journal publishes two issues in a year, i.e., January–June and July–December. It is a peer-reviewed open-access Journal that publishes manuscripts pertaining to clinical and translational investigations of pediatric neurological diseases that will allow clinicians and neurologists to enrich their knowledge of patient management and education, and clinical or experimental research. The aim of the Journal is to publish cutting-edge clinical research from around the world with more focus on the Indian subcontinent. JAOPN is directed at pediatricians, pediatric neurologists and all clinicians and academicians involved in children with neurological disorders.

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Contents

EDITORIAL

Acute Encephalitis Syndrome: Changing Trends and Challenges for India

Amarjeet S Wagh[1], Jasodhara Chaudhuri[2], Varsha V Vaidya[3]

Journal of Academy of Pediatric Neurology (2025): 10.5005/jaopn-11028-0017

Acute encephalitis syndrome (AES) is an important public health problem in India. Acute encephalitis syndrome is a serious neurological condition with significant mortality and morbidity. A lot of research and advancements have happened over the last few decades for the prevention of AES and its acute management to prevent long-term neurological sequelae. Hence, there is a need for constant efforts both at the community and policy makers level to reduce the burden of AES in India.

Definitions

In 2008, term AES was coined by the World Health Organization (WHO) for surveillance and proper reporting of suspected encephalitis cases in India. As per WHO, AES case can be defined as "a person of any age, at any time of the year, with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizure)".

This definition was mainly useful for surveillance purposes and does differentiate various causes of AES. It not only includes viral encephalitis, but also all etiologies of fever and altered sensorium, such as bacterial meningitis, tubercular meningitis, cerebral malaria, and acute disseminated encephalomyelitis.

Hence in 2013, **International Encephalitis Consortium** (IEC) has defined it as per the fulfilment of certain major and minor criteria, where the major criteria is MUST, and it states: Neurological dysfunction manifesting with altered mental status for more than 24 hours without an alternative cause.

Minor criteria includes: 1. Fever >38°C. 2. New focal neurological findings. 3. Cerebrospinal fluid (CSF) pleocytosis >5 cells/mm^3 4. Cranial imaging showing brain parenchymal changes. 5. Electroencephalography findings are consistent with encephalitis.

When minimum two minor criteria is present, it is possible AES. With three minimum criteria, it is labeled as probable AES. Acute encephalitis syndrome is confirmed when there are more than three minor criteria. When there is lab confirmation of the etiological agent then it's a definite case of AES.

These new terminologies have helped clinicians in the proper diagnosis and management of the patients with suspect AES.

Epidemiology

Recently there was an outbreak of AES in Gujrat, and it was mainly attributed to the CHPV virus.

This recent outbreak clearly shows that there has been a significant shift in etiological agent over the last few years.

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In India, the first case of AES was clinically diagnosed in Tamil Nadu in 1955. Over the next 20 years, there were frequent outbreaks, which were mainly restricted to the southern part of the country. Between 1975 till 1999, there were outbreaks that were predominantly of JE viruses. These outbreaks were mostly seen in Uttar Pradesh, Madhya Pradesh, and other northern and eastern parts of the country. From 2000 to 2010, there was a dramatic shift in AES etiology with the emergence of non JE outbreaks mainly caused by Nipah virus (NiV), Chandipura virus (CHPV) and other enteroviruses.

In last decade, along with these new viruses, there are still JE outbreaks happening mainly in Uttar Pradesh, Assam, West Bengal and Tamil Nadu. One more peculiar thing has been observed over the last few years, as there are many cases of para infectious and post infectious causes of AES are also seen.

This rise of probable autoimmune and para infectious causes may contribute to almost 30% of total etiological factors for AES.

This change in etiological spectrum is very important to redefine treatment protocols for AES patients. Over last two decades, significant research has happened on many fronts, like vaccine development, newer diagnostic technologies, use of various software and artificial intelligence (AI) for precise diagnosis, software for better surveillance. These efforts are helping us in reduce the epidemic burden of this disease.

A significant decrease in the burden of vaccine-preventable diseases was seen with the advent of vaccinations against

measles, rubella and mumps, along with improved rabies vaccines as pre-exposure and also post-exposure prophylaxis, and with effective vaccines against Japanese encephalitis since 2006.

Clinical Profile

Acute encephalitis syndrome can be clinicopathologically categorized into 5 various localizations depending on their clinical presentations

1. If focal abnormalities like focal seizures focal neurological deficits are more common, we need to think of focal involvement of cortical grey matter.
2. When features like dystonia dense encephalopathy are prominent, then involvement of deep gray matter involving thalamus and basal ganglia is more likely.
3. When long tract signs are seen early, then diffuse or patchy white matter involvement should be considered more likely.
4. When gait disturbances with mild or no encephalopathy is seen, then localization is mainly at cerebellar level.
5. In case of rapid progression of symptoms with respiratory involvement and multiple cranial nerve involvement, possibility of brainstem encephalitis are more likely.

Despite of significant advancements, the morbidity and mortality is still high in AES.

Predictors of poor outcome in children with AES can include:

- GCS <8 at the time of admission.
- Drug-refractory seizures.
- Invasive ventilation.
- Need of inotropes and mechanical ventilation.
- Etiology of AES.

Infection Triggered Encephalopathy Syndromes (ITES) and Its Implications

As discussed earlier, with advent of research, we are now aware of various autoimmune etiologies for AES. It's been observed that these various entities are nothing but a spectrum of various pathologies with varied clinical presentation. Hence now they are collectively defined as ITES. This umbrella term comprises various clinical, radiological, and pathological presentations of AES. These entities have helped us defining various treatment protocols and in identifying certain fast progressive and serious clinical entities like acute necrotizing encephalopathy of childhood (ANEC) and acute fulminant cerebral edema (AFCE). Infection triggered encephalopathy syndromes is a spectrum that includes ANEC, mild encephalopathy with reversible splenial lesion (MERS), febrile infection related epilepsy syndrome (FIRES), hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome, acute encephalopathy with biphasic seizures with late diffusion restriction (AESD). It is very important that these neuro-immunological conditions be identified appropriately and be treated on time.

Autoimmune encephalitis is one of the commonest para infectious neuro immunological phenomenon and is characterized by a constellation of symptoms like seizures, psychiatric symptoms, hyperkinetic movement disorders, gait disturbances and autonomic disturbances. After clinical suspicion the clinician needs to send the appropriate investigations and start immune modulators in appropriate dosage. Also, ITES spectrum includes fulminant manifestations like ANEC which requires a rapid diagnosis and may respond to newer immune modulators like tocilizumab if used at the appropriate time. With the ever expanding spectrum of AES including the autoimmune entities it is important that clinicians are updated with the recent guidelines and the updated investigation and treatment plan.

- **Way forward**: Lot of efforts are put in by both the government and health authorities to reduce the disease burden of AES in India. **Indian Academy of Pediatrics** (IAP) is taking lead in vaccine research and vaccination campaigns to prevent AES. Indian Academy of Pediatrics is also instrumental in organizing various training modules for pediatricians and other health care workers. Under **presidential action plan** of IAP 2025, various important teaching modules like the module encephalitis awareness, study and evaluation module (**EASE**), and the one health module (prevention of various zoonotic diseases) are rolled over across the country. Such efforts will help in drafting region-specific treatment and prevention protocols. We are sure that vaccine research will further reduce in the incidence of AES in near future.

ORIGINAL RESEARCH

Analysis of Cases of Acute Encephalitis Syndrome in a Pediatric Intensive Care Unit

Sumit Kumar[1], Praveen Kumar[2], Shreya Chauhan[3], Ramakant Sabharwal[4]

Received on: 27 April 2025; *Accepted on:* 21 May 2025; *Published on:* 03 June 2025

Abstract

Context: Acute encephalitis syndrome is a growing problem worldwide with varied etiologies, clinical presentations, and outcomes. The most challenging aspect of encephalitis is its etiological diagnosis. We aimed to analyze the etiological spectrum and evaluate the outcome of patients with acute encephalitis syndrome.

Evidence acquisition: Pediatric patients (6 months to 16 years) admitted to the pediatric intensive care unit (PICU) from 2014 to 2024 with symptoms suggestive of encephalitis were included in the study. A thorough clinical examination and investigation workup were done to rule out the possible etiologies of encephalitis. Investigations included blood tests, cerebrospinal fluid (CSF) study, electroencephalogram (EEG), and neuroimaging. Prospective data were evaluated using the appropriate statistical tool, and the etiological profile and outcome were recorded.

Results: We identified 135 patients with acute encephalitis. The etiology of encephalitis was identified in 113 (84%) patients. Results showed that the most common cause of encephalitis in this study was immune-mediated encephalitis (28%), autoimmune encephalitis, constituting 15% of patients, and acute disseminated encephalomyelitis, constituting 13% of patients. The second most common cause was bacterial encephalitis (20%), followed by viral encephalitis in 18% of patients. Tuberculosis was the most common bacterial infection, and dengue virus was the most common viral infection. Patients with behavioral changes ($p = 0.003$) and super-refractory status epilepticus ($p < 0.0001$) on presentation were found to have more risk for autoimmune encephalitis. Electroencephalogram was abnormal in 84% of patients, but had non-specific findings, however delta brush pattern was seen in a few patients with autoimmune encephalitis. The magnetic resonance imaging (MRI) brain was abnormal in 67 (49%) patients. A positron emission tomography scan was done in two patients of autoimmune encephalitis with negative CSF and MRI findings, and it was abnormal in both cases. Other causes of encephalitis included systemic sepsis (6%) and metabolic causes like hepatic and renal failure (12%). Sixteen percent of patients remained undiagnosed even after an extensive investigation workup was available. There was an abnormal outcome in 44% of patients, particularly in cognitive and behavioral domains, with 3% mortality, and the remaining 53% were discharged without any morbidity. The predictors of poor outcomes were status epilepticus on admission, severe hemodynamic instability secondary to sepsis, and refractory seizures not responding to multiple antiepileptics.

Conclusion: Acute encephalitis syndrome is a serious problem with significant morbidity. Etiological diagnosis is important in improving the treatment outcome and prognosis. Non-infectious causes of encephalitis, like autoimmune encephalitis, are being increasingly recognized. If promptly diagnosed and treated appropriately, autoimmune encephalitis has a favorable immediate outcome.

Keywords: Acute encephalitis syndrome, Autoimmune encephalitis, Etiology.

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Introduction

Encephalitis is defined as inflammation of the brain. Diagnosis is pathological, not a clinical one. However, there are typical clinical findings, most importantly altered mental status (encephalopathy), often accompanied by headache, fever, nausea, and vomiting, and sometimes by seizures and focal neurological deficits.[1] Surrogate clinical markers, including inflammatory changes in the cerebrospinal fluid (CSF) or parenchymal inflammation on neuroimaging, are often used to diagnose it. Acute encephalitis syndrome (AES) is defined as the acute onset of fever with mental status changes (including symptoms such as confusion, disorientation, coma, or inability to talk) and often with new onset of seizures (excluding simple febrile convulsion) in a person of any age at any time of the year.[2] Acute encephalitis syndrome presentation can be as encephalitis, meningitis, or meningoencephalitis and may have infectious and non-infectious causes. The incidence is estimated at 3.5–7.4 per 1,00,000 inhabitants per year.[3–6]

The incidence of encephalitis in tropical regions is 6.3 per 1,00,000, whereas in the western world, the incidence varies between 0.7 and 13.8 per 1,00,000.[7] Encephalitis affects patients of all ages, but the incidence is higher in pediatric patients. The worldwide annual incidence of encephalitis reported ranges between 3.5 and 7.5 cases per 1,00,000 persons and 16 per 1,00,000 children.[8] Infections may include various viruses, bacteria, mycobacteria, rickettsia, and rarely by toxoplasma. Although viral infections are the most common

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causes of infectious encephalitis/encephalopathy, the causative virus can be unknown in up to 60% of cases.[9] Japanese encephalitis virus (JEV) and Dengue virus (DV) are more prevalent in South East Asia, including India. Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are the most common causes of acute infectious encephalitis in other parts of the world. Cerebrospinal fluid viral studies now play a pivotal role in finding the etiology of infectious causes of AES. Commercially available tests, testing for a panel of viruses (pan flavivirus RNA, pan enterovirus RNA, pan paramyxovirus RNA, pan herpes virus DNA) and bacteria with a 1–2 mL CSF sample, using molecular techniques, are available now.[10]

An important differential diagnosis mimicking acute viral encephalitis is acute disseminated encephalomyelitis (ADEM), which may follow an initial respiratory infection, diarrhea, or post-vaccination.

Patients who were empirically diagnosed as viral encephalitis with normal CSF reports are now being increasingly recognized as having autoimmune encephalitis since the discovery of several neuronal surface and cytoplasmic antibodies. Autoimmune encephalitis may be classified as either possible autoimmune, probable autoimmune, definite limbic, or anti-NMDA encephalitis.[11] Presentation varies and depends on the category and the specific autoimmune condition. Clinicians should suspect an autoimmune encephalitis in clinical scenarios of otherwise unexplained CSF fluid pleocytosis or elevated protein, hyperintensities in limbic structures on magnetic resonance imaging (MRI), recent onset systemic symptoms suggestive of malignancy, psychiatric symptoms, or when status epilepticus occurs as part of a subacute neurologic degenerative disorder.

Acute encephalitis is a medical emergency requiring prompt diagnosis and specific antiviral treatment, and other supportive treatment.[12,13]

Thus, differentiating between infectious and non-infectious causes of acute encephalitis syndrome is important because non-infectious immune-mediated cases are mainly treated with corticosteroids, IV immunoglobulin (IVIg), plasmapheresis, and other supportive treatment. Timely, appropriate treatment has a significant influence on survival and the extent of brain sequelae.

This study consisted of identifying patients with acute encephalitis and encephalitis-like syndrome (AES), and then classifying the patients according to clinical and etiological profiles. There is limited data available regarding the etiological spectrum of acute viral encephalitis and related syndromes in Indian children. More so, the data regarding autoimmune encephalitis is scarce. The present study proposes to establish the diagnosis of such cases through clinical details and investigation workup.

Materials and Methods

This is a prospective, observational study conducted in the pediatric intensive care unit (PICU) at Institute of Child Health (ICH), Sir Ganga Ram Hospital, New Delhi, India, a tertiary health care center with the state of art facilities and required diagnostic modalities including research facility catering to all strata of the society. The study was conducted over a period of 3 years, starting from December 4, 2014 to December 4, 2017, after approval by the ethical committee. Patients were clinically evaluated and investigated as per the specified methodology. No extra investigations or procedures were done entirely for study purposes.

Patients fulfilling the inclusion criteria were examined by the clinician. The clinical details, such as demographic details, history, symptoms, and signs during admission, reason for PICU admission, and systemic examination, were noted. After the initial resuscitation including maintaining vitals, maintenance of blood glucose, electrolyte imbalance and aborting active seizures, investigations as blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood culture, urine routine with culture, liver function test (LFT), kidney function test (KFT) were sent and treatment, including antibiotics and antiviral therapy, started accordingly. Electroencephalogram (EEG) was done to look for background cerebral electrical activity, epileptiform activity, and to exclude non-convulsive status epilepticus. Magnetic resonance imaging brain with contrast was done. Eligible patients were subjected for lumbar puncture and CSF studies for cytobiochemistry, gram stain, bacterial antigen (*Streptococcus pneumonia*, group B *Streptococcus*, *Neisseria meningitides*, and *Hemophilus influenza* B), AFB stain and culture and pan neurotropic viruses (pan flavivirus RNA, pan enterovirus RNA, pan paramyxovirus RNA, pan herpes virus DNA) were sent. In case of normal CSF studies, lumbar puncture was repeated after 72–96 hours. Patients in whom lumbar puncture could not be done were excluded from the study. Status epilepticus was defined as a seizure that lasts longer than 5 minutes or two or more seizures without return to the neurological baseline condition in between.[14] Refractory status epilepticus was defined as ongoing seizures despite two appropriately selected and dosed antiepileptic drugs (AEDs), including a benzodiazepine. Glasgow coma scale (GCS) was used to assess impaired consciousness based on motor responsiveness, verbal performance, and eye opening to an appropriate stimulus. A coma was defined as GCS < 8. In patients with a suggestive clinical course and investigations, workup for autoimmune encephalitis, including CSF for autoimmune antibodies (anti-NMDAR antibody, GABA receptor antibody, LGI1 (VGKC type) antibody, CASPR 2 antibody, and GLUR1, GLUR2 antibodies) was sent.[15] Contraindications for lumbar puncture were moderate to severe impairment of consciousness (GCS < 13 or fall in GCS of >2), focal neurological signs (including unequal, dilated or poorly responsive pupils), papilledema, Cushing's triad, immunocompromised patients, systemic shock, coagulation abnormalities like thrombocytopenia (platelet count < 100×10^9/L), ongoing anticoagulant therapy, local infection at the lumbar puncture site, respiratory distress and neuroimaging suggestive of increased intracranial pressure. Enrolled patients were monitored, and the outcome was determined in terms of total duration of hospital stay, mortality, and survival (whether intact or with morbidity). After completion of the study, data were evaluated using an appropriate statistical tool, and the etiological profile and outcome were recorded.

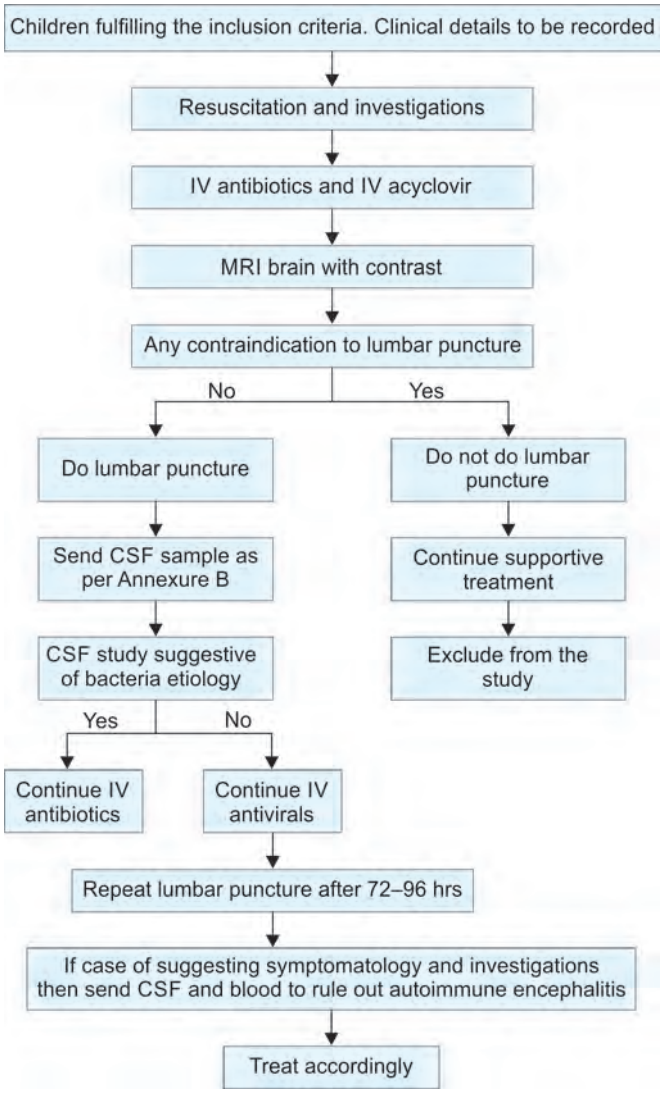
Objectives

- To establish an etiological diagnosis of patients presenting with fever (temperature > 38°C) and encephalopathy (altered level of consciousness persisting for ≥24 hours) with or without seizures, focal neurological deficits, and behavioral changes based on clinical profile and investigations.
- To evaluate the outcome, in terms of mortality, morbidity, or intact survival until discharge from hospital and duration of hospital stay, of enrolled patients.

Statistical Methods

Statistical testing was conducted with the Statistical Package for the Social Sciences System version SPSS 17.0. Continuous variables were presented as mean ± SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as

Flowchart 1: Schematic diagram showing the methodology



frequencies and percentages. *p*-value < 0.05 was considered to be significant (Flowchart 1).

Inclusion Criteria

All children aged from 6 months to 16 years admitted to the pediatric intensive care unit with symptoms of fever (temperature > 38°C) and encephalopathy (altered level of consciousness persisting for ≥24 hours) with or without seizures, focal neurological deficits, and behavioral changes.

Exclusion Criteria

- Age < 6 months or >16 years.
- Left the study in between (left against medical advice or transferred out to another health facility).
- Patients with a confirmed diagnosis before admission.
- Patients in whom lumbar puncture could not be done.
- Refused for informed consent.

Results

In the present study, a total of 135 patients aged 6 months to 16 years presenting with fever (temperature > 38°C) and encephalopathy (altered level of consciousness persisting for ≥24 hours) with or without seizures, focal neurological deficits, and behavioral changes were analyzed according to different characteristics. Male:female ratio was 2.5:1. Out of 135 cases (Table 1), a total of 47 (35%) patients were in the age-group of 6 months to 5 years, 58 (43%) patients were in the age-group >5–10 years and rest 30 (22%) patients were more than 10 years in age (Table 2). A thorough clinical examination and investigation workup were done to elicit the possible etiologies of encephalitis. Investigations included blood serology tests, CSF study, EEG, and neuroimaging. Data was evaluated using the appropriate statistical tool, and the etiological profile and outcome were recorded. Most of the patients had a subacute onset of disease, and none of the patients presented with an acute onset. Out of 135 patients, 80 (59%) patients had presented with chief complaints of fever for more than 24 hours, altered sensorium, and seizures. Thirty-five (43%) patients presented in status epilepticus, and 15 (18%) eventually had refractory status epilepticus. Seven (8%) patients presented in a comatose condition. Twenty-nine (23%) patients out of 54 had behavioral changes in the form of irritability, hallucinations, and inappropriate speech. The remaining 26 patients (32%) had focal neurological deficits with fever and altered sensorium in the form of unequal pupils and hemiparesis (Table 3 and Figs 1 to 3).

Table 1: Sex wise distribution

Sex	*Number of children*	*Percentage (%)*
Male	96	71
Female	39	29
Total	135	100

Table 2: Age-wise distribution

Age distribution	*Number of children*	*Percentage (%)*
6 months–5 years	47	35
>5–10 years	58	43
10 years	30	22
Total	135	100

Table 3: Major presenting features

Major presenting complaint	*Number of patients*	*Percentage (%)*
Fever + altered sensorium + focal neurological deficit	26	20
Fever + altered sensorium + behavioral changes	29	21
Fever + altered sensorium + seizures	80	59
Total	135	100

Sepsis screen was abnormal in 87 (64%) patients, but culture-proven positive sepsis was seen in 12 (8%) patients (Tables 4 and 5). Cerebrospinal fluid pleocytosis was seen in 77 patients (57%) patients and high CSF protein was seen in 38 (28%) patients, but both findings did not vary between patients with different etiologies. However, low CSF glucose (10%) was found mainly in patients with bacterial meningoencephalitis. Cerebrospinal fluid biofire examination was positive in six patients with viral encephalitis and three patients with bacterial meningoencephalitis. Cerebrospinal fluid for the autoimmune antibody panel was positive for anti-NMDA antibodies in seven

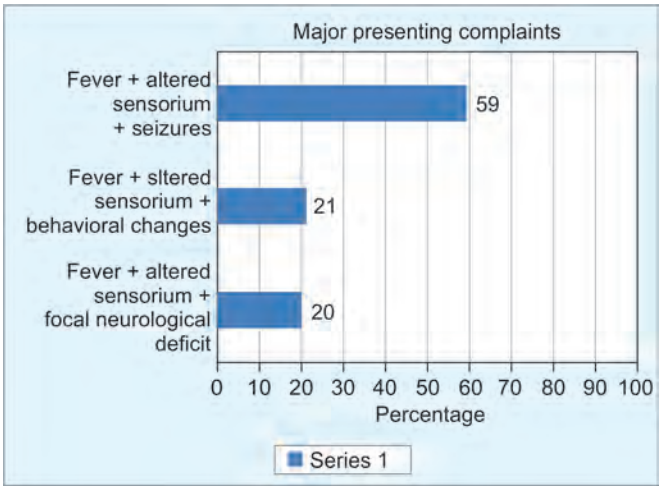


Fig. 1: Major presenting features

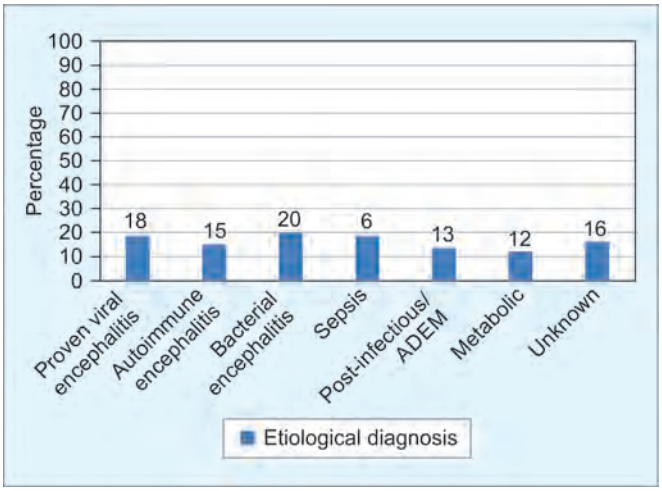


Fig. 2: Etiological diagnosis

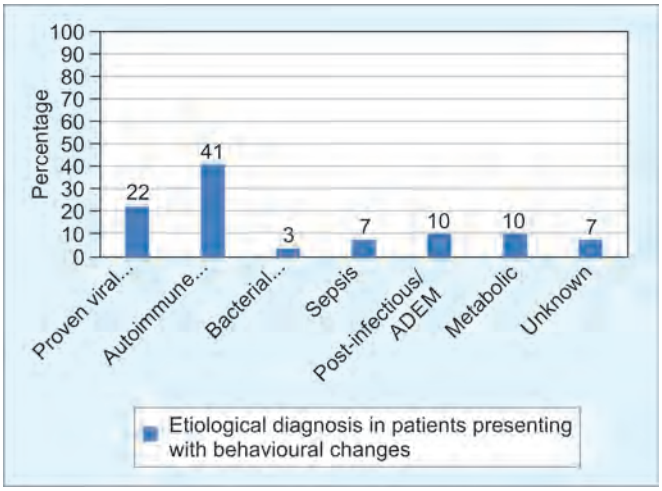


Fig. 3: Etiological diagnosis in patients presenting with behavioral changes

patients. Electroencephalogram was abnormal in all patients but had non-specific findings; however, "delta brush pattern" was seen in nine patients of autoimmune encephalitis. The MRI brain was abnormal in 67 (49%) patients. None of the patients showed any evidence of malignancy. A positron emission tomography (PET) scan was done in two patients of autoimmune encephalitis with negative CSF and MRI findings, and it was abnormal in both cases. Results (Tables 6 to 9) showed that the most common cause of encephalitis in this study was immune-mediated encephalitis (28%), autoimmune encephalitis constituting 15% of patients, and ADEM constituting 13% of patients. The diagnosis of autoimmune encephalitis was made by the new guidelines by Francesc et al.[11] A total of 10 patients (50%) out of the 20 had possible autoimmune encephalitis with focal CNS findings. A total of 3 (15%) had limbic encephalitis with typical MRI changes, and 5 (25%) patients had classical NMDAR encephalitis. The remaining two patients (10%) had probable autoimmune encephalitis with typical MRI features and CSF pleocytosis (Table 10). The second most common cause was bacterial meningoencephalitis (20%), with tuberculosis being the most common bacterial infection. Viral encephalitis was diagnosed in 18% of patients, dengue virus being the most common viral infection (Table 9). There were two cases of SSPE secondary to possible previous measles infection. Other causes of encephalitis included systemic sepsis (8%) and metabolic causes, including hepatic and renal failure (12%). Sixteen percent of patients remained undiagnosed even after an extensive investigation, and workup was available (Figs 4 to 6).

All the patients were started on IV antibiotics and antiviral acyclovir (Table 11). Later on, depending on the clinical scenario and investigation results, antibiotics were stopped in 45% of patients, and antiviral was stopped in 33% of patients. Steroids were given to 46 patients (34%). Indications were tubercular meningitis, autoimmune encephalitis, ADEM, and enteric fever, tubercular meningitis. IV immunoglobulin was given to 15 patients (11%). Indications were mainly autoimmune encephalitis. Plasmapheresis was required in 12 autoimmune encephalitis patients (8%). Mechanical ventilation was needed in 44 patients (32%). Indications were coma, refractory seizures, and severe hemodynamic instability. Anti-tuberculosis drugs were required in 20 diagnosed cases of tubercular meningitis (15%).

Morbidity in the form of behavioral and cognitive dysfunction was seen in almost 35% of patients, and 3% of patients died during the hospital course (Table 12). The mean duration of stay was 15 days. The minimum number of days of hospitalization was 2 days, and the maximum was 71 days.

Discussion

Patients with acute encephalitis syndrome present with fever, altered consciousness with or without seizures, focal neurological deficits, and behavioral changes. The diagnosis is usually presumptive, based on presenting clinical signs and symptoms. Acute encephalitis syndrome can have varied infectious and non-infectious etiologies and outcomes. Our study of 135 patients in the age-group 6 months to 16 years with encephalitis-like presentation seeks to classify and characterize the infectious, non-infectious causes, including immune-mediated/autoimmune encephalitis, encephalopathy secondary to metabolic causes, and other unknown forms of encephalitis.[14–18]

In our study, male to female ratio was 2.5:1 (Table 1) which has a higher male preponderance as compared to the study of California Encephalitis Project (1998–2005) by Glaser et al.[16] where male:female ratio was 1.2:1. In a study by Pillai et al.[17] in Australia, male:female ratio was 1.3:1. In an another study by Granerod et al.[18]

Table 4: Evaluation of 135 cases

	Sepsis screen	*LFT and RFT*	*LP*	*CSF biofire viral markers*	*CSF biofire bacterial antigen*	*CSF autoimmune antibody panel*	*MRI brain*	*EEG*	*PET*
No.	135	135	135	135	135	135	135	135	2
Normal	48	97	49	129	132	128	68	22	0
Abnormal	87	38	86	6	3	7	67	113	2
Comments	Blood culture—10 positive, urine culture—two positive	Abnormal Na-12, BUN, Creat-6, LFT-20	High cell count-77, Protein-38, Sugar-14	SSPE-Ab test, Varicella, Measles—Ab test, EV, HSV—PCR	*E. coli*, Pneumococcal	NMDAR+	Limbic encephalitis-3 ADEM	Delta brush pattern—nine cases	

Table 5: Evaluation of 135 cases—other investigations

Other investigations	*Number of patients*	*Percentage (%)*
Dengue NS1 antigen positive	15	11
Dengue IgM + HAV IgM	1	0.7
Influenza PCR + HAV IgM	1	0.7
Scrub typhus IgM	1	0.7
Widal test	4	3
HEV IgM	1	0.7
ELISA for JE (sent in five pts)	0	0

ELISA, enzyme linked immunosorbent assay; HAV, hepatitis A virus

Table 6: Etiological diagnosis

Diagnosis-wise distribution	*Number of patients*	*Percentage (%)*
Viral encephalitis	24	18
Autoimmune encephalitis	20	15
Sepsis	8	6
Bacterial encephalitis (TBM, Typhus, *E. coli*, Pneumococcal)	27	20
Post-infectious/ADEM	18	13
Metabolic causes	16	12
Unknown	22	16
Total	135	100

TBM, tubecular meningitis

Table 7: Etiological diagnosis in patients presenting with behavioral changes

Diagnosis-wise distribution of patients presenting with behavioral changes	*Number of patients*	*Percentage (%)*
Viral encephalitis	6	22
Autoimmune encephalitis	12	41
Sepsis	2	7
Bacterial encephalitis (TBM, Typhus, *E. coli*, Pneumococcal)	1	3
Post-infectious/ADEM	3	10
Metabolic causes	3	10
Unknown	2	7
Total	29	100

Table 8: Etiological diagnosis in patients presenting with super-refractory status epilepticus

Diagnosis-wise distribution of patients presenting with behavioral changes	*Number of patients*	*Percentage (%)*
Viral encephalitis	2	14
Autoimmune encephalitis	13	86
Sepsis	0	0
Bacterial encephalitis (TBM, Typhus, *E. coli*, Pneumococcal)	0	0
Post-infectious/ADEM	0	0
Metabolic causes	0	0
Unknown	0	0
Total	15	100

Table 9: Etiological diagnosis—proven viral encephalitis

Proven viral encephalitis	*Number of patients*	*Percentage (%)*
Dengue	15	63
Dengue + hepatitis A	1	4
Varicella zoster virus	1	4
Enterovirus	1	4
Influenza + hepatitis A	1	4
Hepatitis E	1	4
Measles	3	13
Herpes	1	4
Total	24	100

Table 10: Etiological diagnosis—autoimmune encephalitis

Type of autoimmune encephalitis	*Number of patients*	*Percentage (%)*
Possible	10	50
Probable	2	10
NMDAR	5	25
Limbic	3	15
Total	20	100

in England, male:female ratio was around 1.1:1. Whether men and boys are more susceptible to encephalitis, or have greater exposure to causative agents, needs to be established. The majority of our patients were in the age-group of >5–10 years (Table 2), which coincides with a similar study by Beig et al.[19] Similar result was shown by a study by Fidan et al.[20], AES being more common in the younger age-group (<15 years).[19–21]

The etiology of encephalitis was identified in 113 (84%) of our patients (Table 6). This is considerably higher than the diagnostic yield in some of the previously reported series by Granerod et al.[18] and Glaser et al.[16] In our study, infectious cause of encephalitis was found in 59 (44%) patients, and non-infectious causes of encephalitis were diagnosed in 54 (40%) of patients. This was

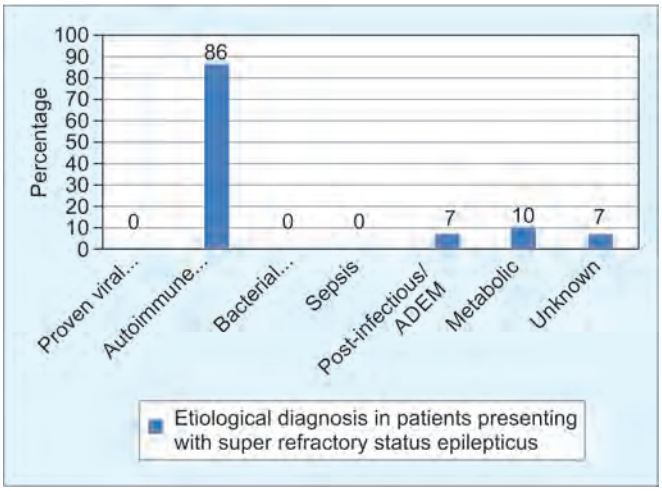


Fig. 4: Etiological diagnosis in patients presenting with super-refractory status epilepticus

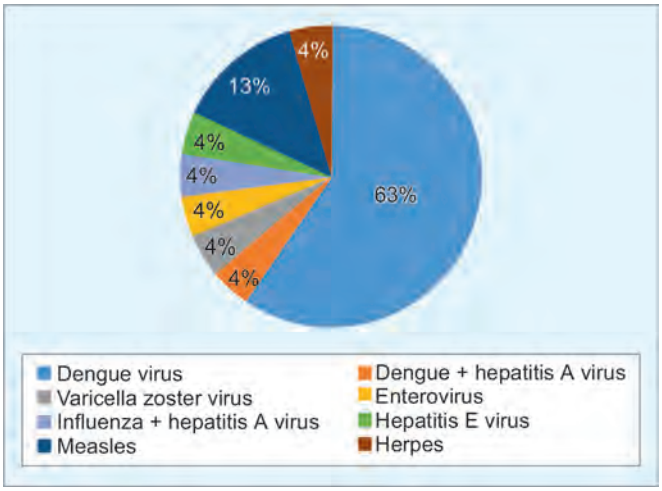


Fig. 5: Proven viral encephalitis

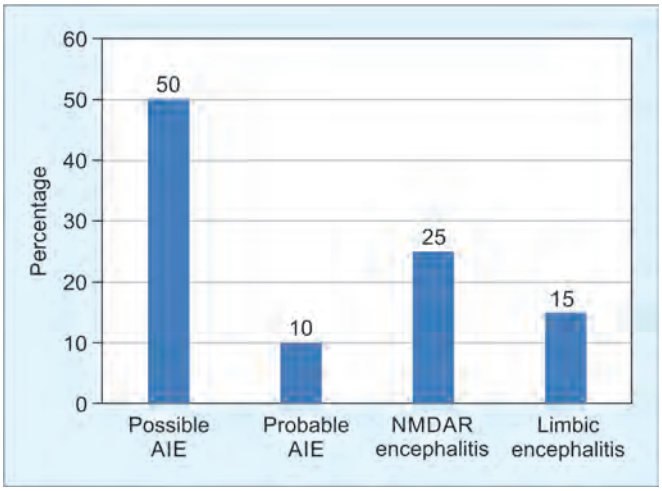


Fig. 6: Autoimmune encephalitis

comparable with the study done by Pillai et al.[17] where an infectious etiology was found in 36% of patients and a non-infectious etiology in 21% of patients. In the study by Glaser et al, infectious etiology was found in 29% of patients and non-infectious etiology in 8% of patients. Our being a tertiary care center with better availability of tests and affordability for patients might have resulted in a better diagnostic yield.

Timely distinction between various causes of acute encephalitis is essential to direct appropriate and specific management for better response, outcomes, and prognostication. We confirmed the well-described clinical findings for viral, bacterial, and mycobacterial causes. However, no single presenting feature, CSF results, could alone or in combination accurately differentiate between different etiologies. All the patients with encephalitis had fever and altered sensorium during the presenting illness (Table 3). More than 50% of patients had headaches, seizures, and lethargy. Irritability, meningeal signs, personality or behavioral changes, and focal neurological deficits were also recorded. The proportion of patients with seizures and irritability varied significantly by cause. The maximum number of patients presenting with seizures were of immune-mediated and proven viral etiology. These diseases tend to manifest with seizures. A total of 35 (43%) patients presented in status epilepticus, out of which 15 patients (18%) did not respond to multiple antiepileptics and needed the use of anesthetic drugs to control seizures and were classified as super-refractory status epilepticus. The majority of such patients were diagnosed as having autoimmune encephalitis ($p < 0.0001$) and responded to immunotherapy. Autoimmune encephalitis has been described to present with refractory status epilepticus.[21,22] By contrast, the incidence of seizures was less in patients with ADEM, varicella zoster virus, and *Mycobacterium tuberculosis* infection. Behavior manifestations and movement disorders are more common features of autoimmune encephalitis than ADEM. Presentation of respiratory symptoms, skin rashes, and gastrointestinal symptoms also varied significantly by cause (Table 3). Respiratory symptoms were more common in patients with ADEM and dengue encephalitis than in any other etiological group. Rash was most common in patients with dengue virus and varicella meningoencephalitis. Dengue and varicella encephalitis are known to have exanthematous presentation. Gastrointestinal symptoms (predominantly vomiting) were present in more than half of all patients with encephalitis and were most common in patients with bacterial etiology, patients with sepsis (7%), and those in whom no cause was found. The systemic findings are helpful in the etiological evaluation. Clinical signs during presentation may give a clue towards autoimmune encephalitis. Movement disorders, sleep disturbances, and behavioral changes ($p = 0.003$) in a setting of seizures, especially in the absence of fever, should alert clinicians to the possibility of autoimmune encephalitis because this symptom commonly occurs in NMDA receptor and voltage-gated potassium channel encephalitides.[23,24] Focal neurological symptoms in the form of hemiparesis, unequal pupils were most common in cases of meningoencephalitis secondary to *Mycobacterium tuberculosis*. Meningeal signs were positive in 11 (20%) patients and mainly comprised patients with bacterial causes of meningoencephalitis and a few cases of encephalitis of unknown causes (Table 10). Glasgow coma scale was ≤12 in 83 (62%) patients, and 7 (8%) patients presented in a comatose condition. These signs help in early suspicion and thus immediate management without any delay.

Serum electrolyte levels showed hyponatremia in 12 (9%) patients, in the range of 130–135 meq/L, and were associated with decreased serum osmolarity in 10 patients. It was thought to be a

Table 11: Treatment details

	IV Antibiotic	*IV Acyclovir*	*IV MP*	*IVIg*	*Plasmapheresis*	*Rituximab*	*Ventilation*
Given	135	90	46	15	12	1	44
Not Given	0	45	89	120	123	134	91
Comment	Discontinued in 62 patients	Discontinued if not proven viral			ADEM-1	NMDAR +ve	Indications: coma, refractory seizures, severe hemodynamic instability

Table 12: Outcome

Outcome	*Number of patients*	*Percentage (%)*	*Comments*
Discharged without disability	71	53	–
Discharged with disability	60	44	–
Death	4	3	Sepsis, MODS, ARDS, Dengue with HLH, Encephalitis with MODS

part of syndrome of inappropriate antidiuretic hormone secretion (SIADH), causing dilutional hyponatremia commonly associated with meningoencephalitis of varied etiologies. Another two patients with hyponatremia were diagnosed with autoimmune encephalitis, which is a common association.

Sepsis workup in blood helped to diagnose AES secondary to systemic sepsis. Hyperleukocytosis in blood was seen in one-fourth of the patients, comprising mainly those with culture-positive sepsis and bacterial causes of encephalitis (Table 4). Decreased blood counts were seen in patients with culture-positive enteric fever and patients with serologic evidence of dengue virus. Enteric fever and dengue illness are known to have leucopenia. C-reactive protein and ESR were high in more than 50% of patients with sepsis and even in non-infectious causes, which were associated with severe hemodynamic instability due to secondary sepsis. Children in the PICU are prone to secondary sepsis. Sepsis was diagnosed as a cause of encephalopathy in eight patients (6%) and was treated with antibiotics. The proportion of cases secondary to sepsis in studies by Granerod et al.[18] and Pillai et al.[17] was 3.5 and 8% of patients, respectively.

High CSF cell count (Table 4) was seen in 77 patients (57%), and high CSF protein in 38 patients (28%). The presence of pleocytosis and abnormal protein in the CSF did not vary significantly between patients with different causes of encephalitis. About 10 patients with viral or immune-mediated encephalitis and an unknown cause had a CSF cell count >5 cells/mm^3. A total of 27 (20%) of patients with bacterial causes of encephalitis had low glucose and high protein in CSF. However, low CSF glucose was found only in bacterial etiology. This is a very important etiological clue. Bacterial causes were also associated with high CSF white cell counts with neutrophilic predominance. One patient with a positive gram stain and bacterial antigen for *Streptococcus pneumoniae* was diagnosed as having pneumococcal meningitis. Abnormal CSF protein concentrations were found more in patients with ADEM and proven viral encephalitis than in patients with immune-mediated causes. Cerebrospinal fluid pleocytosis was seen in 71% of patients in a study by Pillai et al.[17] and 80% of patients in the study by Granerod et al.[18]

Magnetic resonance imaging brain and EEG were done in all 135 patients in the study. Magnetic resonance imaging was abnormal in 67 patients (49%). Magnetic resonance imaging findings were found to be different in patients with different etiologies. Magnetic resonance imaging brain was found to be abnormal in patients with ADEM and tubercular meningitis, as compared to being more normal in patients with autoimmune encephalitis and patients with unknown causes. Acute disseminated encephalomyelitis (ADEM) has been regarded as a clinicoradiological entity. Three patients with limbic encephalitis (15%) had typical hyperintensity in the temporal lobe and thalamic areas. Abnormal MRI was found in 80% of patients in a study done by Pillai et al.[17] and in 60% of patients in a study by Granerod et al.[18] Abnormal MRI in these studies was seen mainly in patients with ADEM and HSV encephalitis. Electroencephalogram (EEG) was abnormal in 32 patients (59.3%). Abnormal EEG findings did not vary among different etiologies. However, nine patients with autoimmune encephalitis had a typical delta brush pattern in the EEG. Delta brush pattern is a rhythmic delta activity 1–3 Hz with superimposed bursts of rhythmic 20–30 Hz beta frequency activity "riding" on each delta wave. It is not specific but suggestive of NMDAR encephalitis.[25] In a study done by Pillai et al.,[17] EEG was abnormal in around 88% of patients, and in a study done by Granerod et al.,[18] EEG was abnormal in 83% of patients.[25]

Positron emission tomography scan was done in two cases of suspected autoimmune encephalitis with negative CSF autoantibodies and normal MRI findings. It showed hypometabolism in various areas of the brain, including bilateral thalami, midbrain, pons, and temporal lobes, typical of autoimmune encephalitis. Studies have shown that even in the normal structural MRI findings, fluorodeoxyglucose positron emission tomography (FDG-PET) may show hypometabolism in the medial temporal lobe and may have potential for clinical course prediction and treatment follow-up.[26] We found an abnormal PET scan helpful in the early step-up of therapy.

The most common infection causing encephalitis was bacterial (20%) (Table 6). The most frequent bacterial infection was *M. tuberculosis* (74%). Studies show that tuberculosis affecting the brain usually presents as chronic meningitis, however, the infection may lead to encephalitis.[27] Tuberculosis constituted 1% of encephalitis patients in the study by Glaser et al.[16] and Granerod et al.[18] The CSF picture of tubercular infection may be atypical and may be similar to those associated with acute viral infections. A total of 4 (15%) patients were diagnosed with enteric fever encephalitis. The identification of tuberculosis and enteric fever is clinically important as these infections still have a high prevalence in developing countries like India, and these patients respond to specific treatment; delay in diagnosis and treatment is associated with serious complications, poor outcome, and high mortality rates.

The second most common infection causing encephalitis was viral, seen in 18% of patients. Dengue virus encephalitis accounted for 53% of the total of 24 patients diagnosed with viral encephalitis (Table 7). Results were in contrast to the studies done by Pillai et al.[17] and Granerod et al.,[18] where viral encephalitis constituted

the most common etiology, around 23–28% of total cases, but the most common viral infection was of EV and HSV. Dengue virus infection is more common in this part of the world.[28–32] Three cases of viral encephalitis were related to the measles virus, out of which there were two cases of post-measles subacute sclerosing panencephalitis (SSPE). Few recent studies in India have shown continued high prevalence of Japanese encephalitis virus and resurgence of Chandipura virus in acute encephalitis outbreaks.[33–37]

Out of 135 patients, immune-mediated encephalitis was the most common etiology, seen in 38 patients (28%). Autoimmune encephalitis (Table 8) was diagnosed in 20 patients (15%). The presence of autoimmune encephalitis is consistent with the recent studies reporting a prevalence of 20–40%.[16,18] Anti-encephalitis was diagnosed in five patients, who had typical clinical features of the disease, with predominant orofacial-facio-brachial movements, psychiatric problems, sleep disturbance, speech disorder, and autonomic features. The high incidence of autoimmune encephalitis in suspected cases of acute encephalitis in our study, especially when presenting with prominent seizures, behavioral changes, mild CSF pleocytosis, and typical EEG changes, suggests that prompt diagnosis and treatment with immunotherapy are effective if given early. A total of 18 (13%) patients had ADEM but without any serological evidence of infection.[29]

Encephalopathy secondary to metabolic causes was seen in 16 patients (12%), hepatic failure being the cause in six patients, nine cases of renal failure secondary to UTI, and one patient had diabetic ketoacidosis. Serum ammonia levels were not significantly high in these patients. Metabolic causes leading to encephalopathy constituted 0.4% patients in study by Glaser et al.[16] Older studies had higher percentage of undiagnosed cases in AES and with the availability of newer tests such as autoimmune and viral serology, advanced MRI techniques and PET scan, cases such as autoimmune encephalitis, metabolic disorders are increasingly being recognized.

Systematic use of modern molecular diagnostics in combination with timely investigation for non-infectious causes might explain the low proportion of cases of unknown causes (Table 6) in 22 cases (16%) compared with the 60% previously described in studies.[5,30] Possible explanations include the failure to identify non-encephalitic syndromic mimics, inadequate case investigation, and the presence of novel infectious or non-infectious encephalitis causes. Treatment of most of the patients with proven viral encephalitis was usually supportive. Antibiotics were continued in 73 patients (54%) with culture-proven sepsis and in patients with high sepsis markers and hemodynamic instability (Table 9). Most of the patients with autoimmune encephalitis responded to immunotherapy in the form of steroids, IVIg, and plasmapheresis. IV immunoglobulin and plasmapheresis were given to patients with autoimmune encephalitis, where seizures were resistant to anti-epileptics and steroids. Our study shows that immunotherapy has the potential for remarkable improvement in patients with autoimmune encephalitis, even if the presentation is late and very severe. Mechanical ventilation was needed in 44 patients (32%), mainly in patients with coma, refractory status epilepticus, severe hemodynamic instability, and sepsis. Therefore, our study supports the current evidence of aggressive treatment of patients with encephalitis, regardless of etiology and severity of presentation, because of the possibility of favorable recovery.[31]

Out of 135 patients, four patients (3%) died during the hospital stay (Table 12). The mortality rate in this study was similar to data quoted in England for cases of viral encephalitis (7%) but lower than those quoted in a recent French study (10%).[32] Three out of four patients (75%) were diagnosed as having autoimmune encephalitis with severe hemodynamic instability, requiring ionotropic support, and one patient had severe sepsis.

Our study confirms that encephalitis is a serious disease with an abnormal outcome in 44% of patients, particularly in cognitive and behavioral domains, with 3% mortality, and the remaining 53% were discharged without any morbidity. In general, the predictors of poor outcomes were status epilepticus on admission, severe hemodynamic instability secondary to sepsis, and refractory seizures not responding to multiple antiepileptics, as in previous studies.[33,34]

The patients with poor outcomes in our study emphasize the importance of future research in this area. The present study demonstrates the varied presentations of clinical and etiologic characteristics of acute encephalitis and contributes to the importance of timely targeted management and treatment options. The recognition of subgroups of patients with encephalitis as described in this report may be useful to clinicians in identifying the various etiologies of encephalitis, selecting the treatment strategies, and anticipating the course of illness and the prognosis for the patient. Second, knowledge of the natural history of a given profile may also be helpful in counseling families. Additional studies, however, are needed to determine the precision of these estimates and the effectiveness of case-specific management strategies.

Conclusion

- Acute encephalitis syndrome is a serious problem with significant morbidity.
- Etiological diagnosis is important in improving the treatment outcome and prognosis.

Non-infectious causes of encephalitis, like autoimmune encephalitis, are being increasingly recognized. If promptly diagnosed and treated appropriately, autoimmune encephalitis has a favorable immediate outcome.

Limitations of the Study

- Ours is a tertiary care referral center in North India, and more than one-third of the patients in this series were referred from peripheral hospitals. So, there is a strong possibility of a referral bias and findings may not be actual representative of the experience in other hospitals.
- A small sample size limits its generalizability.

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ORIGINAL RESEARCH

Clinical and Electrophysiological Characteristics of Generalized Photoparoxysmal Response in Children: A 10-year Retrospective Study

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Abstract

Background: Photosensitivity is characterized by an abnormal response in the electroencephalogram (EEG) during visual stimulation. This phenomenon is called a photoparoxysmal response (PPR). Photoparoxysmal responses can be elicited using intermittent photic stimulation (IPS) during EEG. Photoparoxysmal responses can occur with or without clinical symptoms. Generalized PPR is highly associated with various epilepsy syndromes. Photoparoxysmal response is an important variable in the management of such syndromes.

Aim of study: To study the electrographic and clinical characteristics of children with generalized PPR in EEG.

Methods and procedures: The cases were identified by reviewing the EEG records retrospectively. The study subjects consist of subjects <18 years of age with type IV PPR. Data were retrospectively analyzed with regard to their clinical and EEG findings by examination of patient files and EEG data for a study period from 2011 to 2021. Utilizing a structured proforma, we retrospectively gathered the demographics and EEG data.

Results: During the study period, 28 subjects were identified to have type IV PPR. There was a huge female preponderance (M:F = 1:3) in the study, similar to the previous literature. The majority of the subjects had idiopathic generalized epilepsy (IGE) (39.3%). Among them, five subjects had Juvenile myoclonic epilepsy (JME). More than 50% of the subjects had some form of clinical correlation along with the PPR, most commonly eyelid myoclonia (EEM). It was also seen that PPR was maximum at a frequency range of 8–14 Hz.

Conclusion: Juvenile myoclonus epilepsy, epilepsy with EEM, and photosensitive occipital lobe epilepsy (POLE) were the most common epilepsy syndromes associated with generalized PPR in our study. The electrophysiological features of the subjects in our cohort were similar to the previously reported pediatric and adult studies. Three subjects in our study had photic stimulation-induced generalized tonic-clonic seizure (GTCS) despite following the international protocols. Therefore, in addition to the benefits of photic stimulation (PS), consideration of safety measures is crucial. We could find a significant association between abnormal EEG background and abnormal MRI brain with intellectual disability. Further long-term prospective studies are needed to better characterize photosensitivity in children.

Keywords: Eyelid myoclonia, Idiopathic generalized epilepsies, Photoparoxysmal response, Photosensitivity.

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Introduction

Photosensitivity is characterized by an abnormal electroencephalogram (EEG) response during visual stimulation. This phenomenon is called a photoparoxysmal response (PPR). During EEG, PPRs can be elicited using intermittent photic stimulation (IPS). Photoparoxysmal responses can occur with or without clinical symptoms. When visual stimulation provokes an epileptic seizure, it is called a photosensitive seizure. During IPS, frequencies in the 15–25 Hz range were found to be most likely to trigger seizures.[1] Although the prevalence of photosensitivity in the general population is supposed to be 1/4,000, it is much more common in the pediatric age-group. Various studies report the prevalence of PPR in children from 2 to 5%.[2,3]

Photosensitivity occurs as part of different epilepsy syndromes, the most common being idiopathic generalized epilepsies (IGE).[4] Photoparoxysmal responses that outlast the stimulus as well as self-limiting PPRs (occurring only during the train of stimulus) are associated with seizures.[3] The detection of PPR in EEG depends on many factors, like the duration of recording, technical expertise, and, most importantly, anti-seizure medications (ASM) and type of epilepsy syndrome.[5]

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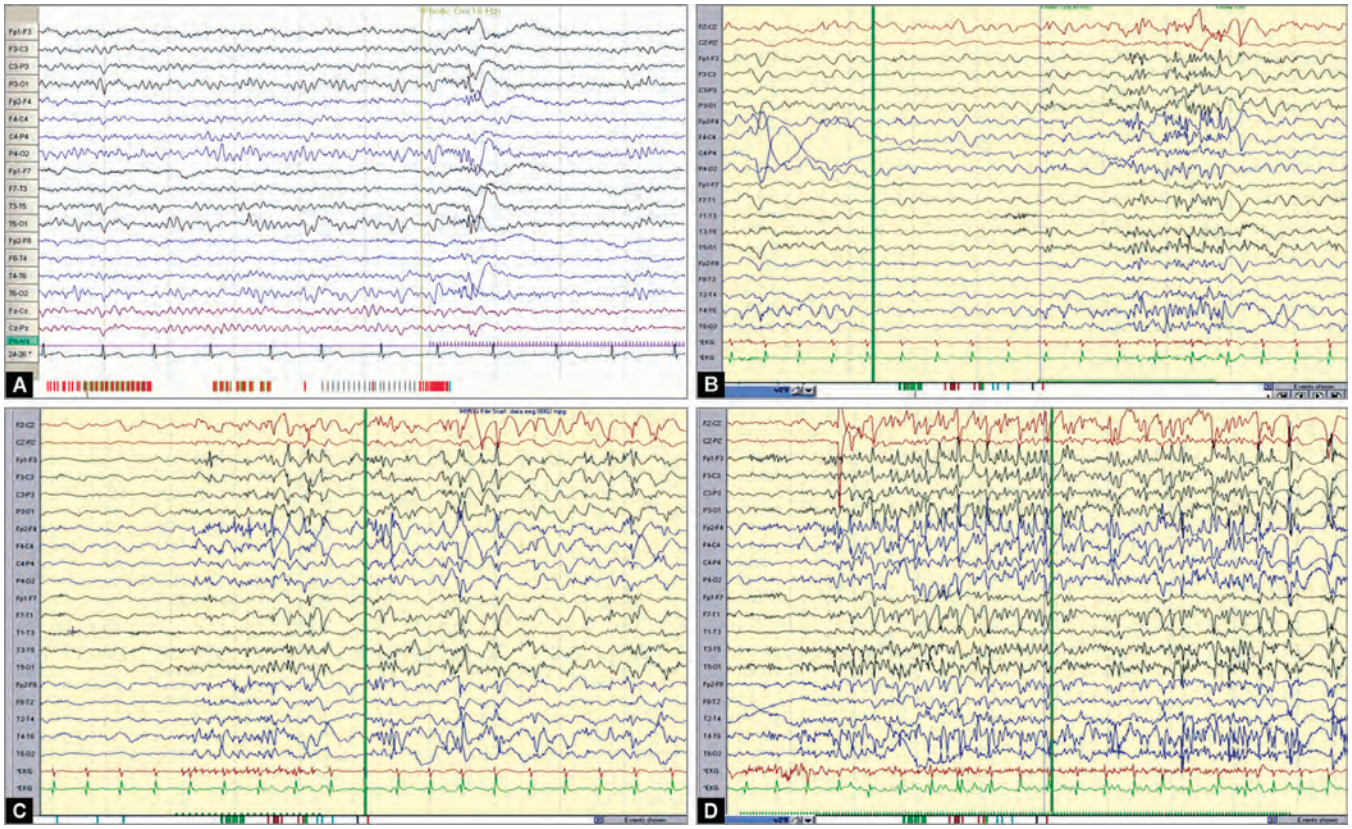
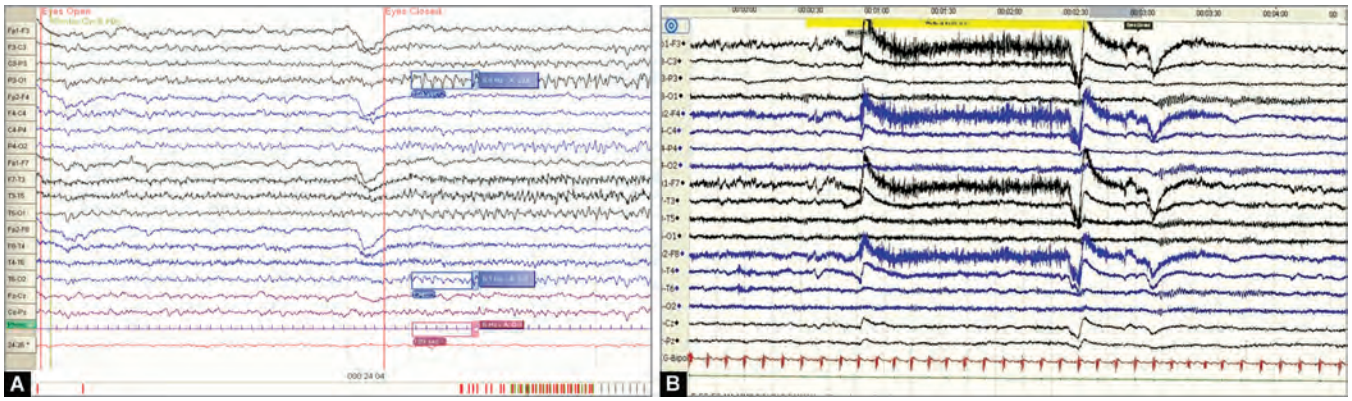
Waltz et al. first described the different pattern of PPR, which is still the most used classification system.[6] As per this system, PPR is divided into four types (Fig. 1):

1. **Type I**: Occipital spikes.
2. **Type II**: Parieto-occipital spikes with biphasic slow wave.



Figs 1A to D: Different grades of PPR during IPS (A) Grade I PPR at 18 Hz; (B) Grade II PPR at 30 Hz; (C) Grade III PPR at 10 Hz; (D) Grade IV PPR at 20 Hz



Figs 2A and B: Physiologic responses to IPS (A) Photic driving response time locked with IPS; (B) Photomyogenic response

3. **Type III**: Parieto-occipital spikes with biphasic slow wave and spread to frontal regions.
4. **Type IV**: Generalized spike/polyspike and wave discharges.

Photic driving and photomyogenic responses are considered physiological response with IPS (Fig. 2).

Methods and Procedures

This was a retrospective study performed at the neuro-electrophysiology lab of Amrita Institute of Medical Sciences and Research Center (AIMS), a tertiary referral center for epilepsy. The cases were identified by reviewing the EEG records done between January 2011 and December 2021. The study included all subjects below 18 years of age who had type IV PPR.[6] The subjects whose clinical and other details were not retrievable were excluded. The demographic, clinical, and electrophysiological data were collected using MS Excel and statistically analyzed using Stata Version 13.0.

Video EEG Recording and IPS Procedure

The video EEG recording was done using a digital video EEG system (Nicolet Biomedical). The recording length varied from 1 hour to 8 hours according to the clinical indication. Oral chloral hydrate was given to sedate the uncooperative subjects. Our video EEG recording consisted of a standard 19-channel scalp EEG, including vertex channels and one electrocardiogram channel. The electrodes

Table 1: Demographic details of the subjects

Variable	*Result, n (%)*
Total number of patients enrolled	28
Age	
Range	4–18 years
Mean	12.3 years
Median	12.5 years
1st and 3rd quartile	7–18 years
Male:Female	7:21 (1:3)
Mean age of seizure onset	6.6 years
History of clinical photosensitivity	3 (10.7%)
Presence of intellectual disability	9 (32%)
History of Febrile Seizures in the past	5 (18%)
Family history of epilepsy	14 (50%)

Table 2: Seizure characteristics in the subjects

Seizure type	
Generalized	15 (53.6%)
Focal/Multifocal	5 (17.5%)
Both	4 (14.3%)
Unknown	3 (10.7%)
No seizures	1(3.6%)
Epilepsy syndrome	
IGE	11 (39.3%)
–JME	–5
–Unclassified	–6
EEM with absences	6 (21.4%)
Benign childhood focal epilepsy	5 (17.9%)
–POLE	–4
–SELECTS	–1
Genetic suspected	5
Structural	0
ASM at the time of performing the EEG	
Yes	21 (75%)
No	7 (25%)
MRI	
Normal	22 (92%)
Abnormal	2
Not done	4

IGE, idiopathic generalized epilepsy; JME, juvenile myoclonic epilepsy; POLE, photosensitive occipital lobe epilepsy; SELECTS, self-limited epilepsy with centro-temporal spikes

(cup electrodes) were attached to the scalp with glue according to the international 10–20 system. The additional channels, like anterior temporal electrodes, monitor for electromyogram, respiration, electro-oculogram, and other transducers that were applied when indicated.

The standardized method of IPS was followed.[7] The photic stimulator was placed symmetrically in front of the patient's eyes, 30 cm from the nasion. The patient was seated and asked to look at the center of the lamp. Flashes at frequencies of 1, 2, 8, 10, 15, 18, 20, 25, 40, 50, and 60 each are given in trains of 5 seconds duration with eye closure, eye closed, and eye open in a room with reduced illumination. In children <4 years of age or with conditions that limit cooperation, eyes were kept closed by the parent or by the technician. Patients with photosensitivity were tested for pattern sensitivity by moving in front of their eyes using seven different standard patterns. The technologist was alerted to stop the stimulation immediately on identifying a type IV PPR since prolonged stimulation can trigger a generalized tonic-clonic seizure (GTCS) in a sensitive patient.

All the EEGs were read and reported by a team of experienced neurotechnologists and pediatric epileptologists.

Results

During the study period, there were 28 subjects detected to have type IV PPR in subjects under 18 years of age (Table 1). Out of 28 subjects, 21 were females (75%) and 7 were males (25%). The age range was 4–18 years, with a mean of 12.3 years. The mean age of seizure onset was observed to be 6.6 years. A history of clinical photosensitivity was present in three subjects (10.7%). In our study, nine subjects (32.1%) had intellectual disability as per the latest definition.[8] Idiopathic generalized epilepsy was the most common epilepsy syndrome among the subjects (n = 11, 39.3%).[9] Among them, five subjects were diagnosed to have Juvenile myoclonic epilepsy (JME). Self-limited focal epilepsy of childhood was diagnosed in five subjects (17.9%). Out of them, four had POLE and one had self-limited epilepsy with centro-temporal spikes (SELECTS).[10] Six subjects (21.4%) had epilepsy with eyelid myoclonia (EEM), previously known as Jeavons syndrome. Five subjects (17.9%) were suspected to have a genetic basis for the epilepsy based on the clinical features and family history. Genetic testing was done for only two and diagnosed Type 2 congenital methemoglobinemia (homozygous mutation CYB5R3) and sunflower syndrome (heterozygous mutation CHD2). None of the subjects had structural epilepsy. Twenty-one subjects were under ASMs at the time of EEG acquisition (75%). Twenty-four subjects had an MRI brain available, and all but two were normal. The abnormal magnetic resonance imaging (MRI) of the subject with Type 2 Congenital Methemoglobinemia showed diffuse cortical and basal ganglia atrophy. The other subject with CHD2-associated sunflower syndrome had non-specific frontal white matter changes. In this study it was seen that PPR was maximum noted at a frequency range of 8–14 Hz.

Out of the 28 subjects, 15 subjects (53.6%) had a clinical correlation associated with photo paroxysmal response (PPR) (Table 2). The most common type of clinical correlate was eyelid myoclonus in nine subjects (32.1%). Three subjects had GTCS during photic stimulation (PS) (10.7%). Six subjects had two types of clinical correlates. Among the 28 subjects enrolled in the study, 21 subjects were on ASM and 7 were drug naïve. Among the 21 subjects, 11 were being treated with levetiracetam, 9 with valproic acid and 3 with clobazam and 1 each with oxcarbazepine and topiramate. Four subjects were on dual ASM, and 17 were on monotherapy.

Using the Chi-square test, the association of different variables with intellectual disability was examined. Statistically significant associations were found ($p < 0.05$) with abnormal MRI brain and abnormal EEG background (Tables 3 and 4).[9,10]

Discussion

Photosensitivity is an important attribute in classifying, managing, and prognosticating childhood epilepsies. Our study aimed at analyzing the demographic, clinical, and electrophysiological features of generalized PPR in children with epilepsy. It also attempted to find the variables associated with intellectual

Table 3: Electroencephalogram and electroclinical characteristics

PPR frequency range	*8–14 Hz*
Clinical correlate with PPR	
Yes	15 (53.6%)
No	13
Types of clinical correlates	
Eyelid myoclonus	9
Limb/axial myoclonus	6
GTCS	3
Absence seizure	2
Focal motor seizure	1
Form of PPR discharge	
Polyspikes	4
Spike and slow waves	4
Mixed	20
PPR outlasting photic stimulation	8 (28.6%)
Eye status during PPR	
Only during eye closure	12 (42.9%)
Both eye closure, eye closed, and eye open	16
IEDs	
Present	25 (89.3%)
Absent	3
Types of IEDs	
Generalized	11
Focal/Multifocal	3
Both	11
Types of focal IEDs present	
Frontal	3
Temporal	6
Central/centro-parietal	2
Occipital	5
Abnormal EEG background	2

GTCS, generalized tonic-clonic seizures; IED, interictal epileptiform discharges; PPR, photoparoxysmal response

Table 4: Intellectual disability and the relation to different study variables

Variable	*Intellectual disability p-value*
PPR outlasting PS	0.701
Abnormal EEG background	**0.033**
Abnormal MRI	**0.047**
IEDs	0.207
Clinical correlate during PPR	0.339
Clinical photosensitivity history	0.175

IED, interictal epileptiform discharges; PPR, photoparoxysmal response

disability. This study is unique and one of its kind since it included only subjects with type IV PPR below 18 years of age. Most of the previous studies have included all types of PPR.

In our study, a total of 28 subjects were included, of whom 21 were females. The female preponderance in our study (M:F = 1:3) was in line with the previous studies.[11–13] Although the study included subjects <18 years, the youngest included was 4 years of age. A study conducted by Binelli et al. concluded that PPR is rare in children <5 years of age.[14] Compared to their study, none of our subjects had Dravet syndrome or any other developmental and epileptic encephalopathies (DEE) or progressive myoclonic epilepsies like neuronal ceroid lipofuscinosis (NCL). Similar to the previous studies, IGE was the most common epilepsy syndrome associated with our study (*n* = 11, 39.3%), with JME the most common type (5/11).[11] The interictal epileptiform discharges (IEDs) were generalized and multifocal with no posterior predominance in our subjects with JME. This was contrary to the findings reported by Bauer et al. that JME with PPR had a statistically significant prevalence of posterior independent IEDs compared to JME without PPR.[15] One of our subjects was a proven case of type II congenital methemoglobinemia with epilepsy. To the best of our knowledge, this is the first time this condition has been reported to be associated with photosensitivity.

The most common focal epilepsy in our cohort was POLE (*n* = 4, 14.3%), and only one subject had SELECTS. This was in stark contrast to the study by Lu et al., who reported type IV PPR in about 9% of subjects with SELECTS.[16] This may be explained by the difference in methodology since Lu et al. included only subjects with at least two EEGs recorded. Comparatively, our study might have missed subjects with transient photosensitivity.[17]

Epilepsy with EEM had a disproportionate representation (*n* = 6, 21.4%) in our study, despite being a rare epilepsy syndrome.[18] Previous pediatric and adult studies also do not report such a high proportion.[12,19] One reason could be that this syndrome was only recently identified as a distinct entity by the Indian League Against Epilepsy (ILAE), and prior research could have categorized them under IGE.[6]

Our study found that the clinical correlates of PS can be EEM, limb/axial myoclonia, GTCS, absences, or focal seizures in the descending frequency (Table 2). It is notable that despite following the protocol of stopping the PS when generalized PPR is detected, three subjects in our cohort had PS-induced GTCS. This underscores the importance of arranging proper safety measures in any epilepsy monitoring unit (EMU) where PS are conducted.[20]

The presence of an abnormal MRI brain or abnormal EEG background was found to be significantly associated with intellectual disability. Hence, we can conclude that in subjects with PPR, the presence of an abnormal MRI brain or abnormal EEG background could predict the development of intellectual disability. Further, those subjects are unlikely to have IGE and need further etiological workup.

Limitations

The retrospective design of the study prevented us from calculating the relative risk associated with different outcomes. The relatively small sample size was a further limitation. Our institution, being a tertiary care epilepsy center, cannot avoid referral bias. The extent of EEG recording varied from 1 hour to 8 hours among the subjects. This may have reduced the rate of picking of PPR in subjects who underwent EEG recording for shorter durations. Nevertheless, the procedure of recording the EEG and performing PS was uniform for all the subjects.

Conclusion

This 10-year retrospective study included children <18 years of age with generalized PPR. JME, epilepsy with EEM, and POLE were the most common epilepsy syndromes associated with generalized PPR in our study. The electrophysiological features of the subjects

in our cohort were similar to the previously reported pediatric and adult studies. Three subjects in our study had photic stimulation-induced GTCS despite following the international protocols. Therefore, in addition to the benefits of PS, consideration of safety measures is crucial. We could find a significant association between abnormal EEG background and abnormal MRI brain with intellectual disability. Further long-term prospective studies are needed to better characterize photosensitivity in children.

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REVIEW ARTICLE

Genetics of Autism Spectrum Disorders

Usha P Dave

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Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with significant genetic and environmental contributions. Advances in genetic research, particularly through whole-exome sequencing and whole-genome sequencing, have led to the identification of numerous risk genes, offering the potential for more accurate and personalized diagnostics and treatment strategies. Despite these advancements, the genetic heterogeneity of ASD and its overlap with other neurodevelopmental disorders continue to complicate diagnosis. Environmental factors, including prenatal exposure to pollutants and maternal health conditions, interact with genetic predispositions to further influence ASD risk. The integration of multi-omics data – genomic, epigenomic, and transcriptomic – holds promise for uncovering the intricate mechanisms driving ASD and improving our understanding of how genetic and environmental factors contribute to its progression. As genetic testing becomes more widespread, it is crucial to address the ethical implications surrounding its use in both clinical and societal contexts. The present review explores significant challenges, the potential for personalized medicine based on genetic findings offering a hopeful future for ASD research and treatment, providing new opportunities to improve outcomes for individuals with ASD.

Keywords: Autism spectrum disorder, Genetics, Neurodevelopmental disorder, Whole-exome sequencing.

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Introduction

Autism spectrum disorder (ASD) is a group of heterogeneous neurodevelopmental disorders characterized by impaired social interaction and communication, along with restricted and repetitive behaviors, and has significant genetic and environmental contributions. It manifests as challenges in verbal and non-verbal communication, social skills, and learning, alongside certain repetitive behaviors, hyper focus, with niche and strong interests.[1,2]

In 1943, Kanner was the first to define autism, providing detailed case descriptions of children showing a lack of social interaction along with intellectual disability (ID).[3] In 1944, Asperger further highlighted the inept social communication and restricted yet intense interests, despite advanced intellect and language skills.[4] A spectrum of autistic conditions was later conceptualized by combining the descriptions by Kanner and Asperger.[3–6] Although ASD can be diagnosed at any age, in the majority of cases, symptoms begin to manifest during the first few years of childhood. Hence, it is termed as a "developmental" disorder, characterized by aloofness, social communication impairments, stereotyped behaviors, and speech regression. Neuroregression is a hallmark of typical autism satisfying diagnostic statistical manual-V (DSM-V) criteria of clinical diagnosis. The substantial variability in symptom severity, cognitive ability, and co-occurring conditions are noticed.[2,7] Autism spectrum disorder is diagnosed four times more often in males than in females (M:F = 4:1). Additionally, the presentation of symptoms is observed to differ in males and females.[8]

Autism spectrum disorder currently affects about 1–2% of global population; however, the prevalence seems to be increasing. The prevalence from 1 to 4 in 10,000 had increased periodically to 1 in 1,000; then 1 to 3 in 100. The most recent U.S. census has reported an alarmingly high rate of 1:64 in children. There are very few systematic studies in Indian population, reporting as 1–3 per 1,000 children, which has recently increased to 1–3 in 100. Individuals across all ethnicities and socioeconomic backgrounds are equally affected by ASD.

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Clinical Features of ASD

Characteristic features of ASD include inadequacies in social communication, such as difficulty in initiating and sustaining conversations, forming relationships, and understanding social cues. Interpretation of facial expressions and maintaining eye contact are some of the common struggles of autistic individuals.[9] They also show repetitive movements like hand-flapping, rocking, stimming, etc. Individuals with ASD often follow strict routines and have intense, specific interests, this can hinder their day to day life to varying degrees.[10]

As the name suggests, ASD brings along a spectrum of ID ranging from mild to severe with executive dysfunction to varying extents, thus facing problems with planning, attention, and working memory. This may also impact their overall adaptability. The language development is impacted and may be non-verbal or exhibit echolalia (they repeat words or phrases), and use of non-verbal cues, like gestures and facial expressions, may be non-existent or inappropriate.[9,11]

Individuals with ASD often show an unusual response to sensory stimuli, being overly sensitive (hyper-reactive) or show little to no response (hypo-reactive) to sounds, lights, textures, or smells.[12,13] Moreover, aggression and tendency to self-harm can be seen in some individuals during distress. Conditions such

as attention-deficit hyperactivity disorder (ADHD), anxiety, and depression often coexist with ASD. Additionally, individuals with ASD experience sleep disturbances as well as gastrointestinal problems like constipation, diarrhea, and abdominal pain. Certain genetic syndromes such as Tuberous sclerosis, Fragile X syndrome, and Rett syndrome are associated with autistic features which help in further diagnosis. Epilepsy is seen as a common comorbidity, with active seizures or simply, electro encephalograph (EEG) abnormalities in ASD–ID combination.[10]

There are several batteries of psychological tests which a clinical psychologist administers in two to three sittings in the environmental setting. The ASD children will often not satisfy complete DSM-V diagnostic criteria and some may show mild to moderate autistic features.

Genetics Factors in ASD

Scientists, while searching for the precise causative factors of ASD for the last two to three decades, have come to the conclusion that ASD is a heterogeneous group and that both environmental and genetic factors may contribute to its etiology. Various twin and familial studies have shown ASD to be highly heritable and have tried to establish a genetic basis as a cause. The ASD association with both common and rare genetic variants/mutations proved important in accurate diagnosis and effective therapy.[11] Several researchers have provided an overview of ASD, with a focus on examining the role of genetics in its development. For example, large-scale genome-wide studies have revealed that rare *de-novo* mutations (spontaneously arising mutations) and common inherited variants both play significant roles in the development of ASD.

About Established Genes in ASDs

Currently, more than 90 genes, with a role of their several variants, are reported to be associated with ASDs.

One prominent example is CHD8, a gene associated with chromatin remodeling that regulates gene expression during brain development. Mutations in CHD8 are strongly linked to ASD with macrocephaly (abnormally large head size), providing a clear genotype–phenotype connection. Another gene, *SCN2A*, encodes a sodium channel subunit critical for neuronal signaling. Mutations in *SCN2A* disrupts ion channel function, leading to both autism and epilepsy in some individuals. SHANK3, a gene involved in synaptic scaffolding, plays a crucial role in synaptic structure and function. Mutations in SHANK3 are associated with both ASD and intellectual disabilities.[14]

In addition to these rare, high-impact mutations, common variants also contribute to ASD risk, though each variant exerts a smaller effect individually. Collectively, these common variants act in a polygenic manner to influence ASD susceptibility. Genome-wide association studies have identified several loci harboring common variants involved in neuronal development and connectivity, further supporting the polygenic nature of ASD.

Many identified risk genes are expressed during critical periods of neurodevelopment – particularly in excitatory and inhibitory neurons, which are essential for balanced brain activity. Disruptions in these neurons are thought to lead to the excitatory–inhibitory imbalances seen in individuals with ASD.[15]

Copy number variants (CNVs), the large deletions or duplications of deoxyribonucleic acid (DNA) segments that can disrupt multiple genes, are more prevalent in individuals with ASD compared to the general population.[7] These CNVs often have a large effect size, contributing significantly to ASD risk by altering key neurodevelopmental pathways. For example, 16p11.2 deletions are among the most well-established CNVs linked to ASD, frequently associated with developmental delays and intellectual disability. Additionally, CNVs affecting synaptic genes, such as SHANK3 deletions, are strongly correlated with ASD, emphasizing their role in the pathogenesis.[14] Figure 1 clearly illustrates the possible role of neuronal and synaptic connectivity in ASD.

Environmental Factors Contributing to Genetic of ASD

Besides genetic factors, some scientists have reported a role of environmental factors in the development of ASD by genetic predispositions. Several prenatal factors have been consistently associated with an increased ASD risk. For instance, advanced maternal and paternal age has been linked to a higher likelihood of ASD in offspring. Additionally, birth asphyxia or preterm delivery have been identified as contributing factors, possibly due to their impact on early brain development.[7] Maternal health conditions such as obesity and gestational diabetes have been linked to higher ASD risk, whereas maternal infections, such as influenza or genitourinary infections during pregnancy, are associated with slight but significant ASD risk, likely due to inflammatory or metabolic disruptions during fetal development.[16]

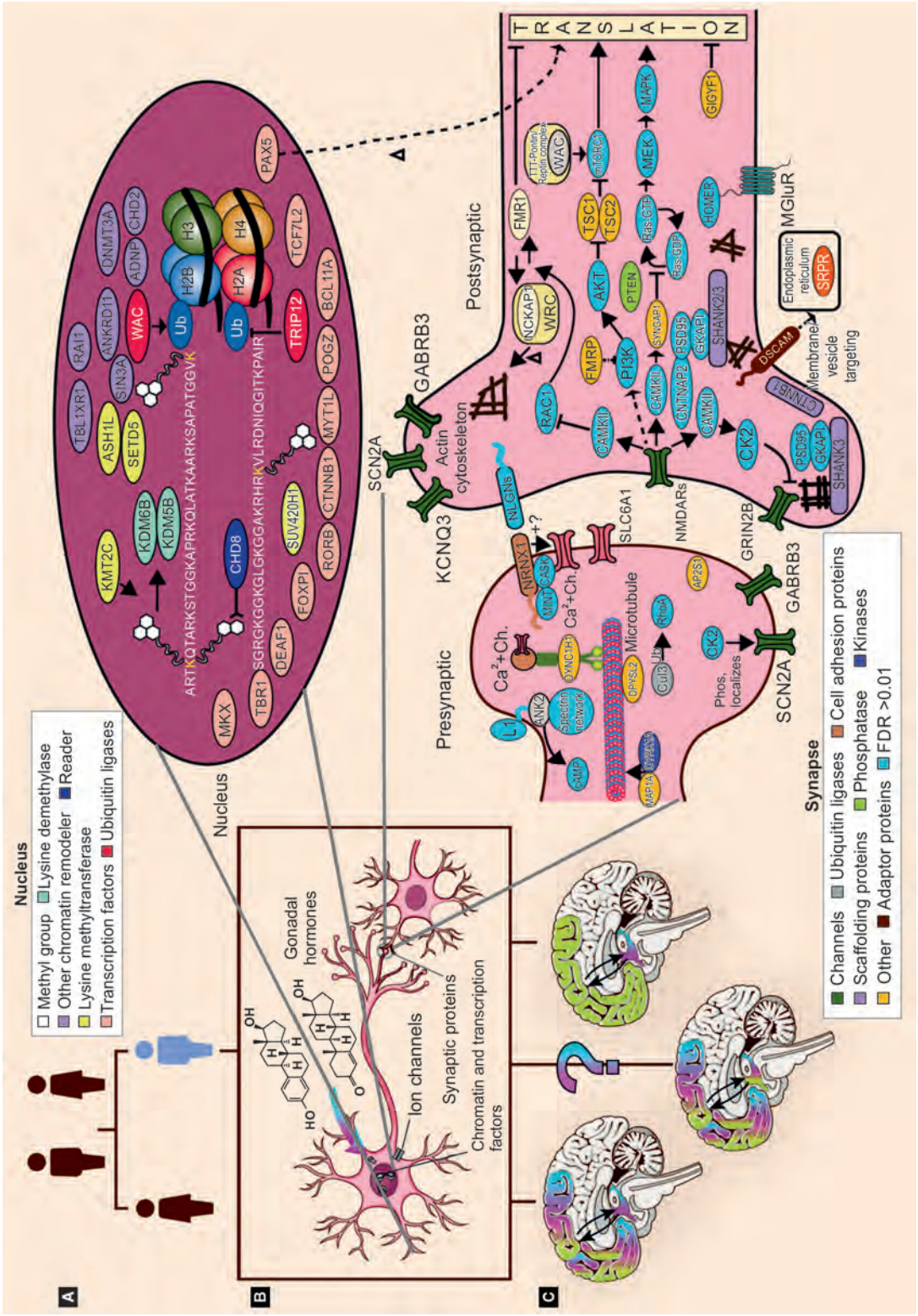
The role of maternal nutrition, especially folic acid supplementation, may reduce the risk of ASD, while nutritional deficiencies during pregnancy could increase vulnerability.[9] Prenatal exposure to medications such as valproate, an anticonvulsant, is strongly associated with neurodevelopmental disorders, including ASD.

In terms of environmental pollutants, exposure to air pollution, especially particulate matter (PM 2.5), during pregnancy and early childhood has been linked to a higher likelihood of ASD, suggesting pollutants may interfere with neurodevelopment during critical windows, contributing to ASD onset.[17] Although post-natal environmental factors such as exposure to toxins or infections have been studied, the most significant environmental risks seem to occur during prenatal development. Importantly, there is no evidence to support a link between vaccinations and ASD, debunking earlier claims that led to vaccine hesitancy.[7]

Diagnosis and Therapeutic Implications

Genetic advances are of tremendous help in the diagnosis of ASD by enabling more precise identification of the genetic underpinnings of the disorder. Whole-exome sequencing (WES), in particular, has proven invaluable by allowing clinicians to identify specific pathogenic variants associated with ASD in individual patients.[18] This approach helps differentiate between idiopathic cases and those tied to distinct genetic syndromes, such as Fragile X syndrome, Rett syndrome, and tuberous sclerosis complex, where ASD is one of the key features.[19,20] This level of specificity in diagnosis is critical for patients with syndromic ASD, who often present with unique comorbidities influencing the choice of therapeutic interventions.

Advances in genetic research, particularly through WES and whole-genome sequencing (WGS), have led to the identification of numerous risk genes, offering the potential for more accurate, personalized diagnostics and treatment strategies. However, despite these advancements, ASD diagnosis remains a significant challenge. The genetic heterogeneity of ASD – where multiple genes can be implicated, and different mutations can cause similar symptoms – complicates diagnosis. Additionally, ASD



Figs 1A to C: The diagram illustrates a simplex autism pedigree, including an affected proband and unaffected parents and siblings (affected status is represented by the purple color). Multiple studies of de novo mutations in ASD leverage in Simons Simplex Collection (24), in which the majority of pedigrees were "quartets," as shown here, comprising a parent-proband trio and at least one unaffected sibling. This structure is ideal for genetic studies of spontaneous mutations, as it allows for the evaluation of spontaneous germline mutation rates within families, comparing affected to unaffected siblings. In panel B, functional annotations of ASD-associated genes highlight the putative roles of sematic structure and function, as well as the regulation of gene expression, particularly enriched for chromatin structure and dynamics. Genes that reached the highest statistical threshold in reference 6 or 7 are included in the diagram, placed to their commonly annotated functional roles and cellular locations. Panel C depicts several models of the possible intersections of ASD pathobiology (green) and sexual differentiation of the brain (pink and blue). On the right, ASD pathogenesis may affect cortical development in regions that interact with sub-cortical structures (arrows) that show differences between males and females to produce sex-biased phenotypes. On the left, sex differences and ASD pathogenesis may converge in regions of the cortex, in populations of cells that remain to be identified, to produce sex differences in ASD. At the center, sexual differentiation and ASD pathogenesis may disrupt sex-typical patterns of development and activity in cortical and subcortical structures to produce sex biases in ASD.
Source: Manoli and State.[14] Am J Psychiatry 2021;178(1):30–38.

shares many features with other neurodevelopmental disorders, leading to overlapping symptoms that can result in misdiagnosis.[21] For instance, distinguishing ASD from intellectual disabilities or language disorders can be difficult without precise genetic information. Advances in genetic testing, such as the integration of WGS and multi-omics approaches, are expected to improve our understanding of the molecular mechanisms behind ASD, potentially allowing for earlier and more accurate diagnoses.[15]

As the genetic mechanism underlying ASD becomes clearer, targeted therapies are emerging. Pharmacogenetics, which tailors drug treatments based on genetic data, holds promise for treating ASD's behavioral and cognitive symptoms. The genetic diversity in ASD and its varying clinical manifestations complicate the development of one-size-fits-all treatments. Nonetheless, emerging personalized genomic medicine offers a promising direction for future ASD research.

Genomics focuses on identifying genetic mutations or variations, epigenomics investigates how environmental factors may modify gene expression without altering the DNA sequence; and transcriptomics examines how gene expression is regulated at the ribonucleic acid (RNA) level. By combining these approaches, researchers build a more comprehensive picture of the biological mechanisms driving ASD, going beyond traditional genetic research to include how genes are expressed and regulated in different environments and exploring for the therapeutic purpose.[18,22] These studies also offer insights into how early-life exposures and genetic predispositions can affect long-term developmental outcomes, which is critical for identifying when and how to intervene.[19] Longitudinal data help track how ASD symptoms evolve over time, aiding in the development of interventions tailored to different life stages.[23]

Conclusion

Despite genomic advancements, the clinical and genetic heterogeneity of ASD, along with its overlap with other neurodevelopmental disorders, continue to make ASD a complex entity for diagnosis and therapy. Environmental factors, including prenatal exposures to pollutants and maternal health conditions, interact with genetic predispositions to further influence ASD risk. The integration of multi-omics data – genomic, epigenomic, and transcriptomic – holds promise for unraveling the intricate mechanisms behind ASD and improving our understanding of how genetic and environmental factors contribute to its progression, as well as the challenges in the potential for personalized genomic medicine. In brief, while ASD presents ongoing challenges, the progress in genetics and personalized medicine holds promise for more effective diagnosis and treatments, offering hope for individuals and families affected by this disorder.

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CASE SERIES

Developmental Epileptic Encephalopathy 25—Epilepsy with Amelogenesis Imperfecta: A Case Series with Novel Variants

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Abstract

A class of neurological conditions known as developmental epileptic encephalopathies (DEE) is defined by developmental delay and epilepsy. Many DEEs are related to gene pathogenic variants and present in the neonatal period to early childhood. There are several genes that are implicated in the etiology. The exact prevalence of childhood-onset DEE is not known. Developmental epileptic encephalopathies 25 (DEE25) caused by mutations in *SLC13A5* gene is one of the rarest types of DEEs, characterized by neonatal-onset seizures, developmental delay, cognitive decline, and amelogenesis imperfecta (AI). Here, we report seven cases of DEE25 that were identified through genetic testing as being caused by homozygous pathogenic variants in *SLC13A5*. Worldwide case reports are scarce, and information regarding genotype, phenotype, and response to various antiseizure drugs is also lacking. The specifics of seven cases are outlined in our case series. Patients 3, 4, and 5 are children from separate households; patients 1, 2, and 7 are sibling pairs.

The *SLC13A5* variant was inherited from both parents, per segregation analysis. It was discovered that every variation, with the exception of one, was novel and not present in the population or databases. The long-term developmental and seizure outcomes of these children are highlighted in this case series. Out of the seven children, only one could walk, and none had seizures under control for more than a year. Endogamous communities had a high frequency of DEE25, as evidenced by the fact that all of the children were products of consanguineous marriages. Further investigation of the intricate biochemical pathways is necessary for focused drug discovery as a result of this information, which complements the scant genotype and phenotype data already available.

Keywords: Amelogenesis imperfecta, Anti-seizure medication, Developmental and epileptic encephalopathy 25, Epilepsy, Epileptic encephalopathy, Genetics, Next-generation sequencing.

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Introduction

Developmental Epileptic Encephalopathy 25 (*SLC13A5*) is an extremely rare illness for which there are very few published case reports worldwide, none of which come from India. The genetics and phenotype of seven Indian patients are described in this case series. *SLC13A5* epileptic encephalopathy is caused by pathogenic variants in the *SLC13A5* gene that cause loss of function and, in turn, result in a deficiency of the sodium/citrate cotransporter.[1] Patients usually begin having seizures in the first week of life, and they also suffer intellectual disability and developmental delay. Individuals with biallelic variations in *SLC13A5* experience intractable seizures that start in infancy, which are followed by developmental delays and hypoplasia or hypodontia of the teeth. The 12 exons of the *SLC13A5* gene, which has both eukaryotic and prokaryotic homologs, are found on chromosome 17p13.1. The exact prevalence of the disease is unknown.[2,3] The natural history, genotype-phenotype correlations have been studied briefly; however, large population-based studies are required and need of disease-causing variants to be unearthed. This case series adds to the existing database literature of DEE25.

Case Description

Here we describe two siblings from two families and children from three unrelated families diagnosed with DEE25.

Cases 1 and 2

Two siblings who were born to third-degree consanguineous parents presented to the clinic. The older female child in the family, aged 11 years, had a history of seizures for 3 days of life. They were generalized tonic seizures, recurrent, and on antiseizure medications (ASM). The seizures decreased in frequency and currently continue to have breakthrough episodes. She has developmental delays in all her domains. She is able to walk independently (unable to run or climb stairs), speak sentences, eat, take her medication, respond to simple commands from her parents, and is not enrolled in school at the age of 11 years.

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The younger male sibling, 9 years old, had the onset of seizures at 21 days of life, which later continued daily in sleep. He was commenced on ASM, and the frequency of seizures had reduced. He has been seizure-free for the past 6 months. Global developmental delay, with motor milestones being more delayed than cognitive delay, is present. At 9 years of age, he is nonambulatory, sits and stands with support, is unable to feed himself, is reaching out to objects, speaks a few words, responds to commands, and is able to indicate toilet needs. He displays an interest in music.

Both siblings have brittle teeth with yellowish discoloration, enamel loss, increased interdental distance, mild gum hypertrophy, and crown disruption suggestive of amelogenesis imperfecta (AI).

Electro encephalogram (EEG) revealed generalized frontally dominant spikes and slow wave discharges during sleep. Both siblings were on a ketogenic diet and did not show any response.

On physical examination, Sibling 1 had upslant palpebral fissures, a broad-based gait, increased toned limbs, and yellow discolored teeth. At 11 years old, she weighed 39 kg, had a height of 131 cm, and a head circumference of 53 cm, which was appropriate for her age.

Sibling 2 had Achilles spasticity, bottom shuffling, choreoathetoid movements, and tremulousness. He had a happy disposition. He had gapped, yellowish, discolored teeth. He weighed 19 kg at age 9 years, had a head circumference of 45 cm, which was small for his age, and a height of 113 cm, which was normal for his age.

The magnetic resonance imaging (MRI) brain and metabolic workup were normal.

Case 3

A 7-year-old female child, born of a third-degree consanguineous marriage, presented with global developmental delay, failure to thrive, speech delay, intellectual disability, microcephaly, and neonatal-onset recurrent seizures (eye and neck deviation to one side, stiffening, and clonic jerks of all limbs lasting for 10 seconds with no associated head drop). On examination, she had a pyramidal sign (left > right), pseudobulbar palsy, mild gastrocnemius spasticity, intermittent distal upper limb dystonia, truncal hypotonia, head lag, and pes planus. Currently, at 7 years of age, she is nonverbal, has poor eye contact, has to pull to sit, and is not bearing weight on her lower limbs. Amelogenesis imperfecta is present: Small, discolored, yellow teeth with gum hypertrophy. Electro encephalogram was abnormal, and the MRI brain was normal. Improvement with ASM and progress in development are noticed. She was started on ASM.

Case 4

A 9-month-old child born of a fifth-degree consanguineous marriage presented with motor delay, seizures of neonatal onset (generalized tonic-clonic seizures), jerky movements in all 4 limbs, and uprolling of the eyes. There is a family history of seizures in his cousin, brother, and paternal grandfather (seizures at 50 years of age) and gestational diabetes in his mother. He had attained partial neck holding and transient tripod sitting. On examination, he had generalized hypotonia. His teeth at 10 months of age were normal. His brain MRI and TMS were normal. The EEG brain revealed multifocal epileptic abnormality.

Case 5

A 17-day-old female baby born to a third-degree consanguineous couple was admitted with seizures. She was born to a 19-year-old second gravida mother at term, singleton pregnancy, lower segment cesarean section (LSCS) delivery in view of previous LSCS, weighed 3 kg, and cried immediately after birth. She presented with multifocal seizures, subtle seizures, and hypotonia from day 2 of her life. On examination, she had microcephaly and hypotonia. Currently, she is 1.4 years old and is not sitting; she is able to grasp and reach out to objects but not transfer objects; she doesn't have eye contact; she turns to sound; and she has no social smile. Electro encephalogram revealed bilateral spike and wave discharges suggestive of multifocal epileptic abnormality, and her MRI brain was normal.

Cases 6 and 7: Siblings

Case 6

Sibling 1, a female baby of third-degree consanguineous parents, was born at term by LSCS in view of non-progression of labor, was small for gestation age, weighed 1.9 kg, and had a delayed cry, for which she was admitted to the neonatal intensive care unit (NICU). The baby had seizures on the first day of life. After discharge from the NICU, she had developmental delays and seizures. Seizures occurred once every 3 months, which included the rolling of eyeballs and tonic-clonic limb movements. After 2 years of age, the frequency of seizures reduced to once a year and was associated with fever. Developmental milestones were delayed in both the motor and cognitive domains. At 9 years of age, she is able to sit, smile, and turn to sound; does not respond to parents; has no monosyllables; and has a happy disposition. On examination, anthropometry is normal for age. She has gum hypertrophy and yellow discoloration in her teeth. She has spasticity in the upper and lower limbs, as well as brisk reflexes. The brain MRI is normal. Electro encephalogram was suggestive of epileptic encephalopathy. Currently, she is on valproate, clobazam, and levetiracetam (Fig. 1).

Case 7

Sibling 2 was born to third-degree consanguineous parents at 34 weeks by LSCS, weighed 2 kg, and cried immediately after birth. He was admitted on the 8th day of life with hyponatremic dehydration. Newborn screening was normal. His multifocal clonic seizures began on the twelfth day of his life. He had 2–3 episodes of seizures every month for a few seconds, followed by postictal drowsiness. His last seizure was status epilepticus generalized tonic-clonic type with post-ictal drowsiness. He was noticed to have a developmental delay. At 2 years old, he was pulling to sit and crawling. At 2.5 years, he was identifying parents and had speech impairment; at 2.9 years, he was standing with support. Currently, at 4 years of age, he is sitting, crawling, and recognizing parents; has no speech; doesn't indicate toilet; and has a happy disposition. On examination, he has 1 large café au lait spot on his face measuring 2 × 3 cm. He has spasticity of the bilateral upper limb, elbow flexor, and hamstring more than adductors with central hypotonia. His anthropometry was appropriate for his age. An MRI of the brain was not done. Electro encephalogram was suggestive of epileptic encephalopathy.

Discussion

A diverse range of monogenic neurodevelopmental illnesses, including early-onset seizures, significant epileptic activity, and aberrant neurocognitive development, are often referred to as DEE. The online mendelian Inheritance in Man database lists 102 genes that are currently classified as being involved in monogenic DEE;

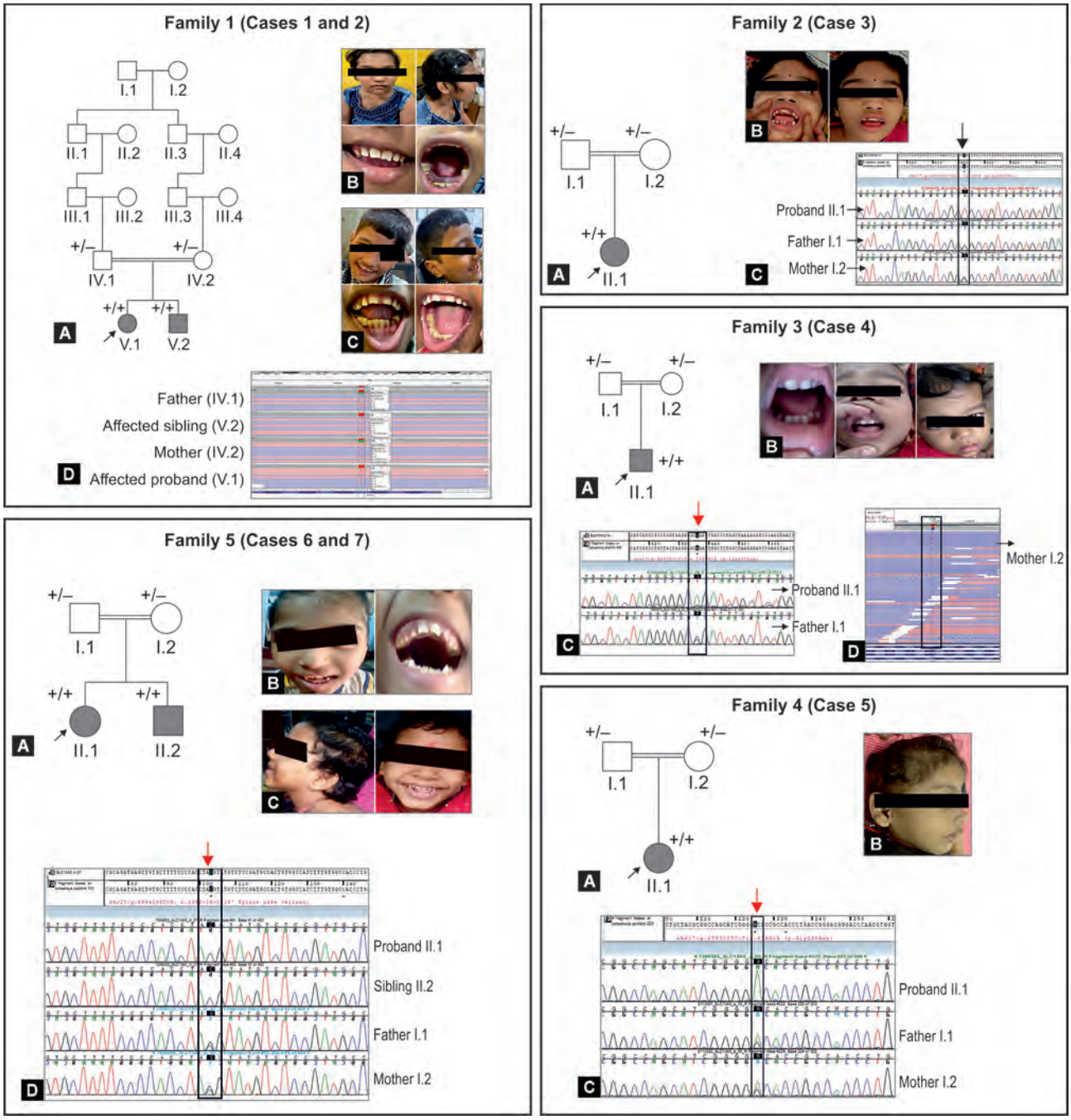

Fig. 1: Schematic representation of the consanguineous partial pedigree of the of the five families with SLC13A5 gene variants following clinical exome sequencing. The affected individuals marked by filled square/circle. The symbol "+" for variant/mutant allele and "–" for wild-type allele is marked in the pedigree corresponding to the zygosity of the variant detected (mapped NM_177550.5 transcript). Individuals marked with"++" are homozygous and individuals with "+/–" are carriers (Family 1 c.1589T > A; p.Val530Asp. Family 2 c.1283G > T; p.Gly428Val. Family 3 c.1249G > A; p.Gly417Arg. Family 4 c.659G > A; p.Gly220Asp. Family 5 c.1056-1G > C). The pedigree, blinded photographs, pedigree, family members, photographs, Sanger chromatograms, and Integrative IGV viewer are represented for each of these variants for all the family members analyzed (represented as A,B,C,D for each family). Family members denoted in the pedigree as I.1, I.2, II.1, II.2

this number has doubled in the last 5 years.[4] Although approved anti-seizure drugs can improve seizure control, developmental verbal and motor delays persist throughout adulthood with this condition, with neonatal seizures frequently being the first presenting symptom.[5–9]

Amelogenesis imperfecta enamel is characterized by its very thin, soft, fragile, pitted, and/or poorly discolored surface. There are several genes implicated in the same.[10]

The year 2014 saw the first determination of the cause of DEE25 by whole exome sequencing in three patients suffering

Table 1: Details of the SLC13A5 variant in the cohort diagnosed with DEE with amelogenesis imperfecta

Family No.	*Variant details (NM_177550.5)*		*In silico prediction tools*	*Segregation – affected sibling*	*Segregation – asymptomatic parents*	*Classification*	*Reported*
Family 1 (cases 1 and 2)	c.1589T>A	p.Val530Asp (Exon 12)	SIFT- D	Homozygous (case 2)	Heterozygous in both	VUS (PM2)	This study
Family 2 (case 3)	c.1283G>T	p.Gly428Val (Exon10)	SIFT, LRT, MT2- D; PP2-PrD	NA	Heterozygous in both	VUS (PM2,PP3)	This study
Family 3 (case 4)	c.1249G>A	p.Gly417Arg (Exon 9)	SIFT, LRT, MT2- D; PP2-PrD	NA	Heterozygous in both	VUS (PM2,PP3)	This study
Family 4 (case 5)	c.659G>A	p.Gly220Asp (Exon 5)	SIFT, LRT, MT2, PP2-D	NA	Heterozygous in both	VUS (PM2,PP3)	This study
Family 5 (cases 6 and 7)	c.1056-1G>C	p. (Intron 7)	MT2, SpliceAI, MaxENTScan- D	Homozygous (case 7)	Heterozygous in both	Likely pathogenic (PVS1, PM2)	VCV001352224.3

The variants detected in family 1, 2, 4, and 5 were absent in the population databases. The variant in family 3 (p.Gly417Arg) had an alternate allele frequency of ~001% in GnomAD and ExAC databases. VUS, variant of uncertain significance. The cDNA annotation for the SLC13A5 gene is based on NM_177550.5 transcript.

from early-onset epileptic encephalopathy. More than 40 bi-allelic *SLC13A5* variations have been identified to date that cause epilepsy; these include nonsense and missense variants, frame shift variants derived from single nucleotide variants, exon deletions, and whole gene deletions. The most prevalent variants are c. 655G>A (p.G219R) and c. 680C>T (p.T227M).[11,12] However, these variants were not found in this case series (Table 1).

The testes, liver, brain, and teeth all exhibit significant levels of expression for the gene *SLC13A5*, which codes for the plasma membrane sodium-coupled citrate transporter (NaCT). Plasma membrane sodium-coupled citrate transporter is present in neurons in the brain and is probably involved in controlling the amount of citrate released by astrocytes, which in turn affects the activity of N-methyl-D-aspartate receptors (NMDARs).[9,13,14]

In this report, we illustrate 7 children (Table 2) with a history of neonatal-onset epilepsy where a homozygous *SLC13A5* variant was found. Most of these children have a similar profile, with early-onset polymorphic epilepsy, developmental delay, and AI appearing later in life. All children were products of consanguineous marriage, which is commonly seen in the South Indian population, correlating with the existing proven theory that genetic diseases have a higher prevalence amongst consanguineous marriages. In our case series, four children were above 5 years old and three were below 5 years old, and it was noticed that AI, or tooth abnormalities, were noticed around 5 years of age in both primary and secondary dentition. Patients 1, 2, 3, and 6 had features of AI, and patients 4, 5, and 7 did not; however, since they had presented at 7 months, 16 months, and 3.6 years of age, respectively, surveillance for tooth manifestations was advised in view of the progressive nature of the condition. Post-NGS results, it was observed that all variants in *SLC13A5* were missense variants except for patient 6 and 7, the sibling pair who harbored a splice site variant. The variant found in them was previously reported in ClinVar-VCV001352224.3 and absent in population databases. This variation, which affects an acceptor splice site in intron 7 of the *SLC13A5* gene results in loss of function of the protein. Variants found in cases 1–5 were missense variants, absent in population and disease databases, and characterized as novel variants. Details of variants are given in Table 1.

All of our patients did not show a good response to any one particular antiseizure medication, and we propose that further research needs to be done to explore targeted therapy. Also, post-genetic testing, since the variants found were novel, the variants were not validated further by functional studies, and we hope that we can fill this gap in the future.

In this case series, we have delineated the clinical characteristics, the response to anti-seizure medication, and the varied genotype, which adds to the existing natural history, phenotype, and genotype database.

The majority of children experience fewer seizures by late childhood, according to the typical evolutionary trend, but three children in our series continued to have seizures (Table 2). No single antiseizure medication (Table 2) was differentially helpful in our cohort, and two children failed the ketogenic diet as well. Similarly, late childhood is the plateau for cognitive and motor deficits, leaving patients severely disabled. Further research is required to establish genotype-phenotype correlations, and *in vitro* and *in vivo* studies are required for targeted therapies.

Conclusion and Future Directions

As far as we are aware, this case series is the first reported from Southeast Asia, and all but one variant found was novel and added to the existing genetic variant database. There were no specific genotype-phenotype correlations, and heterogeneity in disease was found. All children presented with neonatal-onset seizures with significant developmental delays. It is necessary to determine the functional importance of *SLC13A5* c.1589T>A p.Val530Asp, c.1283G>T, c.1249G>A, c.659G>A, and c.1056-1G>C *in vitro* and *in vivo*. The knowledge of the gene variant and its effects on the sodium citrate transporter has future prospects for potential therapies. The genotype and phenotype of this family add to the existing clinical database.

In children with epilepsy and AI, we advise screening for *SLC13A5*, since this would help with therapy, anti-seizure drugs, prognosis prediction, and appropriate genetic counseling to support well-informed reproductive decision-making.

Declaration of Conflicting Interests

Regarding the research, writing, and/or publication of this article, the authors have declared that they have no potential conflicts of interest.

Table 2: Treatment and follow-up

Pt/ gender	*Age at onset/last follow-up*	*Frequency at onset*	*SE during neonatal age*	*Treatment at onset/1st year*	*Seizure during follow-up (F/U)*	*Freq at last F/U*	*Treatment on F/U*	*Development at F/U*	*Additional features*
1.F	DOL-3/ 11 years	15–20/day	Epileptic spasms	Levetiracetam, clonazepam, topiramate, prednisolone	No seizure Since 8 months	0	Perampamil, clonazepam, topiramate	Walk independently (unable to run or climb stairs), speak sentences, although not very clear, she is able to eat, take her medication, responds to simple commands of parents	Involuntary movements, Amelogenesis imperfecta
2.M	21 DOL/ 9 years	15–20/day	Epileptic spasms	Levetiracetam, clonazepam, topiramate, Prednisolone	Seizure free since 6 months	0	Perampamil, clonazepam, topiramate	9 years – not walking, standing with support and sit, can reach out to objects, says a few words, understands commands, likes to listen to songs, indicates toilet	Involuntary mvts, Amelogenesis imperfecta achillis spastiity, bottom shuffling, choreoathetoid movements, tremulousness. He had a happy disposition
3.F	10 DOL/ 7 years	4/day	Focal clonic, generalized clonic	Levetiracetam, phenobarbitone, prednisolone, vigabatrin	Ongoing 3/day non-cluster, focal motor	2–3/day	Clobazam, lacosamide, perampamil, valproate, methylprednisolone	Sits on her own and unsupported, recognizes parents and smiles, incomprehensible sounds, weight bearing	Amelogenesis imperfecta, gum hypertrophy, small teeth, discoloration
4.M	1 DOL/ 6 months	Four episodes/ day on days 1 and 7	Generalized clonic	Phenytoin, levetiracetam, lacosamide, pyridoxine	Fever associated – up rolling of eye balls, jerky movements of all four limbs, aura present persisting without fever	5–6/day	Phenobarbitone, phenytoin, lacosamide, levetiracetam, later added Topiramate and perampaml	Sits without support when made to sit; babbles; recognizes parents; normal vision and hearing	Teeth erupted – upper and lower incisors and lower canines
5.F	17 days/ 1.4 years	Four episodes/ day	Generalized seizures	Phenytoin, phenobarbitone, vigabatrin	Five episodes per day	7–8/day	Phenobarbitone, phenytoin, lacosamide, levetiracetam, later added topiramate and perampamil	Not fixing, turning to sound, no social smile, grasp present	Microcephaly was present
6.F	1 day/ 9 years	2–3 episodes every 3 months	Tonic clonic, multifocal seizures	Levetiracetam	Fever associated seizures	once a year	Valparin, clobazam, levetiracetam	Sitting, smiles, turns to sound, no words, poor response to parents	Gum hypertrophy, teeth discoloration, gaps in teeth
7.M	12 days/ 3.6 years	2–3 episodes every month	Multifocal clonic seizures	Levetiracetam, phenobarbitone, pyridoxine	20 days ago – Status uprolling eye balls and clonic movement of limbs	2 per month	Phenobarbitone, phenytoin, lacosamide, levetiracetam, later added topiramate and perampamil	Stands with support, identifies family members, no words, ankle spasticity, head lag, central hypotonia	Normal teeth

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CASE REPORT

Nonketotic Hyperglycinemia Presenting as HIE MIMIC – A Case Report

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Abstract

Inborn errors of metabolism (IEM) can present as an acute metabolic emergency, resulting in significant morbidity, progressive neurological injury, or death. Nonketotic hyperglycinemia (NKH) is a rare inherited metabolic disorder caused by defects in the glycine cleavage system (GCS). Neonates with NKH develop severe apnea, resulting in acute hypoxemic respiratory failure, requiring respiratory support. This case highlights the importance of early recognition and treatment with sodium benzoate and dextromethorphan, which, when initiated during the neonatal period in patients with attenuated disease, can decrease plasma glycine levels and significantly improve clinical outcomes.

Keywords: Case report, Glycine encephalopathy, Hiccup like movement, Rare disease.

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Introduction

Nonketotic hyperglycinemia (NKH) is an autosomal recessive (AR) genetic disorder with abnormal glycine metabolism caused by the insufficiency of the glycine cleavage system (GCS).[1] It results from a genetic deficiency in the GCS, and mutations have been identified in three of the four GCS proteins: T, H, and P. Mutations in the glycine decarboxylase (GLDC) gene, which encodes the P protein, account for approximately 80% of NKH cases.[2] The buildup of glycine primarily occurs in the brain and spinal cord. Its prevalence in India is not well established.

Nonketotic hyperglycinemia presents in four forms: Neonatal, infantile, late-onset, and transient, with neonatal NKH being the most common and severe.[3,4] We report a case of a neonate with profound hypotonia, myoclonic jerks, respiratory failure, and encephalopathy who was diagnosed with NKH through cerebrospinal fluid (CSF) and serum glycine levels and confirmed by magnetic resonance (MR) spectroscopy and whole exome sequencing.[5] Early treatment with sodium benzoate and dextromethorphan resulted in a significant reduction in glycine levels and the need for respiratory support.[6,7]

Case Description

A term male infant, the firstborn of non-consanguineous parents, weighing 3.2 kg at birth, was born via lower segment cesarean section (LSCS) following an unremarkable pregnancy except for reduced fetal movements. An ultrasound in the second trimester revealed polyhydramnios. The baby had a weak cry after birth, requiring emergency hospitalization in the NICU, ventilator support, and anti-seizure medications. We received the baby on day 11 of life with encephalopathy, hypotonic, and jerky movements. The baby exhibited floppiness and multifocal seizure (myoclonic jerks).[3,4]

Routine laboratory investigations, including hemogram, liver function tests (LFT), and renal function tests (RFT), were normal. Serum ammonia was normal. Arterial blood gas analysis (ABG) and lactate were normal. Newborn screening for inborn errors of metabolism (IEM) was also normal.

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On physical examination, there was no facial dimorphism. On central nervous system (CNS) examination there was generalized hypotonic with absent neonatal reflexes. Continuous electroencephalography (EEG) revealed multifocal sharp wave discharges on EEG originating from both hemispheres. Magnetic resonance imaging (MRI) of the brain, with MR spectroscopy, showed a prominent glycine peak at 3.5 ppm, indicative of NKH (Fig. 1). Serum glycine levels were elevated at 2885 µmol/L.[5] The serum CSF glycine ratio was suggestive of NKH.[8]

A diagnosis of NKH was confirmed, and treatment with sodium benzoate and dextromethorphan was initiated.[1] Follow-up serial CSF serum glycine ratio showed a decrease in values. Significant clinical improvement was observed, with the baby being successfully weaned off ventilator support. Repeat serum glycine levels after treatment decreased to 1165 µmol/L.[5] Follow-up MR spectroscopy showed a reduction in the glycine peak. Whole exome sequencing revealed a genetic variant consistent with glycine encephalopathy type 2. The baby is now 6 months old, thriving well, and started on a ketodiet in view of recurrent seizure.

Magnetic resonance spectroscopy images showed a large glycine peak at 3.5 ppm, and repeat MR spectroscopy 2 weeks after

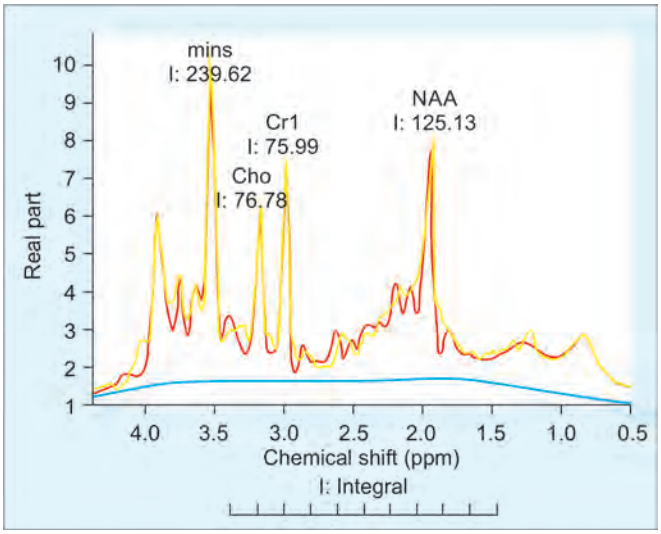

Fig. 1: Magnetic resonance spectroscopy showing a prominent glycine peak at 3.5 ppm

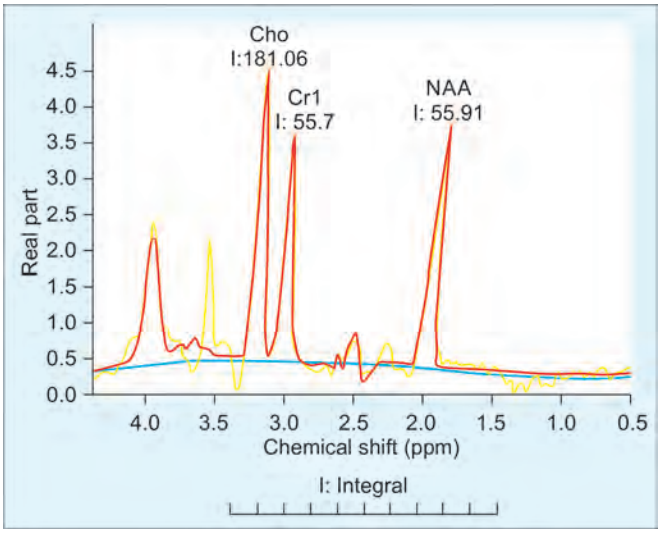

Fig. 2: Magnetic resonance spectroscopy after 2 weeks of initiation of treatment showing regression in the glycine peak

the initiation of treatment showed regression in the glycine peak, consistent with treatment response (Fig. 2).

Discussion

When evaluating a neonate with seizures, other differential diagnoses, including hypoxic-ischemic encephalopathy (HIE), hemorrhage, infarction, infection, trauma, and toxic exposures, must be considered. In our case, the absence of abnormal brain malformations prompted further investigation into possible IEM. Elevated serum and CSF glycine levels led to the diagnosis of NKH and the initiation of treatment. The severity of NKH depends largely on the extent of GCS enzyme deficiency, with individuals carrying two defective alleles typically experiencing a more severe clinical course. In contrast, those with a single defective allele may have a milder phenotype. The transient form of NKH, which resolves between 2 and 8 weeks of age after discontinuing glycine-lowering medication, mirrors the neonatal form but is temporary.

Nonketotic hyperglycinemia results from glycine accumulation, which disrupts myelin formation and excitatory neurotransmission. Glycine interferes with myelin basic protein (MBP) and myelin-associated glycoprotein (MAG) in the corpus callosum and striatum, leading to impaired myelination.[4] It also decreases neuroglycan-2 (NG-2) in the cerebral cortex. Elevated glycine causes excitotoxicity through excessive activation of NMDA receptors, leading to increased intracellular calcium beyond the buffering capacity of the emergency room (ER) and mitochondria, disrupting neuronal homeostasis and causing cell death.[4]

Treatment options for NKH remain limited, as there is no definitive cure. Management typically centers on controlling symptoms, particularly seizures. Treatment strategies aim to lower glycine levels and mitigate the excitotoxic effects of excess glycine. Dextromethorphan acts as an N-Methyl-D-Aspartic acid (NMDA) receptor antagonist, reducing the neurotoxic effects of glycine.[9] Sodium benzoate binds to glycine, forming hippurate, which is excreted in urine.[10,11] Studies have also shown that outcomes depend on genetic mutation and the initiation of therapy. Early recognition and diagnosis of NKH are critical for improving outcomes, as early intervention can help mitigate further neurological damage and enhance the quality of life for affected individuals. Given the rarity of NKH, a thorough evaluation of patients presenting with relevant neurological symptoms is necessary, as under diagnosis remains a concern.

Conclusion

Neonatal cases presenting with persistent hiccups, seizures, hypotonic, diminished reflexes, difficulty with breastfeeding, abdominal distension, and swallowing difficulties should raise suspicion for NKH.[2] A history of pre-birth hiccup-like movements may suggest severe NKH, likely due to glycine accumulation in utero. Prenatal indicators such as polyhydramnios and abnormal fetal movements could aid in early diagnosis.

This case underscores the critical importance of early diagnosis and adherence to proper management protocols for NKH. In this instance, suboptimal management, exemplified by limited access to EEG, genetic testing, and long-term follow-up, emphasizes the need for adherence to established clinical guidelines. Effective management involves the prompt initiation of anticonvulsants, glycine-lowering agents like sodium benzoate, and NMDA receptor antagonists such as dextromethorphan.[11]

Additionally, a multidisciplinary approach, including collaboration between neurology, genetics, and metabolic specialists, is vital to addressing the complex needs of these patients. Ongoing follow-up is essential to track developmental milestones, seizure management, and glycine levels, ultimately improving patient outcomes. Genetic counselling and testing should be offered to all families, as identifying mutations in NKH-related genes can significantly inform prognosis and treatment strategies. Comprehensive patient care also requires attention to potential gastrointestinal, cardiovascular, and orthopedic complications.

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CASE REPORT

A Diagnostic Challenge: Adolescent Anti-NMDAR Encephalitis Presenting as Functional Neurological Disorder—A Case Report

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Abstract

Anti-NMDAR encephalitis can present with prominent psychiatric and behavioral symptoms, especially in adolescents, often leading to misdiagnosis. We present the case of a 15-year-old girl who initially manifested with behavioral disturbances, apparent functional neurological symptoms, and interpersonal stressors in her parents. Despite normal neuroimaging and electroencephalogram (EEG) findings, her progressive clinical course with eventual seizure activity led to a diagnosis of anti-NMDAR encephalitis confirmed on cerebrospinal fluid (CSF) testing. Immunotherapy led to seizure control, but behavioral issues persisted, underlining the neuropsychiatric burden of the illness. This case emphasizes the need for high clinical suspicion of autoimmune encephalitis in adolescents with atypical behavioral and functional symptoms and highlights the importance of long-term neuropsychiatric follow-up.

Keywords: Adolescent psychiatry, Anti-NMDAR encephalitis, Autoimmune encephalitis, Case report, Functional neurological disorder, Pediatric neuroimmunology.

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Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder commonly affecting children and adolescents, often presenting with neuropsychiatric symptoms.[1–3] The initial presentation may mimic primary psychiatric illnesses or functional neurological disorders, especially in adolescents.[4] Early recognition and immunotherapy are critical for improved outcomes.[2] This report discusses a diagnostically challenging case that underscores the interface of psychiatry and neurology in pediatric practice.

Case Presentation

A 15-year-old girl with normal birth and developmental history presented with behavioral changes over a few months. Symptoms included unilateral limb weakness that used to last for hours, she would not walk on her own, and sometimes may show bizarre abnormal limb movement while being unresponsive for some time. Events would occur with varied severity in the presence of the treating doctor and her father. Multiple events used to occur in a day.

She was stubborn and difficult to handle at times by her parents though was doing good at school. Her diet and sleep was appropriate. No history of such particular events. She was the only child, emotionally very close to her father, and described as pampered and willful since early childhood by her mother. The family dynamic was strained, with significant parental conflict.

Initial workup by two neurologists (adult and pediatric) included normal magnetic resonance imaging (MRI) brain (plain), normal electroencephalogram (EEG) (twice) which captured events though no EEG correlates, and unremarkable labs including antistreptolysin-O (ASO) titer, thyroid stimulating hormone (TSH), FT3/FT4, and homocysteine. She was diagnosed with a functional neurological disorder and managed by psychiatry with fluoxetine, risperidone, and psychotherapy. She improved somewhat but continued to have behavioral outbursts and remained selectively unresponsive to her mother. Despite these concerns, she maintained normal academic performance and social behavior at school, which further complicated the clinical picture.

Few months later, she had a new episode of staring spell with lip smacking and prolonged unresponsiveness lasting 10–15 minutes, followed by focal motor twitchings over the left angle of her mouth f/b limbs and urinary incontinence. Repeat EEG showed mild slowing over the right temporal region. Magnetic resonance imaging brain with epilepsy protocol was again normal. Given the evolution of symptoms, autoimmune encephalitis was considered. cerebrospinal fluid (CSF) testing confirmed anti-NMDAR antibodies.

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She received intravenous methylprednisolone and intravenous immunoglobulin (IVIG), followed by an antiepileptic drug. While she remained seizure-free, behavioral issues persisted, and she was subsequently treated with rituximab. At present, she continues to receive psychiatric medications and a single antiepileptic drug, with improved seizure control and mild residual behavioral issues. Magnetic resonance imaging pelvis was negative for ovarian teratoma.

Discussion

This case illustrates the broad phenotypic spectrum of anti-NMDAR encephalitis, particularly in adolescents where psychiatric symptoms may predominate.[4] Functional neurological features, such as limb weakness and non-epileptic unresponsiveness, can mimic conversion disorder.[4,5] The presence of family stressors, a strong emotional attachment to one parent, and preserved functioning at school further complicated the diagnosis.

The NMDAR is highly expressed in the hippocampus and limbic system, which are involved in emotion, memory, and behavior—explaining the neuropsychiatric dominance in many adolescent presentations.[1] Importantly, her clinical evolution with a new seizure-like event prompted re-evaluation and a shift in diagnostic consideration. The delay in diagnosis reflects the subtle and evolving nature of autoimmune encephalitis and underscores the importance of considering organic causes even in the presence of apparent psychosocial triggers.[2,3]

The persistence of behavioral disturbances despite immunotherapy suggests a residual neuropsychiatric burden, reinforcing the need for ongoing psychiatric support even after seizure control.[4,5] Longitudinal follow-up with a multidisciplinary approach is vital for optimizing functional recovery.

Conclusion

Anti-NMDAR encephalitis should be considered in adolescents with atypical behavioral disturbances, especially when symptoms are persistent, bizarre, or resistant to psychiatric management.[2,4] Close collaboration between neurology and psychiatry is essential for early recognition and appropriate management.[5]

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CASE REPORT

Clues in the Claw: Hirayama Disease in a Young Adolescent Male

Subash Kumar Patra[1], Ruchika Tamrakar[2], Sambita Panda[3]

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Abstract

Background: Hirayama disease (HD) is a rare, self-limiting motor neuron disorder predominantly affecting adolescent males, characterized by unilateral or asymmetric muscular atrophy of the distal upper extremities.

Objectives: To review the etiology, clinical course, and management strategies of HD, emphasizing the importance of early recognition and interdisciplinary care coordination.

Case presentation: A 17-year-old male presented with progressive weakness and atrophy of the right hand, initially affecting the middle finger and subsequently involving all fingers over a year. A similar progression was noted in the left hand starting in December 2020. There were no sensory deficits, but the patient experienced difficulty in daily activities and handwriting changes. Neurological evaluations and imaging studies led to the diagnosis of HD.

Conclusion: Early diagnosis of HD is crucial to prevent irreversible neurological damage. Clinicians should consider HD in adolescents presenting with insidious-onset upper limb weakness and atrophy.

Keywords: Adolescent motor neuron disease, Case report, Cervical myelopathy, Hirayama disease, Muscular atrophy.

Journal of Academy of Pediatric Neurology (2025): 10.5005/jaopn-11028-0013

Introduction

Hirayama disease (HD), first described in 1959, is a benign, self-limiting motor neuron disease characterized by painless weakness and amyotrophy in the forearm and hand of a single upper limb, typically presenting between adolescence and the third decade of life.[1] The disease often stabilizes spontaneously a few years after onset. It is hypothesized that during neck flexion, compression of the spinal cord by the dura mater induces chronic microcirculatory changes in the territory of the anterior spinal artery, leading to HD.[2]

Etiopathogenesis

Several theories have been proposed regarding the pathogenesis of HD:

- Contact pressure theory (1960): Suggests that degenerative spurs compress the spinal cord during flexion.[2]
- Tight dural canal theory (1987): This prominent theory suggests that the dura mater, particularly at the back of the C2 and C3 vertebrae, has increased looseness. When the neck bends forward, this slack permits the spinal cord to shift abnormally toward the front. This repeated movement can lead to subtle cervical trauma and reduced blood flow (microischemia) to the anterior horn cells. Over time, these changes may result in spinal cord damage and degeneration, especially impacting the nerve roots associated with C7 and C8.[2]
- Growth imbalance hypothesis: Proposes that disproportionate growth between the vertebral column and dural canal during growth spurts results in increased dural laxity, permitting anterior displacement of the posterior dura.[3]
- Posterior longitudinal ligament structure variation: Suggests that unequal distribution of elastic ligaments securing the posterior dura mater may allow localized cord displacement, as observed in some surgical and cadaveric studies.[3]
- Venous congestion hypothesis: Hirayama suggested that bending the neck forward raises pressure within the spinal cord, which slows down blood flow in the posterior epidural venous plexus. This venous stagnation can cause swelling and contribute to compression of the spinal cord.[4]

Epidemiology

Hirayama disease predominantly affects males, with a peak onset between 15 and 17 years of age. While initially reported in Japan, cases have been documented across Asia, including China, Taiwan, Malaysia, India, and Sri Lanka, North America, and Europe. Unilateral muscle weakness generally develops slowly and tends to appear during the early stages of adolescence, often around the time puberty begins. Usually, the condition stabilizes within 1–4 years after it begins, although in some cases, progression can continue

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Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

Fig. 1: A 17-year-old male with Hirayama disease

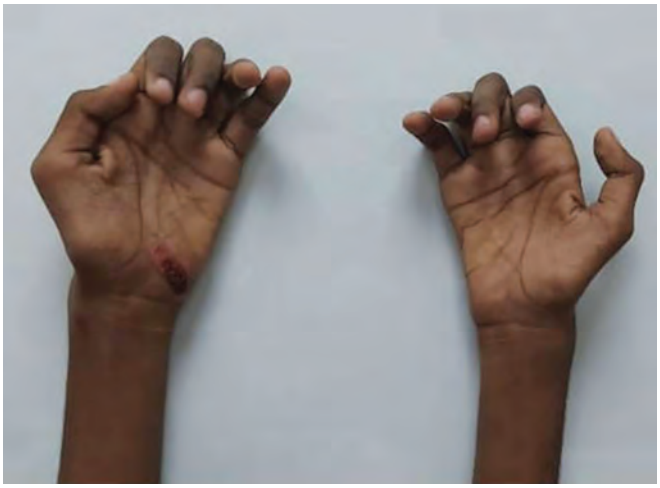

Fig. 3: Ventral aspect of bilateral hand and wrist

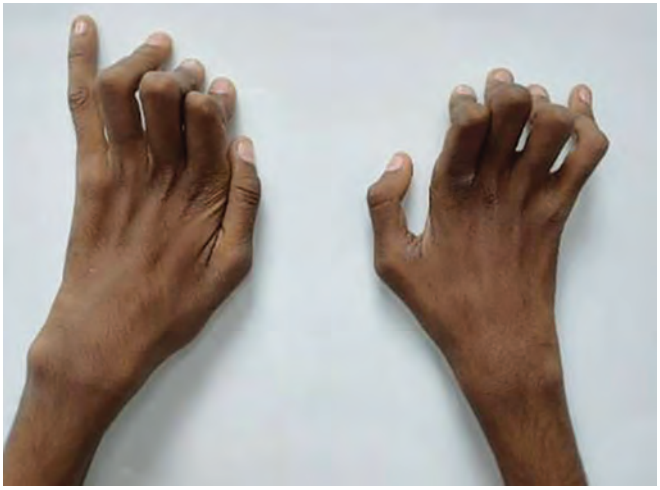

Fig. 2: Dorsal aspect of bilateral hand and wrist

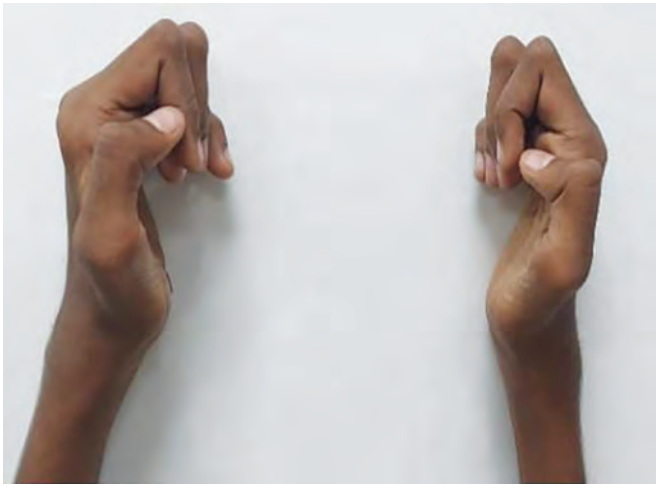

Fig. 4: Lateral aspect of bilateral hand and wrist

into the early 20s. Studies have noted a higher incidence of right-sided involvement in HD, with a ratio close to 2.8:1, irrespective of hand dominance. While rare, instances involving both upper limbs have been observed in this same age-group and are regarded as the most severe form of the condition.[1,2]

Case Presentation

A 17-year-old male (Fig. 1) presented to the pediatric outpatient department with a 4-year history of progressive wasting and weakness of right hand, initially affecting the middle finger, then third and fourth digits and subsequently involving all fingers over a year, starting from the proximal interphalangeal joints and progressing distally. A similar progression of clawing was noted in the left hand 2 years after onset of initial symptoms (Figs 2 to 5). There was no history of paresthesia, loss of sensation, loss of power or motor functions, while in due course, patient gradually experienced difficulty in daily activities and changes in handwriting. Neurological evaluations and imaging studies were conducted.

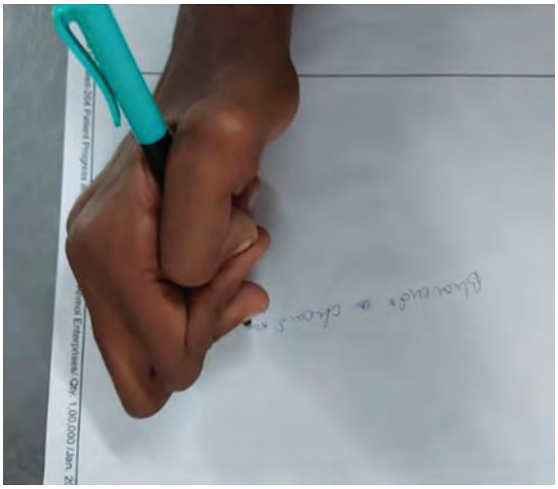

Fig. 5: Image showing posture of hand of patient while writing with his right hand

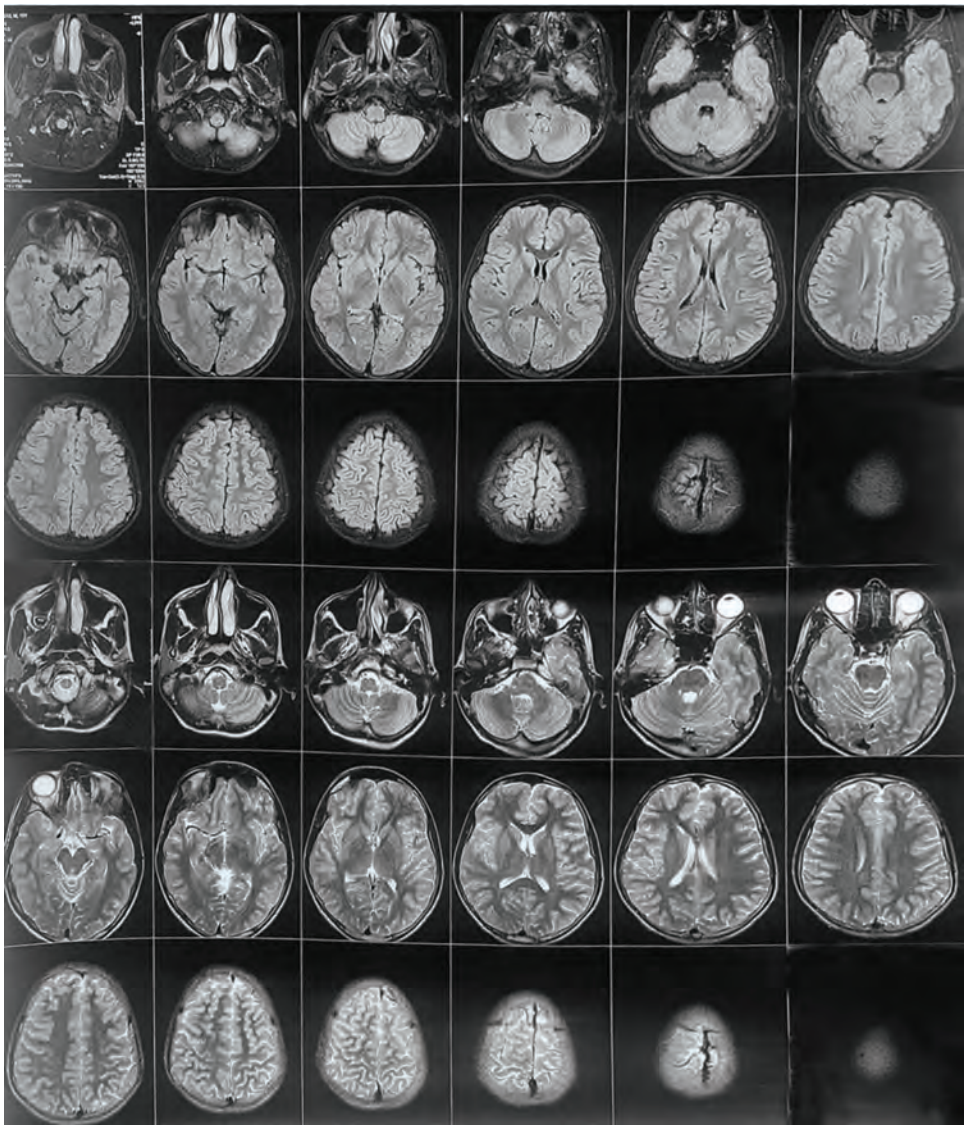

Fig. 6: T2-weighted MRI of brain (coronal section)

Investigations

- Nerve conduction study: Nerve conduction study revealed abnormal compound muscle action potential and sensory nerve action potential, suggesting predominantly motor, severe axonal polyneuropathy.
- Electromyography: Showed neurogenic pattern of involvement of cervical and lumbar myotomes.
- Magnetic resonance imaging (MRI) of brain and spine: Magnetic resonance imaging of brain was unremarkable. Spinal MRI demonstrated loss of lumbar lordosis and mild disc bulging at L4–L5, compressing the dural sac (Figs 6 and 7).

Differential Diagnosis

The differential diagnosis for HD includes:[5]

- Upper motor neuron lesions:
  - Amyotrophic lateral sclerosis
  - Ossified posterior longitudinal ligament
  - Toxic neuropathy
  - Spinal muscular atrophy
  - Cervical spondylotic myelopathy
- Lower motor neuron lesions:
  - Syringomyelia
  - Myotonic dystrophy
  - Pronator syndrome
  - Peripheral nerve entrapment syndromes

Discussion

Hirayama disease is an uncommon, benign neurological condition characterized by muscular atrophy of unilateral or asymmetric bilateral upper limbs. Despite global case reports, awareness remains limited, leading to potential underdiagnosis.[2] Diagnosis relies on clinical evaluation, nerve conduction studies, and,

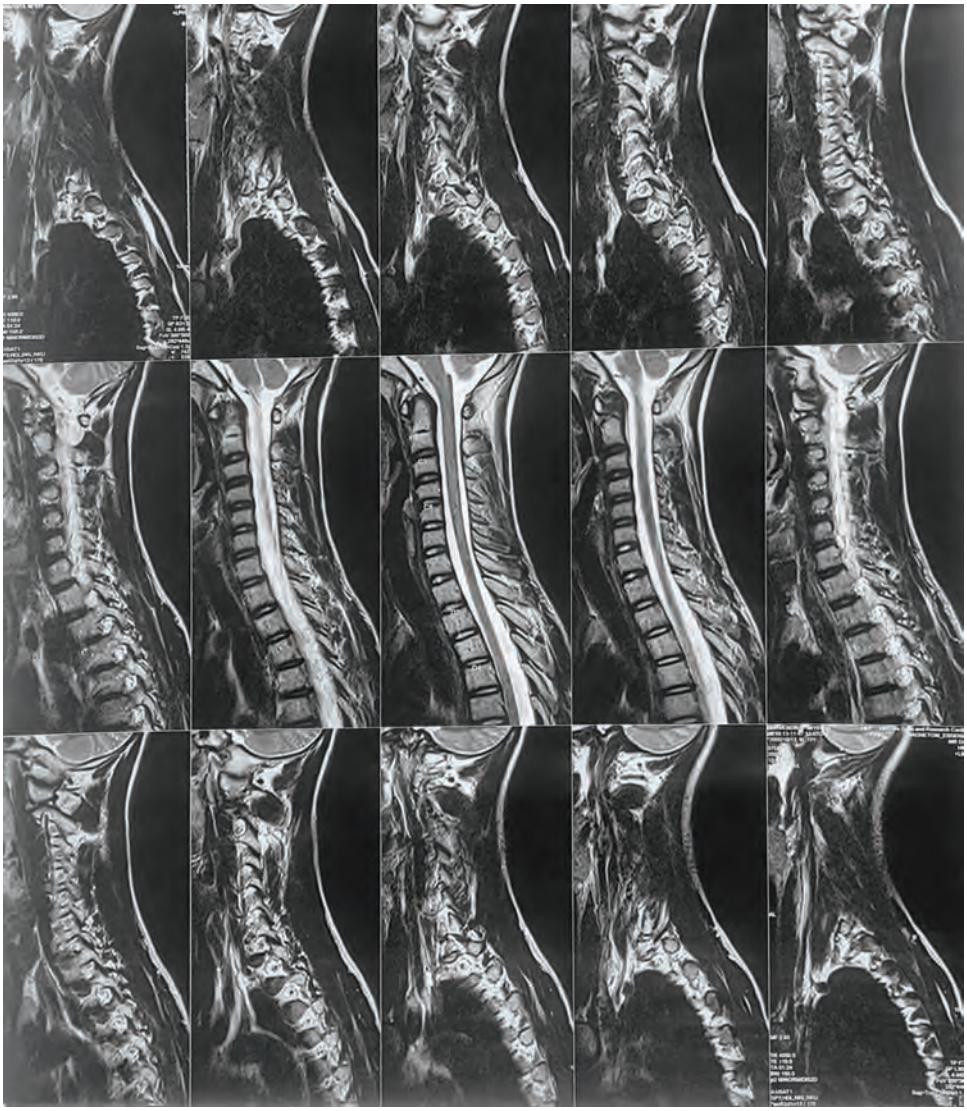

Fig. 7: T2-weighted MRI of spine (sagittal section)

critically, cervical spine MRI during neck flexion, which may reveal anterior displacement of the posterior dura and spinal cord compression. Early recognition is vital to prevent irreversible spinal cord damage.[4,6] Treatment is primarily supportive, including physiotherapy, antioxidants, multivitamins, and long-term cervical braces.[6] Studies emphasize the importance of timely diagnosis and management to avoid serious and permanent injury to the cervical spinal cord. Therefore, in juvenile patients presenting with gradually developing limb weakness, HD should be included in the differential diagnosis and confirmed through cervical flexion MRI.[7]

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CASE REPORT

Transaminitis as a Red Herring: A Misdiagnosed Case of Duchenne Muscular Dystrophy—A Case Report

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Abstract

Introduction: Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder characterized by progressive muscle weakness and elevated creatine kinase (CK) levels. However, early signs may be misinterpreted, especially when biochemical abnormalities such as transaminitis are present. Elevated liver enzymes due to muscle degeneration can mimic hepatic disease, delaying the correct diagnosis.

Case description: A 6.3-year-old male presented with persistently elevated liver enzymes and sonographic hepatic abnormalities. He was initially evaluated at another hospital for suspected metabolic liver disease. At our clinic, detailed neuromuscular examination revealed Gowers' sign, valley sign, and calf pseudo hypertrophy. Serum CK was significantly elevated. Whole exome sequencing (WES) identified a hemizygous pathogenic variant in the DMD gene (c.531-2A > C), confirming the diagnosis of DMD. A heterozygous variant in the Focadhesin (FOCAD) gene was also detected but deemed unrelated to the phenotype.

Discussion: This case emphasizes that elevated liver enzymes in children without hepatic symptoms should prompt evaluation for neuromuscular disorders. Misinterpretation can lead to diagnostic delay. Genetic testing played a crucial role in uncovering the correct diagnosis guiding clinical management and family counseling.

Conclusion: Duchenne muscular dystrophy may present with atypical biochemical findings, such as isolated transaminitis. A multidisciplinary approach and early genetic testing are key to avoiding misdiagnosis, ensuring timely intervention, and providing appropriate genetic counseling to affected families.

Keywords: Duchenne muscular dystrophy, Genetic counseling, Genetic diagnosis, Misdiagnosis, Neuromuscular disorders, Transaminitis.

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Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive neuromuscular disorder that primarily affects males and is caused by mutations in the DMD gene located on the X chromosome. The absence of dystrophin, a cytoskeletal protein critical for maintaining muscle fiber stability, leads to muscle degeneration and progressive weakness.[1] Clinical manifestations typically begin between 2 and 5 years of age, with affected children showing delays in motor milestones, difficulty in running and climbing stairs, and characteristic findings such as Gowers' sign and calf pseudohypertrophy.[2]

Despite the well-characterized phenotype, early signs may be overlooked or misattributed, particularly when symptoms overlap with other systemic conditions.[3] Elevated transaminases serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT), commonly associated with liver pathology, are also observed in DMD due to ongoing muscle fiber damage and subsequent release of intracellular enzymes.[4] This often leads to an initial misdiagnosis, especially when neuromuscular features are subtle or not thoroughly evaluated.

In this case, the patient was initially assessed at another center for persistent transaminitis and sonographic hepatic abnormalities and was diagnosed with suspected metabolic liver disease. However, further clinical deterioration in motor function, family history suggestive of X-linked inheritance, and comprehensive evaluation at our clinic led to the suspicion of a neuromuscular disorder. Genetic testing ultimately confirmed the diagnosis of DMD, underscoring the importance of genetic testing in atypical presentations.[5]

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This case highlights the diagnostic pitfalls that may arise when elevated liver enzymes are interpreted in isolation, without consideration of neuromuscular causes.[6] It also illustrates the critical role of genetic testing in unraveling underlying etiologies and enabling timely diagnosis and management.[7]

Case Description

A 6.3-year-old male child, born to non-consanguineous parents, presented with a 7-month history of persistently elevated liver enzymes. He was initially evaluated at another center for asymptomatic transaminitis, where laboratory investigations showed

Table 1: Initial laboratory investigations

Test	*Purpose*	*Findings*
Liver function tests (LFTs)	Evaluate liver enzyme levels	SGOT: 247 U/L (↑), SGPT: 272 U/L (↑), mild hyperbilirubinemia
Abdominal ultrasonography (USG)	Assess liver structure and echotexture	Coarse hepatic echotexture, increased hepatic echogenicity
Whole exome sequencing	Identify potential genetic/metabolic disorders	FOCAD: c.4132+2C>A (heterozygous), DMD: c.531-2A>C (hemizygous pathogenic)
Serum creatine kinase (CK)	Assess muscle injury/damage	CK: 1892.34 U/L (↑)
Neuromuscular examination	Evaluate for clinical signs of muscular dystrophy	Positive Gowers' sign, valley sign, and calf pseudohypertrophy
Family history assessment	Investigate pattern of inheritance, pedigree analysis	Male relatives with similar phenotype, consistent with X-linked DMD

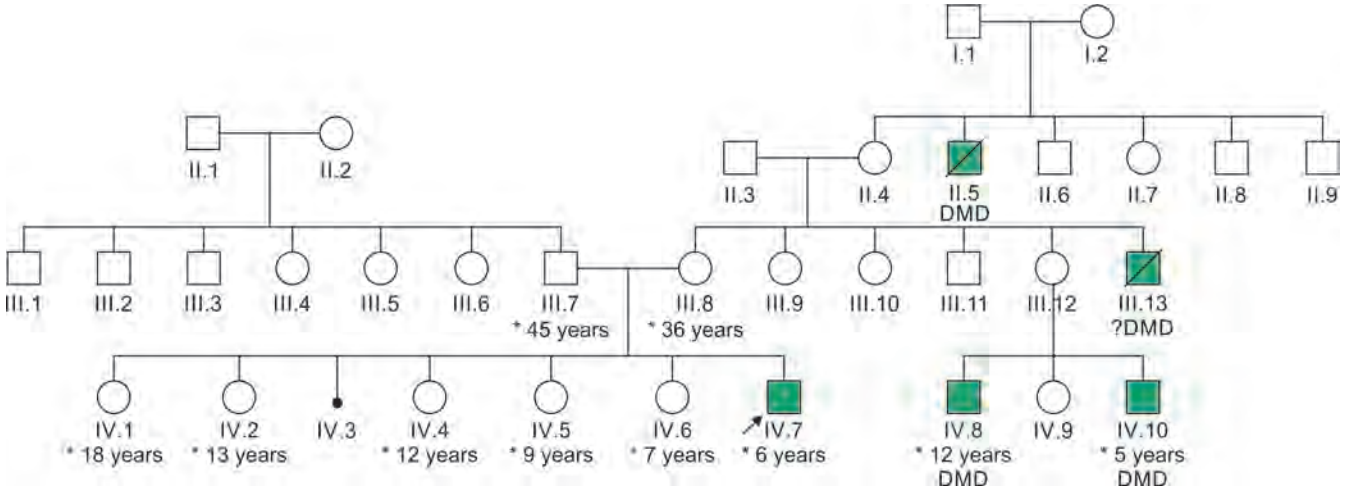

Fig. 1: Family pedigree showing multiple male individuals affected in subsequent generations

elevated SGOT at 247 U/L and SGPT at 272 U/L. Bilirubin levels were within normal limits. An abdominal ultrasound revealed coarse hepatic echotexture with increased echogenicity, raising clinical suspicion of a metabolic liver disorder. No detailed neuromuscular assessment was performed at that time, whole exome sequencing (WES) was done, and the child was referred for genetic evaluation to investigate potential underlying metabolic causes.

When evaluated at our genetic clinic, the history revealed subtle but consistent motor difficulties that had been overlooked. The child had long-standing issues with rising from the floor and climbing stairs and exhibited a waddling gait, which had not been previously assessed in detail. Physical examination revealed classical signs suggestive of a neuromuscular disorder, including a positive Gowers' sign, calf muscle pseudo hypertrophy, and a prominent valley sign. There was no evidence of hepatosplenomegaly or jaundice.

Further laboratory workup at our clinic revealed a markedly elevated serum creatine kinase (CK) level of 1892.34 U/L, which raised suspicion for an underlying muscular dystrophy. Whole exome sequencing was revealed: (1) a heterozygous likely pathogenic variant in the Focadhesin (FOCAD) gene (c.4132+2C>A), associated with autosomal recessive congenital liver disease online men Delian inheritance in man (OMIM 619991) and (2) a hemizygous pathogenic variant in the DMD gene (c.531-2A>C), consistent with DMD (OMIM 310200), and the finding was considered incidental in this case. The FOCAD mutation was ruled out as heterozygous and does not correlate with clinical presentation (Table 1).

A detailed family history revealed male relatives with similar motor weakness in early childhood, suggesting X-linked inheritance (Fig. 1). Based on clinical features, family history, elevated CK levels, and genetic confirmation, a diagnosis of DMD was established. The incidental liver findings and transaminitis were attributed to muscle degeneration commonly seen in DMD. Genetic counseling was provided to the family regarding the implications of the diagnosis, recurrence risk, and options for carrier testing and future reproductive planning.

Discussion

Duchenne muscular dystrophy is a progressive X-linked recessive neuromuscular disorder caused by mutations in the DMD gene, that result in the absence or severe reduction of dystrophin, a critical structural protein in muscle fibers.[1] While DMD typically presents with signs of muscle weakness between ages 2 and 5 years, such as difficulty rising from the floor, climbing stairs, and waddling gait, these signs may be subtle or misinterpreted, especially when biochemical findings suggest an alternate diagnosis.[2]

In the present case, the child was initially misdiagnosed with metabolic liver disease at another center due to persistently elevated liver enzymes and hepatic echogenicity on ultrasound.

Table 2: Multidisciplinary management plan for DMD

Specialty	*Role and interventions*
Neurology	• Baseline assessment of motor function and muscle strength (e.g., North star ambulatory assessment)
	• Initiate corticosteroid therapy (e.g., prednisone or deflazacort) as per guidelines
	• Monitor progression and refer for clinical trial opportunities
Cardiology	• Baseline electrocardiogram (ECG) and echocardiography (ECHO)
	• Annual cardiac monitoring to detect early cardiomyopathy
	• Consider ACE inhibitors or beta-blockers if cardiac dysfunction is detected
Pulmonology	• Baseline and annual pulmonary function tests (PFTs) once child is old enough or symptomatic
	• Monitor for nocturnal hypoventilation
	• Discuss early respiratory support planning in later stages
Physiotherapy and rehabilitation	• Daily stretching exercises to prevent contractures
	• Promote ambulation with assistive devices if needed
	• Monitor and manage scoliosis
	• Occupational therapy for ADLs and adaptive equipment
Nutrition and dietetics	• Nutritional assessment, especially if on long-term corticosteroids
	• Prevent obesity and ensure adequate calcium/vitamin D intake
	• Monitor for steroid-induced side effects like osteoporosis and weight gain
Psychological support	• Genetic counseling for patient and family to address emotional impact
	• Behavioral support, especially if cognitive or learning difficulties are present
	• Connect with patient support groups (e.g., Bharath MD Foundation, IAMD in India)

ACE, angiotension converting enzyme; ADLs, activity of daily livings

However, transaminitis is a well-recognized biochemical feature of DMD, resulting from muscle breakdown rather than hepatocellular injury.[3] Enzymes such as aspartate aminotransferase (AST) (SGOT) and alanine aminotransferase (ALT) (SGPT), though traditionally liver-specific, are also abundantly present in skeletal muscle tissue. In DMD, their persistent elevation in the absence of liver-specific symptoms should prompt a neuromuscular evaluation.[8]

The detection of a heterozygous FOCAD variant associated with autosomal recessive liver disease through WES further complicated initial impressions. However, the child's phenotype and inheritance pattern did not support a primary liver disorder. Ultimately, WES provided a definitive diagnosis by identifying a pathogenic splice-site variant in the DMD gene, underscoring the utility of genomic testing in atypical or misleading clinical scenarios.[5] Although the gold standard choice of genetic test for DMD is Multiplex ligation Probe Amplification for large exonic deletions and duplications.

This case emphasizes the importance of thorough neuromuscular assessment in children with unexplained hypertransaminasemia and highlights the risk of diagnostic delay when symptoms are interpreted in isolation. Moreover, genetic counseling played a vital role in informing the family about the diagnosis, X-linked inheritance, carrier testing for the mother, and reproductive options for future pregnancies. In disorders like DMD, early genetic diagnosis facilitates timely initiation of multidisciplinary care, family planning, and potential enrollment in clinical trials (Table 2).[9]

Conclusion

This case highlights how DMD can present with non-specific findings such as elevated liver enzymes, leading to initial misdiagnosis. A high index of suspicion, combined with detailed clinical evaluation and timely genetic testing, is essential in identifying underlying neuromuscular disorders. Genetic testing proved invaluable in clarifying the diagnosis, allowing appropriate counseling and multidisciplinary management. Early recognition of DMD enables timely intervention, improves quality of life, and provides families with crucial reproductive and prognostic information.

Clinical Significance

This case underscores the importance of considering neuromuscular causes such as DMD in children presenting with isolated transaminitis. Early signs of DMD may be subtle and misattributed to hepatic pathology, delaying accurate diagnosis and intervention. Genetic testing can play a pivotal role in uncovering hidden diagnoses and guiding appropriate management. Timely recognition enables early initiation of multidisciplinary care and informed genetic counseling for families.

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