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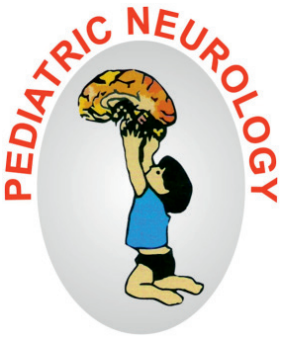

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Journal of Academy of Pediatric Neurology

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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

ORIGINAL RESEARCH

A Study of Clinical Profile and Prognostic Factors in Pediatric Patients with Guillain–Barré Syndrome

Disha A Mehta[1], Jolly G Vaishnav[2], Anuya V Chauhan[3]

Received on: 15 July 2025; *Accepted on:* 29 August 2025; *Published on:* 14 November 2025

Abstract

Aim and background: To study the clinical presentation, epidemiology, diagnostics, management, complications, outcomes, disease progression (using Hughes disability grading), and prognostic factors (age, sex, antecedent illness, Medical Research Council (MRC) score, duration of weakness, time to peak weakness, autonomic dysfunction, electrophysiology, ventilatory support) in patients with Guillain–Barré syndrome (GBS).

Materials and methods: This prospective analytical study was conducted at BJ Medical College, Ahmedabad (January 2023–June 2024). It included children (1–12 years) with GBS diagnosed as per Asbury criteria and NCV studies, admitted to the pediatric intensive care unit/ward. Detailed analysis of history, investigations, and treatment was done. Prognostic factors and ventilation needs were assessed. Patients were monitored from admission to discharge and followed for 6 months using Hughes grading. Data analysis was performed using appropriate statistical methods.

Results: A total of 95 GBS patients meeting the inclusion criteria were enrolled. Most (50.5%) were aged 5–9 years, with a male predominance (62.1%). Cases peaked between July and October, with respiratory illness being the most common antecedent (38.9%). Bilateral lower-limb weakness was the most frequent presentation (69.4%). Cranial nerve affection was most commonly seen in form of bulbar palsy (40%). The acute motor axonal neuropathy subtype was found to be most common (35.7%), lower MRC scores, autonomic instability, and bulbar palsy predicted ventilation needs. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) patients showed the most significant improvement over time.

Conclusion: Early diagnosis and intervention are crucial in managing GBS. Lower MRC scores, autonomic instability, and bulbar involvement predict poorer outcomes, including the requirement of ventilatory support. Seasonal patterns and antecedent illnesses influence disease presentation and progression. All GBS subtypes showed significant improvement in disability over time, especially AIDP.

Clinical significance: There should be close monitoring of lower-limb weakness, respiratory issues, autonomic instability, MRC scores, and development of bulbar palsy to prognosticate patients and improve outcomes. Public health awareness, comprehensive rehabilitation, and regular follow-ups support recovery, as evidenced by significant disability improvements over time.

Keywords: Hughes disability grading, Medical Research Council score, Prognostic predictors.

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Introduction

Acute flaccid paralysis (AFP) is a rapidly progressing paralysis (≤4 weeks) characterized by flaccid limbs with diminished tone and deep tendon reflexes.[1] Common causes include Guillain–Barré syndrome (GBS), poliomyelitis, transverse myelitis, traumatic neuritis, and post-diphtheritic neuropathy. Despite India's polio-free certification (2014), non-polio AFP (NPAFP) cases have risen, possibly linked to repeated Oral Polio Vaccine campaigns, which may alter gut microbiota and contribute to paralysis.[2] Guillain–Barré syndrome is an autoimmune peripheral neuropathy causing rapidly ascending paralysis, sensory deficits, and autonomic dysfunction, often triggered by infection. Pediatric GBS can lead to severe weakness, respiratory failure and requires intensive care. While recovery is common, early rehabilitation minimizes long-term deficits. Respiratory and autonomic complications are major mortality risks.

Objective

To study the clinical presentation, epidemiology, diagnostics, management, complications, outcomes, disease progression (using Hughes disability grading), and prognostic factors (age, sex, antecedent illness, Medical Research Council (MRC) score, duration of weakness, time to peak weakness, autonomic dysfunction, electrophysiology, ventilatory support) in GBS patients.

[1–3]Department of Pediatrics, BJ Medical College, Ahmedabad, Gujarat, India

Corresponding Author: Disha A Mehta, Department of Pediatrics, BJ Medical College, Ahmedabad, Gujarat, India, Phone: +91 9426234138, e-mail: mehtadisha186@gmail.com

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Conflict of interest: None

Materials and Methods

This prospective, analytical study was conducted at BJ Medical College, Civil Hospital, Ahmedabad, from January 2023 to June 2024 (1.5 years).

Inclusion Criteria

Children aged 1–12 years diagnosed with GBS (Asbury criteria, NCV studies) and admitted to the pediatric intensive care unit/ward.

Exclusion Criteria

Infants, children >12 years, asymmetrical symptoms, sharp sensory levels, or other neurological conditions (e.g., myasthenia gravis,

botulism, poliomyelitis, porphyria, diphtheria, drug/toxin-induced neuropathy). Ethical approval was obtained, and informed consent was taken.

Patient data (demographics, clinical history, neurological/systemic exams, MRC sum score, cranial nerve and respiratory assessment, sensory/autonomic evaluation) were recorded. Investigations included blood tests, stool analysis, NCV, cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI), and Hughes disability grading for motor deficits. Treatment involved intravenous immunoglobulin (IVIG), plasmapheresis, steroids, analgesics, physiotherapy, and supportive care. Acute flaccid paralysis reporting was done for all cases. Prognostic factors and mechanical ventilation needs were assessed. Patients were monitored from admission to discharge and followed up for 6 months using Hughes disability grading. Data were analyzed using Microsoft Excel and statistical methods.

Diagnostic Criteria (Asbury's)

- Required: Progressive weakness (≥1 limb), distal areflexia with proximal areflexia/hyporeflexia.
- Supportive: Symmetrical deficits, mild sensory involvement, CN involvement (esp. CN VII), autonomic dysfunction, CSF findings (↑protein, white blood cell (WBC) ≤10/μL), NCV changes.
- Against diagnosis: Asymmetrical weakness, early/persistent bowel/bladder dysfunction, CSF WBC >50/μL, sensory level.
- Exclusion criteria: Isolated sensory involvement, other polyneuropathies.[3]

MRC Sum Score

It is grading system used for assessment of muscle power.

Functions Assessed

- Upper extremity: Wrist flexion, forearm flexion, shoulder abduction.
- Lower extremity: Ankle dorsiflexion, knee extension, hip flexion.

Score for Each Movement

0: No visible contraction.
1: Visible muscle contraction, but no limb movement.
2: Active movement but not against gravity.
3: Active movement against gravity.
4: Active movement against gravity and resistance.
5: Active movement against full resistance.

- Maximum score – 60 (normal).
- Minimum score – 0 (quadriplegia).

Hughes Disability Grading

The Hughes disability score, also called as the GBS disability score. It assesses functional impairment in patients with GBS using a scale from 0 to 6. Each score corresponds to varying degrees of disability.[4]
0 – Healthy.
1 – Minor symptoms or signs of neuropathy, but capable of manual work/capable of running.
2 – Able to walk without support of stick (5 m across an open space) but incapable of manual work/running.
3 – Able to walk with a stick, appliance, or support (5 m across an open space).
4 – Confined to bed or chair bound.
5 – Requiring assisted ventilation (for any part of day or night).
6 – Death.

Table 1: Demographic and antecedent illness characteristics in Guillain-Barré syndrome patients

Profiling parameters	*No. of patients (N = 95)*	*Percentage (%)*	*Chi-square test p-value*
Age (years)			
<5	31	32.6	0.0003
5–9	48	50.5	
10–12	16	16.9	
Sex			
Male	59	62.1	0.0183
Female	36	37.8	
Season			
Winter (November–February)	22	34.4	0.465
Summer (March–June)	17	26.5	
Monsoon (July–October)	25	39	
Antecedent illness			
Respiratory	37	38.9	0.0099
Gastrointestinal	26	27.3	
Other febrile illness	9	9.4	
None	23	24.2	

Results

This prospective study was carried out from January 2023 to June 2024 at Civil Hospital, Ahmedabad. A total of 95 patients with GBS who fulfilled inclusion criteria were enrolled in the study.

The majority of patients (50.5%) were in the 5–9-year age-group, 32.6% of patients were <5 years, and 16.9% patients were between 10 and 12 years of age. The *p*-value was 0.0003, suggesting that the observed distribution of patients across age-groups was statistically significant (Table 1).

In the present study, out of 95 patients, 59 (62.1%) were male and 36 (37.8%) were female. Thus, preponderance of males was found. The *p*-value was approximately 0.0183, which is less than the common alpha level of 0.05. This indicates a statistically significant difference in the proportion of males and females in the sample. The male-to-female ratio was 2.1:1 in <5 years of age-group, 1.5:1 in the 5–9 years of age-group, and 1.2:1 in the 10–12 years of age-group (Table 1).

The maximum number of patients presented between the months of July and October. The *p*-value was 0.465, which is much greater than the common alpha level of 0.05. This indicates that there is no statistically significant difference in the distribution of patients across different seasons (Table 1).

In this study, out of 95 patients, 72 (75.7%) patients had a preceding illness. The most common preceding illness was a respiratory infection, observed in 37 (38.9%). The *p*-value of 0.0099 is less than the common significance level of 0.05, indicating that the distribution of antecedent illnesses is significantly different (Table 1).

The maximum number of patients presented with paraparesis (69.4%), followed by quadriparesis in 30.5% of cases. Difficulty in breathing was seen in 48.7% of cases, and difficulty in swallowing

Table 2: Clinical profile of patients with Guillain–Barré syndrome

Presenting complaints	*No. of patients (N = 95)*	*Percentage (%)*
All four-limb weakness	29	30.5
Lower limb weakness	66	69.4
Difficulty in respiration	47	48.7
Difficulty in swallowing	38	40
Change in voice	26	27.3
Sensory symptoms	25	26.3
Autonomic disturbance	36	37.8
Cranial nerve involvement		
Bulbar	38	40
Facial	10	10.5
Oculomotor	4	4.2
Abducent	2	2.1
Duration of weakness on admission		
Within a day	13	13.68
2–3 days	47	49.47
4–5 days	20	21.05
6–7 days	6	6.3
8–10 days	3	3.1
>10 days	6	6.3
MRC score		
51–60	3	3.1
41–50	12	12.6
31–40	12	12.6
21–30	18	18.9
11–20	24	25.2
0–10	26	27.3

Table 3: Investigation and treatment of patients with GBS

Subtypes on electromyography-nerve conduction velocity	*No. of patients (N = 95)*	*Percentage (%)*	*Chi-square test p-value*
AMAN	34	35.7	<0.0001
AIDP	18	18.9	
AMSAN	16	16.8	
Miller Fischer variant	4	4.2	
AMAN + AIDP	2	2.1	
Unclassified	17	17.8	
Normal EMG-NCV	4	4.2	
Albumino-cytologic dissociation in CSF	13 (*N* = 20)	65	
Caudal enhancement in spine MRI	19 (*N* = 26)	73	
Treatment			
IVIG	69	72.6	
Plasmapharesis	15	15.7	
MPS	4	4.2	
Symptomatic	7	7.3	

EMG-NCV, electromyography-nerve conduction velocity

in 40% of cases. In this study, sensory symptoms were reported in 26.3% patients, and autonomic disturbances were observed in 37.8% patients (Table 2).

The most common cranial nerve involvement was in the form of bulbar involvement, observed in 40% of cases, followed by the facial nerve (10.5%), oculomotor nerve (4.2%), and abducent nerve (2.1%). In this study, the most commonly involved cranial nerves were the 9th and 10th cranial nerves. The *p*-value was < 0.0001. There is a statistically significant difference in the involvement of different cranial nerves among the patients.

In this study, 60 (63%) patients presented to the hospital within 72 hours of the onset of weakness. The *p*-value of < 0.0001 indicates that there is a highly significant difference in the distribution of the number of patients across different days of weakness on admission.

In this study, 52.5% of patients had an MRC score of less than 20 on admission, which suggests greater severity of disease on admission. The mean MRC sum score in the study was 24.4 (Table 2).

In this study, the acute motor axonal neuropathy (AMAN) subtype was the most common, observed in 34 patients (35.7%), followed by acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in 18 patients (18.9%), AMSAN in 16 patients (16.8%), Miller Fisher variant in 4 patients (4.2%), and a mixed variety of AMAN and AIDP in 2 patients. In 17 patients, NCV studies could not be performed. In this study, the *p*-value was <0.0001. There was a statistically significant difference in the distribution of subtypes among the patients (Table 3).

In this study, CSF examination was done in 20 patients, of whom 13 (65%) showed albuminocytological dissociation. Magnetic resonance imaging was done in 26 patients, and 19 patients (73%) showed caudal enhancement (Table 3).

In this study, 69 patients (72.6%) were treated with IVIG, 15 patients (15.7%) were treated with plasmapheresis, 4 patients (4.2%) were treated with methylprednisolone, and 7 patients who were ambulant were treated symptomatically (Table 3).

Out of 60 patients admitted within 3 days of the onset of weakness, 34 patients required ventilation, while 26 did not.

There was a greater requirement for ventilation in those patients who had lesser duration of weakness on admission, which might indicate rapid progression. However, the *p*-value was not found to be statistically significant.

Out of 38 patients with bulbar involvement, 28 required ventilator support, while 10 patients not requiring ventilatory support. Among 56 patients without bulbar involvement, 19 patients required ventilatory support and 37 patients did not require ventilatory support.

The *p*-value (0.00035) is much smaller than the common significance level of 0.05, indicating a statistically significant association between bulbar involvement and the need for a ventilation. Bulbar involvement was found to be a prognostic factor for ventilator requirement.

Out of 37 patients with autonomic instability, 25 patients (67%) required ventilator support. Among 58 patients without autonomic instability, 22 patients (37.93%) required ventilatory support.

The *p*-value (0.00581) is smaller than the common significance level of 0.05, indicating a statistically significant association between autonomic instability and the need for a ventilator.

There was no statistically significant association between sensory system involvement and the need for a ventilator.

There was no statistically significant association between the type of GBS and the requirement for a ventilatory support.

Among the 33 patients with the AMAN subtype, 27.2% had mild disability (grade 0–II) on admission, increasing to 64.7% by 6 months. Of the 17 AIDP patients, initial severe disability was common, but 81.2% achieved mild disability by 6 months, showing significant improvement. The 15 AMSAN patients had an even distribution of disability at admission, with all reaching mild disability (grade 0–II) by 6 months. Overall, all subtypes showed progressive recovery over time, with AIDP and AMSAN patients demonstrating more pronounced functional improvement compared with the AMAN variety.

Discussion

In this study, the highest proportion of patients (50.5%) were in the 5–9-year age-group, consistent with findings from Nasiri et al.[5] (45.6%). This suggests that GBS may have a peak incidence during middle childhood, potentially due to increased exposure to triggering infections or differences in immune system maturation. The distribution of patients across age-groups was statistically significant, indicating possible underlying factors such as environmental exposure, access to healthcare, or epidemiological trends.

The male-to-female ratio was 1.6:1, aligning with Adhikari et al.[6] (1.64:1, India, 2023) and slightly lower than that reported by Chaweekulrat and Sanmaneechai[7] (2.3:1, Thailand, 2022) and Rangan et al.[8] (2.3:1, India, 2021).

A majority of cases (39%) occurred between July and October, coinciding with the monsoon season. Although the seasonal distribution did not yield a statistically significant *p*-value, the trend supports findings from Adhikari et al., who observed 62% of cases in the same period. The monsoon season is typically associated with an increased incidence of gastrointestinal and respiratory infections, including *Campylobacter jejuni*, a known GBS trigger. The lowest case frequency was recorded during the winter months. Despite the non-significant seasonal pattern, continuous public health surveillance and year-round awareness programs are recommended. Respiratory infections were the most frequent antecedent illness (38.9%), followed by gastrointestinal infections (27.3%) and other febrile illnesses (9.4%). This pattern was consistent with Chaweekulrat and Sanmaneechai (respiratory 39%, gastrointestinal 12.2%, febrile 9.8%) and Adhikari et al. (respiratory 53.3%, febrile 22.2%, gastrointestinal 17.8%). The observed differences in antecedent illness distribution were statistically significant ($p = 0.0099$), suggesting the influence of regional infectious disease epidemiology, healthcare-seeking behavior, and environmental factors. Further studies of socio-economic and genetic determinants could provide more information (Table 1).

At admission, 52.5% of patients had an MRC sum score <20, indicating greater disease severity. A highly significant association ($p < 0.0001$) was found between MRC score categories and the need for mechanical ventilation, provides the utility of MRC score as a prognostic marker. Although patients with a shorter duration of weakness on admission tended to require more ventilation – suggesting rapid disease progression – the association was not statistically significant ($p = 0.172$). This however suggests the need for early clinical recognition and intervention (Table 2).[9]

Electrophysiological subtyping revealed that AMAN was the predominant variant in the present study, similar to Yadav et al.,[10] and consistent with findings in pediatric populations in India and neighboring countries. Conversely, AIDP was more prevalent in studies by Nasiri et al. and Kalita et al.[9] These regional differences may reflect underlying genetic, environmental, or infectious determinants influencing GBS subtype presentation.

Albuminocytological dissociation on CSF analysis was found in 76.9% of cases, consistent with its high diagnostic specificity for GBS. Additionally, caudal enhancement on spine MRI was observed in 66.6% of patients. However, such enhancement is not pathognomonic for GBS and can also occur in other conditions, such as post-diphtheritic polyneuritis, cauda equina syndrome, arachnoiditis, tumors, arteriovenous malformations, and trauma; therefore, it should be interpreted in clinical correlation.[11]

Intravenous immunoglobulin was the primary treatment, administered to 88.9–92% of patients across referenced studies (Yadav et al., Nasiri et al., Adhikari et al., Rangan et al.). In this study, one patient received both IVIG and plasmapheresis, and two received a second dose of IVIG. A relatively higher percentage of plasmapheresis usage was noted in this study, likely due to its availability at the treating center (Table 3).

Statistical analysis showed significant associations between the need for ventilatory support and the presence of bulbar involvement ($p = 0.00035$) as well as autonomic instability ($p = 0.00581$). Patients with these complications were more likely to require mechanical ventilation. In contrast, there were no significant associations between ventilator requirement and antecedent illness type ($p = 0.385$), sensory involvement ($p = 1.0$), or GBS subtype ($p = 0.272$). These findings emphasize the importance of monitoring for cranial nerve and autonomic involvement to anticipate respiratory deterioration (Table 4).

Across all GBS subtypes, significant improvement in disability grades was noted from admission through discharge and at 3-month, and 6-month follow-ups. The AIDP group demonstrated highly significant recovery ($p < 0.00001$), while the AMAN and acute motor and sensory axonal neuropathy (AMSAN) subtypes also showed statistically significant improvements ($p < 0.05$). These findings support early and aggressive supportive care and rehabilitation to improve functional outcomes (Table 5).

Conclusion

This study highlights the importance of early recognition of prognostic markers and early interventions in GBS. Lower MRC scores, autonomic instability, and bulbar involvement are significant predictors of poor outcomes, including the need for ventilatory support. Seasonal patterns and antecedent illnesses also play a significant role in the clinical presentation and progression of GBS. Significant improvements in disability grades were observed across all GBS subtypes over time, particularly in AIDP type of GBS.

Clinical Significance

Due to possibility of rapid progression of disease, early detection and prompt interventions are crucial. Healthcare providers should

Table 4: Association between clinical variables and need for mechanical ventilation in Guillain-Barré syndrome patients

Characteristics	*Requiring ventilation*	*Not requiring ventilation*	*Chi-square test p-value*
Bulbar involvement			
Yes	28	10	0.0003
No	19	37	
Autonomic instability			
Yes	25	12	0.0058
No	22	36	
Sensory system involvement			
Yes	13	12	0.1
No	34	35	
Subtype of GBS			
AMAN	8	26	0.27
AIDP	8	10	
AMSAN	6	10	
Antecedent illness			
Respiratory	22	15	
Gastrointestinal	11	15	0.385
Other febrile illness	4	5	
None	10	13	
Duration of weakness on admission			
Within 3 days	34	26	0.172
4–5 days	8	12	
>6 days	5	10	
MRC score			
51–60	–	3	
41–50	–	12	
31–40	3	9	<0.0001
21–30	6	12	
11–20	16	8	
0–10	21	5	

Table 5: Type of GBS and its functional outcome

Type of GBS	*Grade*	*No. of patients on admission (N = 65)*	*%*	*No. of patients on discharge (N = 65)*	*%*	*No. of patients on 3 months follow-up (N = 56)*	*%*	*No. of patients on 6 months follow-up (N = 43)*	*%*	*Chi-square test p-value*
AMAN		(*N* = 33)		(*N* = 33)		(*N* = 29)		(*N* = 17)		0.0004
	0–II	9	27.2	14	42.4	18	62	11	64.7	
	III–IV	17	51.5	19	57.5	11	37.9	6	35.2	
	V	7	21.21	0	0	0	0	0	0	
AIDP		(*N* = 17)		(*N* = 17)		(*N* = 16)		(*N* = 16)		<0.0001
	0–II	2	11.7	7	41.1	10	62.5	13	81.2	
	III–IV	8	47	10	58.8	6	37.5	3	18.7	
	V	7	41.1	0	0	0	0	0	0	
AMSAN		(*N* = 15)		(*N* = 15)		(*N* = 11)		(*N* = 10)		0.002
	0–II	5	33.3	10	66.6	9	81.8	10	100	
	III–IV	5	33.3	5	33.3	2	18.1	0		
	V	5	33.3	0	0	0		0		

be particularly vigilant for signs of weakness in the lower limbs and respiratory difficulties, as these are common early symptoms. Public health strategies should include awareness campaigns about potential triggers and symptoms of GBS. Monitoring, management strategies, and resource allocation for high-risk groups may help reduce mortality and morbidity. Given their significant association with poor outcomes, autonomic instability, lower MRC scores, and bulbar palsy should be closely monitored and managed in GBS patients to improve prognosis and reduce mortality. Further studies with this perspective are required so that a comprehensive scoring system can be developed to prognosticate the course of GBS, which will go a long way in improving the outcome. Comprehensive rehabilitation programs and regular follow-ups are recommended to track and support patient recovery. The significant improvements observed in disability grades over time highlight the effectiveness of such interventions.

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ORIGINAL RESEARCH

Basal Ganglia Stroke in Children Following a History of Fall: A Study of Five Cases with Mineralizing Angiopathy

Habib G Pathan[1], Syed M Hashmi[2], Aarthi A Karikalvalaven[3], Fateen Shareef[4]

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Abstract

Aims and background: Arterial ischemic stroke is a significant cause of stroke in pediatric patients. Trauma-induced endothelial injury and fibrin accumulation can cause ischemia of cerebral parenchyma, resulting in a distinct clinico-radiological entity. Basal ganglia stroke is often associated with mineralization of lenticulostriate arteries.

Materials and methods: A retrospective analysis was conducted on consecutive children with basal ganglia stroke and mineralization of lenticulostriate arteries from a tertiary care center in South India. The study group was formed by children with mineralization in the distribution of the lenticulostriate arteries and basal ganglia infarcts. Their demographic data, clinical and radiological characteristics, treatment response, neurodevelopmental outcome, and recurrence of stroke were noted.

Results: Among all the children who suffered arterial ischemic strokes during the study period, only five infants with basal ganglia ischemic stroke and mineralization of the lenticulostriate arteries were included. All five cases had a history of fall or trauma. The study group was formed by children before 24 months of age, and the majority had hemiparesis. The follow-up period was brief, but all patients showed a partial or complete recovery.

Conclusion: Basal ganglia stroke in children with a history of falls may be caused by mineralizing angiopathy. Early detection and timely management of risk factors may prevent recurrence and improve neurodevelopmental outcomes.

Clinical significance: Basal ganglia stroke in infants following trauma is a distinct clinico-radiological entity. Early detection of the lenticulostriate arteries can be detected on radiological investigations, and timely treatment with aspirin and cilostazol can lead to partial to complete recovery.

Keywords: Basal ganglia stroke, Epilepsy, Focal deficits, Head trauma, Lenticulostriate arteries, Mineralizing angiopathy, Pediatric neurology, Post-traumatic, Seizures, Stroke.

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Introduction

Arterial Ischemic stroke has an incidence of 5/1,00,000 in children, making it one of the most common causes of stroke in the pediatric age group.[1] Ischemic stroke can be ascribed to endothelial injury following trauma. Basal ganglia stroke has been reported to occur in infants in association with minor falls and is well recognized as occurring secondary to mineralization of lenticulostriate arteries.[2] Trauma impact on the skull causes a stretching and shearing effect on vessels in the brain parenchyma. The traumatic endothelial intimal lesion is followed by fibrin accumulation, leukocyte reaction, and white thrombus formation, which occludes the lumen. This vessel obstruction causes ischemia of cerebral parenchyma with clinical symptoms after a symptomless latency period.[3] This presents as a distinct clinico-radiological entity.

In this article, we have described five cases of pediatric basal ganglia stroke following minor head trauma with mineralizing angiopathy of lenticulo-striate arteries on imaging.

Materials and Methods

The study was conducted at the Child Neurology Division, Department of Pediatrics, attached to a tertiary care center from South India. Consecutive cases of basal ganglia stroke showing mineralization of lenticulostriate arteries were selected from the neurology unit databases. Participants were identified retrospectively from September 2020 to June 2021, and the follow-up period was up to August 2021. The hospital ethics committee cleared the study. All children with subcortical stroke who presented at the pediatric unit during this period were included. The study group was formed by children with mineralization in the distribution of the lenticulostriate arteries and basal ganglia infarcts. Their demography, history of trauma/fall, weakness, seizures, and neurological symptoms and signs were noted. Other relevant history, such as developmental, family, and similar past history, was

[1]Department of Pediatrics, Deccan College of Medical Sciences, Hyderabad, Telangana, India

[2,3]Department of Radiodiagnosis, Deccan College of Medical Sciences, Hyderabad, Telangana, India

[4]Deccan College of Medical Sciences, Hyderabad, Telangana, India

Corresponding Author: Aarthi A Karikalvalaven, Department of Radiodiagnosis, Deccan College of Medical Sciences, Hyderabad, Telangana, India, Phone: +91 9000835137, e-mail: aarthiabirami1251994@gmail.com

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Table 1: Case details in the study

Case number	*1*	*2*	*3*	*4*	*5*
Sex	M	M	F	M	M
Age	11 m	60 m	24 m	10 m	12 m
History of trauma	Yes	Yes	Yes	Yes	Yes
Acute dystonia	Yes	Yes	No	No	No
Hemiparesis (R, L)	(Yes, no)	(No, yes)	(Yes, no)	(Yes, no)	(No, yes)
Speech	Normal	Expressive aphasia	Normal	Normal	Normal
Focal seizures	Yes	No	Yes	No	Yes
Mineralization (R)	Linear calcification in two arteries	Linear calcification in two arteries	Linear calcification in two arteries	Linear calcification in four arteries	–
Mineralization (L)	Linear calcification in three arteries	Linear calcification in two arteries	Linear calcification in three arteries	Linear calcification in four arteries	–
Previous episodes	2 m	36 m	None	None	None
Recurrence	Yes	Yes	No	No	No
Treatment given	Aspirin, cilostazol	Aspirin, cilostazol	Aspirin, cilostazol	Aspirin, cilostazol	Aspirin, cilostazol
Neurodevelopmental outcome	Partial recovery	Complete recovery	Partial recovery	Partial recovery	Partial recovery
Follow-up time	10 m	3 m	3 m	5 m	2 m

F, female; L, left; M, male; m, months; R, right

elicited. Treatment response, neurodevelopmental outcome, and recurrence of stroke were documented during the follow-up period. The brief follow-up period is a limitation of this study.

The details of physical examination and systemic examination, such as anthropometry and any evidence of organomegaly, were documented. Magnetic resonance imaging (MRI) and non-contrast computed tomography (NCCT) of the brain with axial and coronal sections were carried out in all infants except one, where neurosonography (NSG) was performed. Complete blood count and echocardiography were performed in all cases. The details of the cases are shown in Table 1.

Results

Among all the children who suffered arterial ischemic strokes during the study period, only five infants with basal ganglia ischemic stroke and mineralization of the lenticulostriate arteries detected using CT formed the study group. The demographic data, clinical and radiological characteristics, and follow-up details of the study group are summarized in Table 1.

In all the cases, five of five cases had a history of fall or trauma. All of the cases at initial presentation were before 24 months of age, and the majority of the (three of the five) cases were under the age of 18 months. None experienced loss of consciousness. Among these, two of the five infants reported a recurrence which were also precipitated by a fall. One case of recurrent stroke had expressive aphasia, and four of the five recovered partially. Hemidystonia was reported (two out of five) post minor head trauma, following which both cases had recurrence in later life. Of the three infants who did not experience a recurrent stroke, all three had residual hemiparesis. In total, four out of five had residual hemiparesis.

Brain CT demonstrated characteristic, mineralizing angiopathy of lenticulostriate arteries which is the primary reason for infarction of the basal ganglia.[4] Axial CT showed linear hyperdensities through he inferior sections of the lentiform nuclei in all infants. On coronal and sagittal views, the linear hyperdensities were noted along the anatomical distribution of the lenticulo-striat arteries. These lesions had attenuation values between 56 and 88 HU, suggestive of mineralization. The number of mineralized arteries varied from two to five on each side. The radiological findings are shown in Table 2 with a few radiological images in Figure 1.

All patients were treated with aspirin and cilostazol. Rehabilitative physiotherapy was advised for all.

Discussion

Acute ischemic stroke involving the basal ganglia in infants after mild head trauma is strongly clinically correlated, as this phenomenon has been reported for over a decade. The association of basal ganglia calcification with minor head trauma was suggested in 10 out of 16 infants in a report from China by Yang et al. in 2013.[5]

The correlation between acute dystonia and recurrence is not well established in the existing studies reporting this phenomenon. This topic needs further research as there are no significant studies or reporting on it.

Jain et al. reported that the predisposition of lenticulostriate arteries to mineralize seems to be age-related.[6] The majority of patients in the Lingappa study were under the age of 18 months.[7] In our study, all cases were under the age of 60 months at presentation, and three cases were under the age of 18 months.

Dystonia

Lingappa et al. reported the appearance of dystonia in 16 of 23 infants, whereas Gowda et al. reported 28 of 38 cases showing dystonia. Dystonia was noted in two out of five of our cases.

All the cases that had recurrence (two out of five), one had complete neurological recovery, and one had partial recovery. As reported by Gowda, all children with recurrence had residual neurological deficits.[4]

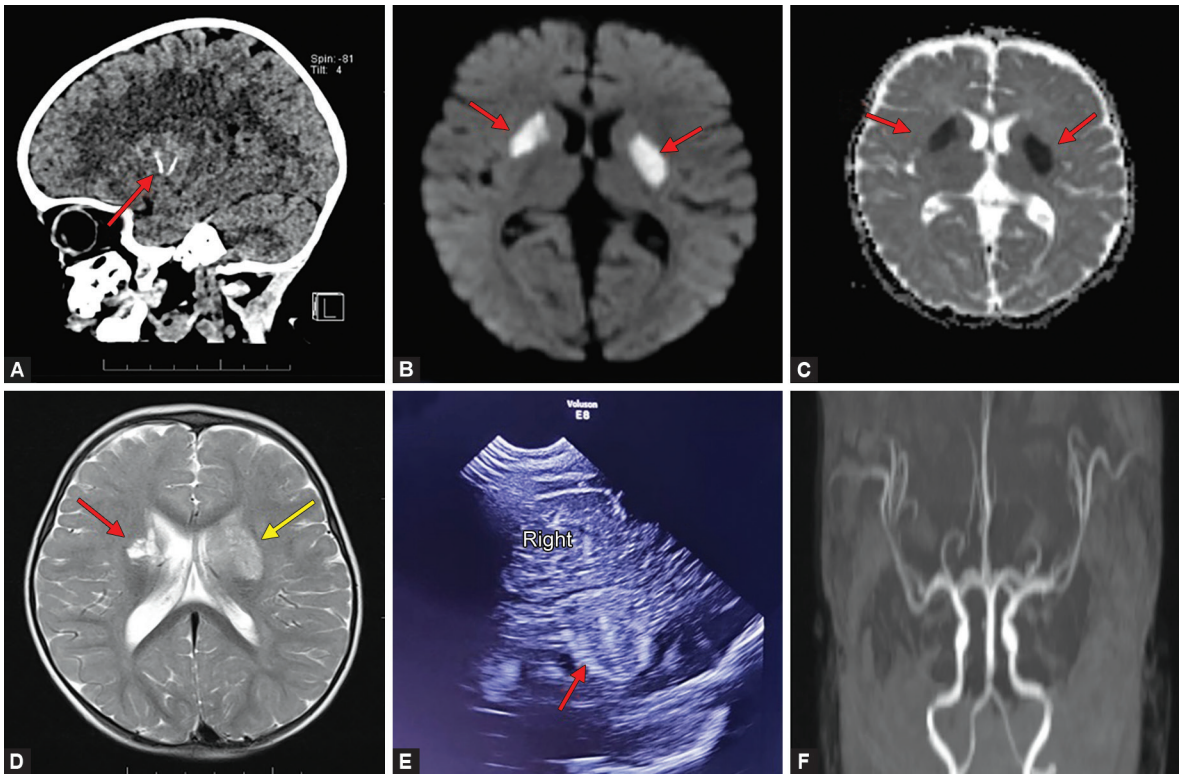
Mineralization

MRI is not the most sensitive modality when it comes to identifying mineralization. When a capsuloganglionic (CG) infarct is identified

Table 2: Radiological findings in each of the cases in the study

Case number	*1*	*2*	*3*	*4*	*5*
Sex/Age	*M/11 months*	*M/60 months*	*F/24 months*	*M/10 months*	*M/12 months*
CT findings	Linear calcifications in the bilateral CG region. Three arteries on the left and two arteries on the right are involved	Linear calcifications in bilateral CG regions with hypodense SOL in the left CG region Two arteries are involved on both sides	Linear calcifications in the bilateral lentiform nucleus Three arteries are involved on the left, and two arteries are involved on the right.	Linear calcifications in bilateral (CG) region Four arteries are involved on both sides	Not done
DWI and ADC	Diffusion restriction in the left CG region	Diffusion restriction in the right CG region and corona radiata	Diffusion restriction in the left CG region and corona radiata	Diffusion restriction in the bilateral CG region	Diffusion restriction in the right CG region and corona radiata
MRI findings	T2 and FLAIR hyperintensities in the left CG region Gliosis in the right CG region	T2 and FLAIR hyperintensities in the right CG region and corona radiata Area of gliosis in the left CG region	T2 and FLAIR hyperintensities in the left CG region and corona radiata Gliotic area in the right CG region and corona radiata	T2 and FLAIR hyperintensities in the bilateral CG region	T2 and FLAIR hyperintensities in the right CG region and corona radiata
SWI	Normal	Blooming in bilateral CG regions	Normal	Blooming in bilateral CG regions	Normal
MR angiogram	Normal	Normal	Normal	Normal	Normal
Neurosonogram (NSG)	Not done	Not done	Not done	Linear echogenic hyperechoic foci in the bilateral CG region	Not done

CG, capsuloganglionic; DWI, diffusion weighted imaging; F, female, M, male; MRI, magnetic resonance imaging; SOL, space occupying lesion; SWI, susceptibility weighted imaging



Figs 1A to F: (A) Sagittal CT sections of the brain showing linear calcifications in the left CG regions most likely representing the calcified lenticulostriate arteries (red arrow); (B and C) DWI and ADC mapping of another patient with diffusion restriction in bilateral CG regions suggestive of fresh infarcts; (D) MRI of another patient showing T2 hyperintensity in the left CG region (yellow arrow) with an area of gliosis in the right CG region (red arrow); (E) NSG showing linear echogenic hyperechoic foci in the right CG region marked by the red arrow; (F) Normal MR angiogram

on an MRI in the age group of 6 months to 60 months, it is preferable to do a thin-sliced multiplanar reconstruction CT to delineate linear calcification in lenticulostriate vessels. If mineralizing angiopathy of lenticulostriate arteries is clearly noted in the CT scan, then further investigations to discern the cause of stroke become unnecessary. This condition shows a good prognosis when treated with standard antithrombotic therapy, according to Baby et al.[8] It has also been associated with a higher risk of thalamic infarcts after minor trauma, also known as mineralizing vasculopathy (different from that caused by radiotherapy).[9]

Recurrence, Outcomes, and Speech Defects

Lingappa study reported that of the 22 infants reported, five showed a recurrence precipitated by a fall. Four of the five recurrence cases had residual weakness, dysarthria, motor, and speech delay. Gowda et al. reported eight cases of recurrence, with one case of dysarthria, three with motor and speech delay, and all recurrent cases experiencing residual hemiparesis. In our study, there were two cases of recurrence, which were also precipitated by a fall, and one of those had expressive aphasia. One case recovered completely, and the other had residual hemiparesis. Good long-term neurodevelopmental outcomes were reported by Lingappa, except in cases of recurrent stroke. In our series, no such correlations could be made, and a longer follow-up period is required to make a statement on any such correlation. Bhardwaj et al. reported a second stroke occurring 18 months after the first, with a fall provoking the recurrence, indicating the need for sustained long-term follow-up.[2]

Follow-up

The mean duration of follow-up in the Lingappa study was 11.36 months, while the Gowda study had a mean of 8.31 months, and the recovery in the non-recurrent cases (17) was in 6 months of follow-up. Yang et al. had a median follow-up of 12 months, reporting complete recovery of patients from 2 weeks to 13 months. The average follow-up period of our study was 4.6 months, with the longest follow-up period being 10 months.

Treatment

Some studies have ascribed the recurrence of stroke to the absence of aspirin prophylaxis. In the indexed series, all patients were given antiplatelet therapy, despite which only one case showed complete recovery. No correlation could be made out from our study, ascribing the lack of aspirin therapy to recurrence or recovery. However, Toelle et al. reported complete recovery of five patients over the course of 12 months without antiplatelet or anticoagulant therapy.[10] Yang et al. reported one recurrent stroke in their series, though antiplatelet agents were not used. Lingappa et al. reported three out of five cases of recurrent stroke despite being on antiplatelets. According to Bhardwaj et al., the stroke is believed to be "mechanical" and related to shearing of vessels post-trauma, and aspirin may not necessarily prevent the occlusion. Further research is required to determine the role of antiplatelet agents in recovery and recurrence.

Conclusion

The manifestation of acute recurrent transient dystonia/focal deficits/focal seizures in patients as the presenting symptom is unique to infarcts of the basal ganglia region occurring due to occlusion of lenticulostriate arteries.[7]

Mineralizing angiopathy of lenticulostriate arteries presenting as basal ganglia stroke post-trauma is a distinct entity with a long-term neuro-developmental outcome. Computed tomography scans are not routinely advised following trivial trauma, but the presence of neurological deficits and long-term sequelae of mineralizing angiopathy in later life warrants a change in guidelines to require a CT scan in all cases following trivial trauma, as already advised by Bhardwaj et al.

Clinical Significance

- Mineralizing angiopathy is an often-overlooked cause of pediatric stroke.
- Thin-section spiral CT with multiplanar reconstructions (coronal and sagittal sections) is necessary in children developing focal deficits following trivial trauma.
- Diagnosis can be confirmed based on radiological findings alone; no further investigations are required.
- The condition has a favorable prognosis with judicious care and management.

Orcid

Habib G Pathan https://orcid.org/0009-0001-0378-2912
Syed M Hashmi https://orcid.org/0009-0006-5968-2853
Aarthi A Karikalvalaven https://orcid.org/0009-0000-0015-3099
Fateen Shareef https://orcid.org/0009-0005-6467-7613

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REVIEW ARTICLE

Neurodevelopmental Disorders and L-carnosine: A Clinical Perspective

Pramod Jog[1], Puja Kapoor[2], Ranjith Kumar M[3], Arpit Doshi[4], Neel Patel[5], Ashwin Kotamkar[6], Shailesh Pallewar[7], Amit Qamra[8], Aaditi Phadke[9], Prabhojit Mohanty[10], Anjalika Atrey[11]

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Abstract

Neurodevelopmental disorders (NDDs) affect approximately 15% of children and adolescents worldwide. Neurodevelopmental disorders, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), pose significant challenges in diagnosis, care, and treatment. L-carnosine, a naturally occurring dipeptide with antioxidant and neuroprotective properties, has shown therapeutic potential in managing NDDs. The complex interplay of genetic, environmental, and epigenetic factors in NDDs necessitates a comprehensive treatment approach. L-carnosine, a naturally occurring dipeptide with antioxidant, anti-inflammatory, and neuroprotective properties, has shown therapeutic potential in managing NDDs. Clinical studies have demonstrated that L-carnosine supplementation can improve behavioral symptoms, cognitive function, and social communication in children with ADHD and ASD. This review explores the potential therapeutic effects of L-carnosine on NDDs and implications for clinical practice. The findings suggest that L-carnosine could be a valuable complementary treatment option in the comprehensive management of NDDs, offering a promising avenue for improving the lives of affected individuals.

Keywords: Attention deficit hyperactivity disorder, Autism spectrum disorder, L-carnosine, Neurodevelopmental disorders, Specific learning disorders.

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Introduction

Neurodevelopmental disorders (NDDs) affect children and adolescents and are characterized by cognitive, communication, behavioral, and motor impairments due to abnormal brain development. The DSM-5 classifies NDDs into six main categories: it covers a wide spectrum of conditions, including attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), specific learning disorders (SLD), Intellectual disabilities, communication disorders, and motor disorders, including tic disorders (Fig. 1).[1] Managing NDDs poses several challenges, including difficulties in diagnosis due to overlapping symptoms, the need for tailored interventions, and limited access to resources for affected individuals and their families. Furthermore, the comorbidities of NDDs complicate treatment strategies.[2] A dipeptide composed of beta-alanine and histidine, L-carnosine, is primarily found in muscle and brain tissue. It possesses antioxidant properties and may play a role in neuroprotection and cognitive function, making it a subject of interest in the context of NDDs. This review aims to explore the potential therapeutic effects associated with L-carnosine on key NDDs, its mechanism of action, benefits

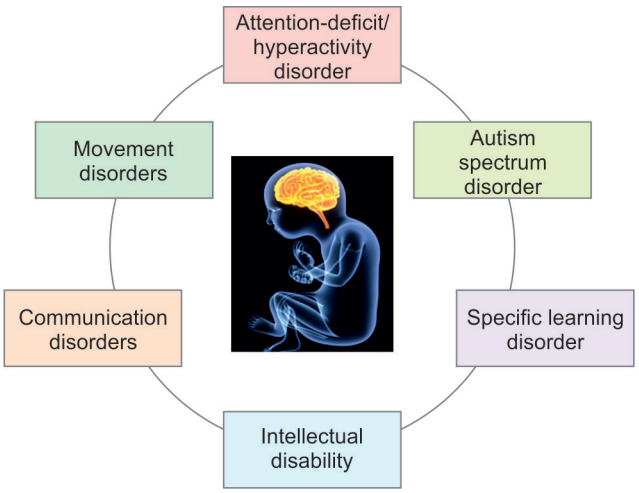

Fig. 1: Types of NDDs

[1]Department of Family Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Center, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pune, Maharashtra, India

[2]Department of Pediatric Neurology, Continua Kids – Child Development Centers, Gurugram, New Delhi, India

[3]Department of Pediatric Neurology, Shri Ramchandra Medical College, Chennai, Tamil Nadu, India

[4]Senior Consultant Pediatrician, Dr. Doshi's Clinic, Borivali, Mumbai, Maharashtra, India

[5–9]Department of Medical Affairs, Macleods Pharmaceuticals Ltd., Mumbai, Maharashtra, India

[10]Consultant Psychiatrist, Altiuz Hospital, Mumbai, Maharashtra, India

[11]Senior Consultant Psychiatrist, Criticare Asia Multispeciality Hospital, & Phoenix Hospital, Mumbai, Maharashtra, India

Corresponding Author: Neel Patel, Department of Medical Affairs, Macleods Pharmaceuticals Ltd., Mumbai, Maharashtra, India, Phone: +91 9898489742, e-mail: neelpatel12121993@gmail.com

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in cognitive and behavioral symptoms, and its relevance in clinical practice.

Epidemiology of Key NDDs

Around 15% of children and adolescents worldwide suffer from NDDs.[3,4] Approximately 5–11% of people worldwide suffer from ADHD, 3–10% from specific learning disorder (SLD), and 0.70–3% from ASD.[5] In India, the prevalence of ADHD varies between 1.6 and 14%. Attention deficit hyperactivity disorder (ADHD) has been identified in about 7% of school-age children. Depending on their comorbidities, the kind of ADHD, and the sort of care they get, the affected children display different behavioral problems. In India, the prevalence of ASD is estimated to be around 1.5%, and the prevalence of SLD is reported to vary from 3 to 10%. The incidence of SLD in India is reported to range from 3 to 10%.[6,7]

Pathophysiology

Attention Deficit Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder is marked by hyperactivity and/or difficulties with maintaining attention that are not appropriate for the individual's developmental level, often interfering with their social, academic, and occupational functioning. The pathophysiology of ADHD includes intricate interplays between environmental and genetic variables. Key mechanisms include alterations in neurotransmitter systems, particularly dopamine and norepinephrine, and structural/functional changes in brain regions controlling attention and executive function.[8,9] Figures 2 and 3 depict the pathophysiology and developmental impact of ADHD.

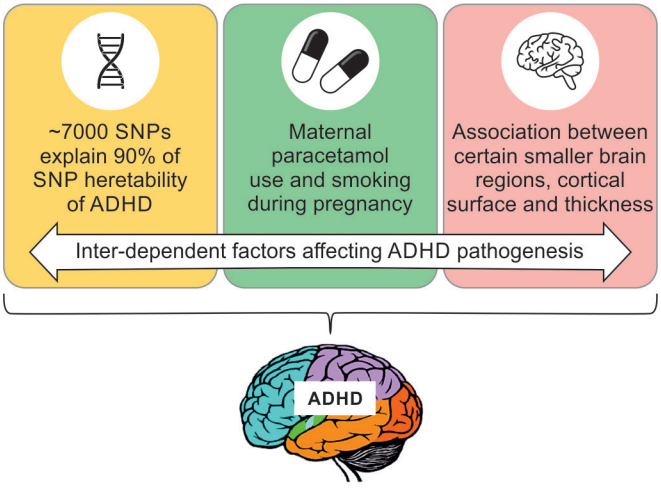

Fig. 2: Pathophysiology of ADHD
ADHD, attention deficit/hyperactivity disorder; SNPs, single-nucleotide polymorphisms

Autism Spectrum Disorder (ASD)

Autism spectrum disorder has become a typical neurodevelopmental condition that manifests as difficulties interacting with others, delayed language development, repetitive bodily motions, and significantly worsened social connect. Environmental factors that may contribute to the susceptibility to ASD include screentime, air pollution, heavy metals exposure, maternal heath, medications during pregnancy, birth complications etc. Genetic risk factors related to neurodevelopment, brain communication, and social interaction yield important insights into the genesis of ASD since the illness is strongly inheritable. Additionally, data indicates that epigenetic factors such as noncoding RNA, histone modification, and DNA methylation are important in the development of ASD.[10,11] Over the past 20 years, the link between oxidative stress (OS) and ASD has been emphasized considerably. Autism spectrum disorder is significantly impacted by reactive species of nitrogen and oxygen (ROS and RNS). Figures 4 and 5 depict diverse etiologies and relationships among the main determinants of ASD.

Specific Learning Disorders (SLDs)

The hallmark of SLDs is their inability to acquire important academic abilities. These challenges with learning new skills are caused by a combined effect of genetic, epigenetic, and environmental variables that impair the brain's capacity to process or perceive information.[12] The term "developmental learning disorder" has been replaced by the *International Classification System of Diseases 11th Revision (ICD-11)*. This involves difficulties with reading, writing, calculation, and other learning disabilities.

Current Treatment Approaches

Attention Deficit Hyperactivity Disorder (ADHD)

Simultaneous use of pharmaceutical and non-pharmacological intervention options is generally supported by the numerous studies on therapies for pediatric and adult ADHD. Attention deficit hyperactivity disorder is treated with drug therapies that include psychostimulants and non-stimulants. Individual variability defines it. Methylphenidate (MPH) and amphetamines belong to the category of psychostimulants, whereas non-stimulant medications include atomoxetine (ATX), bupropion, modafinil, tricyclic antidepressants (TCAs), venlafaxine, and alpha-2-adrenoceptor agonists.

Many individuals typically prefer alternative therapies like psychosocial intervention techniques. Psychosocial strategies, namely psychoeducation, cognitive-behavioral therapy, mindfulness-based

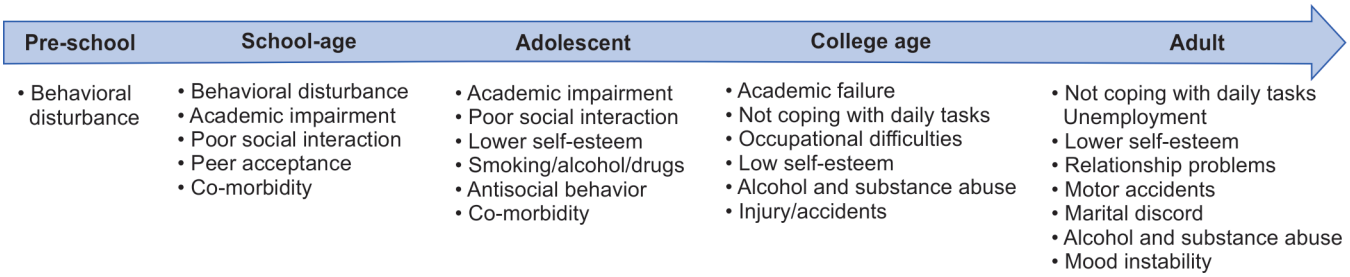

Fig. 3: Developmental impact of ADHD

training, and dialectical behavior therapy, are commonly used to assist individuals with ADHD in having fewer symptoms.[13]

Autism Spectrum Disorder (ASD)

The main objective of the treatment of ASD is to maximize the child's long-term functional autonomy as well as quality of life by minimizing the key characteristics of ASD, promoting socialization, facilitating learning and development, lowering maladaptive behaviors, and educating and supporting families. A spectrum of therapies, including speech therapy, applied behavioral analysis, and sensory integration therapy, is recommended as part of the treatment for autism, because there is presently no cure for the condition. Medication is used to address behavioral problems. aggressiveness, hyperactivity, stereotypies, and sleep difficulties. Repetitive and stereotyped behavior has been treated with mood stabilizers including valproate, selective serotonin reuptake inhibitors (SSRIs), and second-generation antipsychotics.[14]

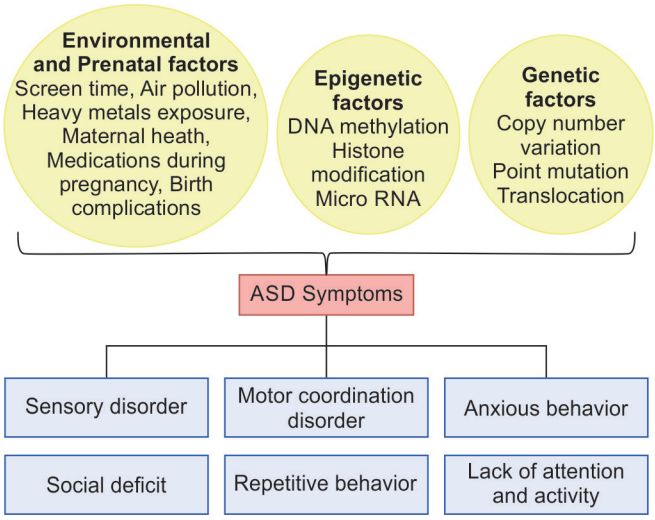

Fig. 4: Diverse etiology of autism spectrum disorders

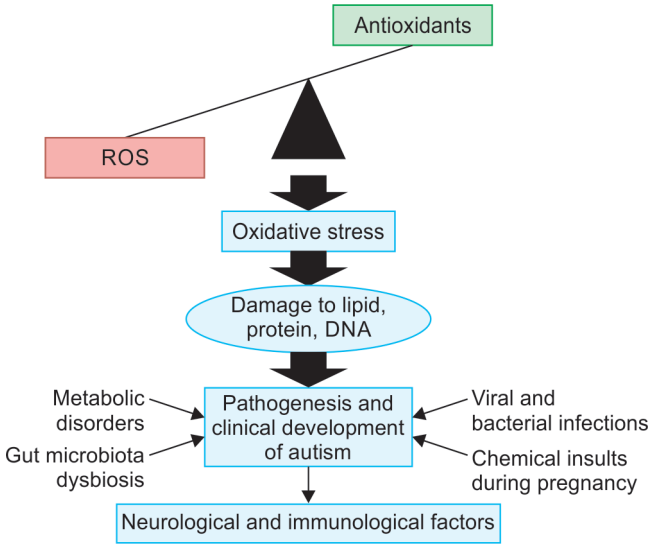

Fig. 5: Relationship among the main determinants of ASD

Specific Learning Disorders (SLDs)

The main objectives of managing SLD are to address the disorder's basic problems, its adverse effects on the child and relatives, and concurrent illnesses that are linked to it. Effective evaluation and management of SLD require a multidisciplinary approach involving professionals such as a pediatrician, psychologist, special educator, speech and language therapist, and occupational therapist.[15]

L-carnosine and its Properties

The water-soluble endogenous dipeptide carnosine (β-alanine-L-histidine) was discovered in Russia by Gulevitsch in 1900. L-histidine and beta-alanine are converted to carnosine by the enzyme carnosine synthase, which is then broken down by the enzyme carnosinase. Age (carnosine concentration decreases with age), gender (males have higher levels), and food (vegetarian diet has a lower level of carnosine in the skeletal tissues) all affect the body's carnosine levels. Among its numerous health benefits, it has anti-oxidant, ion-chelating, anti-glycating, anti-inflammatory, pH buffering, and anti-aging properties.[16]

β-alanine, which is produced by the liver's breakdown of thymidine, uracil, and dietary dipeptides, and L-histidine, undergoes an enzymatic process that is catalyzed by carnosine synthase to produce L-carnosine.[17] The molecule exists in several natural variants, including anserine, ophidine/balenine, homocarnosine, carcinine, and acetylcarnosine. Its degradation is exclusively catalyzed by two types of carnosinase enzymes: serum carnosinase (CN1) found in serum and brain tissue, and tissue carnosinase (CN2) expressed only in tissues. Due to high CN1 activity, circulating carnosine is rapidly broken down within 2–3 hours post-meal, making it undetectable during fasting. This tightly controlled enzymatic degradation process, unaffected by common peptidases or non-enzymatic mechanisms, indicates well-regulated carnosine metabolism.[18] Figures 6 and 7 depict the synthesis and degradation of carnosine (Tables 1 and 2).

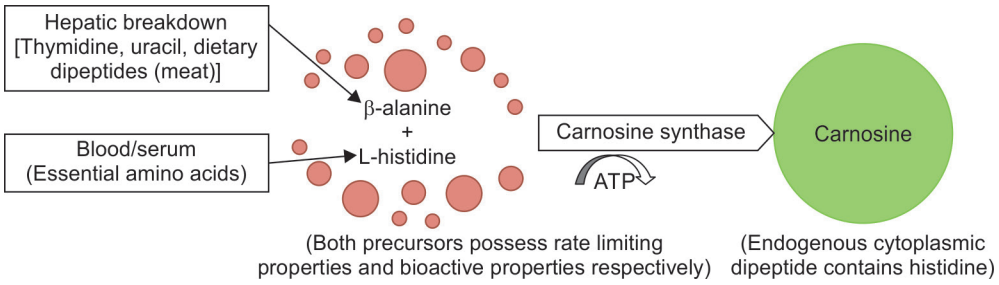

Fig. 6: Synthesis of carnosine from precursor amino acids
ATP, adenosine triphosphate

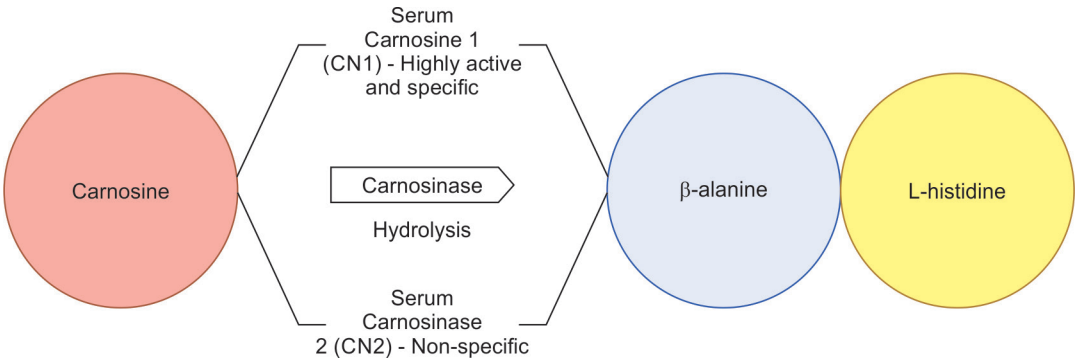

Fig. 7: Degradation process of carnosine

Table 1: Epidemiology of NDDs

Prevalence	*ADHD (%)*	*ASD (%)*	*SLD (%)*
Global	5	1.5	5
Indian	1.6–14	1.5	3–10

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; SLD, specific learning disability

Table 2: Diagnosis of specific learning disorder with specifiers

Academic domains	*Impaired subskills*
With impairment in reading	Word reading accuracy Reading rate or fluency Reading comprehension
With impairment in written expression	Spelling accuracy Grammar and punctuation accuracy Clarity or organization of written expression Number sense
With impairment in mathematics	Memorization of arithmetic facts Accurate or fluent calculation Accurate math reasoning

L-carnosine possesses significant antioxidant action through the mechanisms of metal ion chelation, ROS scavenging, and peroxyl radical neutralization. It lowers intracellular ROS and OS-induced apoptosis by enhancing superoxide dismutase (T-SOD) activity and decreasing NADPH oxidase (Nox) 4 expression in cellular investigations using human kidney tubular epithelial (HK2) cells. Furthermore, L-carnosine inhibits lipid oxidation and neutralizes oxidized products by forming complexes with transition metals and superoxide, hydroxyl radicals.[19] Figure 7 depicts: Degradation process of carnosine. Figure 8 depicts: Anti-oxidant effect of L-carnosine.

Role of L-carnosine in Key NDDs

In the treatment of two neurodevelopmental diseases, ADHD as well as ASD, L-carnosine has shown therapeutic potential. L-carnosine has been shown in clinical research to assist children with these illnesses improve their behavior and cognitive abilities, including their capacity for communication and concentration. Neuroprotection and neurotransmitter modulation are an important part of its mechanisms of action.[20,21]

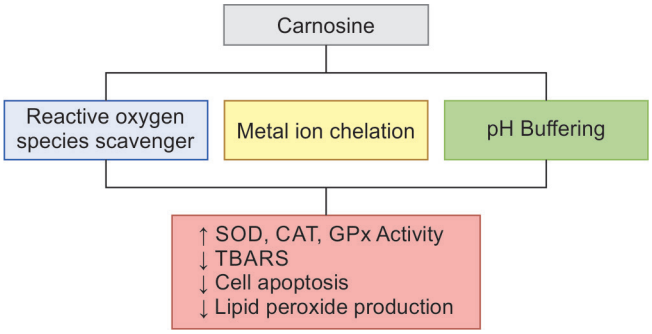

Fig. 8: Schematic overview of the anti-oxidant effect of L-carnosine
CAT, catalase; GPx, glutathione peroxidase; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances

Clinical Evidences of L-carnosine in Key NDDs

Ghajar et al.[22] included 56 medication-free children and adolescents with an ADHD diagnosis, ages 6–17, for an 8-week randomized, double-blind with placebo-controlled study. Patients were randomly assigned to receive either a placebo plus methylphenidate (0.5–1.5 mg/kg/d) or L-carnosine (800 mg/d in two different doses) for eight weeks. Teacher and Parent ADHD rating IV scale (ADHD-RS-IV) was used to assess the patients. Fifty patients completed the study, and they were all assessed at weeks four and eight. The time × treatment interaction had a significant impact on the parent ADHD-RS's total and inattention subscales using the general linear model repeated measures ($p = 0.041$ and $p = 0.030$, respectively). There was no significant difference between the two groups in terms of improvements in the Teacher ADHD-RS or the inattention and hyperactivity subscale scores ($p = 0.956$ and 0.281, respectively) ($p = 0.705$). In the study, no significant variance in the adverse effects between the two groups. According to the study's findings, children with ADHD may benefit from using L-carnosine as an additional drug (Fig. 9).

Chez et al.[23] evaluated whether giving 800 mg L-carnosine per day would yield notable improvements in 31 children with autism spectrum disorders (21 boys, 10 girls, mean age = 7.45 years of age) in the placebo-controlled, double-blind study of 8 weeks. As outcome measures, the clinical global impressions of change, the Gilliam autism rating scale, the childhood autism rating scale, and the expressive and receptive one-word picture vocabulary tests were utilized. The placebo group did not significantly change

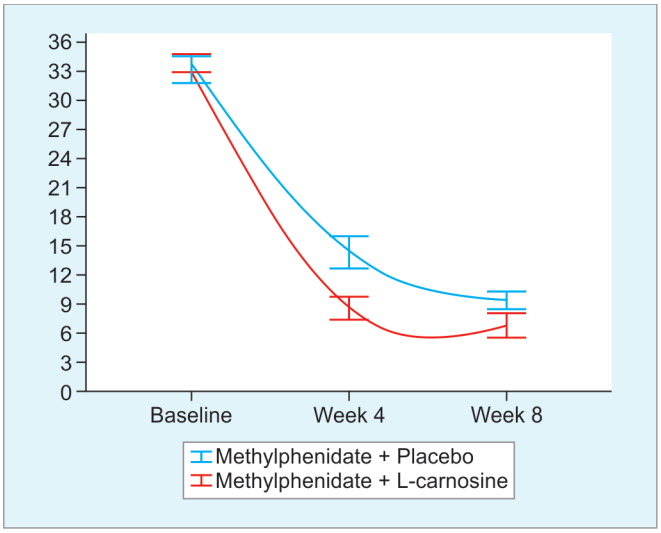

Fig. 9: Repeated measure for comparison of the effects of two treatment groups on total parent ADHD rating scale score (Adapted from Ghajar et al.)[22]—treatment interactions significantly affected Parent ADHD-RS scores over the 8-week trial. Differences in behavior were noted between the two treatment groups

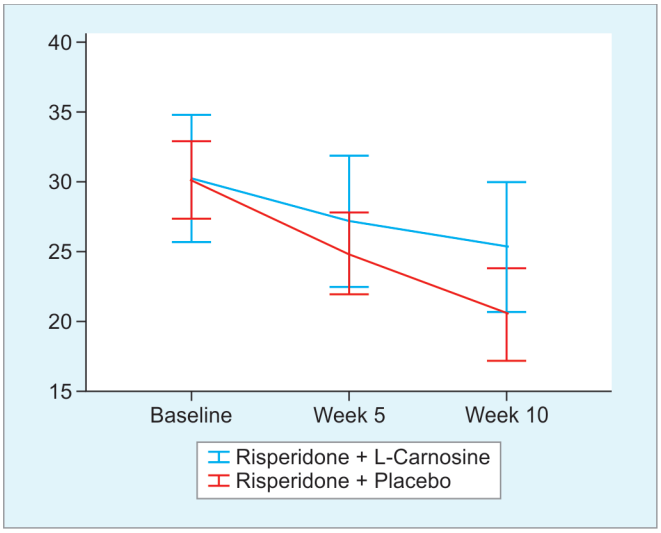

Fig. 10: Comparison of ABC-C hyperactivity/non-compliance subscale scores between L-carnosine and placebo group (Adapted from Hajizadeh-Zakerr et al.)[24]—at week 10, the L-carnosine group experienced a noticeably higher score decrease in the hyperactivity/non-compliance subscale than the placebo group [MD (95% CI) = 5.05 (0.39–9.70), t (40) = 2.19, p-value = 0.034]

between baseline and eight weeks. At 8 weeks, the L-carnosine group demonstrated statistically significant improvement on the receptive one-word picture vocabulary test and the Gilliam autism rating scale (total score and the behavior, socialization, and communication subscales) (all $p < 0.05$). Although statistical significance was not reached, improvements were shown on other outcome measures, including the childhood autism rating scale ($p = 0.07$) and clinical global impression ($p = 0.06$). According to the authors, L-carnosine may improve neurologic function.

A 10-week randomized, double-blind, placebo-controlled study was carried out by Hajizadeh-Zaker et al.[24] to investigate the efficacy and tolerability of L-carnosine as a supplement to risperidone in drug-free children who have ASD aged 4–12 who had a score of irritability subscale more than or equal to 12 on the aberrant behavior checklist community (ABC-C) scale. At baseline, five weeks later, and 10 weeks later, children were assessed. A total of 50 children were randomized to one of two groups: 25 got Risperidone and L-carnosine (800 mg/day in two separate doses), and 25 got Risperidone and a placebo. During the trial period, both arms were prohibited from using any additional medications or psychosocial therapy. Since each arm had four discontinuations overall, 21 participants from each arm finished the research. Applying the general linear model repeated measurements for time treatment association did not result in a significant improvement in the irritation subscale scores. When compared to the placebo group, the L-carnosine group significantly decreased hyperactivity/noncompliance scores on the ABC-C ($p = 0.044$), but stereotypical behavior, lethargy, or social withdrawal and inappropriate speech subscale scores did not significantly improve. According to these findings, L-carnosine may benefit children with ASD who are hyperactive and noncompliant when taken with risperidone (Fig. 10).

Treatment effect of L-carnosine in the medical management of pediatric cognitive disorders was studied by Moorthy M et al. The study participants included a wide range of neurodevelopmental problems, including pediatric patients with cognitive impairments such as ADHD, ASD, epilepsy, cerebral palsy (CP), and dyslexia. A total of 300 children were enrolled, 150 of them received L-carnosine, and the other 150 received a multivitamin placebo. The trial was conducted for ten weeks. The ratio of men to females was 70:30, with the mean age of the males being 7.1 years and the girls being 8 years. The dosage of liquid L-carnosine was 10–15 mg/kg. The placebo group did not show any discernible changes in cognitive results, according to comparative analysis. However, among other NDDs, the L-carnosine group demonstrated statistically significant increases in cognitive function across ADHD ($p < 0.00001$), ASD ($p < 0.00001$), epilepsy ($p < 0.00001$), dyslexia ($p < 0.00001$), and CP ($p < 0.0001$). Additionally, social communications, language domains, memory, learning capacity, and behavior all showed statistically significant improvements. Overall, the study's results indicated that L-carnosine has neuroprotective properties and that giving it to children with cognitive problems improves their cognitive performance statistically significantly, surpassing a placebo as a treatment.[25] Table 3 depicts a summary of clinical studies of L-carnosine.

Conclusion

L-carnosine is a natural dipeptide with antioxidant and neuroprotective properties. In the treatment of neurodevelopmental diseases, primarily ADHD, and ASD, it is showing promise as a therapeutic agent. Several double-blind, randomized, placebo-controlled trials have repeatedly shown that L-carnosine supplementation can significantly improve behavioral symptoms, cognitive function, and social communication in children with

Table 3: Summary of clinical studies of L-carnosine

Authors	*Population*	*Intervention*	*Key findings*
Ghajar et al.[22]	Fifty-six medication-free children/adolescents, 6–17 years old, with a diagnosis of ADHD	L-carnosine (800 mg/d in two divided doses) plus MPH (0.5–1.5 mg/kg/d) or placebo plus MPH (0.5–1.5 mg/kg/d) for 8 weeks	Significant effect was observed for time × treatment interaction on total and inattention subscales of the Parent ADHD-RS using the general linear model repeated measures ($p = 0.041$ and 0.030, respectively) Improvements in the Teacher ADHD-RS were not significantly different between the two arms ($p = 0.705$), as well as inattention and hyperactivity subscale scores ($p = 0.956$ and 0.281, respectively)
Chez et al.[23]	Thirty-one children (21 male, 10 female, mean age = 7.45 years) with autism spectrum disorders	Eight hundred milligrams of L-carnosine daily, 8 weeks, double-blind, placebo-controlled study	In the L-carnosine group, after 8 weeks, statistically significant improvements on the Gilliam autism rating scale (total score and the behavior, socialization, and communication subscales) and the receptive one-word picture vocabulary test (all $p < 0.05$) were seen in children Improved trends were noted on other outcome measures like clinical global impression ($p = 0.06$) and childhood autism rating scale ($p = 0.07$), though statistical significance was not reached
Hajizadeh-Zaker et al.[24]	Fifty patients were randomly assigned to receive either L-carnosine ($n = 25$) or placebo ($n = 25$) in trial arms who met the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013) Criteria for diagnosis of ASD	Fifty children were randomized, 25 in L-carnosine (800 mg/day in two divided doses) plus Risperidone arm and 25 in placebo plus Risperidone arm. No other drugs or psychosocial therapies were allowed during the study period in both arms	Significant reduction in hyperactivity/noncompliance scores on the aberrant behavior checklist-community (ABC-C) in the L-carnosine group compared to placebo ($p = 0.044$), although no significant improvements were observed in lethargy/social withdrawal, stereotypic behavior, and inappropriate speech subscale scores On the irritability subscale scores no significant difference was seen using a general linear model repeated measures for time treatment interaction
Moorthy et al.[25]	Pediatric patients presenting with cognitive disorders secondary to various neurological conditions, including ASD, ADHD, CP, epilepsy, and dyslexia	Three hundred children were enrolled, 150 on L-carnosine and 150 on placebo (multivitamins). Study duration: 10 weeks. liquid L-carnosine was used at a dose of 10–15 mg/kg	Comparative analysis revealed that the placebo group did not exhibit significant changes in cognitive outcomes L-carnosine group demonstrated statistically significant enhancements in cognitive function across various neurodevelopmental disorders, including ASD ($p < 0.00001$), ADHD ($p < 0.00001$), CP ($p < 0.0001$), Epilepsy ($p < 0.00001$), and dyslexia ($p < 0.00001$) Statistically significant improvement was also seen in language domains, social communications, memory, behavior, and learning ability

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder

these disorders. When used as an adjunctive therapy alongside conventional treatments, such as MPH for ADHD or risperidone for ASD, L-carnosine appears to enhance therapeutic outcomes while maintaining a favorable safety profile. According to these findings, L-carnosine may offers a valuable adjunctive therapy option in the comprehensive treatment of NDDs, offering a promising avenue for improving the lives of affected individuals.

Orcid

Pramod Jog https://orcid.org/0000-0003-2542-8516
Neel Patel https://orcid.org/0009-0001-3575-0560
Ashwin Kotamkar https://orcid.org/0009-0000-9219-6992
Shailesh Pallewar https://orcid.org/0009-0000-6084-4553
Amit Qamra https://orcid.org/0000-0002-4456-2959

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CASE REPORT

An Unusual Case of TH Mutation Presenting with Titubation: Movement Disorder

Ayush Khare[1], Jayshree Mahigh[2], Dixa Shah[3], Brij Mehta[4], Nitish Vora[5], Sanjiv Mehta[6], Siddharth Shah[7]

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Abstract

Introduction: Tyrosine hydroxylase (TH) is a key enzyme in catecholamine biosynthesis, playing a crucial role in dopamine (DOPA) production. Tyrosine hydroxylase deficiency has a broad clinical spectrum ranging from DOPA-responsive dystonia to severe infantile encephalopathy. Although classically presenting with hypokinesia, rigidity, and dystonia, atypical phenotypes can mimic other neurological disorders, often leading to misdiagnosis and delayed treatment.

Case description: In a family of four, the patient's elder sister having an uneventful birth, had global developmental delay and presented as a cerebral palsy (CP) mimic, initial investigations and magnetic resonance imaging (MRI) Brain were normal, on suspicion of genetic abnormality, whole exome sequencing was done showing homozygous mutation in TH gene and DOPA trial was started, following which there is marked improvement. The patient, a 6-month-old male, had an uneventful birth, was neurodevelopmentally normal till 5 months of age, when parents noticed head titubation. Neurological examination revealed rhythmic oscillatory movements without signs of spasticity, dystonia, or developmental regression. more in the morning and increased crying, these movements also improved with a low dose of DOPA.

Discussion: This case highlights an unusual presentation of TH deficiency with isolated titubation as an early sign. It underscores the expanding phenotypic variability of the disorder and the potential for misdiagnosis, particularly when the presentation deviates from classical motor findings. Early recognition and treatment with DOPA replacement can result in significant clinical recovery. Moreover, the presence of a similarly affected sibling earlier diagnosed as CP mimics emphasizes the need for heightened clinical suspicion and appropriate workup in familial cases of unexplained movement disorders.

Keywords: Case report, Cerebral palsy mimic, Dopa-responsive dystonia, Movement disorder, Tyrosine-hydroxylase.

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Introduction

Tyrosine hydroxylase (TH) deficiency is a rare autosomal recessive disorder affecting the catecholamine biosynthetic pathway. Tyrosine hydroxylase catalyzes the conversion of tyrosine to L-dopamine (DOPA), a rate-limiting step in the synthesis of DOPA, norepinephrine, and epinephrine. Mutations in the TH gene can lead to a spectrum of neurological phenotypes, ranging from progressive infantile hypokinetic-rigid syndrome, dopa-responsive dystonia (DRD), to more severe encephalopathy-like presentations.[1,2]

Movement disorders associated with TH deficiency often include hypokinesia, rigidity, and dystonia. Titubation, characterized by rhythmic tremor of the head or trunk, is uncommon and may be confused with cerebellar pathologies or benign movement variants in infancy.

We report a case of a 6-month-old infant with normal early development who presented with new-onset titubation-like movements and was subsequently diagnosed with TH deficiency. Notably, the patient's older sibling had a prior diagnosis of cerebral palsy (CP) mimic, which on genetic testing represents the same underlying genetic condition.

Case Description

This case involves a nuclear family of four, including two siblings affected by TH deficiency, each presenting with differing phenotypic severity and clinical features.

The first affected child, a female, is the elder sibling who was born full-term via normal vaginal delivery following an uneventful pregnancy and perinatal period. Despite a normal birth history, her developmental milestones were significantly delayed across all domains. She exhibited poor head control, delayed sitting, and had not achieved independent ambulation by the expected age. Clinically, she presented with increased muscle tone and postural abnormalities suggestive of CP. But no perinatal insult raises suspicion of an alternate diagnosis. Initial investigations, including metabolic screening and 3 Tesla magnetic resonance imaging (MRI) of the brain, were unremarkable. Given the atypical features and lack of clear structural abnormalities, a genetic etiology was considered. A therapeutic trial of low-dose L-DOPA/carbidopa was initiated, which resulted in marked clinical improvement, particularly in motor control and tone, supporting the diagnosis

[1–7]Department of Pediatric Neurology, Royal Institute of Child Neurosciences, Ahmedabad, Gujarat, India

Corresponding Author: Ayush Khare, Department of Pediatric Neurology, Royal Institute of Child Neurosciences, Ahmedabad, Gujarat, India, Phone: +91 7389710163, e-mail: drayushkharemd@gmail.com

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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.

of a DOPA-responsive dystonia secondary to TH deficiency. Later on, whole-exome sequencing revealed pathogenic homozygous (inheritance- autosomal recessive) missense variation in exon 6 of the TH gene (chr11:g.2167905C>T; c.698G>A; p.Arg233His) that results in amino acid substitution of Histidine for Arginine at codon 233 (p.Arg233His; ENST00000381178.5). Following this diagnosis.

The second case involves her younger brother, a 6-month-old male, who also had an uneventful birth and normal early development until approximately 5 months of age. At that point, his parents observed involuntary, rhythmic head movements characterized by a side-to-side oscillation—consistent with titubation. These movements were more prominent in the morning and exacerbated by emotional stimuli such as crying. Notably, there were no accompanying features of spasticity, dystonia, nystagmus, truncal ataxia, or developmental regression. On examination, the infant was alert and interactive with preserved eye contact and normal limb tone, strength, and reflexes. Birth history was uneventful. He was born at term via lower segment caesarean section with normal Apgar scores and no perinatal complications. In light of his sibling's diagnosis, early genetic screening was pursued and confirmed the same homozygous TH gene mutation. A low-dose DOPA trial was initiated with prompt clinical response, resulting in a significant reduction of the titubation over subsequent weeks.

Together, these two cases demonstrate the variable phenotypic expression of TH deficiency within a single family—ranging from a CP mimic with generalized motor delay in one sibling to isolated head titubation in the other. The early recognition of a movement disorder pattern, coupled with family history and genetic confirmation, enabled the timely initiation of dopaminergic therapy with notable improvement in both children.

Discussion

This case illustrates a non-classical presentation of TH deficiency with isolated titubation in an infant who had otherwise normal early development. The absence of classical hypokinesia or rigidity initially led to diagnostic ambiguity. However, the presence of a similarly affected sibling with a prior diagnosis provided a crucial diagnostic clue.

Tyrosine hydroxylase deficiency has variable phenotypes, broadly classified as:

- Type A (mild form): Presents in childhood with DRD and diurnal fluctuation.
- Type B (severe form): Early infantile onset with profound hypokinesia, rigidity, and poor prognosis.
- Intermediate forms: Present with complex movement disorders including tremor, dystonia, and ataxia.[2,3]

Hoffman and associates proposed that signs of DOPA deficiency include increased muscle tone, hypokinesia, dystonia, oculogyric crises, distal chorea, ptosis, and hypersalivation.[4] Additionally, several nonspecific manifestations may arise from DOPA deficiency, such as epileptic encephalopathy, cognitive decline, microcephaly, oromotor difficulties, pyramidal tract dysfunction, and truncal hypotonia. Although the sibling in this case presented with the classical symptoms of TH deficiency, the patient presented with the unique symptom of titubation, which was not described in earlier studies.[2]

Importantly, this case reinforces the need to reconsider "CP" diagnoses in the absence of clear perinatal risk factors or structural brain abnormalities, especially when dopaminergic therapy yields improvement. Genetic testing for TH and other neurotransmitter synthesis disorders should be considered in such cases.

Treatment with levodopa/carbidopa remains the mainstay and is often highly effective, especially when initiated early. In this case, the favorable response highlights the importance of early recognition and intervention in improving outcomes.[5]

Clinical Implications

This case underscores the clinical variability of TH deficiency and its potential to masquerade as more common pediatric movement or developmental disorders. Demonstrating that non-classical, subtle presentations of TH deficiency, such as titubation or isolated tremor, should prompt evaluation for neurotransmitter disorders, especially in the context of a family history of unexplained developmental delay or CP-like syndromes. Misdiagnosis as CP can delay effective therapy, and this case supports a low threshold for initiating cerebrospinal fluid (CSF) neurotransmitter studies and targeted genetic testing in similar scenarios. Timely diagnosis and initiation of levodopa therapy can lead to marked clinical improvement and may prevent long-term disability.

Orcid

Ayush Khare https://orcid.org/0000-0003-3724-4845

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CASE REPORT

Mycophenolate Mofetil as First-line Induction and Maintenance Therapy with cPACNS: A Case Report

Divya Agrawal[1], Praveen Kumar[2], Ramakant K Sabharwal[3]

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Abstract

Aim and background: To report our experience in successfully treating a child with primary central nervous system vasculitis (cPACNS) using mycophenolate mofetil (MMF) as a first-line agent for both induction and maintenance therapy. This is probably the first case report from India in which MMF has been used as a first-line agent in a child with cPACNS.

Case description: A previously healthy 7-year-old boy presented with nausea, vomiting, and left-sided weakness. Magnetic resonance imaging revealed multiple infarcts and cerebellar mass effect, with angiographic findings suggestive of vasculitis. Extensive workup excluded secondary causes. He was diagnosed with cPACNS and treated with pulse steroids, followed by oral steroids and MMF for induction and maintenance therapy. The patient showed continuous gradual neurological improvement, and a 3-month follow-up and subsequently 2-year follow-up showed no new infarcts. Mycophenolate mofetil was well tolerated.

Conclusion: This case underscores the utility of oral MMF as a first-line agent for both induction and maintenance therapy in cPACNS, especially in settings where regular hospital visits are challenging for intravenous cyclophosphamide.

Clinical significance: Early diagnosis and a tailored treatment approach using MMF can provide effective disease control and minimize hospital burden in pediatric cPACNS, improving outcomes in real-world scenarios.

Keywords: Case report, Childhood primary angiitis of the central nervous system, Cyclophosphamide, Mycophenolate mofetil, Steroids.

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Introduction

Childhood primary angiitis of the central nervous system (cPACNS) is an increasingly recognized cause of recurrent childhood stroke and neurological deficits. This condition presents with focal or diffuse neurological symptoms and can lead to devastating long-term neurological sequelae if left untreated. We present a case of cPACNS in a child who was managed effectively using mycophenolate mofetil (MMF) as a first-line therapy. To our knowledge, this is the first case report from India in which MMF has been used as a first-line induction and maintenance agent for a child with cPACNS.

Case Description

A previously healthy 7-year-old male, with an unremarkable birth and developmental history, developed nausea, vomiting, and decreased appetite, for which the child was admitted locally and was managed conservatively. There was no history of fever, trauma, or recent illness. Magnetic resonance imaging (MRI) of the brain was done (Fig. 1) which was suggestive of T2/ Fluid-attenuated inversion recovery (FLAIR) hyperintensity in right cerebellar hemisphere, right thalami, right parasagittal, and left parietotemporal region, showing diffusion restriction on diffusion weighted image (DWI) images with mass effect on pons and medulla. Magnetic resonance angiography (MRA) was reported as normal. The patient was then referred to our institute. On physical examination, vital signs were stable. The patient was drowsy. Vertical gaze restriction and bilateral plantars extensor were noted. The child was started on enoxaparin along with other supportive treatments. A 2D echocardiography (2D ECHO) was normal. Fundus examination was normal. Magnetic resonance imaging of the brain was repeated with vessel wall imaging. It was suggestive of a subacute infarct involving the bilateral cerebral hemispheres and a swollen right cerebellar hemisphere, showing patchy areas of restriction with a linear area of blooming and mass effect, including displacement of the right hemipons and effacement of the fourth ventricle, leading to supratentorial mildly prominent lateral and third ventricles. Encephalomalacia was noted in the left cerebellar hemisphere. Magnetic resonance angiography vessel wall imaging (Fig. 2) on post-contrast images showed vessel wall enhancement in the left mid P1 segment,

[1–3]Department of Pediatric Neurology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Corresponding Author: Divya Agrawal, Department of Pediatric Neurology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India, Phone: +91 8006980734, e-mail: Divya.agrawal42@gmail.com

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Conflict of interest: Dr Praveen Kumar is associated as the Zonal Editor: North in the editorial Board member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and his research group.

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.

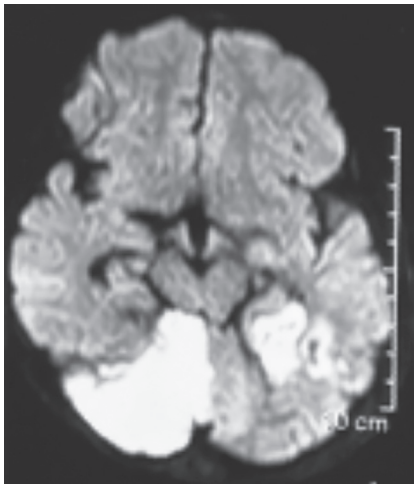

Fig. 1: Axial DWI MRI showing diffusion restriction in the right cerebellar hemisphere and left temporoparietal region suggestive of acute infarct

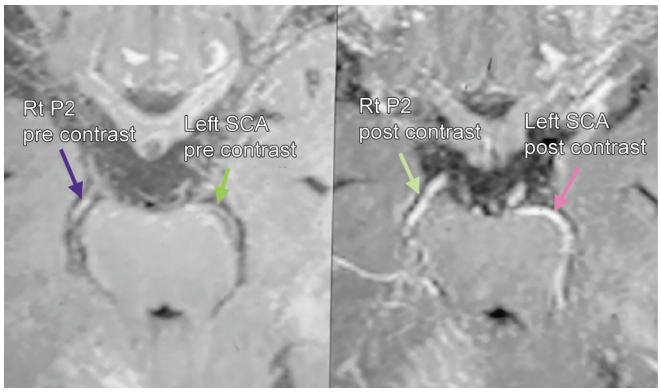

Fig. 2: Pre and post contrast MR vessel wall imaging- Post contrast images showing vessel wall enhancement in the right P2 segment with vessel wall enhancement left superior cerebellar artery

right P2 segment, with vessel wall enhancement left superior cerebellar artery. Vessel wall enhancement was also seen in the terminal intradural vertebral artery on the right side. In view of MRI findings suggestive of vasculitis, intravenous pulse doses of methylprednisolone were administered for 5 days, followed by oral prednisolone. Autoimmune workup, including antinuclear antibody (ANA), extractable nuclear antigen (ENA), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) antibodies, and infectious panel including sepsis screen, viral markers, varicella zoster serology, and Mantoux test were negative for vasculitis secondary to systemic disease. The thrombophilia panel, which included cytoplasmic antineutrophil cytoplasmic antibody (cANCA), perinuclear antineutrophil cytoplasmic antibody (pANCA), β2 glycoprotein IgG/IgM, prothrombin gene mutation (G20210A), methylenetetrahydrofolate reductase (MTHFR) gene polymorphism, factor V (Leiden) gene mutation, anticardiolipin antibodies IgG/IgM, factor V Leiden (APC-R), antithrombin functional assay, protein C, protein S, lipoprotein A, von Willebrand factor (VWH) antigen testing came negative. Gradually physiotherapy was started. Enoxaparin was discontinued after 5 days, while aspirin was continued. The parents were counseled and discussed about need for monthly cyclophosphamide injection vs oral MMF, and the risk of recurrence was discussed. The patient was started on oral MMF @600 mg/m^2/day in two divided doses, with the dose gradually increased weekly to 1000 mg/m^2/day. The patient showed significant improvement, including recovery from hemiparesis. Follow-up MRI after 3 months showed no new ischemic changes and improvement in vessel caliber. Steroids were gradually stopped after 6 months. The patient continued on low-dose aspirin and MMF for maintenance and was regularly monitored for adverse effects. A repeat MRI at 2 years showed residual gliosis with no fresh infarcts, and on vessel wall imaging no evidence of any active disease was seen.

The choice of oral MMF over intravenous cyclophosphamide was guided by the available, albeit limited, literature evidence of efficacy as induction and maintenance therapy, financial considerations and the practical advantage of oral administration, reducing the need for frequent hospital visits.

Discussion

Childhood primary angiitis of the central nervous system is an uncommon yet increasingly identified inflammatory condition affecting the brain's blood vessels in otherwise healthy children. It can present with a broad spectrum of neurological signs, such as persistent seizures, focal deficits, cranial nerve abnormalities, significant cognitive impairment, and altered levels of consciousness. Childhood primary angiitis of the central nervous system presents a therapeutic challenge due to its rarity and varied clinical presentation. Early diagnosis and aggressive immunosuppressive therapy have shown favorable outcomes. In 1988, Calabrese and Mallek outlined diagnostic criteria for primary central nervous system (CNS) angiitis, which include the development of a neurologic or psychiatric deficit without another identifiable cause, evidence of angiitis confined to the CNS based on either classic angiographic findings or histopathology, and the exclusion of systemic vasculitis or other conditions that could resemble the disease radiologically or histologically.[1] Most of which are still relevant today. Recent classification of cPACNS is based on vessel size, with three subtypes recognized: Angiography-positive nonprogressive (APNP) and angiography-positive progressive (APP) disease, affecting the large/medium-sized vessels, and angiography-negative (AN) disease, affecting small cerebral vessels.[2,3]

In general, the recommended treatment approach involves initiating intravenous pulse steroid therapy for induction, followed by high-dose oral prednisone with gradual tapering over a period of 3–12 months, along with intravenous anticoagulation therapy initially, followed by long-term antiplatelet therapy. In angiography-positive progressive cPACNS and angiography-negative cPACNS, 6 months of IV cyclophosphamide therapy, with trimethoprim/sulfamethoxazole as part of induction, and maintenance therapy with mycophenolate mofetil/mycophenolic acid is also recommended.[4] The efficacy of other immunosuppressive agents, including azathioprine, methotrexate, and rituximab is still unknown.[5,6]

Mycophenolate mofetil is an immunosuppressive pro-drug of the active metabolite of mycophenolic acid. It works by selective inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH). Inosine monophosphate dehydrogenase is essential for de novo synthesis of guanine nucleotides; hence, this inhibition limits the proliferation of T and B lymphocytes and dampens the immune response. Mycophenolate mofetil is being widely used in pediatric patients for prevention of organ transplant rejection and in the management of various conditions, such as lupus nephritis, steroid resistant nephrotic syndrome (SRNS), juvenile dermatomyositis, and CNS disorders like autoimmune encephalitis

and relapsing MOGAD. Mycophenolate mofetil has also been used as induction and maintenance therapy in patients resistant to cyclophosphamide/rituximab.[7] The recommended pediatric dose is typically 600 mg/m^2/day twice daily, increased up to 1000 mg/m^2/day, and may be adjusted based on clinical response and tolerability.[7] Mycophenolate mofetil is generally well tolerated, but its adverse effect profile includes gastrointestinal disturbances, leukopenia, increased risk of infections, hepatotoxicity, and rarely, progressive multifocal leukoencephalopathy. Routine monitoring involves complete blood counts, liver and renal function tests, and vigilance for infections, with periodic review of immunization status and growth parameters to ensure safe long-term use. Our patient tolerated MMF well with no adverse effects.

We also chose MMF based on available literature evidence of efficacy as induction and maintenance therapy, the convenience of follow-up for this outstation patient, and financial limitations.[8,9]

This case highlights the importance of early recognition and pragmatic management of cPACNS in resource-limited settings. Selecting MMF as the first-line immunosuppressive agent in this context proved effective, minimizing hospitalization and ensuring better compliance and continuity of care.

Conclusion

This case underscores the importance of timely diagnosis and individualized treatment in cPACNS. The successful use of MMF as a first-line induction and maintenance therapy demonstrates its potential as an effective alternative to cyclophosphamide, particularly in resource-limited settings, or in a setting where regular hospital visits are not possible. The patient's significant neurological recovery and stable radiological findings on follow-up reinforce the role of MMF in managing both the acute and chronic phases of cPACNS.

Clinical Significance

This report contributes to the growing evidence supporting MMF as a safe and effective immunosuppressive agent in the treatment of cPACNS. Its oral administration, lower toxicity profile, and cost-effectiveness make it a viable alternative to cyclophosphamide, especially in settings where access to IV medications and frequent hospital visits may be challenging. This case advocates for increased awareness, early diagnosis, and judicious use of MMF to improve long-term neurological outcomes in children with cPACNS.

Orcid

Praveen Kumar https://orcid.org/0000-0002-9172-2767

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CASE REPORT

Congenital Myasthenic Syndrome with ALG2 Mutation Presenting as Progressive Ascending Paralysis: A Case Report

Ananya Mohanty[1], Bijay K Meher[2], Jyoti R Satapathy[3]

Received on: 23 September 2025; *Accepted on:* 24 October 2025; *Published on:* 14 November 2025

Abstract

Aims and background: Congenital myasthenic syndromes (CMSs) are a heterogeneous group of disorders characterized by impaired neuromuscular transmission due to genetic defects in endplate proteins, particularly involving glycosylation pathways. Congenital myasthenic syndrome severity varies from mild symptoms to progressive weakness and respiratory crises, often misdiagnosed as acquired conditions. We report a rare case of ALG2-related CMS mimicking Guillain–Barré syndrome (GBS).

Case description: A 10-year-old girl presented with a 5-day history of fever, followed by ascending limb weakness and respiratory distress. She had areflexia, slurred speech, and ptosis. A similar episode occurred 3 years prior, and her elder sibling had died following a similar illness. She was initially treated as GBS with intravenous immunoglobulin (IVIG) and steroids without improvement. Whole exome sequencing ultimately revealed a homozygous ALG2 mutation, confirming CMS14 (CDG type Ii). Pyridostigmine led to partial ptosis improvement but no significant respiratory recovery. She remained ventilator-dependent and succumbed after 5 months from ventilator-associated pneumonia.

Conclusion: Congenital myasthenic syndrome can mimic acute flaccid paralysis and should be considered in atypical, treatment-refractory neuromuscular presentations. Early diagnosis can guide specific therapy and alter outcomes.

Clinical significance: Early recognition of CMS, especially ALG2-associated subtypes, allows for initiation of targeted therapies such as pyridostigmine or combination regimens, potentially improving prognosis and preventing fatal complications.

Keywords: ALG2 mutation, Case report, Congenital myasthenic syndrome, Glycosylation defect, Guillain–Barré mimic, Progressive paralysis.

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Introduction

Congenital myasthenic syndromes (CMSs) represent a group of genetically heterogeneous disorders resulting from defects in neuromuscular transmission. Glycosylation pathway defects, such as mutations in the ALG2 gene, lead to subtypes like CMS14, which may present with limb-girdle weakness and respiratory compromise. These rare syndromes can mimic acquired conditions, like Guillain–Barré syndrome (GBS), leading to delayed or missed diagnosis. Timely identification and initiation of appropriate treatment is essential for improving outcomes in affected children.

Case Description

A 10-year-old female child weighing 20 kg from Balasore district of Odisha, presented with complaints of a low-grade fever for 5 days, followed by weakness of both the lower and upper limbs for 3 days. On past history, the patient had a similar event 3 years back of lower limb weakness, which was evaluated on an outpatient basis but was lost to follow-up. Sibling loss occurred at the age of 13 years with a similar history. On examination, the patient had a heart rate (HR) = 120/minute, respiratory rate (RR) = 30/minute, SPO_2 = 99% with a non-rebreather mask (NRM), blood pressure (BP) = 50th–90th. On systemic examination, the patient was conscious and responsive to her mother, had slurring of speech. On cranial nerve examination, B/l ptosis was present (3rd cranial nerve affected), B/l pupil equally reacted to light, and the gag reflex was absent (9th and 10th nerve might be affected); examination of all other cranial nerves was normal. On motor system examination, all four limbs were hypotonic (lower limb > upper limb); power across all joints of the lower limb was 2/5 and power across all joints of the upper limb was 4/5. All deep tendon reflexes (DTRs) of the upper limbs were preserved, while knee jerk and ankle jerk of both the lower limbs were absent. Bilateral plantar reflex was unresponsive, ankle contractures were present (Fig. 1). Areflexia was present, bowel and bladder intact, and no signs of autonomic instability present except tachycardia. The Glasgow Coma Scale (GCS) = 15/15. She was started empirically on antibiotics, and IVIG was planned suspecting it as a case of GBS. On the next day, the patient developed paradoxical breathing and was intubated (Figs 2 and 3). A serum CPK was done to rule out muscular dystrophies (34) which came out to be normal. Patient was unresponsive to pulse therapy of methylprednisolone, so a whole exome sequencing was done after suspecting congenital myopathy,

[1–3]Department of Pediatrics, SCB Medical College and Hospital, Cuttack, Odisha, India

Corresponding Author: Ananya Mohanty, Department of Pediatrics, SCB Medical College & Hospital, Cuttack, Odisha, India, Phone: +91 9439255599, e-mail: ananyamohanty.1597@gmail.com

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Conflict of interest: None

Patient consent statement: A written informed consent was obtained from the patient for the publication of details, which can include photographs and/or videos and/or case history to be published in any printed/online journals.

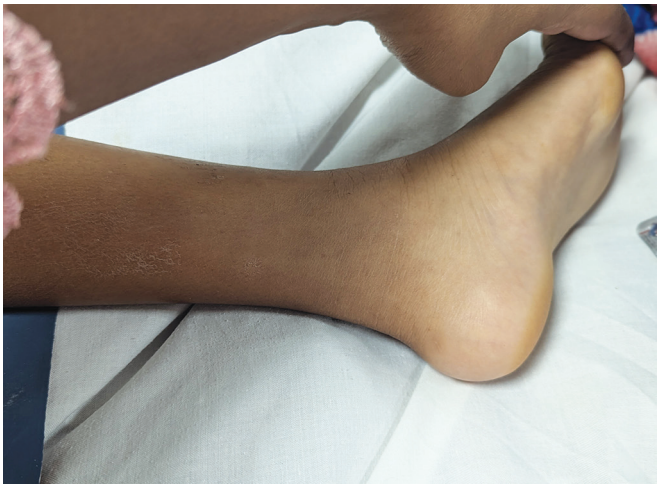

Fig. 1: Ankle contractures on presentation along with history of gait abnormalities

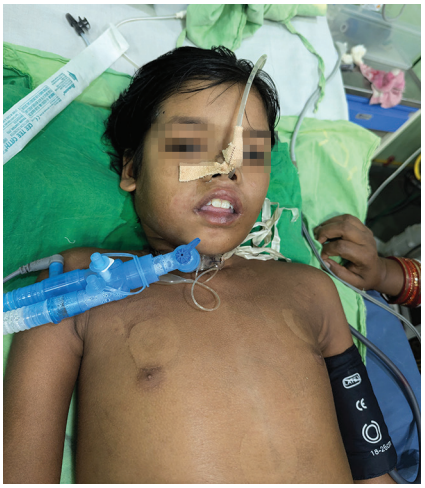

Fig. 4: Improvement of ptosis after pyridostigmine

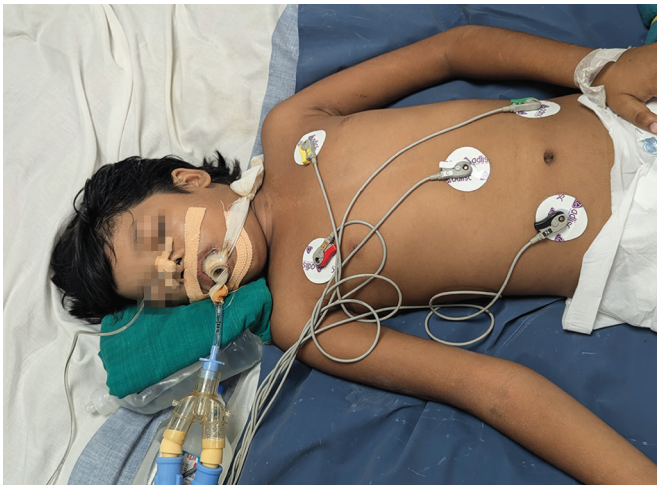

Fig. 2: Deterioration of respiratory symptoms and intubation on day 2

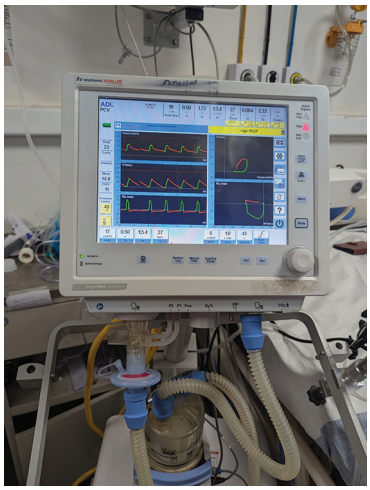

Fig. 3: Initial ventilator requirements

which came out to be homozygous for ALG2 gene associated with myasthenic syndrome congenital 14, CDG1l congenital disorder of glycosylation type li CDG1l:607906.

Initially the patient was treated with GBS and IVIG, but the respiratory pattern did not improve and ventilator requirements increased, with no chest signs and cerebrospinal fluid (CSF) polymerase chain reaction (PCR) and culture, along with blood culture, being largely normal, so methylprednisolone was also added along with IVIG, suspecting it to be a case of autoimmune encephalitis. As serum CPK was normal, dystrophinopathy and myopathy were ruled out. Due to significant past history and a family history, whole exome was planned. Pyridostigmine was started; ptosis improved, but respiratory efforts did not improve (Fig. 4). The patient remained in mechanical ventilator for 5 months and died due to ventilator-associated pneumonia and its complications.

Discussion

Congenital myasthenic syndrome is caused by mutations in genes such as ALG2, ALG14, and DPAGT1, affect the glycosylation process, which is critical for neuromuscular junction integrity. ALG2 encodes alpha-1,3-mannosyltransferase; mutations lead to impaired glycosylation and neuromuscular dysfunction.[1,2] Most CMS14 patients show a limb-girdle phenotype, with preserved ocular and bulbar function in some cases. The heterogeneity in presentation and response to treatment complicates diagnosis and management. Some patients show early, persistent weakness resembling congenital myopathy or muscular dystrophy. Limb-girdle CMS with acetylcholinesterase (AChE) inhibitor response or muscle biopsy tubular aggregates suggests GFPT1 mutations, while others should first be screened for DOK7, then GFPT1 if negative.[3]

A single report of heteroallelic mutations in one individual in ALG2 has previously been reported, which caused a severe multisystem disorder, termed CDG type Ii (MIM 607906), which is genotypically similar to my case report.[4]

Therapy for CMS often includes AChE inhibitors like pyridostigmine. Combination regimens with 3,4-diaminopyridine, albuterol, or fluoxetine have shown benefit in some subtypes. Early recognition and appropriate therapy initiation are crucial, as standard immunotherapy is ineffective in CMS.[5]

Conclusion

Congenital myasthenic syndrome-14 due to ALG2 mutation is a rare but important differential diagnosis in children presenting with progressive paralysis. Genetic testing should be considered in recurrent or refractory cases. Early targeted therapy may alter the disease trajectory and reduce morbidity.

Clinical Significance

Misdiagnosis of CMS as GBS can delay critical treatment. Awareness and early recognition of CMS subtypes enable targeted therapy such as pyridostigmine, potentially improving patient outcomes and preventing avoidable complications.

Orcid

Ananya Mohanty https://orcid.org/0009-0008-0221-8798
Bijay K Meher https://orcid.org/0000-0003-2908-3092

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CASE REPORT

A Baby with Acute Encephalopathy, Refractory Hyponatremia, and Hypertension: A Case Report

Gajalakshmi S H[1], Jigna N Bathia[2], Hriday De[3], Deblina Dasgupta[4], Priyankar Pal[5]

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Abstract

Autoimmune encephalitis (AE) is an expanding group of clinical syndromes that can occur at all ages (from <1 year to adult), but more commonly affects young adults and children. It is a rare cause of encephalopathy that has been increasingly recognized over the last decade. Most of these disorders are severe and potentially fatal; however, if recognized in a timely manner and treated with immunotherapy, patients often respond well with good outcomes. Here, we present a 7-month-old baby girl with seronegative AE, presenting with encephalopathy, hypertension, and refractory persistent hyponatremia. Prompt treatment with aggressive immunotherapy improved her neurological symptoms. This case highlights the association of hyponatremia, hypertension, and the importance of timely immunotherapy in AE.

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

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Key Learning Points

- Autoimmune encephalitis (AE) is a broad spectrum of diseases which needs further investigation and studies to detect potential antibodies.
- Seronegative AE has more severe neurological impairment and poor outcome compared to seropositive AE.
- Autoimmune encephalitis might be associated with unusual features like electrolyte imbalance (hyponatremia, hypokalemia) and SIADH which is not mentioned in literature especially in pediatrics population.
- FDG-PET imaging aids in early diagnosis of AE especially in seronegative AE and helps in characterizing the type of AE based on metabolic patterns.
- Autoimmune encephalitis is not a monophasic illness. Relapse have been noted even after 5–10 years.
- Aggressive immunotherapy plays a critical role in treatment and to achieve good prognosis. Rituximab is effective in refractory cases.

[1–3]Department of Pediatrics, Institute of Child Health, Kolkata, West Bengal, India

[4]Department of Pediatric Nephrology, Institute of Child Health, Kolkata, West Bengal, India

[5]Department of Pediatric Rheumatology, Institute of Child Health, Kolkata, West Bengal, India

Corresponding Author: Gajalakshmi S H, Department of Pediatrics, Institute of Child Health, Kolkata, West Bengal, India, Phone: +91 8050197776, e-mail: gajalakshmishgaja@gmail.com

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Conflict of interest: None

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.

Introduction

Autoimmune encephalitis is an expanding group of clinical syndromes that can occur at all ages (from <1 year to adult), but it more commonly affects young adults and children. It is a rare cause of encephalopathy that has been increasingly recognized over the last decade. Although its exact mechanism remains unclear, current research indicates that autoimmune antibodies target synaptic proteins, triggering brain inflammation.[1] It has a wide clinical spectrum that ranges from typical limbic encephalitis to syndromes with complex neuropsychiatric symptoms such as altered sensorium, loss of memory, cognition, psychosis, seizures, electrolyte imbalance, autonomic dysregulation, or coma.[1–3] Seronegative AE refers to a subgroup of AE where the patient does not have detectable antibodies in cerebrospinal fluid (CSF) or serum. The possible reasons for the absence of antibodies maybe decreasing serum antibodies or the existence of unidentified antibodies which are yet to be discovered or the non-availability of tests to detect the less common serotypes.[4] This makes the diagnosis and treatment more challenging. Early recognition and treatment prevent relapse and reduce long-term neurological sequelae. Management of AE is mainly by using immunosuppressants. First-line therapy includes steroids and intravenous immunoglobulins (IVIG).[5–12] Second-line immunotherapy, such as rituximab or cyclophosphamide, should be considered if the symptoms do not subside with the first-line therapy.[6,12–14]

Case Presentation

A 7-month-old baby girl presented with complaints of generalized tonic-clonic seizures for 90 min. The convulsions were aborted by benzodiazepine at the emergency, and the baby was admitted for further evaluation. After thorough history and physical examination,

it was found that she was a full-term *in vitro* fertilization born baby with no significant birth or past history. The present history started 2 days ago when the parents noticed that the baby was drowsy and had low-grade fever (100–101°F) following vaccination. Examination findings revealed that the vitals were stable. Systemic examination including the central nervous system was normal. There was post-ictal drowsiness and a few crepitations on chest auscultation.

Investigations

Routine blood investigations were sent. The laboratory workup was unremarkable: TLC – 15,900/mm^3, N57L38; C-reactive protein (CRP): 0.57mg/L (normal range ≤1 mg/L), hyponatremia: 113 mmol/L (normal range 135–145). Liver and kidney function tests were within the normal limits. Urine for routine examination and culture sensitivity was unremarkable. Procalcitonin level was 0.05 ng. Blood culture was negative. Infective causes like dengue, malaria, scrub typhus, and enteric fever were ruled out. Lumbar puncture revealed CSF with normal transparency, 0 leukocytes/mL, 57 mg/mL glucose, and 25 mg/L protein (normal findings). Gram stain and culture were negative.

Management

The baby was admitted, stabilized, and started on Levetiracetam and antibiotics. Routine investigations were normal except for hyponatremia and hypertension (99th percentile for that age and sex). The hyponatremia was resistant to repeated 3% NaCl correction. The hypertension (BP: 110/70 ± 10 mm Hg) persisted despite two anti-hypertensives (Amlodipine and Prazosin) at maximum dosage. Magnetic resonance imaging (MRI) of the brain did not reveal any significant findings other than mildly dilated ventricles. Electroencephalography was normal. Cerebrospinal fluid studies, including the AE antibody panel, were normal. Echocardiography, non-contrast CT (NCCT) of the brain, fundus examination, and USG of kidneys as a part of hypertension workup were also normal. Lumbar puncture showed normal CSF. Gram stain and culture were negative. Laboratory workup was unremarkable except for hyponatremia: 113 mmol/L (normal range 135–145). C-reactive protein was 0.57 mg/L (normal range ≤1 mg/L), and no infection was detected. Considering a immune/inflammatory cause, the baby was administered intravenous immunoglobulin and methylprednisolone pulse therapy for 5 days. However, there was no improvement in her clinical condition. Further evaluation of the hyponatremia revealed raised urinary sodium excretion (211 mEq/L, normal range <20 mEq/L), raised urinary osmolality (561 mOsm), low serum osmolality (269 mOsm), along with raised urinary urates (Table 1). With a provisional diagnosis of syndrome of inappropriate ADH secretion (SIADH), fluid restriction and tolvaptan (6 mg/kg/day) was started. The hyponatremia gradually improved over the next few days (Fig. 1).

Due to ongoing encephalopathy, a repeat MRI was performed, revealing only mildly dilated ventricles. The imaging findings, combined with CSF results and the prolonged duration of illness, made acute disseminated encephalomyelitis less likely. As the hypertension persisted and a neuroendocrine or para-neoplastic cause was suspected, Fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) scan was done, which revealed increased areas of uptake in bilateral mesial temporal cortices, thalami, basal ganglia, and brain stem, with globally reduced metabolism in rest of the brain (Fig. 2). Persistent encephalopathy, normal CSF studies, normal MRI brain, unexplained hypertension (autonomic/central), and diffuse FDG uptake on PET-CT all pointed toward a final diagnosis of seronegative AE with secondary SIADH refractory to first-line immunotherapy.

Table 1: Table of investigations supporting SIADH

Investigation	*Value*
Serum osmolality	269 mOsm (280–295)
Urine osmolality	561 mOsm
S. sodium	125 mEq/L (135–145)
Urinary sodium	211 mEq/L (<20 mEq)

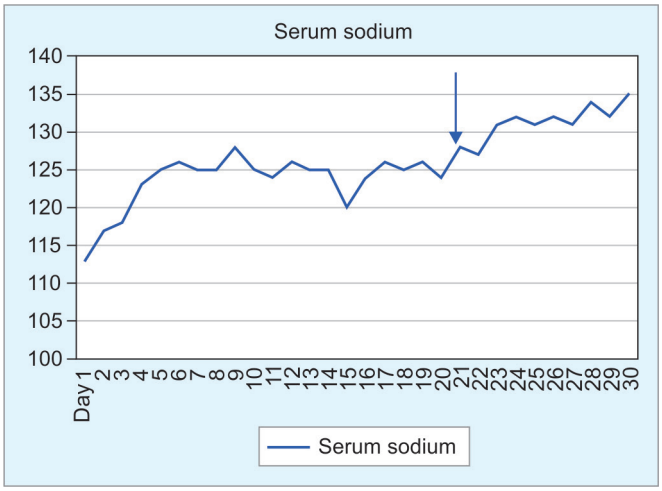

Fig. 1: Trend of sodium. Blue arrow indicates introduction of oral Tolvaptan

Outcome

The baby was started on injection Rituximab (750 mg/m^2) after the final diagnosis. Drowsiness gradually improved over the next 7 days, and she was discharged. A second dose of Rituximab was given after 15 days. On follow-up, tolvaptan and anti-hypertensives have been gradually tapered off and stopped over the next 9 months. She gradually regained her milestones. The child was asymptomatic for the next 15 months and was under regular follow-up.

Later, she developed abnormal movements – myoclonic jerks were noticed by her parents. Repeat imaging did not reveal any significant abnormalities. Considering a relapse of encephalitis, a pulse dose of intravenous methylprednisolone was administered, followed by two doses of Rituximab (750 mg/m^2) was repeated. Currently, the child is asymptomatic and remains under follow-up.

Discussion

Autoimmune encephalitis is a growing group of broad-spectrum clinical syndromes that can affect individuals of all ages, though it is more common in children and young adults. It is a rare but increasingly recognized cause of encephalopathy. While the exact mechanism is still not fully understood, research suggests that autoimmune antibodies target synaptic proteins, leading to brain inflammation.[1–3] In more 50% of cases, antibodies are absent or undetectable with the techniques available currently. This subgroup is categorized as seronegative AE. It requires further study

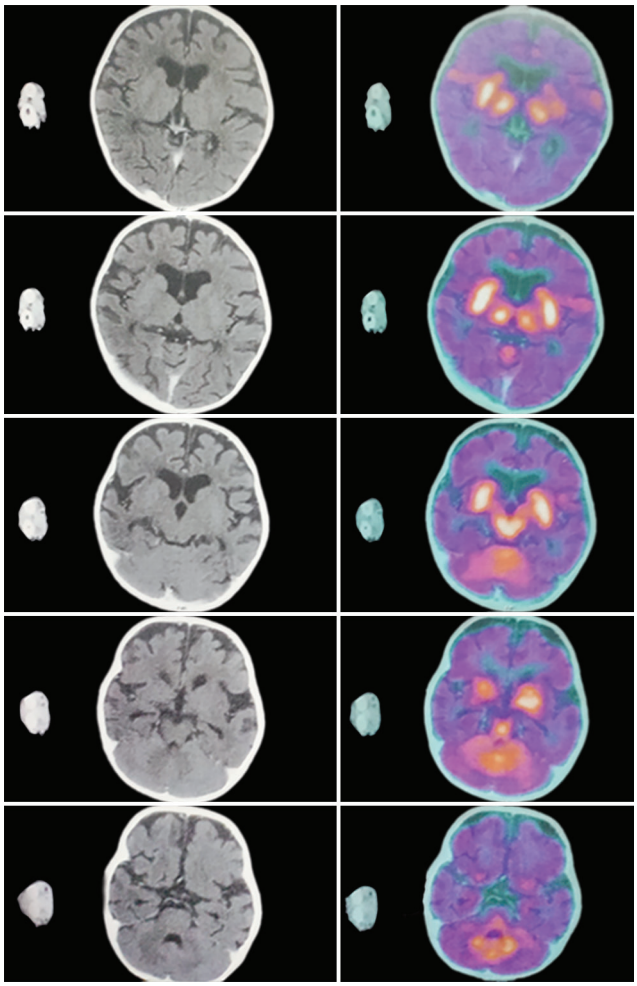

Fig. 2: PET-CT findings. Increased FDG uptake in B/L mesial temporal cortices, thalami, basal ganglia, brainstem with globally reduced metabolism in rest of the brain

and investigation to identify potential antibodies. They have more severe neurological impairment and poor outcome when compared to seropositive AE.[4,15–17] Prompt diagnosis and exclusion of other causes, such as viral encephalitis, are crucial. Evidence indicates that management with earlier initiation of immune-suppressive treatment facilitates better recovery in this potentially fatal condition.[4,6] When AE involves a particular area of the brain, such as the cortical area, focal neurologic deficits such as language dysfunction, motor deficits, and focal seizures occur. Limbic system involvement causes behavioral disturbances, electrolyte imbalance, and cognitive decline. Limbic encephalitis is a subtype where limbic structures of the brain are affected (mesial temporal lobes).[4,7] Diagnosis of AE is based on integration of clinical and test results, including neurological (MRI), electroencephalogram, and immunological (CSF study) results, combined with the exclusion of other diseases (viral encephalitis) that could mimic the observed symptoms. PET-CT imaging has emerged as a crucial tool in the early diagnosis of AE, particularly when MRI results are normal or nonspecific, and studies have shown that PET-CT is more sensitive than MRI in detecting AE, especially in seronegative AE. Basal ganglia hypermetabolism is a characteristic feature in anti-CASPR2 and anti-LGI1 AE, often accompanied by temporal hypermetabolism.[9–11]

This case highlights the association of hyponatremia (secondary SIADH) with AE, which was refractory to repeated sodium correction and responded well to use of tolvaptan.[16,17]

Conclusion

Seronegative AE (antibody negative but possible AE) represents a broader spectrum of disorders that can present with unusual and unexplained symptoms, such as electrolyte imbalance and autonomic dysregulation.[2,3] The disease's association with electrolyte imbalance (hyponatremia, hypokalemia) is seen in leucine-rich glioma-inactivated 1 antibody (LG I1) antibody encephalitis, which is not mentioned in literature, especially in the pediatric population.[5,7,8] FDG-PET imaging aids in early diagnosis, especially when MRI is unremarkable with negative serum and CSF autoantibody profiles, enhancing diagnostic accuracy.[9–11] Aggressive immunotherapy plays a critical role to achieve a good prognosis.[5,6] However, first-line immunotherapy (i.e. corticosteroids) and their efficacy has limited role in seronegative AE. Studies have shown that seronegative AE responds better to second-line immunotherapy (Rituximab and Cyclophosphamide).[5,6,8,12] Rituximab shows an favorable prognosis rate in refractory patients, with particularly greater effectiveness in pediatric population.[13–15]

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CASE REPORT

Recurrent Acute Flaccid Quadriparesis: Unmasking Hereditary Coproporphyria after a Diagnostic Odyssey

Preeti Joon[1], Kathirvel M[2], Nayankumar G Tada[3], Kuldeep Singh[4]

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Abstract

Background: Acute flaccid paralysis (AFP) is a syndrome of rapid-onset weakness and areflexia, most commonly caused by Guillain-Barré syndrome (GBS). Hereditary coproporphyria (HCP) is a rare, autosomal dominant acute hepatic porphyria that represents a frequently overlooked etiology. Caused by a coproporphyrinogen oxidase (*CPOX*) gene mutation, HCP leads to the accumulation of neurotoxic porphyrin precursors, causing acute neurovisceral attacks. These attacks can progress to a severe motor neuropathy that mimics AFP. The absence of cutaneous photosensitivity in many cases and the resemblance of its neuropathy to more common conditions often lead to significant diagnostic delay, particularly in patients with recurrent, unexplained weakness.

Objectives:

- To present HCP as a rare, treatable cause of recurrent AFP in children.
- To highlight the diagnostic challenge and underscore the utility of simple clinical clues, like urine discoloration, in resource-limited settings.
- To emphasize the critical importance of reanalyzing prior genetic data when clinical suspicion for a specific disorder remains high.

Case presentation: A 7-year-old male presented with recurrent acute flaccid quadriplegia, respiratory distress, abdominal pain, vomiting, and severe syndrome of inappropriate antidiuretic hormone secretion (SIADH)-mediated hyponatremia. The diagnostic clue was photosensitive dark-red urine. Prior whole-exome evaluations from outside for tubulopathies were negative. Whole-exome sequencing reanalysis confirmed HCP via a pathogenic *CPOX* variant (c.746C>G). This case highlights HCP as a rare cause of recurrent AFP. It was initially mismanaged as a tubulopathy before exome sequencing re-analysis identified the correct porphyria diagnosis.

Conclusion: This case highlights a classic yet rare presentation of acute neurovisceral porphyria in a pediatric patient and the importance of re-analysis of the exome on strong suspicion.

Keywords: Case report, Coproporphyria, Exome, Givosiran, Hemin, Neurovisceral crisis, Re-analysis, Recurrent acute flaccid paralysis, Syndrome of inappropriate antidiuretic hormone secretion.

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Introduction

Acute flaccid paralysis (AFP) is a syndrome characterized by rapidly evolving diffuse muscle weakness (critical course), muscular hypotonia, and deep or abolished hypoactive reflexes. It is a sudden disease that develops in hours to weeks, and the acute term refers to neurological disability in this range. The time of AFP evolution varies and depends on the etiology. Acute flaccid paralysis in children under 15 years old, Guillain-Barré Syndrome (GBS), was identified as the most frequent cause. Other documented etiologies included myelitis, post-vaccine poliomyelitis, tick bite paralysis, porphyria, tumors, trauma, a range of other miscellaneous causes, and a notable proportion of cases where the definitive etiology remained undefined. Recurrent AFP is not a standard medical term but describes multiple episodes of this syndrome in a single patient, which is a very rare clinical presentation. Hereditary coproporphyria (HCP) is a rare autosomal dominant disorder caused by pathogenic variants in the coproporphyrinogen oxidase (*CPOX*) gene. It is characterized by acute neurovisceral attacks, which are potentially life-threatening and indistinguishable from other acute hepatic porphyrias (AHP) and/or chronic blistering cutaneous photosensitivity, similar to that seen in porphyria cutanea tarda (PCT) or variegate porphyria (VP). This variable presentation makes a timely diagnosis challenging. Rare homozygous cases exhibit more severe phenotypes, including a distinct form known as harderoporphyria, which features prominent hematologic manifestations. Hereditary coproporphyria is an autosomal dominant condition caused by a partial deficiency in coproporphyrinogen oxidase enzyme activity due to a mutation in the *CPOX* gene. The prevalence of HCP has been estimated at approximately 2–5 per million population.[1,2] In a study from the

[1]Department of Pediatric Neurology, Radiant Children Hospital, Jodhpur, Rajasthan, India

[2]Department of Medical Genetics, Apollo Hospital, Chennai, Tamil Nadu, India

[3]Department of Medical Genetics, IKDRC, Ahmedabad, Gujarat, India

[4]Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Corresponding Author: Preeti Joon, Department of Pediatric Neurology, Radiant Children Hospital, Jodhpur, Rajasthan, India, Phone: +91 7678361617, e-mail: ps1337085@gmail.com

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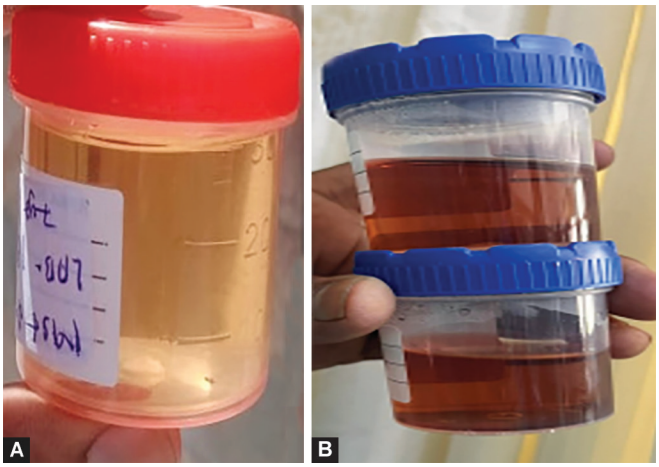
European Porphyria Network, the relative incidence for symptomatic acute intermittent porphyria (AIP) vs VP vs HCP was 1.00 to 0.62 to 0.15.[2] In individuals heterozygous for a pathogenic *CPOX* variant, half-normal enzyme activity suffices for baseline heme synthesis. However, when hepatic heme demand increases, upregulation of ALAS1 leads to the accumulation of coproporphyrinogen III. This substrate auto-oxidizes to coproporphyrin III, resulting in its diagnostic elevation in urine and feces during and after acute attacks, which characterizes HCP. Clinically, AHPs are characterized by severe, potentially life-threatening acute attacks, alongside chronic symptoms that impair daily functioning and quality of life. Acute attacks typically present with severe abdominal pain, a range of neurological disturbances, and psychiatric symptoms. Cutaneous photosensitivity is also a feature in patients with HCP and VP.[3–5] These attacks are frequently precipitated by factors such as certain medications, alcohol, fasting, infections, hormonal fluctuations, or stress, and often necessitate emergency medical intervention. Consequently, a key component of management is the vigilant avoidance of known triggers.[5] While treatments involving carbohydrate loading and hemin infusions can be effective and may shorten the duration and lessen the intensity of acute attacks, they are not curative.[2,3] We report a case of HCP that presented with recurrent episodes of AFP. The initial episodes were managed as tubulopathies at an outside facility but were correctly identified as porphyria upon re-analysis of exome sequencing data.

Case Description

A 7-year-old male with a normal developmental history presented with a 15-day history of acute-onset, progressive generalized weakness affecting all four limbs. This episode was the most recent in a series of recurrent attacks over the past one and a half years. The current weakness began with difficulty walking and rising from a sitting position, later progressing to the upper limbs and resulting in functional impairment such as the inability to self-feed or comb hair. Associated symptoms included poor oral intake, nonprojectile vomiting, diffuse abdominal pain, respiratory difficulty, reduced urine output, and calf pain at rest. His previous history included three previous hospitalizations for similar episodes, featuring combinations of abdominal pain, vomiting, abnormal movements, altered sensorium, and generalized weakness. During these prior admissions, he was managed as a case of Bartter or Gitelman syndrome, for which the child was managed conservatively and had gradual improvement in weakness. Outside investigations reviewed had dyselectrolytemia (hyponatremia, hypokalemia) and urinary pH-5, but no evidence of metabolic acidosis was found. A previous whole-exome sequencing, performed one year earlier at an outside facility for suspected tubulopathy, had returned negative. On examination during the current episode, the child was in respiratory distress but had an intact Glasgow Coma Scale. Neurological examination revealed hypotonia, diminished deep tendon reflexes, and profound weakness (power 0/5 on the MRC scale in all limbs) with peripheral muscle wasting (Fig. 1 – follow-up image). He was also hypertensive. Initial laboratory investigations showed significant dyselectrolytemia, including hyponatremia (124 mEq/L) and hypokalemia (3.1 mEq/L), with biochemical findings consistent with syndrome of inappropriate antidiuretic hormone secretion (SIADH). There was no metabolic acidosis to suggest a primary tubulopathy. A clinical suspicion of porphyria was raised and supported when a urine sample turned dark red upon sunlight exposure (Fig. 2). Although urinary porphobilinogen (PBG) testing, MRI brain and spine, nerve conduction studies could not be performed due to financial constraints; hence, a re-analysis of prior whole-exome sequencing data was pursued. This identified a heterozygous autosomal dominant mutation in the *CPOX* gene (c.746C>G, p. Pro249Arg), confirming the diagnosis of HCP (OMIM #121300). No family history of similar complaints was reported, though parental segregation testing was not performed due to affordability issues. The child was managed conservatively with IV fluids, electrolyte correction, respiratory support H3FNC, and supplementation with pyridoxine and vitamin E. On a 2-month follow-up, he had significantly improved and was able to walk with support.

Fig. 1: Showing peripheral neuropathy in the bilateral lower limb > upper limb



Figs 2A and B: (A) Urine before exposure to sunlight; (B) Urine showing a change in color on exposure to sunlight

Discussion

Hereditary coproporphyria is a rare metabolic disorder caused by a deficiency of the enzyme *CPOX*, resulting from an autosomal dominant mutation in the *CPOX* gene. This defect leads to the accumulation of toxic porphyrin precursors in the body.[6] Acute flaccid paralysis has a broad differential diagnosis, including recurrent chronic inflammatory demyelinating polyneuropathy (CIDP), channelopathies (periodic paralysis), tubular disorders,

toxic neuropathy, tick bite paralysis, and AIP. Recurrent cause of AFP includes CIDP, periodic paralysis, and AIP. Among these, the AHP represent an important but frequently overlooked category.[6] Similarly, in the present case, the child was initially managed elsewhere as a case of tubular disorder. Acute hepatic porphyria is often not suspected initially due to its rarity and nonspecific clinical presentation, even in severe cases. Consequently, diagnostic testing should be considered even when clinical suspicion is low. The limited availability of rapid, qualitative testing for urinary PBG, a simple and reliable assay capable of quickly confirming or excluding the diagnosis, poses a significant barrier to timely diagnosis.[7] Porphyrias are a group of uncommon metabolic diseases, each resulting from impaired function of a specific enzyme in the eight-step heme biosynthetic pathway.[7] These disorders are broadly classified as hepatic or erythropoietic based on the initial organ where heme precursors accumulate. Notably, the four AHPs cause neurological symptoms, most often manifesting as acute attacks in adults, and are biochemically defined by increased concentrations of the porphyrin precursors delta - aminolevulinic acid (ALA) and PBG, as well as porphyrins themselves.[7] While ALA and PBG are established biomarkers, their direct contribution to neurotoxicity has not been definitively established. Alternative theories suggest that localized heme deficiency in neural or vascular tissues may underlie symptoms, possibly by limiting the synthesis of hemoproteins such as nitric oxide synthase, thereby promoting vasospasm and neural dysfunction.[8,9] Abdominal pain is the most frequent presenting symptom in AHP. The pain is typically diffuse and poorly localized and is commonly accompanied by gastrointestinal disturbances such as nausea, vomiting, constipation, bloating, and abdominal distension. Importantly, as the underlying cause is neurological rather than inflammatory, classic signs of an acute abdominal condition, such as tenderness, fever, or leukocytosis, are usually absent.[7,10] Hyponatremia may result from hypothalamic involvement and the SIADH. Peripheral sensory neuropathy, causing extremity, chest, and back pain, is common. Axonal motor neuropathy is often a later feature of severe attacks, usually beginning proximally in the upper extremities and, as in our patient, may progress to quadriparesis and respiratory failure.[7,11,12] Hereditary coproporphyria may be associated with chronic blistering cutaneous manifestations, similar to those seen in PCT or VP.[10] Our case had no cutaneous manifestations or photosensitivity. The diagnosis of AHP is established by finding a marked elevation of urinary PBG, which can occur in AIP, VP, and HCP. Due to the non-affordability of quantitative urinary PBG screening, a simple bedside test was performed in which the child's urine was exposed to sunlight and showed a color change, further supporting the possibility of porphyria. This patient's *CPOX* mutation has not been previously reported or functionally studied in the literature, so it is presently classified as a variant of unknown significance (VUS). However, the severe manifestations of AHP in this patient, along with the absence of *HMBS* or *PPOX* mutations, strongly suggest that this is a pathogenic *CPOX* mutation. Similar findings have been reported by Upchurch et al.[13] Symptomatic and supportive management of acute AHP attacks is essential and includes opioids for pain, antiemetics, sedatives, and close monitoring for autonomic and motor dysfunction and electrolyte abnormalities. Specific treatments that downregulate hepatic ALAS1 include glucose loading, hemin, and givosiran. Glucose loading is generally considered only for mild attacks.[13] Our case was managed conservatively with supportive measures.

Conclusion

This case establishes HCP as a critical, though rare, etiology for recurrent acute flaccid quadriparesis in children. It underscores that the absence of cutaneous features does not exclude the diagnosis, which can be guided by classic neurovisceral signs and simple bedside clues like darkening urine. The diagnostic odyssey, initially confounded by dyselectrolytemia, highlights the perils of premature diagnostic anchoring on tubulopathies. Ultimately, it demonstrates that definitive diagnosis in complex cases may rely on the re-interrogation of existing genetic data when clinical suspicion remains high. This approach is paramount for enabling timely, targeted management of this treatable neurometabolic disorder.

Orcid

Preeti Joon https://orcid.org/0000-0002-5344-4655

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