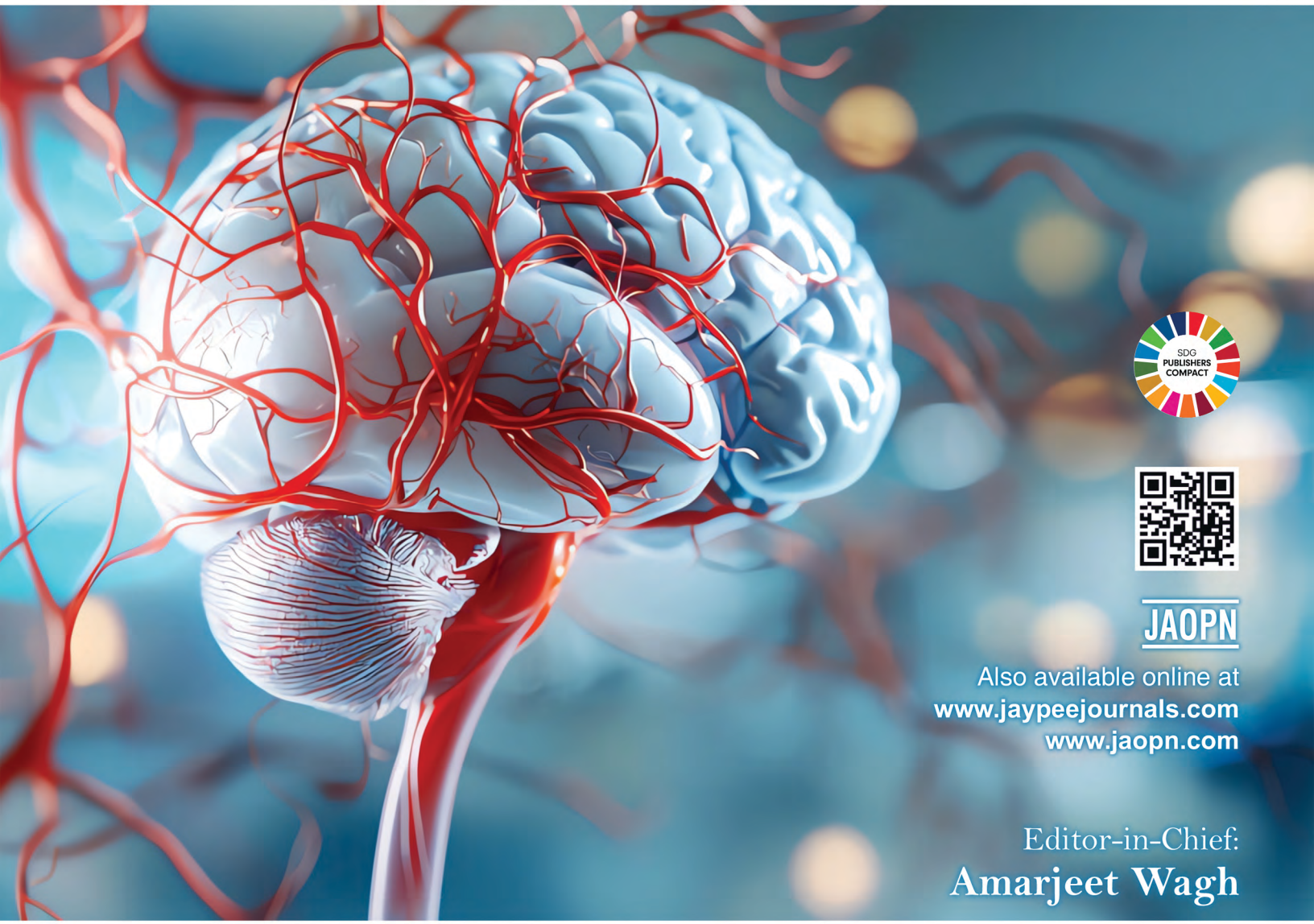
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Thanks and regards

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EDITORIAL

Folinic Acid, Paracetamol, and Vaccines in Autism Spectrum Disorder: An Evidence-based Appraisal of Mechanism, Confounding, and Myths

Sheffali Gulati[1], Shubha SN[2]

Keywords: Acetaminophen, Autism spectrum disorder, Cerebral folate deficiency, Evidence-based medicine, Folate receptor alpha, Leucovorin, Measles, mumps, and rubella vaccine, Vaccination hesitancy.

Journal of Academy of Pediatric Neurology (2026): 10.5005/jaopn-11028-0033

Autism spectrum disorder (ASD) affects approximately 1 in 100 children globally, with recent surveillance estimates of 1 in 31 children in the United States.[1,2] In India, the INCLEN multisite population-based study of 3,964 children aged 2–9 years found ASD prevalence comparable to the published global literature.[3] Despite decades of research, no medication has been proven to improve the core symptoms of ASD.[4] This has resulted in two contrasting problems: Enthusiasm for treatments without sufficient evidence and the persistence of myths despite strong evidence against them. These three examples illustrate the importance of applying the same rigorous standard of evidence to every claim.

Folinic acid (leucovorin) has a plausible biological rationale for use in autism. In cerebral folate deficiency, autoantibodies against folate receptor alpha impair folate transport, and leucovorin restores central folate metabolism.[5] Yet it is increasingly prescribed without testing the autoantibodies or cerebrospinal fluid 5-methyltetrahydrofolate that identify a likely responder. The only robust randomized trial (48 children) showed benefit confined to autoantibody-positive participants, and the larger 2024 trial often cited alongside it was retracted in 2026.[6,7] Folinic acid is therefore a reasonable biomarker-guided trial, not a treatment for unselected ASD.

Early studies suggested that taking paracetamol during pregnancy might increase the risk of autism. However, later research showed that this finding was largely due to confounding factors. A sibling-controlled study involving 2.48 million children found no association between prenatal paracetamol exposure and autism (hazard ratio 0.98), and a 2026 meta-analysis of 43 studies reached the same conclusion.[8–10] Paracetamol remains the antipyretic of choice in pregnancy when indicated.

Two Danish national cohort studies found no association between the measles, mumps, and rubella (MMR) vaccine or thimerosal and autism.[11,12] These findings were supported by a meta-analysis involving more than 1.2 million children and by studies showing that autism rates continued to rise even after thimerosal was removed from vaccines.[13,14] The challenge now is to communicate this evidence clearly, as measles cases continue to increase.

A plausible mechanism is not proof of efficacy. Clinicians should neither prescribe unproven therapies because they seem biologically convincing nor avoid safe interventions because of disproven fears. For folinic acid, biomarkers, not biological plausibility alone, should guide treatment.

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Both authors contributed to the conception, drafting, and critical revision of this editorial and approved the final version.

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ORIGINAL RESEARCH

Vitamin D Status in Children with Epilepsy on Antiepileptic Drugs

Samridhi[1], Manmeet K Sodhi[2], Harmohinder K Attri[3], Pallavi Sharma[4]

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Abstract

Aim and background: Epilepsy is one of the most common neurological disorders in children, requiring long-term antiepileptic drug (AED) therapy. Antiepileptic drugs have been shown to disrupt vitamin D metabolism, raising the possibility of a deficiency with prolonged use. This study intended to establish the prevalence of vitamin D deficiency in children with epilepsy on AED therapy and to explore its relationship with the type and duration of treatment.

Materials and methods: A prospective cross-sectional study was conducted on 100 epileptic patients aged 2–15 years receiving AED therapy for more than 3 months. Serum 25(OH) vitamin D, calcium, phosphorus, and alkaline phosphatase were measured. Data were analyzed using SPSS version 22.

Results: Among 100 participants, 48% were vitamin D deficient (mean 10.95 ± 4.75 ng/mL), 28% insufficient (mean 17.17 ± 2.28 ng/mL), and 24% sufficient (mean 28.77 ± 6.28 ng/mL). There was a substantial inverse relationship ($p = 0.001$) between vitamin D levels and the duration of both seizures and AEDs. Children on polytherapy had significantly lower vitamin D levels than those on monotherapy ($p = 0.001$), although no notable difference was found among individual AEDs ($p = 0.069$).

Conclusion: Vitamin D deficiency is highly prevalent among children with epilepsy on long-term AED therapy, particularly in those receiving multiple drugs or prolonged treatment.

Clinical significance: Routine screening and supplementation of vitamin D should have a major role in the management of pediatric epilepsy patients on long-term AED therapy.

Keywords: Antiepileptic drugs, Bone metabolism, Epilepsy, Pediatric, Polytherapy, Vitamin D deficiency.

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Introduction

Epilepsy is a chronic neurological disorder recognized by recurrent, unprovoked seizures triggered by aberrant, excessive, or synchronized neuronal activity occurring in the brain. It affects approximately 50 million people worldwide, accounting for nearly 1% of the global population, making it one of the most prevalent neurological conditions.[1] Although epilepsy can affect individuals of any age, it occurs more commonly among children and older adults. A community-based study conducted in North India observed the prevalence rates of active epilepsy as 4.07 per 1,000 population, with higher rates in rural (6.99 per 1,000) than urban regions (5.48 per 1,000).[2,3] The International League Against Epilepsy (ILAE) classifies seizures as per the mode of onset into focal and generalized types.[4]

Following an initial neurological insult such as trauma, stroke, or infection, the process of epileptogenesis transforms a normal brain into one predisposed to spontaneous seizures.[5] This process involves multiple stages, including acute neuronal injury, synaptic reorganization, and chronic structural alterations like hippocampal sclerosis and cortical atrophy, leading to a sustained hyperexcitable state.[6] Understanding epileptogenesis has significant therapeutic implications for early identification and intervention to prevent chronic epilepsy, using agents that target neuroinflammation, oxidative stress, and ion channel dysfunction.[7]

Management of epilepsy primarily involves long-term use of antiepileptic drugs (AEDs) aimed at seizure control and improving quality of life. However, chronic AED therapy is often associated with systemic adverse effects, including hepatotoxicity, nephrotoxicity, endocrine, psychiatric, and particularly skeletal manifestations like osteopenia and osteoporosis.[8,9] These adverse outcomes are partly attributed to AED-induced disturbances in vitamin D metabolism.

Vitamin D is a fat-soluble vitamin essential for calcium and phosphorus homeostasis and bone mineralization. It is synthesized in the skin upon ultraviolet-B exposure and obtained from dietary sources including eggs, butter, and fish liver oils.[10,11] Vitamin D is converted in the liver to 25-hydroxyvitamin D [25(OH)D] and subsequently in the kidneys to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the active form of Vitamin D, which regulates calcium absorption and bone health.[12] Beyond skeletal functions, vitamin D also modulates immune and cellular processes. Deficiency of this vitamin is a major global health issue, with prevalence exceeding 90% in developing countries and 15–50% in developed nations.[13]

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Despite abundant sunlight, vitamin D deficiency (VDD) is highly prevalent in India, affecting 70–90% of the population due to factors like limited sun exposure, dietary inadequacy, and sociocultural practices.[14] Chronic VDD contributes to skeletal manifestations such as rickets and osteomalacia, muscle weakness, and delayed growth in children, along with extraskeletal consequences including immune dysfunction and neurocognitive effects.[15]

The relationship between bone mineral metabolism and AED use was first described in 1960, with subsequent studies confirming that AEDs alter calcium, phosphorus, and parathyroid hormone levels, leading to decreased bone density and elevated fracture risk.[16,17] The mechanism involves hepatic enzyme induction by certain AEDs, enhancing the vitamin D catabolism and hence reducing its bioavailability.[18,19] Enzyme-inducing drugs such as phenytoin, phenobarbital, and carbamazepine are particularly implicated, while non-enzyme-inducing AEDs like valproate and lamotrigine have minimal impact.[20,21]

Given the high burden of both epilepsy and vitamin D deficiency in India, understanding their interrelationship is essential for optimizing management strategies, improving skeletal health, and enhancing overall quality of life in patients on prolonged AED therapy.

The present study intended to ascertain the prevalence of vitamin D deficiency in children with epilepsy, receiving various antiepileptic drug regimens. The specific objectives were to assess the vitamin D status among children on monotherapy and polytherapy and to evaluate the effect of the duration of antiepileptic drug therapy on serum vitamin D levels.

Materials and Methods

This prospective cross-sectional study was conducted in the Department of Paediatrics, in collaboration with the Department of Biochemistry, at the Government Medical College (GMC), Amritsar, from June 2023 to May 2024. The Institutional Ethics Committee granted the ethical clearance, and written informed consent was obtained from the parents or guardians of all participants before inclusion. The study population comprised children aged 2–18 years diagnosed with epilepsy and receiving AED therapy for more than 3 months to ensure adequate and clinically meaningful exposure to medicine for quantifiable effects on vitamin D metabolism and related biochemical markers to occur. Detailed socio-demographic and clinical parameters, including age, gender, type of epilepsy, number of AEDs, and duration of therapy, were recorded in a structured proforma. Children with suspected metabolic bone disease, chronic hepatic or renal disease, or those whose parents declined consent or assent were not included in the study.

Epilepsy was defined according to the 2017 operational definition by the International League against Epilepsy (ILAE) as a disorder of the brain characterized by either two or more unprovoked (or reflex) seizures occurring more than 24 hours apart, one unprovoked (or reflex) seizure with a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures over the next 10 years, or the diagnosis of an epilepsy syndrome. The enrolled patients were on various antiepileptic regimens that were broadly categorized as old or new AEDs. Old AEDs included carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and valproic acid, whereas new AEDs included lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, zonisamide, felbamate, and gabapentin. Based on their effects on hepatic cytochrome P450 enzymes, the drugs were further grouped as enzyme-inducing AEDs—such as carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and topiramate—and non-enzyme-inducing AEDs, including valproate, gabapentin, tiagabine, lamotrigine, and vigabatrin. This distinction was of clinical importance because enzyme-inducing AEDs accelerate vitamin D metabolism, predisposing patients to deficiency and subsequent alterations in skeletal health.

Upon enrollment, venous blood samples were collected to estimate serum 25-hydroxyvitamin D [25(OH)D], calcium, phosphorus, and alkaline phosphatase levels. Vitamin D estimation was performed using the chemiluminescence immunoassay (CLIA) technique on an automated analyzer, providing a quantitative measure of serum 25(OH)D. Based on serum concentration, vitamin D status was categorized as deficient (<12 ng/mL), insufficient (12–20 ng/mL), or sufficient (>20 ng/mL). For statistical purposes, children with insufficient and sufficient levels were grouped as non-deficient, while those with deficiency formed the deficiency group. Appropriate supplementation was planned according to the laboratory results.

All the collected data were compiled and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were quantified as frequencies and percentages. Intergroup comparisons of mean vitamin D levels were made using the independent *t*-test and one-way ANOVA. Associations between categorical variables were determined using the Chi-square (χ^2) test. The mean was calculated using the sum of all observations divided by the total number of observations ($\bar{x} = \Sigma x/n$), and the standard deviation was derived using the formula $s = \sqrt{[\Sigma(x - \bar{x})^2/(n - 1)]}$. The Chi-square statistic was computed using $\chi^2 = \Sigma[(O - E)^2/E]$, where O represents the observed value and E the expected value. Degrees of freedom were calculated as (number of rows – 1) × (number of columns – 1). A p-value of less than 0.05 was considered statistically significant.

This analysis aimed to establish the prevalence of vitamin D deficiency among epileptic children receiving different antiepileptic drugs, to compare vitamin D status among those on monotherapy and polytherapy, and to determine the effect of duration of therapy on vitamin D levels.

Observations and Results

A total of 100 children with epilepsy receiving AED therapy were included in the study. The demographic and clinical distribution of cases is summarized in Table 1. The majority of children (56%) were between 2 and 5 years of age, followed by 23% aged 6–10 years and 21% aged 11–15 years. Males constituted 53% of the study population, while females constituted 47%, indicating a slight male predominance. Generalized seizures were more common (77%) compared to focal seizures (23%). The majority of children (66%) had a seizure duration of 1–5 years, and a similar proportion (62%) had been on AED therapy for 1–5 years, suggesting that most participants had moderate-term disease and treatment duration.

Vitamin D and related biochemical parameters are presented in Table 2. Nearly half (48%) of the study participants were vitamin D deficient (<12 ng/mL), while 28% had insufficient levels (12–20 ng/mL), with only 24% having sufficient vitamin D (>20 ng/mL). The mean serum vitamin D concentration among all subjects was

16.97 ± 8.52 ng/mL. Mean serum calcium and phosphorus levels were lowest in the deficient group and increased progressively with higher vitamin D levels, showing a statistically substantial association (p = 0.014 for both). Serum alkaline phosphatase (ALP) levels were highest in the sufficient group but did not reach statistical significance (p = 0.058).

The relationship between clinical variables and vitamin D levels is presented in Table 3. A progressive decline in mean vitamin D levels was noted with longer seizure duration and longer AED exposure. Children with seizures for less than one year had a mean vitamin D level of 24.12 ± 8.92 ng/mL, which decreased to 7.32 ± 4.05 ng/mL in those with seizures lasting 11–15 years (p = 0.001). Similarly, vitamin D levels declined from 22.78 ± 8.57 ng/mL in children on AEDs for less than one year to 7.32 ± 4.05 ng/mL in those treated for 11–15 years (p = 0.001).

The association between therapy type, specific drugs, and vitamin D status is detailed in Table 4. Children on monotherapy had higher mean vitamin D levels (19.10 ± 8.41 ng/mL) than those on polytherapy (13.90 ± 7.79 ng/mL), with a statistically significant difference (p = 0.001). Among individual AEDs, phenobarbitone users showed the highest mean vitamin D levels (23.31 ± 6.74 ng/mL), followed by levetiracetam (21.52 ± 13.64 ng/mL) and phenytoin (20.78 ± 7.10 ng/mL), whereas valproate users had comparatively lower levels (16.78 ± 8.07 ng/mL), although this difference has statistical relevance (p = 0.069).

Table 1: Demographic and clinical profile of the study population

Variable	*Category*	*No. of cases*	*Percentage (%)*
Age-group (years)	2–5	56	56.0
	6–10	23	23.0
	11–15	21	21.0
Gender	Male	53	53.0
	Female	47	47.0
Type of epilepsy	Generalized	77	77.0
	Focal	23	23.0
Duration of seizures (years)	<1	8	8.0
	1–5	66	66.0
	6–10	18	18.0
	11–15	8	8.0
Duration of AED therapy (years)	<1	13	13.0
	1–5	62	62.0
	6–10	17	17.0
	11–15	8	8.0

Most participants were aged 2–5 years, with a male predominance and generalized seizures being the most common type. The majority had seizure duration and AED use between 1 and 5 years

Discussion

Demographic and Clinical Profile

Epilepsy is a prevalent neurological disorder that causes recurrent episodes of seizures and requires long-term management with anti-seizure medication. In the Indian subcontinent, where micronutrient deficiencies are already widespread, children receiving prolonged antiepileptic therapy are particularly susceptible to nutritional deficiencies, not due to the disease itself but because of the metabolic effects of these drugs.

The present study, titled "Vitamin D Status in Children with Epilepsy on Antiepileptic Drugs," was undertaken in the Department of Paediatrics, Government Medical College, Amritsar, over a period of 1 year. A total of 100 children aged 2–18 years were

Table 3: Duration of seizures and AED therapy in relation to vitamin D levels

Variable	*Duration (years)*	*Mean vitamin D (ng/mL)*	*SD*	*p-value*
Seizure duration	<1	24.12	8.92	**0.001**
	1–5	18.17	7.86	
	6–10	13.67	7.87	
	11–15	7.32	4.05	
AED duration	<1	22.78	8.57	**0.001**
	1–5	17.95	7.79	
	6–10	13.51	8.08	
	11–15	7.32	4.05	

Statistically significant inverse relationship between vitamin D levels and both seizure duration and AED therapy duration, indicating that longer disease and treatment exposure are associated with greater vitamin D depletion; Bold values indicate statistically significance

Table 4: Comparison of vitamin D levels by type and duration of AED therapy

Parameter	*Category*	*Mean vitamin D (ng/mL)*	*SD*	*p-value*
Type of AED	Monotherapy	19.10	8.41	**0.001**
	Polytherapy	13.90	7.80	
Individual AED	Levetiracetam	21.53	13.64	0.069
	Phenobarbitone	23.31	6.74	
	Phenytoin	20.78	7.10	
	Valproate	16.78	8.07	

Children on AED polytherapy exhibited significantly lower vitamin D levels than those on monotherapy. Although not statistically significant, valproate users tended to have lower vitamin D levels compared to other AED groups; Bold values indicate statistically significance

Table 2: Vitamin D status and biochemical parameters in epileptic children on AED therapy

Vitamin D status	*No. of cases*	*Mean vitamin D (ng/mL) ± SD*	*Serum calcium (mg/dL) ± SD*	*Serum phosphorus (mg/dL) ± SD*	*ALP (U/L) ± SD*
Deficient	48	10.95 ± 4.75	8.86 ± 1.12	8.86 ± 1.12	301.96 ± 108.02
Insufficient	28	17.17 ± 2.28	9.21 ± 0.77	9.21 ± 0.77	332.82 ± 117.34
Sufficient	24	28.77 ± 6.28	9.57 ± 0.78	9.57 ± 0.78	372.04 ± 131.17
Total/mean	**100**	**16.97 ± 8.52**	**9.13 ± 0.99**	**9.13 ± 0.99**	**327.42 ± 118.73**
p-value			**0.014**	**0.014**	0.058

Significant association between vitamin D deficiency and lower mean serum calcium and phosphorus levels, whereas alkaline phosphatase showed an increasing but statistically non-significant trend with higher vitamin D concentrations; Bold values indicate statistically significance

enrolled, of whom 53% were males and 47% females. The majority of participants (56%) belonged to the 2–5 years age-group, followed by 23% aged 6–10 years and 21% aged 11–15 years. Generalized seizures were predominant (77%) compared to focal seizures (23%).

No significant relationship was observed between age, gender, or seizure type and vitamin D levels in this study. This finding contrasts with the observations of Shellhaas et al.,[22] who observed that female gender, increased BMI, and focal epilepsy were directly correlated with an increased risk of vitamin D deficiency.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency remains a widespread concern in India despite abundant sunlight throughout the year. Cultural practices, limited outdoor exposure, and dietary inadequacies contribute to this paradoxical situation. Studies from North India, including Narang et al.,[23] have reported VDD prevalence as high as 62–95.7% in infants, while the Comprehensive National Nutrition Survey (2016–2018)revealed deficiency rates of 18.2% among children aged 5–9 years and around 23.9% among adolescents aged 10–19 years of age.[24]

In our study, 48% of children were vitamin D deficient (mean 10.95 ± 4.74 ng/mL), 28% were insufficient (mean 17.16 ± 2.27 ng/mL), and only 24% achieved sufficiency (mean 28.77 ± 6.28 ng/mL). The deficiency increased with age, ranging from 35.7% in children aged 2–5 years to 76.2% in those aged 11–15 years. This demonstrates that older children with longer seizure duration and prolonged AED exposure are at greater risk of deficiency.

Concurrent analysis of serum calcium, phosphorus, and ALP levels revealed corresponding biochemical alterations. Deficient children had lower calcium and phosphorus levels, while ALP levels were marginally raised, suggesting subclinical bone metabolism disturbance. Unlike Razazian et al.,[25] who reported normal calcium and vitamin D levels but elevated ALP, our findings indicate both biochemical and nutritional depletion in deficient cases.

Effect of Duration of AED Therapy

An inverse association of statistical significance was observed between vitamin D levels and duration of AEDs ($p = 0.001$). Children receiving AEDs for less than one year have a mean vitamin D level of 22.78 ng/mL, which progressively declines to 7.32 ng/mL after 11–15 years of treatment. This clearly demonstrates a cumulative effect of prolonged AED exposure, likely due to hepatic enzyme induction that accelerates vitamin D catabolism, disrupts calcium absorption, and adversely affects bone health.

These results are in agreement with those of Baek et al.[26] and Azad et al.,[27] who both identified duration of AED use as a key factor influencing vitamin D depletion. A significant variation was noted in vitamin D levels between children on AEDs for more than two years and those who were treated for less than 2 years ($p = 0.03$), further reinforcing the association between therapy duration and deficiency severity.

Comparison of Monotherapy and Polytherapy

The present study also compared vitamin D levels between children receiving monotherapy and those on polytherapy. Monotherapy was more common (59%), while 41% were receiving multiple drugs. Mean vitamin D levels were significantly higher in the monotherapy group (19.10 ± 8.41 ng/mL) compared to the polytherapy group (13.90 ± 7.80 ng/mL) ($p = 0.001$).

This finding can be ascribed to the synergistic pharmacologic effect of multiple drugs, which may enhance hepatic metabolism of vitamin D, leading to accelerated depletion. No significant association was found between age-group and type of therapy ($p = 0.788$*), indicating that age does not influence therapy choice.

Similar findings were summarized by Lee et al.[28] and Fong et al.,[29] who highlighted polytherapy as a significant predictor of vitamin D deficiency in children with epilepsy. The collective evidence indicates that children on multiple AEDs represent a high-risk group requiring closer biochemical monitoring and early preventive supplementation.

Impact of Individual AEDs

The study also assessed the impact of individual AEDs on vitamin D status based on their metabolic properties. Antiepileptic drugs are classified as enzyme-inducing (e.g., carbamazepine, phenytoin, phenobarbitone) and non-enzyme-inducing (e.g., valproate, levetiracetam). Although enzyme inducers are known to enhance vitamin D catabolism, our study did not find a statistically significant difference in vitamin D levels among different drugs ($p = 0.069$*).

While valproate users exhibited lower mean vitamin D levels (16.78 ng/mL) compared to those on phenobarbitone (23.31 ng/mL) or levetiracetam (21.53 ng/mL), this variation was not significant. This suggests that other confounding factors, such as duration of therapy, sunlight exposure, and dietary intake, may play a stronger role.

Chaudhuri et al.[30] similarly reported reduced vitamin D levels with both enzyme-inducing and non-inducing AEDs, irrespective of their mechanism of action. Ginige et al.[31] also observed no significant difference between carbamazepine and valproate monotherapy, whereas Ramelli et al.[32] reported pronounced deficiency in children on enzyme-inducing AEDs. The lack of uniformity among studies may reflect differences in population characteristics, drug exposure, and baseline nutritional status.

Supplementation Status

Only 8% of the children in the present study were receiving vitamin D supplementation, while 92% were not. This highlights a critical gap in preventive nutritional care for epileptic children. Considering the widespread deficiency and its impact on skeletal and extra-skeletal systems, it is imperative to incorporate routine screening and vitamin D supplementation into epilepsy management protocols.

Clinical Implications

The findings of this study substantiate the need for regular biochemical monitoring of vitamin D, calcium, and phosphorus in children on prolonged AED therapy. The duration of treatment and the use of multiple drugs significantly increase the risk of deficiency, regardless of the specific agent used. Early recognition and correction through supplementation and lifestyle modification can prevent the long-term skeletal complications associated with chronic deficiency.

Comparison with Literature

The results of the present study are in agreement with previous international and Indian data, which report vitamin D deficiency rates ranging from 40% to 65% among pediatric epilepsy patients. The duration of AED therapy and use of polytherapy have repeatedly emerged as key determinants of vitamin D status. Our findings align closely with Baek et al.[26] and Azad et al.,[27] confirming that the longer the duration and the higher the number of AEDs, the lower the serum vitamin D concentration.

Limitations

A single center cross-sectional study with a limited sample size, hence the findings could not be generalized to a wider population. Also, having no control group is another major limitation, but the primary reason for that was the high prevalence of vitamin D deficiency across the general population. This widespread deficiency reduces the value of comparing Vitamin D levels between healthy children and those on AEDs, as both groups are likely to exhibit suboptimal levels.

Conclusion

The study provides compelling evidence that children with epilepsy on long-term AED therapy are at significantly increased risk of vitamin D deficiency. The duration of drug exposure and the use of multiple AEDs are the primary determinants of decline in vitamin D levels, while the type of individual drug appears less influential. Routine screening and supplementation should form an integral part of epilepsy management to maintain optimal bone health and prevent associated complications.

Declarations

Data Availability

Available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Institutional Ethics Committee, Government Medical College, Amritsar (No. 398/D-26/2022 Batch).

Informed Consent

Written informed consent was obtained from parents/guardians of all participants.

Artificial Intelligence (AI) Disclosure

The authors state that no AI is used in the study performed.

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Authors' Contributions

Samridhi conducted the study and prepared the manuscript; Manmeet K Sodhi supervised and reviewed the clinical aspects; Harmohinder K Attri supervised biochemical analysis and interpretation.

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ORIGINAL RESEARCH

Demographic and Clinical Characteristics of Children with Autism Spectrum Disorder at a Tertiary Neurodevelopmental Center in Central India: A Retrospective Study Using the Indian Scale for Assessment of Autism

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Abstract

Background: Autism spectrum disorder (ASD) represents a growing public health concern in India, yet published clinical data from Central India, particularly from private tertiary neurodevelopmental centers, remain scarce. The Indian Scale for Assessment of Autism (ISAA), mandated under the Rights of Persons with Disabilities Act 2016 for disability certification, offers a contextually appropriate severity instrument, but its application in retrospective clinical research from Tier-2 cities is underreported.

Objective: This study examined the demographic and clinical characteristics, geographic catchment profile, and ISAA-based severity distribution of children diagnosed with ASD at Little Brain Center (LBC), a private tertiary neurodevelopmental center in Nagpur, Maharashtra (MH).

Methodology: A retrospective descriptive study was conducted using digitized case records of 30 children (aged 2 years 2 months to 7 years 11 months) with ICD-10 F84.0 diagnoses registered at LBC. Variables extracted included age, sex, location, state of origin, and ISAA scores. Descriptive statistics were computed; severity categories were stratified by sex, age-group, and geographic residence type.

Results: The sample comprised 27 males and 3 females (M:F = 9:1). Mean age was 57.4 months (SD = 17.5). Seventeen cases (56.7%) were classified as moderate severity, and 13 (43.3%) as mild; no severe cases were recorded. Numeric ISAA scores were available for all 30 participants, with a mean score of 101.83 (SD = 16.08; range: 71–123). The center drew patients from 16 locations across four states [MH, Madhya Pradesh (MP), Chhattisgarh (CG), Uttar Pradesh (UP)], with 22 (73.3%) from MH and 6 (20%) from MP.

Conclusion: These findings document a pronounced male preponderance exceeding global and Indian clinical norms, a geographic catchment spanning multiple states indicative of severe diagnostic scarcity in Central India, and a predominantly mild-to-moderate severity distribution consistent with earlier clinical presentation trends. The study establishes an empirical baseline for ASD clinical profiling in Vidarbha and Central India, with implications for regional health policy and diagnostic service planning.

Keywords: Autism spectrum disorder, Central India, Geographic catchment, ICD-10 F84.0, India, Indian Scale for Assessment of Autism, Retrospective, Tertiary care, Vidarbha.

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Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent impairments in social communication and interaction, alongside restricted, repetitive patterns of behavior, interests, and sensory responses.[1,2] Its manifestation across developmental stages is variable, and its recognition in low- and middle-income countries (LMICs) is systematically complicated by limited diagnostic infrastructure, scarce trained specialists, cultural barriers to help-seeking, and the absence of community-based screening programs.[3] India, with a population exceeding 1.4 billion and an estimated child population of approximately 480 million, confronts a particularly acute version of this challenge.

Epidemiological data on ASD in India remain limited in both quantity and quality. The most comprehensive meta-analysis of Indian prevalence studies, conducted by Chauhan et al., reported a pooled community-based prevalence of 0.09% in urban settings and 0.11% in rural settings among children aged 0–18 years, figures almost certainly representing significant underestimates given ascertainment methodology limitations, and substantially lower than the 1-in-31 (approximately 3.2%) prevalence reported among 8-year-olds in the United States.[4,5] These estimates derive almost exclusively from urban centers in South and North India, with negligible data from Central Indian states including

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Maharashtra (MH), Madhya Pradesh (MP), and Chhattisgarh (CG). The clinical realities of a private tertiary neurodevelopmental center serving the Vidarbha region of MH, and its multi-state referral network, are therefore entirely undocumented in the peer-reviewed literature.

India's policy framework for ASD was significantly strengthened by the Rights of Persons with Disabilities (RPWD) Act of 2016, which formally recognized ASD as a certifiable disability category. Under this legislation, the Indian Scale for Assessment of Autism (ISAA) was mandated as the standard instrument for disability severity certification. The ISAA, developed by the National Institute for the Mentally Handicapped (now National Institute for Empowerment of Persons with Multiple Disabilities) and validated against the Childhood Autism Rating Scale (CARS) across 10 Indian centers, comprises 40 items distributed across six domains: social relationships and reciprocity, emotional responsiveness, speech-language and communication, behavior patterns, sensory aspects, and cognitive component.[6–8] Scores range from 40 to 200, with thresholds at 70 (mild), 107 (moderate), and 154 (severe). Despite its legislative mandate, published retrospective clinical research utilizing ISAA as a primary severity measure is sparse, and no study to date has reported ISAA-based profiles from Vidarbha or Central India. Little Brain Center (LBC), a private tertiary neurodevelopmental clinic in Nagpur, MH, is among the few centers in Central India offering integrated ASD diagnostic and therapeutic services and functions as a *de facto* regional referral hub, drawing patients from across MH and neighboring states. No clinical research has previously characterized the demographic composition, geographic catchment, or severity profile of this population.

Against this background, the present study is framed around the following research question: What are the demographic, geographic, and ISAA-based clinical severity characteristics of children with ASD registered at LBC, Nagpur, and what patterns emerge across sex, age, geographic residence, and state of origin? By systematically describing the profile of this hitherto undocumented clinical cohort, the study aims to contribute an empirical foundation for future analytical and policy-relevant research in Central India.

Review of Literature

Global and Indian Epidemiological Context

Global estimates of ASD prevalence have risen substantially over successive decades, reflecting improved diagnostic recognition, broadened diagnostic criteria from DSM-IV to DSM-5, and expanded surveillance capacity, rather than a genuine increase in biological incidence. The World Health Organization currently estimates a global prevalence of approximately 1 in 100 children. Within India, Chauhan et al., in the first systematic review and meta-analysis of Indian community-based ASD prevalence, identified only four eligible population studies, underscoring the fundamental paucity of reliable epidemiological infrastructure.[4] Their pooled estimates of 0.09–0.11% contrast sharply with US Centers for Disease Control estimates of 2.3% (1 in 44 children), reflecting the well-documented gap between true prevalence and identified prevalence in resource-constrained settings. Nagpur and the broader Vidarbha region have produced no community prevalence data to date.

The ISAA as a Clinical and Policy Instrument

The development of a culturally and linguistically appropriate autism assessment tool for India was motivated by the recognized inadequacy of Western instruments, including the autism diagnostic observation schedule (ADOS) and autism diagnostic interview-revised (ADI-R), in capturing autistic presentations within Indian socio-cultural contexts, and by their prohibitive cost and intensive training requirements. The ISAA was field-tested on a sample of $N = 1,247$ participants across 10 Indian centers and demonstrated strong criterion validity against the CARS ($r = 0.765$, $p < 0.001$), high internal consistency (Cronbach's $\alpha = 0.93$), and acceptable inter-rater reliability (range: 0.62–0.81 across domains).[6] Manohar et al. subsequently critiqued the ISAA's limitations in children below 3 years of age and called for re-validation against contemporary gold-standard tools such as ADOS-2.[8] These critiques notwithstanding, the ISAA remains the only legislatively mandated, open-access, Indian-normed severity instrument available for routine clinical use, making it the appropriate primary measure for retrospective chart-based studies of Indian ASD cohorts.

Sex Ratio in ASD Clinical Samples

The male predominance in ASD diagnoses is among the most replicated findings in the literature. Loomes et al., in the first systematically derived meta-analytic estimate of the male-to-female ratio (MFR), reported a pooled male-to-female odds ratio (MFOR) of 4.20 (95% CI: 3.84–4.60), with higher-quality studies yielding a more conservative MFOR of 3.32.[9] Posserud et al. confirmed that this predominance is greater in childhood clinical samples and decreases with age, potentially reflecting ascertainment bias and the later identification of autistic females.[10] Indian clinical series consistently report MFRs at the higher end of international ranges, with some reporting ratios of 5:1–8:1, attributed to lower female help-seeking, reduced awareness of female ASD phenotypes among clinicians, and possible under-referral of girls to specialist centers. The present cohort's observed ratio of 9:1 exceeds most reported Indian benchmarks and warrants discussion.

Geographic Determinants of ASD Diagnosis in India

A persistent structural determinant of ASD diagnostic access in India is geographic proximity to specialist care. Autism spectrum disorder neurodevelopmental diagnostic services are heavily concentrated in metropolitan centers, NIMHANS Bengaluru, AIIMS New Delhi, and KEM Mumbai, with almost no equivalent capacity in Tier-2 cities, district hospitals, or rural settings. This concentration produces two interrelated phenomena: First, diagnostic delay at the population level, as families in peripheral districts lack local access to assessment; and second, long-distance referral patterns to the few available specialist centers. Dey et al., in a nationwide scoping exercise on autism community priorities in India, identified access to timely diagnosis as the most consistently reported unmet need, particularly in non-metropolitan settings.[3] The geographic profile of LBC's catchment, spanning four states and 16 locations, with patients traveling from districts 100 to 340 km distant, represents a direct empirical index of this structural diagnostic void.

Age at Presentation in Indian ASD Samples

International guidelines advocate for ASD screening at 18 and 24 months and diagnostic evaluation before the age of 3, given the well-established relationship between age at intervention initiation and developmental outcome. In Indian clinical settings, mean age at first specialist presentation is consistently 4–6 years, with even greater delays documented in rural and lower-socioeconomic-status populations. The present cohort's mean presentation age of 57.4 months (approximately 4.8 years) is consistent with this

documented pattern and reflects systemic delays that begin with limited community awareness, progress through primary and pediatric care avoidance or inadequacy, and culminate in referral to specialist centers only once behavioral divergence becomes impossible to dismiss in educational contexts.

Methodology

Research Design

This study employed a retrospective descriptive design. Clinical records maintained at LBC were systematically reviewed, and demographic, geographic, and ISAA-based severity data were extracted using a standardized proforma developed for this study. No experimental manipulation was performed; no primary data were collected. The study was exempted from formal ethical review on the grounds that it involved retrospective analysis of routinely collected, fully anonymized clinical data, consistent with standard provisions under Indian biomedical ethics guidelines.

Setting

Little Brain Center is a private tertiary neurodevelopmental clinic in Nagpur, MH, established and directed by Dr Amarjeet Wagh. It provides integrated services including neuropsychological assessment, occupational therapy, speech-language therapy, and parent counseling for children with ASD and related neurodevelopmental conditions. Nagpur is the administrative capital of the Vidarbha sub-region of MH. It occupies a central geographic position in India, which partially explains its function as a cross-state referral hub.

Sample

The study sample comprised 30 children ($N = 30$) with documented ICD-10 F84.0 (Childhood Autism) diagnoses from digitized records held at LBC. Records were included if they: (a) contained a confirmed clinical diagnosis of F84.0; (b) included at least age and location data; and (c) were registered within the period for which digital records were available (2018–2024). Records were excluded if ASD diagnosis was absent, unconfirmed, or if the primary diagnosis was a related but distinct condition (F84.1 Atypical Autism; F84.5 Asperger's Syndrome). An additional 100+ paper-based records exist at LBC and are the subject of a planned phase 2 data extraction; the present report constitutes a phase 1 analysis of the digital cohort.

Data Extraction Instrument

A structured data extraction proforma was developed and piloted on five records prior to full extraction. Variables extracted included: (1) age at time of most recent registration (recorded as years and months); (2) sex (male/female/other); (3) location of family residence (city/town/village); (4) state of residence; (5) urban/rural classification, assigned based on Census of India 2011 population thresholds (urban = population ≥ 100,000); (6) ISAA total score (numeric, where recorded); and (7) ISAA severity category (mild: 70–106; moderate: 107–153; Severe: ≥154).

Measures

ISAA

The ISAA is a 40-item, 5-point Likert-rated severity scale developed by the National Institute for Mentally Handicapped, Government of India.[3] Scores range from 40 to 200; the clinically established thresholds define no autism (<70), mild autism (70–106), moderate autism (107–153), and severe autism (>153). Internal consistency is high (Cronbach's $\alpha = 0.93$); criterion validity against CARS is $r = 0.765$ ($p < 0.001$). The ISAA is available in multiple Indian languages and requires minimal training, making it feasible for routine clinical administration. Of the 30 records examined, all 30 now contain full numeric ISAA scores following completion of phase 1 digital data extraction; severity category (mild/moderate/severe) was independently recorded in the original clinical files for every case.

Statistical Analysis

All statistical analyses were performed using Jamovi. Descriptive statistics were computed for all continuous variables (mean, standard deviation, median, range). Frequency distributions and proportions were calculated for categorical variables (sex, ISAA category, state of origin, urban/rural residence). Cross-tabulations were constructed for ISAA severity by sex, age-group (≤3 vs >3 years), and residence type (urban vs rural). Exploratory mean ISAA score comparisons were conducted for sex, residence type, age-group, and state of origin subgroups where $n \geq 2$; formal inferential tests were not conducted given the exploratory, descriptive nature of the study and the small subgroup sizes in certain strata. Accordingly, all findings are reported at the descriptive level and interpreted with due caution regarding generalization.

Results

Sample Characteristics

Table 1 presents the full case-level profile of the 30 participants. Table 2 summarizes the descriptive statistics across key variables.

Sex Distribution

Of the 30 participants, 27 (90.0%) were male, and 3 (10.0%) were female, yielding a MFR of 9:1. All three female participants (LBC-009, LBC-022, LBC-024) were from different geographic locations (Nagpur, Yavatmal, Balaghat), precluding any location-specific interpretation of female under-representation. Two of the three female cases were classified as mild severity; one was classified as moderate.

Age at Presentation

Participant ages at registration ranged from 2 years 2 months to 7 years 11 months. The mean age was 57.4 months (SD = 17.5; approximately 4 years 9 months), and the median age was 55.5 months. Three participants (10.0%) were aged 3 years or younger at the time of registration. The youngest recorded case (LBC-023) was 2 years 2 months; the other two cases were LBC-018 (2 years 11 months) and LBC-029 (2 years 10 months), suggesting a small but meaningful subset with earlier diagnostic pathways. The majority ($n = 27$; 90.0%) presented after the age of 3.

Geographic Catchment and State Distribution

Patients at LBC were registered from 16 distinct locations across four Indian states, with location data now complete for the full sample ($N = 30$). Maharashtra accounted for the largest proportion ($n = 22$; 73.3%), followed by MP ($n = 6$; 20.0%), CG ($n = 1$; 3.3%), and UP ($n = 1$; 3.3%). Within MH, Nagpur was the most frequent location ($n = 9$; 30.0% of total), followed by Amravati ($n = 3$) and Yavatmal ($n = 3$). Gadchiroli, a predominantly tribal, economically marginalized district designated as a Left Wing Extremism-affected region by the

Table 1: Case-level profile of the ASD cohort at LBC (*N* = 30)

Case ID	*Age*	*Sex*	*Location (State)*	*ISAA category (Score)*
LBC-001	4 y 0 m	M	Amravati, MH	Moderate (109)
LBC-002	4 y 6 m	M	Dhamangaon, MH	Moderate (121)
LBC-003	5 y 6 m	M	Nagpur, MH	Moderate (107)
LBC-004	5 y 9 m	M	Mul, MH	Mild (86)
LBC-005	5 y 0 m	M	Gadchiroli, MH	Moderate (113)
LBC-006	5 y 0 m	M	Nagpur, MH	Moderate (119)
LBC-007	6 y 0 m	M	Chhattisgarh, CG	Moderate (123)
LBC-008	6 y 0 m	M	Amravati, MH	Moderate (108)
LBC-009	6 y 0 m	F	Nagpur, MH	Mild (74)
LBC-010	7 y 11 m	M	Chhindwara, MP	Moderate (114)
LBC-011	4 y 5 m	M	Amravati, MH	Moderate (107)
LBC-012	7 y 0 m	M	Yavatmal, MH	Mild (96)
LBC-013	4 y 6 m	M	Betul, MP	Mild (81)
LBC-014	6 y 11 m	M	Meerut, UP	Mild (76)
LBC-015	4 y 1m	M	Lakhandur, MH	Mild (91)
LBC-016	7 y 9 m	M	Dalaghat, MH	Mild (95)
LBC-017	3 y 1m	M	Nagpur, MH	Moderate (107)
LBC-018	2 y 11 m	M	Nagpur, MH	Moderate (108)
LBC-019	3 y 1m	M	Yavatmal, MH	Moderate (114)
LBC-020	5 y 1m	M	Akola, MH	Mild (90)
LBC-021	4 y 1m	M	Nagpur, MH	Mild (71)
LBC-022	3 y 1m	F	Yavatmal, MH	Mild (79)
LBC-023	2 y 2 m	M	Seoni, MP	Moderate (113)
LBC-024	5 y 2 m	F	Balaghat, MP	Moderate (116)
LBC-025	3 y 10 m	M	Jabalpur, MP	Mild (90)
LBC-026	5 y 3 m	M	Nagpur, MH	Moderate (120)
LBC-027	3 y 7 m	M	Gadchiroli, MH	Mild (84)
LBC-028	4 y 9 m	M	Nagpur, MH	Moderate (118)
LBC-029	2 y 10 m	M	Nagpur, MH	Mild (102)
LBC-030	4 y 2 m	M	Seoni, MP	Moderate (123)

CG, Chhattisgarh; ISAA, Indian Scale for Assessment of Autism; LBC, Little Brain Center; MH, Maharashtra; MP, Madhya Pradesh; UP, Uttar Pradesh

Table 2: Descriptive statistics—demographic and clinical variables (*N* = 30)

Variable	*Value/Frequency*	*Notes*
Total sample	*N* = 30	—
Sex: Male	27 (90.0%)	—
Sex: Female	3 (10.0%)	—
MFR	9:1	—
Age range	2 y 2 m–7 y 11 m	—
Mean age (months)	57.4 months (4.78 years)	SD = 17.5
Median age (months)	55.5 months	—
ISAA score range	71 – 123	*n* = 30
Mean ISAA score	101.83	SD = 16.08
Median ISAA score	107.0	—
ISAA: Mild (70–106)	13 (43.3%)	Numeric ISAA available for all cases (*N* = 30)
ISAA: Moderate (107–153)	17 (56.7%)	Numeric ISAA available for all cases (*N* = 30)
ISAA: Severe (>153)	0 (0%)	—
States represented	4 states	MH, MP, CG, UP
Unique locations	16	Across four states
MH cases	22 (73.3%)	—
MP cases	6 (20.0%)	—
CG cases	1 (3.3%)	—
UP cases	1 (3.3%)	—
Location unrecorded	0 (0%)	All 30 cases have recorded location
Urban residence	20 (66.7%)	Of 30 (full sample)
Rural residence	10 (33.3%)	Of 30 (full sample)

CG, Chhattisgarh; ISAA, Indian Scale for Assessment of Autism; MFR, male-to-female ratio; MH, Maharashtra; MP, Madhya Pradesh; UP, Uttar Pradesh

Government of India, contributed two cases, both classified as moderate severity, indicating that diagnostic pathways are being activated even from highly underserved contexts.

Twenty cases (66.7%) were from urban areas; 10 (33.3%) from rural areas, with residence type now recorded for the complete sample (*N* = 30). Table 3 provides the full location-level breakdown of the catchment profile.

Discussion

Principal Findings

This study offers the first published retrospective clinical description of ASD patients registered at a private tertiary neurodevelopmental center in Central India. Three findings stand out as clinically and epidemiologically significant: (a) a MFR of 9:1, substantially exceeding globally and nationally reported benchmarks; (b) a multi-state geographic catchment spanning 16 locations across MH, MP, CG, and UP, indicating that LBC functions as a *de facto* regional diagnostic hub for a population with no local access to specialist ASD care; and (c) a severity distribution concentrated entirely within mild and moderate ISAA categories, with a mean numeric score of 101.83 (now available for the full sample of 30 cases), consistent with earlier clinical presentation but potentially reflecting detection bias favoring more overtly symptomatic presentations.

The MFR: Magnitude and Implications

The observed 9:1 MFR significantly exceeds the meta-analytically derived global estimate of approximately 3:1–4:1 and is higher than most published Indian clinical series. Multiple converging explanations warrant consideration.[9] First, at the biological level, male sex is an established risk factor for ASD through mechanisms including the female protective effect hypothesis and sex-differential gene dosage effects.[9] Second, at the clinical and ascertainment level, autistic females frequently present with less overt behavioral symptoms, engage in more sophisticated social camouflaging strategies, and are less likely to be referred for specialist assessment by schools or pediatricians, particularly in contexts where awareness of the female ASD phenotype

Table 3: Geographic catchment profile of LBC ASD cohort location-level breakdown

Location	*n*	*Urban/ Rural*	*State*	*Note*
Nagpur	9	Urban	MH	Tertiary referral hub; highest single-city count
Amravati	3	Urban	MH	Divisional HQ; 160 km from LBC
Yavatmal	3	Urban	MH	Known access gap district
Gadchiroli	2	Rural	MH	Tribal, underserved district
Seoni	2	Rural	MP	Cross-state; 130 km
Chhindwara	1	Urban	MP	Cross-state
Betul	1	Urban	MP	Cross-state; ~220 km
Balaghat	1	Urban	MP	Cross-state; ~280 km
Jabalpur	1	Urban	MP	Cross-state; ~340 km
Dhamangaon	1	Rural	MH	—
Mul	1	Rural	MH	—
Lakhandur	1	Rural	MH	—
Dalaghat	1	Rural	MH	—
Akola	1	Urban	MH	—
Meerut	1	Urban	UP	Outlier; ~900 km from LBC
CG (city NR)	1	Rural	CG	City-level data not recorded

CG, Chhattisgarh; LBC, Little Brain Center; MH, Maharashtra; MP, Madhya Pradesh; NR, Not recorded; UP, Uttar Pradesh

among frontline practitioners is limited.[10] Third, at the social and cultural level, in many Central Indian communities, parents may be less likely to seek clinical consultation for daughters exhibiting developmental differences either because atypical behavior in girls is more socially tolerable or because the opportunity costs of long-distance specialist visits are borne differently by sex. The finding that all three female cases in this cohort came from distinct geographic locations, one of which (Balaghat, MP) required a cross-state journey of approximately 280 km, adds circumstantial weight to the hypothesis that female ASD in this region is systematically under-identified and under-referred rather than genuinely rarer.

Geographic Catchment as Evidence of Diagnostic Scarcity

The geographic distribution of LBC's patient base constitutes, in itself, a form of evidence. If adequate ASD diagnostic infrastructure existed in districts like Gadchiroli, Yavatmal, Seoni, Balaghat, or Chhindwara, families would not need to travel distances of 100–340 km to reach a specialist. The presence of patients from Meerut, UP, approximately 900 km from Nagpur, likely reflects the absence of adequate pediatric autism diagnostic services in that specific family's local network rather than a geographic preference for LBC. Dey et al., in a nationwide scoping of autism community priorities, identified "access to diagnosis" as the single most consistently articulated unmet need across geographic, socioeconomic, and cultural strata.[3] The LBC catchment pattern translates that abstract finding into concrete spatial evidence: Families with autistic children in Central India are willing to travel across state boundaries for specialist assessment, and this willingness itself reflects the diagnostic void they inhabit.

The higher mean ISAA scores observed among MP cases compared to MH cases may reflect severity-based help-seeking, i.e., that families from more distant states seek specialist care only when symptom severity is sufficient to overcome the friction of travel, though this hypothesis requires larger samples for testing. It is also possible that diagnostic delay in MP leads to later presentation of more severe presentations, independent of true underlying severity distribution differences.

Severity Distribution and ISAA Score Profile

The absence of severe ISAA classifications in this cohort is noteworthy. Three possible explanations merit consideration. First, the sample may genuinely underrepresent severe ASD because the most cognitively and behaviorally impaired children are less likely to be brought to a private clinic, given both the financial costs and the lower expectation of rehabilitative benefit among caregivers. Second, the period from which digital records were drawn may pre-date systematic ISAA administration for the most severe cases; paper records containing severe cases may be present in the un-digitized portion of the archive. Third, the ISAA itself, as Manohar et al. have noted, and as diagnostic accuracy data confirm, may have floor effects for the youngest children in the cohort, potentially leading to underscoring of severity in children below 3 years.[8,11] The slightly higher mean scores among children aged ≤3 years do not support this last explanation, but are based on small subgroup sizes.

The mean ISAA score of 101.83 (SD = 16.08), now calculated across the full sample of 30 cases following completion of numeric data extraction, sits close to the ISAA development sample's mean of 106.09 across autism centers in India, consistent with a broadly comparable severity profile with a modest skew toward milder presentations.[3] The notable ISAA score spread (range: 71–123) within this ostensibly homogeneous ICD-10 F84.0 sample affirms the clinical heterogeneity of ASD presentations and the importance of severity stratification in clinical planning.

Age at Presentation

The mean presentation age of 57.4 months (approximately 4 years 9 months) replicates the pattern of diagnostic delay consistently documented in Indian clinical series and indicates that the majority of children in this cohort did not access specialist diagnostic care during the period when early intervention evidence is strongest (before 36 months). That three children (10.0%) were registered at or below the age of 3 suggests that a minority with earlier-stage awareness, more accessible referral networks, or more overt symptomatology did reach specialist assessment within the recommended window. Reducing mean age at first presentation toward the 18–36-month range, as recommended by international guidelines, requires upstream interventions at the level of primary pediatric care, Anganwadi and ASHA worker training, and community awareness challenges that exceed the capacity of any single tertiary center but for which tertiary data, such as that presented here, provide the baseline evidence.

Implications

Clinical Implications

The pronounced male-to-female imbalance in this cohort urges LBC and similar centers in Central India to develop female-sensitive screening pathways actively. This includes training clinicians in recognition of the female ASD phenotype, typically characterized by less overt repetitive behavior, greater social mimicry, and more internalized distress, and creating referral protocols that specifically include girls who present with social difficulties but do not show stereotypic male ASD presentations. The absence of severe-classified cases points to a potential detection gap at the more impaired end of the spectrum, likely concentrated in lower-income and rural households where awareness and access remain lowest.

Policy Implications

The multi-state geographic catchment of LBC carries a direct policy implication: The establishment of at least one public-sector ASD diagnostic facility in each of the districts from which LBC currently draws cross-state referrals would dramatically reduce the diagnostic burden borne by families in MP and CG. District-level public hospitals in Gadchiroli, Yavatmal, Seoni, and Balaghat represent minimum viable sites for training a neuropsychologist or trained clinical psychologist in ISAA administration and ICD-10 ASD diagnostic protocol, under a hub-and-spoke model anchored to tertiary centers like LBC. National missions under the National Mental Health Programme (NMHP) and the Ayushman Bharat scheme could support such capacity-building.

Research Implications

This study establishes an empirical baseline, the first from Vidarbha and Central India, for future analytical research. The present descriptive phase 1 findings are designed to inform the variable selection, power calculations, and hypotheses of phase 2, which will incorporate paper-based records and extend the sample to 80–100 cases with full comorbidity data, intervention histories, and complete ISAA numeric scores. The research question framing can then evolve from description to analysis, specifically examining associations between geographic distance, sex, age at presentation, and ISAA severity, with appropriate inferential statistical tests.

Limitations and Future Directions

Several limitations constrain the inferential scope of these findings. First, the sample size of 30 is insufficient for subgroup-level inferential analysis; observed differences across sex, age, and geographic subgroups must be treated as hypothesis-generating rather than confirmatory. Second, the retrospective data collection window spans several years of clinical intake at LBC, during which case-recording practices may have evolved gradually; temporal drift in how severity was documented cannot be fully excluded. This is unlikely to have materially affected the present descriptive statistics but should be borne in mind when comparing cases registered in different periods. Third, the retrospective design and reliance on clinical records preclude the collection of data on key confounders, including socioeconomic status, parental education, perinatal history, comorbid intellectual disability, and language profile. Fourth, as a private clinic sample, LBC patients likely over-represent families with financial capacity to access private specialist care and underrepresent the lowest socioeconomic strata in the catchment region. Fifth, the urban/rural classification used here relies on Census of India 2011 data and does not account for the within-urban heterogeneity of access to specialist services. Sixth, the study cannot establish causality, incidence rates, or prevalence from a clinical convenience sample.

Future research directions include as follows: Systematic extraction and analysis of LBC's 100+ paper-based records; integration of comorbidity and developmental history data; analysis of the association between distance to LBC and ISAA severity as a test of the severity-based help-seeking hypothesis; longitudinal follow-up of re-assessed cases to document ISAA score trajectory under intervention; and replication of this descriptive framework at other private and public neurodevelopmental centers in Central India to enable multi-site comparison.

Conclusion

This retrospective descriptive study provides the first empirical clinical profile of ASD patients registered at a private tertiary neurodevelopmental center in Central India. A MFR of 9:1, a geographic catchment spanning four states and 16 locations, and a mean presentation age of 57.4 months collectively document three converging diagnostic access failures: Gender-based under-referral, geographic scarcity of specialist services, and delayed community recognition. ISAA-based severity data, now available as numeric scores for all 30 cases, show a mean score of 101.83 concentrated in the mild-to-moderate range, with no severe cases documented. These findings establish a clinically grounded, empirically quantified baseline for ASD in the Vidarbha–Central India corridor and offer actionable evidence for regional diagnostic infrastructure planning, clinical protocol development, and the prioritization of female-sensitive and geographically equitable ASD services.

Clinical Significance

This study offers Central Indian clinicians an empirically grounded profile of ASD presentation at a regional tertiary neurodevelopmental center, with direct implications for early identification and referral planning. The markedly skewed MFR observed (9:1) underscores the need for heightened clinical vigilance for autism in girls, who often present with subtler, camouflaged symptoms and may otherwise be under-referred for specialist assessment. The predominance of mild-to-moderate ISAA severity at presentation, together with a mean presentation age of nearly 5 years, highlights a critical window for earlier screening within primary pediatric care, Anganwadi, and ASHA-level community health programs. The documented multi-state catchment further reinforces the practical case for decentralized diagnostic services, offering clinicians and policy planners concrete evidence to guide referral protocols and resource allocation for neurodevelopmental care across Vidarbha and adjoining states.

Ethical Approval

This study involved a retrospective review of de-identified, routinely collected clinical records and did not involve direct patient contact, intervention, or the reporting of identifiable information. In accordance with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017), retrospective, anonymized record-based studies of this nature are exempt from mandatory Institutional Ethics Committee (IEC) review. All data were fully anonymized before analysis, and no patient-identifiable information is reported anywhere in this manuscript.

Data Availability Declaration

The datasets analyzed during the current study are derived from confidential clinical records maintained at LBC, Nagpur, and are not publicly available due to patient privacy and confidentiality obligations. De-identified data may be made available by the corresponding author upon reasonable request and subject to institutional approval.

Artificial Intelligence (AI) Disclosure

During preparation of this manuscript, the authors did not use any generative AI or AI-assisted technologies to generate scientific content, data, analysis, or conclusions. Statistical analyses were conducted using standard, non-generative software. Claude AI tool was used solely for language editing, grammar checking, and formatting assistance; the authors reviewed and took full responsibility for the final content.

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Authors' Contributions

AW conceptualized and designed the study, supervised data collection, and critically reviewed the manuscript for important intellectual content. SS contributed to data extraction, statistical analysis, and drafting of the manuscript. SM contributed to the literature review, data curation, and interpretation of findings. PK contributed to data verification, formatting, and critical review of the manuscript. SH contributed to clinical data acquisition and interpretation of the neuropsychological assessment data. PJ contributed to reference verification and critical revision of the manuscript. SC contributed to data collection and clinical documentation. NJ contributed to manuscript review and administrative coordination of the study. All authors read and approved the final version of the manuscript.

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ORIGINAL RESEARCH

Predictive Utility of Pediatric Status Epilepticus Severity Score for Short- and Long-term Outcomes in Children: A Tertiary Care Longitudinal Study

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Abstract

Background and objectives: Status epilepticus (SE) represents a critical neurological emergency in pediatric patients, associated with significant morbidity and mortality. Prompt identification of individuals at risk for adverse outcomes is crucial for effective management and treatment strategies. The pediatric SE severity score (STEPSS) serves as a practical tool for early prognostic assessment in SE. This study aims to assess the efficacy of STEPSS in forecasting both short-term and long-term functional outcomes among children experiencing SE.

Materials and methods: The prospective longitudinal observational study was conducted at a tertiary care teaching hospital. Children aged 2 months to 12 years were included as future patients for SE. Whenever possible, the STEPSS was calculated at the initial presentation and before antiseizure medications were given. Short-term functional outcomes were assessed at discharge or 2 weeks after admission using the Pediatric Overall Performance Category (POPC) scale, whereas long-term functional outcomes were evaluated at 6 months using the modified Rankin scale (mRS). The relationship of STEPSS with functional outcomes was investigated using the Chi-square test, and the discriminatory ability of STEPSS was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: A total of 93 children were enrolled in the study, and 81 completed the six-month follow-up period. Most were 2 years or younger (61.7%), and there was a small percentage of males (54.3%). Generalized convulsive SE was the most common presentation (87.6%). Pediatric SE severity score was very accurate in predicting poor functional outcomes, with an area under the ROC curve (AUC) of 0.68 (95% CI: 57.8–78.2) for POPC and 0.63 (95% CI: 52.7–73.9) for the mRS. The STEPSS was generally associated with worse short-term ($\chi^2 = 9.17$, $p = 0.002$) and long-term ($\chi^2 = 4.71$, $p = 0.03$) functional outcomes.

Conclusion: At this stage of development, STEPSS is a practical bedside scoring system that offers a modest predictive value for both early and late functional outcomes of pediatric SE. More large multicenter studies are needed before routine clinical implementation.

Keywords: Modified Rankin scale, Outcome prediction, Pediatric neurology, Pediatric Overall Performance Category, Pediatric status epilepticus severity score, Status epilepticus.

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Introduction

Status epilepticus (SE) is a frequent neurological crisis observed in pediatric populations characterized by elevated morbidity rates despite advancements in critical care protocols and antiseizure treatments. The International league against epilepsy (ILAE) defines convulsive SE as continuous convulsive seizures lasting ≥5 minutes or recurrent seizures with no recovery of consciousness, and nonconvulsive SE (NCSE) as electroencephalography (EEG) confirmation when there are no obvious motor symptoms.[1,2] If recognized and treated too late, the system can suffer permanent neuronal injury, systemic complications, long hospitalization, and poor neurodevelopment. Pediatric SE is reported in every child from 10 to 73 per 100,000 a year, and is mainly associated with infants and young children. In low- and middle-income countries like India, acute symptomatic etiologies such as central nervous system (CNS) infections, metabolic disturbances, and structural brain lesions are common and often worse for neurodevelopment.[3–5] Early identification of children at risk for adverse outcomes is also important for timely management, resource allocation, and family counseling. While several prognostic scores have been proposed, the adult-based SE severity score (STESS) has limited application in children due to the different seizure characteristics and etiologies.[1,2] The pediatric SE severity score (STEPSS) was developed as a simple bedside tool that is based on readily available clinical variables (Table 1). While initial studies have shown promising predictive value, evidence from resource-limited settings remains lacking. The prospective longitudinal study was conducted to validate the utility of STEPSS in predicting short-term functional outcomes using

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Table 1: Components of the STEPSS

Variable	*Category*	*Score*
Age	≥2 years	0
	<2 years	1
Level of consciousness	Alert, somnolent or confused	0
	Stuporous or comatose	1
Seizure type	Partial, absence or myoclonic	0
	Generalized convulsive SE	1
	NCSE in coma	2
Previous seizure history	Present	0
	Absent or unknown	1
Total STEPSS score	Sum of all component scores	0–6

NCSE, nonconvulsive status epilepticus; SE, status epilepticus; STEPSS, pediatric status epilepticus severity score. Higher STEPSS scores indicate greater disease severity and an increased probability of an unfavorable clinical outcome

the Pediatric Overall Performance Category (POPC) scale and long-term functional outcomes using the modified Rankin Scale (mRS) in children with SE at a tertiary care hospital.

Materials and Methods

Study Design and Setting

This prospective longitudinal observational study was carried out in the Department of Pediatrics at Medical College and Hospital, Kolkata, India, from June 2023 to December 2024. Children eligible for enrollment in the study were recruited after written informed consent was obtained from parents or legal guardians. Children aged 2 months to 12 years were screened for SE in the same way. Status epilepticus was diagnosed according to the ILAE operational definition of continuous convulsive seizures lasting ≥5 minutes or recurrent seizures without recovery of consciousness. As clinically recommended, suspected NCSE was confirmed via EEG. We enrolled 93 children, and 81 of them completed the 6-month follow-up.

Inclusion Criteria

Children with all of the following criteria were eligible:

- Age 2 months to 12 years.
- Diagnosis of convulsive or NCSE according to the ILAE operational definition.
- Presentation during the study period.
- Provided written informed consent from a parent or legal guardian.

Exclusion Criteria

- Children were excluded if they were born with major congenital anomalies or pre-existing neurological disorders that had influenced neurological assessment.
- Lack of parental or guardian consent.
- Missing baseline clinical information required for calculation of STEPSS.
- Death within the first 24 hours of admission. Children who died within the first 24 hours were excluded since the predefined outcome measures (POPC) and mRS are not evaluated beyond the acute stages. Therefore, we were not able to assess these outcomes in this subgroup. This was already recognized as one of the likely sources of selection bias.

Sample Size

Due to the unavailability of preliminary Indian data correlating predictive performances related specifically to STEPSS during design timeframes, it was impractical to establish sample sizing requirements; hence, consecutive eligible patients encountered throughout study durations underwent convenience sampling, ultimately leading to 93 initial recruits and final outcome analyses, including solely those 81 participants who completed follow-up.

Data Collection

Demographic and clinical information, including age, sex, seizure type, seizure duration, previous seizure history, level of consciousness at admission, and probable etiology, were collected using a standardized case record form. Etiology was divided into pediatric epilepsy categories according to the pediatric epilepsy classification. The STEPSS was calculated early after admission, ideally before antiseizure medication was administered. STEPSS comprises four factors at the bedside: Age, seizure type, level of consciousness, and previous seizure history. Scores ranged from 0 to 6, with higher scores reflecting more severe cases.

Outcome Assessment

For short-term functional outcomes, which were assessed at hospital discharge or 2 weeks after admission (if not the same time), the POPC score was used. Pediatric Overall Performance Category scores of 1–2 were considered favorable, and 3–6 were unfavorable. Long-term functional outcome was measured 6 months after discharge using the mRS for outpatient visits and structured telephone interviews. Modified Rankin Scale scores of 0–2 were classified as favorable and 3–6 as unfavorable.

Statistical Analysis

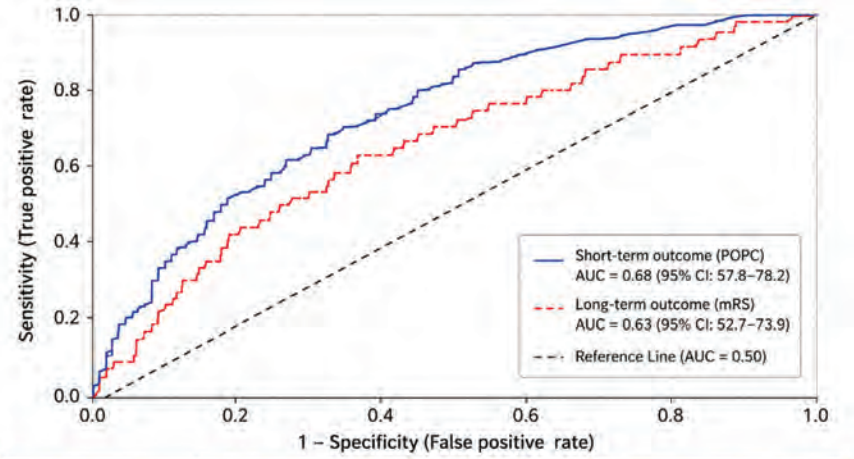
Statistical analysis was performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Continuous variables were given as mean ± standard deviation or median (interquartile range), while categorical variables were given as frequencies and percentages. The relationship between STEPSS and functional outcomes was analyzed with the Chi-square or Fisher's exact test as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of STEPSS, and the area under the curve (AUC) and 95% confidence intervals were calculated (Fig. 1). The optimal cut-off values were obtained from the Youden index. A p-value < 0.05 was considered statistically significant.

Results

In total, 93 children with SE were enrolled during the study period. Twelve of these were lost to follow-up before 6 months, leaving 81 patients (87.1%) for the final analysis.

Baseline Characteristics

The demographic and clinical characteristics of the study population are summarized in Table 2. The majority of children were aged ≤2 years (50/81, 61.7%), and 31 (38.3%) were older than 2 years. There was a slight male predominance, with 44 (54.3%) males and 37 (45.7%) females. Generalized convulsive SE was the most common seizure type, as it was diagnosed in 71 (87.6%) children, and NCSE was reported in 7 (8.6%) children. In the rest of the population, there were other seizure semiologies.



Outcome	AUC	95% Confidence interval	Predictive accuracy	Interpretation
Short-term outcome (POPC)	0.68	57.8–78.2	Moderate	Moderate discriminative ability
Long-term outcome (mRS)	0.63	52.7–73.9	Fair	Fair predictive accuracy

ROC curve analysis demonstrated that STEPSS had moderate predictive ability for short-term outcome (AUC = 0.68) and fair predictive ability for long-term outcome (AUC = 0.63).

Fig. 1: Receiver operating characteristic analysis of STEPSS. Receiver operating characteristic curves for the predictive performance of the STEPSS for short-term outcome (POPC) and long-term outcome (mRS). The AUC for short-term outcome was 0.68 (95% CI: 57.8–78.2), which indicates a moderate discriminative ability, while for long-term outcome it was 0.63 (95% CI: 52.7–73.9), indicating fair predictive accuracy. The diagonal reference line is not discriminating against (AUC = 0.5)

Table 2: Baseline characteristics

Variable	*n (%)*
Male	44 (54.3)
Female	37 (45.7)
Age ≤2 years	50 (61.7)
Age >2 years	31 (38.3)
Generalized convulsive SE	71 (87.6)
NCSE	7 (8.6)
Other seizure types	3 (3.7)

Data are presented as *n* (%), where *n* is the number of patients and % is the percentage of the total study population (*n* = 81). NCSE, nonconvulsive status epilepticus; SE, status epilepticus. Age was set at ≤2 years and >2 years at presentation. Other seizure types included focal convulsive and mixed seizure semiology

Short-term Outcome

Short-term functional outcomes based on POPC scores at either hospital discharge or 2 weeks after admission categorized patients into favorable outcomes (POPC score of 1–2) or unfavorable outcomes (POPC score of 3–6). Table 3 displays POPC score distributions. Receiver operating characteristic curve analysis indicated that STEPSS had limited ability to predict unfavorable short-term outcomes, with an AUC measuring at only 0.68 (95% CI: 57.8–78.2%). A cutoff value of STEPSS ≥3 emerged as optimal based on maximum Youden index findings; sensitivity (Sn) stood at 72%, specificity (Sp) at 60%, positive predictive value (PPV) at 62%, and negative predictive value (NPV) at 70%, respectively, as illustrated in Table 4. A significant association was observed between STEPSS categories and short-term functional outcomes ($\chi^2 = 9.17$; $p = 0.002$), indicating that children exhibiting STEPSS scores ≥3 had a greater likelihood of experiencing unfavorable short-term results compared to those with lower scores.

Table 3: Short-term functional outcome of children with SE assessed using the POPC scale (*n* = 81)

POPC score	*Functional outcome*	*Number (%)*
1	Normal function	34 (42.0)
2	Mild disability	21 (25.9)
3	Moderate disability	14 (17.3)
4	Severe disability	6 (7.4)
5	Coma or vegetative state	3 (3.7)
6	Death	3 (3.7)
Favorable outcome (POPC 1–2)		55 (67.9)
Unfavorable outcome (POPC 3–6)		26 (32.1)

Short-term outcome was assessed at hospital discharge or 2 weeks after admission, whichever occurred earlier. Pediatric Overall Performance Category scores 1–2 were considered favorable outcomes, whereas scores 3–6 were considered unfavorable outcomes. POPC, Pediatric Overall Performance Category; SE, status epilepticus

Long-term Outcome

The long-term functional outcome is measured at 6 months using the mRS. The patients were classified as having favorable (mRS 0–2) or unfavorable (mRS 3–6) outcomes. The mRS scores are shown in Table 5. The ROC analysis showed modest predictive performance of STEPSS for long-term outcome, with an AUC of 0.63 (95% CI: 52.7–73.9%) (Fig. 1). The correlation between STEPSS and long-term functional outcome was statistically significant ($\chi^2 = 4.71$, $p = 0.03$).

Discussion

In this prospective longitudinal study, we assessed the predictive value of the STEPSS in children with SE. Pediatric SE severity score

Table 4: Diagnostic performance of STEPSS in short-term outcome

STEPSS cut-off	*Sn (%)*	*Sp (%)*	*PPV (%)*	*NPV (%)*	*Youden index*
≥2	85	40	55	75	0.25
≥3	72	60	62	70	0.32
≥4	50	80	70	65	0.30

Diagnostic performance was measured to predict a poor short-term outcome. The optimal cut-off was determined using the highest Youden index, with STEPSS having the highest overall balance between Sn and Sp. NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; STEPSS, pediatric status epilepticus severity score; Youden index, sensitivity + specificity – 1

Table 5: Long-term functional outcome at 6 months assessed using the mRS ($n = 81$)

mRS score	*Functional outcome*	*Number (%)*
0	No symptoms	10 (12.3)
1	No significant disability	19 (23.5)
2	Slight disability	31 (38.3)
3	Moderate disability	9 (11.1)
4	Moderately severe disability	7 (8.6)
5	Severe disability	3 (3.7)
6	Death	2 (2.5)
Favorable outcome (mRS 0–2)		60 (74.1)
Unfavorable outcome (mRS 3–6)		21 (25.9)

Long-term functional outcome was assessed 6 months after discharge. Modified Rankin scale scores 0–2 were considered favorable outcomes, whereas scores 3–6 were considered unfavorable outcomes. mRS, modified Rankin scale

was associated with both early and 6-month functional outcomes and performed well in predicting outcomes, with AUCs of 0.68 in the POPC and 0.63 in the mRS at each time point. These results indicate that STEPSS can be a useful bedside instrument for early risk assessment, and should be added to, not replaced by, clinical assessment.[6] We found that most children in our study are younger than 2 years old (61.7%) and there is a slight male predominance (54.3%). Generalized convulsive SE was the most common (87.6%). This aligns with previous reports that SE is most prevalent in early childhood due to the increased susceptibility of the immature brain and the high incidence of acute neurological illnesses in this age group.[7,8] Neurological outcomes improved with time. 67.9% of children had favorable short-term outcomes (POPC 1–2), and 74.1% of children had positive 6-month outcomes (mRS 0–2). This indicates that neurological recovery is still possible after the acute stage and that long-term follow-up is important. Based on ROC analysis, STEPSS was found to have moderate accuracy in predicting both short- and long-term prognostic results. A score of ≥3 was the best choice for Sn and Sp, as in a previous validation study.[9,10] At this stage, STEPSS achieved 72% Sn and 60% Sp for predicting unfavorable short-term results. Although these estimates were slightly lower than previously reported, patient characteristics, etiological spectrum, referral patterns, and healthcare settings could account for the difference.[11,12] Higher STEPSS scores were significantly associated with unfavorable short-term ($\chi^2 = 9.17$, $p = 0.002$) and long-term ($\chi^2 = 4.71$, $p = 0.03$) outcomes. The results suggest that STEPSS approaches children at higher risk, and those who require more frequent monitoring and escalation of care should be considered. One of the simplest benefits of STEPSS is that it is based on clinical variables at the bedside and does not require lab tests, neuroimaging, or EEG, which is very suitable when working with limited resources.[13,14] Early detection of high-risk patients could help to plan treatment, better allocate resources, and to counsel a patient if a prognostic result is obtained. Pediatric status epilepticus severity score showed only a moderate predictive performance, and the multiple reasons for SE outcomes were different. Factors such as the etiology of the patient, seizure duration, treatment delay, neuroimaging results, EEG abnormalities, and systemic complications affect prognosis and should be considered in future prediction models. This study had several limitations. It was performed at a single tertiary center with a relatively small sample size and thus was not generalizable. There were 12 children who were lost during follow-up, and multivariable analysis was not employed. In addition, analysis of outcomes by individual etiologies was not done. Finally, our study provides external validation of STEPSS in the Indian pediatric population and supports its use as a simple bedside score for early prognostic assessment in SE. The clinical, etiological, neuroimaging and electrophysiological aspects of the prediction for neurological outcomes need to be addressed through larger multicenter studies.

Limitations of the Study

- This was a single-center study at a tertiary referral hospital with a relatively small sample size and therefore not generalizable.
- Twelve patients were lost to follow-up, so attrition bias may have been present in the long-term outcome assessment.
- The observational design was not able to control for possible confounders through multivariable analysis.
- Pediatric SE severity score was not compared to other prognostic scores, and there was no evaluation of neuroimaging, EEG findings, treatment delay, and etiological subgroups. We need larger multicenter studies to externally validate STEPSS before it can be accepted for clinical practice.

Conclusion

The STEPSS was shown to be very good at predicting short-term and long-term functional outcomes in children with SE. A score of ≥3 was the best combination of Sn and Sp for identifying those at risk of poor outcomes. As a simple bedside score based on readily available clinical conditions, STEPSS is useful for early risk stratification, especially in resource-limited settings. However, it should be applied in conjunction with a clinical assessment as a general assessment tool rather than simply as a prognostic tool. More robust multicenter prospective studies incorporating etiological, neuroimaging, electroencephalographic, and laboratory variables are needed to further validate and improve its predictive accuracy.

Clinical Significance

The Pediatric SE severity score is a practical bedside score that can be used at presentation without any laboratory testing or neuroimaging. Higher scores were significantly associated with poorer short-term and long-term outcomes. Although STEPSS has moderate predictive power, it can aid in early risk stratification, better monitoring and treatment escalation, and support caregiver counseling, especially in resource-limited settings. It should be used in addition to, not as a replacement for, comprehensive clinical assessment.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Medical College and Hospital, Kolkata (Approval No. MC/KOL/IEC/NON-SPON/2069/06/2023; 14 June 2023). Informed consent from parents or legal guardians of all children was obtained prior to enrollment.

Data Availability Declaration

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Artificial Intelligence (AI) Disclosure

The authors only used OpenAI for language editing, grammar, formatting and text, as well as for improving the readability of the manuscript. The AI tool was not used for data creation, data collection, data analysis, interpretation of the results or scientific conclusions. All the content was carefully reviewed, verified and approved by the authors. In addition, the authors are fully responsible for the accuracy and integrity of the content.

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Authors' Contributions

Prasanta Nayak: Data collection, formal analysis, methodology, and writing of the manuscript. Amrit Hazra, Sourav Nandi: Investigation and manuscript review. Kalpana Datta: Conceptualization, supervision and critical revision of the manuscript. All authors have contributed to the design and interpretation of the data and have read and approved the final manuscript.

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ORIGINAL RESEARCH

Clinical, Neurodevelopmental, and Radiological Profile of Children with Neonatal Hypoglycemic Brain Injury: A Novel Scoring System for Predicting Neurodevelopmental Outcome

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Abstract

Background: Neonatal hypoglycemic brain injury (NHBI) may cause long-term developmental, epileptic, and visual morbidity. The relationship between magnetic resonance imaging (MRI) injury burden and developmental outcome remains incompletely defined.

Objective: To describe the clinical, neurodevelopmental, and MRI profile of children with static encephalopathy attributed to NHBI and to examine the association between an MRI-based injury score and developmental quotient (DQ).

Methods: This cross-sectional study included children aged 0–5 years with static encephalopathy attributed to neonatal hypoglycemia, assessed at a tertiary child neuroscience center in Ahmedabad between August 2022 and December 2023. Development was screened with the Trivandrum Developmental Screening Chart and DQ. Magnetic resonance imaging was scored for white matter, cortical, and deep gray matter abnormalities and graded as mild (0–4), moderate (5–8), or severe (≥9).

Results: Among 92 children (mean age, 38.54 months), developmental delay (DD) was present in 71 (77.2%) and epilepsy in 67 (72.8%); 35.8% of children with epilepsy had drug-refractory epilepsy. Cortical visual impairment occurred in 54 (58.7%). Parieto-occipital injury was the commonest MRI pattern (54/92, 58.7%). Magnetic resonance imaging score correlated inversely with DQ (Pearson $r = -0.388$; 95% CI: −0.549 to −0.199; $p < 0.001$), and MRI injury grade was associated with DD severity ($p = 0.004$).

Conclusion: Neonatal hypoglycemic brain injury was associated with substantial developmental, epileptic, and visual morbidity. The study MRI score showed an association with developmental outcome but requires prospective multicenter validation before routine prognostic use.

Keywords: Cortical visual impairment, Developmental delay, Developmental quotient, Epilepsy, Hypoglycemic brain injury, Magnetic resonance imaging, Neonatal hypoglycemia.

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Introduction

Neonatal hypoglycemia is common, and severe or prolonged episodes may result in permanent brain injury. Established neonatal hypoglycemic brain injury (NHBI) is associated with developmental impairment, epilepsy, and cortical visual dysfunction.[1,2] Magnetic resonance imaging (MRI) typically shows posterior cerebral involvement, particularly in the occipital and parietal regions.[1] A practical method for quantifying MRI burden and relating it to later development may strengthen follow-up and prognostic assessment. This study describes the clinical, neurodevelopmental, and MRI profile of children with NHBI and evaluates the association between a structured MRI injury score and developmental quotient (DQ).

Methods

Study Design and Participants

This cross-sectional observational study was conducted in the outpatient department of the Royal Institute of Child Neurosciences, Ahmedabad, from August 2022 to December 2023. Children aged 0–5 years with clinical and/or radiological evidence of static encephalopathy attributable to neonatal hypoglycemia were included. Children born before 37 completed weeks of gestation, those with another established cause of static encephalopathy, inborn errors of metabolism presenting with hypoglycemia, or pre-existing structural brain malformations were excluded.

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Clinical and Developmental Assessment

Demographic and neonatal data included sex, birth weight, delivery mode, neonatal symptoms, and neonatal seizures. Neurological assessment documented head circumference, tone, dystonia, and other movement abnormalities. Development was screened using the Trivandrum Developmental Screening Chart

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across gross motor, fine motor, language, and social domains. Domain DQs were averaged; developmental delay (DD) was categorized as mild (DQ ≥ 66%), moderate (DQ 34–66%), or severe (DQ < 34%), as defined in the source study. For children above 2 years, the current DQ and DQ at 1 year of age were obtained from their previous data. Epilepsy was defined as more than one unprovoked seizure. Drug-refractory epilepsy denoted persistent seizures despite more than two adequately dosed antiseizure medications with documented compliance. Cortical visual impairment, behavioral difficulties, and autistic features were recorded clinically; no formal DSM-5 diagnostic questionnaire was used for autistic features.

MRI Assessment and Scoring

Magnetic resonance imaging examinations (1.5 or 3 T) were reviewed primarily on axial T2-weighted or FLAIR sequences. The study scoring system incorporated white matter abnormalities in the occipital, parietal, temporal, and frontal lobes and corpus callosum, including gliosis/hyperintensity, cystic change, and volume loss, together with cortical and deep gray matter involvement (including basal ganglia and thalamus). A scoring chart was formed as in Table 1. Total scores were graded as mild (0–4), moderate (5–8), or severe (≥9). In a blinded pilot assessment of 30 children by two senior neuroradiologists, inter-rater agreement was high (Cohen $\kappa = 0.84$).

Table 1: MRI Scoring system proforma

Areas involved	*Right*	*Left*
White matter		
Occipital lobe		
Gliosis (<50%) (score 1)		
Gliosis (>50%) (score 2)		
Cystic changes (score 2)		
Occipital pole (score 1)		
Parietal Lobe		
Hyperintensities/gliosis (score 1)		
Cystic changes (score 2)		
Frontal Lobe		
Hyperintensities/Gliosis (score 1)		
Cystic changes (score 2)		
Temporal Lobe		
Hyperintensities/Gliosis (score 1)		
Cystic changes (score 2)		
Corpus callosum		
Anterior thinning (score 1)		
Posterior thinning (score 1)		
Ventricles		
WM volume loss (score 1)		
Gray matter		
Cortex		
Basal ganglia		
Thalamus		

MRI, magnetic resonance imaging

Statistical Analysis

Analyses were performed in SPSS version 28. Pearson correlation assessed the association between MRI score and DQ. The association between MRI injury grade and DD severity was tested with statistical significance set at p-value < 0.05.

Results

Clinical and Neurodevelopmental Outcomes

The cohort included 92 children: 75 boys (81.5%) and 17 girls (18.5%). The mean age at assessment was 38.54 months. Seventy-five children had neonatal hypoglycemic seizures; the remaining 17 presented with reduced feeding, lethargy, or weight loss. Developmental delay was identified in 71 children (77.2%), with moderate delay predominating across infancy, toddlerhood, and early childhood (Table 2).

Focal seizures with or without aura were the most frequent seizure type (63.0% of children with epilepsy), followed by epileptic spasms (19.6%), myoclonic seizures (9.8%), and atonic seizures (6.5%). Developmental delay severity was associated with epilepsy in toddlers ($p = 0.02$) and children aged 3–5 years ($p = 0.003$), but not in infancy ($p = 0.22$).

MRI Patterns and Association with DQ

Magnetic resonance imaging showed a predominantly posterior injury pattern. Parieto-occipital involvement was most common, followed by isolated occipital involvement (Table 3). Of 10 children with extensive injury beyond the posterior regions, 8 (80.0%) had epilepsy; among those with epilepsy, 62.5% had drug-refractory epilepsy.

Based on the above patterns of injuries and their associations with DD, we graded the severity of the MRI scores into mild (0–4), moderate (5–8), and severe (≥9). These severity grades were compared with the severity of DD, which showed a statistically significant association ($p = 0.004$) between the severity of MRI

Table 2: Key clinical findings and neurodevelopmental outcomes

Outcome	*n/N (%)*
Vaginal delivery	47/92 (51.1)
Birth weight >2.5 kg	63/92 (68.5)
Documented neonatal hypoglycemic seizures	75/92 (81.5)
Developmental delay	71/92 (77.2)
Epilepsy	67/92 (72.8)
Drug-refractory epilepsy	24/67 (35.8)
Cortical visual impairment	54/92 (58.7)
Behavioral difficulties	27/92 (29.3)
Autistic features	26/92 (28.3)

Table 3: MRI injury patterns ($N = 92$)

MRI pattern	*n*	*%*
Isolated occipital involvement	24	26.1
Parieto-occipital involvement	54	58.7
Occipital-pole involvement	4	4.3
Extensive involvement	10	10.8

MRI, magnetic resonance imaging

Table 4: MRI grades vs DD in NHBI

Developmental delay severity	*MRI grades*			*p-value*
	Mild (0–4)	*Moderate (5–8)*	*Severe (≥9)*	
Mild	6	2	2	0.004
Moderate	24	32	2	
Severe	4	15	5	
Total	34	49	9	

DD, developmental delay; MRI, magnetic resonance imaging; NHBI, neonatal hypoglycemic brain injury

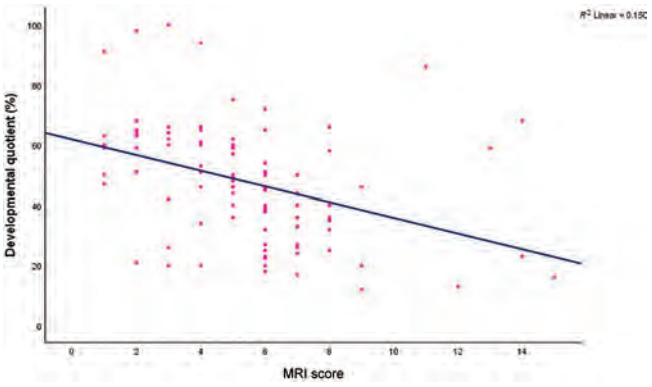


Fig. 1: Pearson correlation in NHBI

grades and DD. Detailed analysis is shown in Table 4 (MRI grades with DD).

Total MRI score correlated inversely with DQ (Pearson $r = -0.388$; 95% CI: −0.549 to −0.199; $p < 0.001$). Higher MRI injury grade was associated with more severe DD ($p = 0.004$) (Fig. 1).

Discussion

In this cohort of children with established NHBI, DD, epilepsy, and cortical visual impairment were frequent. The MRI distribution was predominantly posterior, with parieto-occipital involvement accounting for more than half of cases. These findings are consistent with the recognized vulnerability of posterior cerebral regions to neonatal hypoglycemia and support routine long-term surveillance that includes developmental, epileptic, and visual assessment.[3]

The structured MRI score was inversely associated with DQ, and categorical MRI severity was associated with DD severity. The score may therefore provide a useful research framework for expressing radiological burden in established NHBI.

Limitations

The study is limited by its cross-sectional design and tertiary referral setting, which may introduce selection and referral bias and underrepresent milder NHBI. Because the cohort comprised children with established static encephalopathy, the findings do not estimate the incidence of sequelae among all neonates with hypoglycemia. The scoring system also requires prospective validation in larger, independent multicenter cohorts, including evaluation of its ability to predict epilepsy, visual impairment, and domain-specific developmental outcomes.

Clinical Significance

Neonatal hypoglycemic brain injury was associated with substantial long-term developmental, epileptic, and visual morbidity in this cohort of 92 children. Posterior cerebral injury, especially parieto-occipital involvement, was the predominant MRI pattern. The study MRI score was associated with developmental outcome and is promising as a research tool; prospective multicenter validation is needed before routine clinical prognostication.

Declarations

Ethical Approval

This study was discussed in the Ethics Committee, but in view of the observational study no formal approval was taken for the same. However, written informed consent was obtained from the guardians of the patients for enrolling their kids into the study.

Data Availability Declaration

The results or the data generated during the study are not publicly available due to ethical and confidential restrictions, but can be obtained from the corresponding author on reasonable request.

Artificial Intelligence (AI) Disclosure

The author has used AI-assisted technologies like ChatGPT and takes full responsibility for all AI-generated content.

Acknowledgments

The authors declare that no funding, technical or administrative support was received for this study.

Authors' Contributions

All authors have read and approved the final content of the manuscript and have made significant contributions to this study.

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CASE REPORT

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease Presenting as Focal Seizures in a 5-year-old Child – A Case Report

Kuruvasangam M Kumar[1], Kulandaivel Murugiah[2], Aishwarya Aparajithan[3], Muthulakshmi Ramalingam[4], Dhinesh Ram[5], Lavaniya Ravichandran[6]

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Abstract

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an immune-mediated demyelinating disorder of the central nervous system (CNS), increasingly recognized in the pediatric population. It frequently presents as acute disseminated encephalomyelitis (ADEM), a monophasic syndrome characterized by multifocal neurological symptoms and encephalopathy.

We report a case of a 5-year-old previously healthy girl who presented with new-onset right focal seizures and irritability. Neuroimaging revealed multifocal, ill-defined, T2 FLAIR bilateral frontoparietal sulcal and subcortical hyperintensities with post-contrast enhancement suggestive of a demyelinating process. Serological testing identified the presence of myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) antibodies, confirming the diagnosis of MOGAD.

The child responded well to high-dose intravenous methylprednisolone, followed by a tapering course of oral steroids, with significant clinical improvement at follow-up.

Keywords: Acute disseminated encephalomyelitis, Case report, Demyelination, Myelin oligodendrocyte glycoprotein antibody-associated disease, Oligoclonal bands.

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Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory demyelinating disorder of the central nervous system (CNS) characterized by the presence of antibodies targeting myelin oligodendrocyte glycoprotein (MOG). Unlike multiple sclerosis (MS) and aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), MOGAD represents a distinct clinical entity with unique clinical, radiological, and immunological features.

This case report aims to contribute to the growing body of literature on MOGAD by detailing its clinical presentation, radiological and immunological profile, treatment response, and outcome.

Case Presentation

A 5-year-old developmentally normal female child presented with right focal seizures involving the right upper limb and twitching of the right side of the face. The child also exhibited irritability and behavioral changes for 2 days prior to admission. There was a history of a varicella infection 5 months earlier.

On examination, the child was drowsy but arousable, with a Glasgow Coma Scale (GCS) score of 12/15 (E3V4M5). There were no focal motor deficits, cranial nerve palsies, or signs of meningeal irritation. Fundus examination was normal.

Baseline laboratory investigations, including complete blood count, serum electrolytes, renal and liver function tests, and inflammatory markers, were within normal limits. Cerebrospinal fluid (CSF) analysis revealed acellular fluid with normal protein and glucose levels. Cerebrospinal fluid bacterial cultures, viral PCR panel, and tuberculosis workup were negative (Figs 1 and 2).

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Source of support: Nil

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.

Electroencephalogram (EEG) was normal. Magnetic resonance imaging (MRI) of the brain revealed few ill-defined revealed multifocal, ill-defined, T2 FLAIR bilateral frontoparietal sulcal and subcortical hyperintensities with post-contrast enhancement. There was no diffusion restriction or blooming on gradient echo (GRE) sequences, suggestive of demyelination. Magnetic resonance imaging of the spine and optic nerve were normal.

Given the clinical presentation, imaging features, and the absence of infectious etiology, a diagnosis of acquired demyelinating syndrome was considered. Serology was positive for

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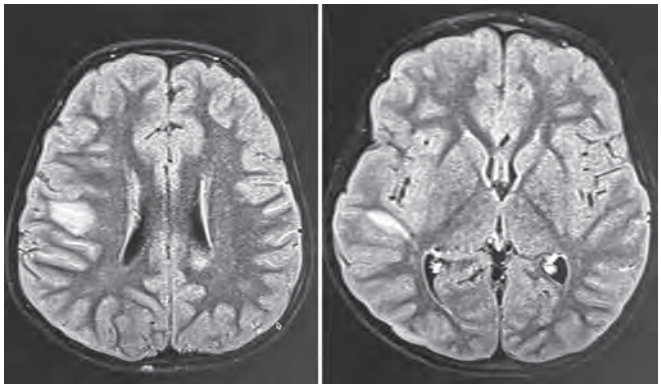


Fig. 1: Few ill-defined T2/FLAIR patchy subcortical hyperintensities with patchy enhancement on T1 post-contrast images in the right frontotemporal-parietal lobes and left parietotemporal lobes. There was no diffusion restriction or blooming on GRE sequences, suggestive of demyelination

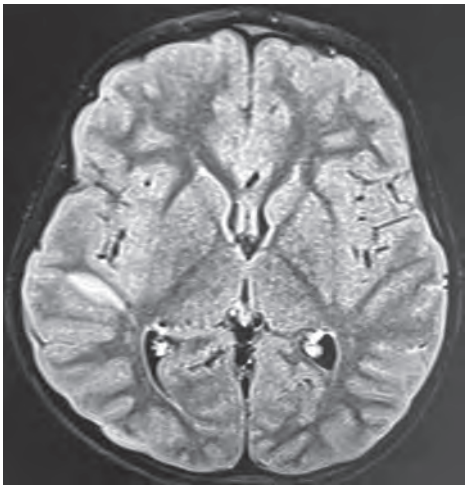


Fig. 2: Subcortical right parietal FLAIR hyperintensities

serum anti-MOG antibodies. Cerebrospinal fluid oligoclonal bands (OCBs) were also positive, confirming the diagnosis of MOGAD.

The child was started on pulse intravenous methylprednisolone at 30 mg/kg/day for 5 days, followed by a tapering course of oral prednisolone for 3 months. Seizure control was achieved with sodium valproate. The child showed rapid clinical improvement, with cessation of seizures and normalization of sensorium within 1 week.

The patient remained clinically stable and relapse-free during a 3-month follow-up period on maintenance oral steroids and antiepileptic therapy. She returned to school with good academic performance (Figs 3 and 4).

Discussion

Myelin oligodendrocyte glycoprotein is a surface protein on the myelin sheath that functions as a cellular adhesion molecule, contributing to oligodendrocyte stability and microtubule network integrity.[1] Antibodies against MOG are associated with a broad spectrum of acquired demyelinating syndromes, including optic neuritis, myelitis, acute disseminated encephalomyelitis (ADEM), NMOSD, encephalitis, and aseptic meningitis.[2]

Myelin oligodendrocyte glycoprotein antibody-associated disease is now recognized as a distinct disease entity, separate

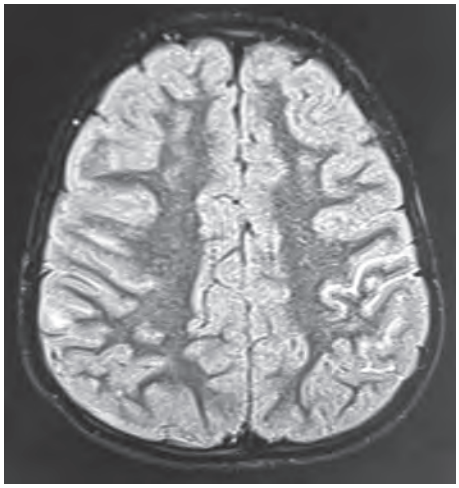


Fig. 3: The T2 FLAIR image showing bilateral frontoparietal sulcal and subcortical hyperintensities

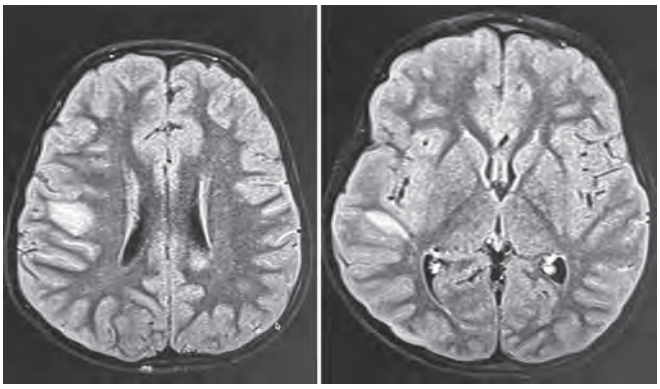


Fig. 4: Post-contrast images showing patchy enhancement in the right parietal sulci region

from MS and AQP4-IgG-positive NMOSD, with unique clinical, radiological, and immunopathological characteristics.[3] The most common manifestations of MOGAD include acute optic neuritis, with or without transverse myelitis, and ADEM, especially in younger children.[4]

Our patient presented with new-onset focal seizures and encephalopathy, in the absence of fever or infectious markers. According to the International MOGAD panel, the diagnostic approach should include neuroimaging, CSF analysis, and serum antibody testing.[5] The detection of MOG-IgG by a cell-based assay is considered the gold standard due to its high sensitivity and specificity.[6]

Typical MRI findings in MOGAD include large, confluent, poorly demarcated lesions that often resolve overtime, differentiating it from MS.[4] In this case, MRI showed patchy subcortical hyperintensities, bilateral frontoparietal hyperintensities, which, along with the clinical profile, supported the diagnosis.

An important observation in this case was the presence of OCBs in CSF. Although OCBs are classically associated with MS, they have been reported transiently in approximately 10–20% of MOGAD cases, particularly in the acute phase.[6] Unlike MS, OCBs in MOGAD do not predict chronic disease progression or relapses and are usually transient. Our patient's relapse-free course over 6 months further supports this distinction.[1]

Seizures in MOGAD are hypothesized to result from cortical irritation due to inflammatory demyelination.[7,8] Recent literature suggests that seizures, including cortical encephalitis, may be part of a distinct MOGAD phenotype in children.[8] Immunotherapy and antiepileptic drugs usually lead to good seizure control and favorable outcomes.

The early identification of MOGAD is critical, as it influences treatment strategies and prognosis.[9] Although many patients experience good recovery, some may develop residual neurological deficits, especially after severe or recurrent relapses.[10]

This case illustrates a pediatric presentation of MOGAD with ADEM-like features and transient OCB positivity. Early diagnosis using MOG-IgG serology helped prevent misdiagnosis as pediatric MS and allowed timely initiation of appropriate immunotherapy, leading to a favorable clinical outcome.

Limitations of the Study

This report describes a single case of MOGAD, and therefore the observations may not be generalizable to a wider population. In addition, long-term follow-up was limited, restricting assessment of sustained neurological and cognitive outcomes. Nevertheless, this case provides clinically relevant insights into an uncommon presentation of MOGAD with focal seizures.

Conclusion

Myelin oligodendrocyte glycoprotein antibody-associated disease should be considered in the differential diagnosis of children presenting with acute focal seizures and encephalopathy, especially when neuroimaging suggests demyelination. Although oligoclonal band positivity is typically associated with MS, it can occasionally occur transiently in MOGAD without indicating a relapsing course. Prompt diagnosis and timely initiation of immunotherapy are crucial to achieving excellent clinical recovery and favorable long-term outcomes.

Clinical Significance

This case emphasizes that MOGAD can present with focal seizures and encephalopathy in young children, even in the absence of overt infectious features. Recognition of this presentation is important to avoid misdiagnosis as epilepsy or pediatric multiple sclerosis. Early serological testing and timely initiation of immunotherapy can result in excellent neurological recovery and favorable outcomes.

Ethical Approval

Formal ethical approval was not required for this case report as per institutional policy, as it involves a single patient with no identifiable information disclosed. Written informed consent for publication of clinical details and accompanying images was obtained from the patient's parent(s)/legal guardian(s). The study complies with the principles of the Declaration of Helsinki.

Data Availability Declaration

- No new data were generated or analyzed in this study.

Acknowledgments

The authors declare that no funding, technical, or administrative support was received for this study.

Authors' Contributions

- Case acquisition: Prof Dr Kulandaivel.
- Patient management: Prof Dr Kulandaivel.
- Data curation: Dr Manoj Kumar.
- Literature review: Dr Aishwarya.
- Writing – Original draft: Dr Aishwarya.
- Writing – Review and editing: Prof Dr Kulandaivel, Dr Aishwarya
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CASE REPORT

A Tale of Two Infants with Early Motor Delay and Dystonia: Unmasking a Neurotransmitter Transporter Defect behind a Normal Magnetic Resonance Imaging – A Case Report

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Abstract

Infantile dystonia with hypotonia and normal magnetic resonance imaging (MRI) often leads clinicians through an exhausting diagnostic maze. We report two infants who presented with axial hypotonia and dystonia, preserved cognition, and normal neuroimaging, ultimately diagnosed with *SLC18A2* vesicular monoamine transporter 2 (VMAT2) deficiency. The first child failed to respond to levodopa and worsened with pramipexole but improved modestly with trihexyphenidyl. The second exhibited partial benefit with pramipexole after failing levodopa. Both highlight the importance of considering neurotransmitter storage disorders in "dystonic cerebral palsy (CP) mimics." Vesicular monoamine transporter 2 deficiency differs from dopamine-synthesis defects by its lack of levodopa response and variable dopamine-agonist sensitivity. When biochemical neurotransmitter testing is unavailable, sequential drug trials and genetic confirmation remain practical diagnostic strategies.

Keywords: Case report, Dystonic cerebral palsy mimic, Infantile dystonia, Neurotransmitter disorder, *SLC18A2*, Vesicular monoamine transporter 2 deficiency.

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Introduction

Infants presenting with motor delay and dystonia but normal neuroimaging frequently raise suspicion for dystonic cerebral palsy. However, when perinatal and structural causes are excluded, a neurotransmitter disorder (NTD) or genetic basal-ganglia disease should be considered.

Most dopaminergic NTDs—*GCH1*, *TH*, and *SPR*—represent synthesis defects and are dramatically responsive to levodopa.[1] In contrast, *SLC18A2* vesicular monoamine transporter 2 (VMAT2) deficiency is a storage/transport defect, producing infantile parkinsonism-dystonia largely unresponsive to levodopa and variably responsive to dopamine agonists.[2]

We describe two infants who exemplify a structured diagnostic approach to "early dystonia with normal magnetic resonance imaging (MRI)," highlighting therapeutic trials, molecular confirmation, and differing treatment responses.

Case Description

Case 1

A 4-month-old boy, born at term (2.8 kg) of nonconsanguineous parents, presented with poor head control and drooling. Sucking and swallowing were intact. Anthropometry was normal (weight: 5.8 kg; head circumference: 40 cm, within normal range).

Neurological examination revealed truncal > appendicular hypotonia, preserved reflexes, and dystonia (oromotor and limb). Eye contact, social smile, and visual tracking were appropriate.

Routine investigations [complete blood count (CBC), electrolytes, calcium profile, creatine phosphokinase (CPK), homocysteine, uric acid] and MRI brain were normal. Given the pattern of central hypotonia with dystonia and a normal MRI, a NTD was suspected.

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Source of support: Nil

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.

A levodopa/carbidopa (Syndopa Plus) trial for 1 month yielded no benefit. Subsequent trihexyphenidyl (Bexol) therapy produced mild improvement in dystonia and limb control.

Tandem mass spectrometry and serum prolactin were normal. Whole-exome sequencing revealed a homozygous likely pathogenic variant in *SLC18A2* (exon 14, c.1208T>A; p.Met403Lys); both parents were heterozygous carriers.

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A pramipexole trial resulted in worsening rigidity and irritability, necessitating withdrawal. The child stabilized on trihexyphenidyl and physiotherapy. At 12 months, he remained hypotonic but socially interactive.

Case 2

A 3-month-old boy with an unremarkable perinatal history presented with severe oromotor and appendicular dystonia and head lag but normal social interaction and tracking. Reflexes were brisk. Magnetic resonance imaging brain and basic metabolic tests were normal.

After levodopa/carbidopa failure, further evaluation [Tandem mass spectrometry (TMS), prolactin] was normal. Whole-exome sequencing identified compound heterozygous pathogenic variants in *SLC18A2*:

- Exon 3: c.169dup (p.Ala57GlyfsTer27)
- Exon 15: c.1395del (p.Leu466SerfsTer40)

Each parent carried one variant. Diagnosis: Vesicular monoamine transporter 2 deficiency (autosomal recessive).

A pramipexole trial achieved partial dystonia reduction and improved hand use at 6-month follow-up, documented using the Barry–Albright Dystonia Scale.[3] Motor delay persisted.

Discussion

These infants represent the quintessential diagnostic dilemma of early dystonia with normal neuroimaging. When structural, metabolic, and perinatal causes are excluded, clinicians should suspect a monoaminergic NTD.

Diagnostic Approach

- Normal MRI: Excludes basal-ganglia lesions or hypoxic injury.
- Brisk reflexes, preserved cognition: Favor central hypotonia over neuromuscular pathology.
- Lack of levodopa response: Argues against dopamine-synthesis defects.
- Genetic confirmation: Critical when cerebrospinal fluid (CSF) neurotransmitter assay [homovanillic acid (HVA), 5-HIAA] is unavailable, as in our setting.

Pathophysiology

Vesicular monoamine transporter 2, encoded by *SLC18A2*, transports dopamine, serotonin, and norepinephrine into synaptic vesicles. Loss-of-function mutations cause vesicular monoamine depletion, leaving synthesis intact but release impaired.[2] Consequently, levodopa fails—dopamine cannot be stored or released—whereas dopamine agonists (e.g., pramipexole) may variably activate postsynaptic receptors.[4] Vesicular monoamine transporter 2 deficiency represents a "packaging failure" — monoamines are synthesized but not released effectively. Other NTDs are "production failures" — neurotransmitters are not synthesized at all.

Therapeutic Variability

Our first case deteriorated on pramipexole but improved modestly with trihexyphenidyl, while the second showed partial benefit with pramipexole. This variability has also been noted in previous reports, likely reflecting residual transporter activity or receptor sensitivity.[2,5]

Although CSF neurotransmitter analysis remains the diagnostic gold standard, whole-exome sequencing offers a pragmatic first-line approach when biochemical assays are inaccessible.[5] Early identification guides therapy, counseling, and prognosis.

Limitations

This report is limited by the small number of cases and the absence of cerebrospinal fluid neurotransmitter analysis. However, genetic confirmation and therapeutic response patterns provide strong diagnostic support.

Conclusion

Early dystonia with hypotonia and a normal MRI mandates evaluation beyond cerebral palsy. *SLC18A2* (VMAT2) deficiency represents a dopamine-storage disorder distinguishable from levodopa-responsive NTDs. Sequential pharmacologic trials—levodopa, dopamine agonist, and anticholinergic—coupled with timely genetic testing, provide a cost-effective diagnostic route.

Our two contrasting cases expand the phenotypic spectrum, emphasizing that dopaminergic responsiveness in VMAT2 deficiency is variable rather than absent, and that a thoughtful, stepwise approach remains the neurologist's most valuable tool.

Clinical Significance

This case report highlights vesicular monoamine transporter 2 deficiency as an important and often overlooked cause of early-onset dystonia with normal neuroimaging.

Ethics Approval and Consent to Participate

Ethics committee approval was not required for this study as it is a descriptive case report. Written informed consent for publication was obtained from the parents or guardians of the patients.

Data Availability Declaration

No new data were generated or analyzed in this study.

Acknowledgments

The authors declare that no funding, technical, or administrative support was received for this study.

Authors' Contributions

Case acquisition: Dr Nishant Rathod and Dr Vishal Patel.
Patient management: Dr Nishant Rathod and Dr Vishal Patel.
Data curation: Dr Nishant Rathod.
Literature review: Dr Nishant Rathod.
Writing – Original draft: Dr Nishant Rathod.
Writing – Review and editing: Dr Chetan Bhalgamiya.
Visualization/Figures: Dr Nishant Rathod.
Supervision: Dr Nishant Rathod.

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CASE REPORT

Genetic Testing in Pediatric Neurology: A Case-based Approach to *PLA2G6*-associated Disorders

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Abstract

Genetic disorders represent a significant subset of pediatric neurology, often presenting diagnostic and management challenges. Here, we report three cases of pediatric patients presenting with neurodevelopmental delay and neurodegeneration, later diagnosed with mutations in the *PLA2G6* gene. The first case involves a 1-year-6-month-old female diagnosed with neurodegeneration with brain iron accumulation-2A (NBIA-2A), the second case is a 2-year-old male diagnosed with infantile neuroaxonal dystrophy (INAD), and the third case is a 4-year 6-month-old female presenting with progressive neuroregression and motor difficulties, with genetic findings consistent with *PLA2G6*-related neurodegeneration. All conditions were confirmed via next-generation sequencing (NGS), emphasizing the role of genetic testing in achieving accurate diagnoses, guiding clinical management, and informed family planning. This report discusses clinical presentations, genetic findings, diagnostic methodologies, and their implications for personalized care in pediatric neurology. Genetic counseling is essential in *PLA2G6*-related neurodegeneration to explain the diagnosis, inheritance, prognosis, and recurrence risks, while supporting informed family decisions.

Keywords: Case report, Genetic counseling, Genetic testing, Neurodegeneration, Pediatric neurology, *PLA2G6*.

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Introduction

Genetic neurological disorders constitute a significant subset of pediatric neurology, often presenting with clinical heterogeneity that complicates diagnosis and management. Traditional diagnostic modalities, including neuroimaging and metabolic studies, are frequently insufficient to establish definitive diagnoses, particularly in early disease stages.[1] The emergence of next-generation sequencing (NGS), including whole-exome sequencing (WES), has revolutionized the diagnostic landscape by enabling the identification of pathogenic variants that would otherwise remain undetected. The *PLA2G6* gene encodes group VI phospholipase A2, an enzyme essential for phospholipid metabolism and membrane remodeling. Pathogenic variants in *PLA2G6* are implicated in autosomal recessive neurodegenerative disorders, including NBIA-2A and infantile neuroaxonal dystrophy (INAD).[2] Neurodegeneration with brain iron accumulation-2A is typically characterized by progressive dystonia, Parkinsonism, and cognitive decline due to iron accumulation in the basal ganglia.[2,3] In contrast, INAD presents within the first 2 years of life with developmental regression, hypotonia, and cerebellar atrophy, ultimately leading to severe neurodegeneration.[4] Despite their distinct phenotypes, both disorders share overlapping molecular mechanisms, including oxidative stress and mitochondrial dysfunction, which contribute to progressive neuronal damage.[5] Given the autosomal recessive inheritance pattern of these disorders, genetic confirmation is essential not only for diagnostic purposes but also for genetic counseling, risk assessment in family members, and potential future therapeutic interventions. This report presents three pediatric cases of *PLA2G6*-associated neurodegeneration diagnosed via WES, emphasizing the critical role of genetic testing in pediatric neurology.[6]

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

Clinical Description

Case 1

A 1-year-6-month-old female was born to consanguineous parents and evaluated at the pediatric neurology clinic due to concerns of developmental delay, speech delay, and hypotonia. Clinical examination revealed hyperextensible knees, irritability, and dysmorphic facial features, including sparse eyebrows, mild frontal bossing, arched eyebrows, and up-slanted palpebral fissures. Developmental history showed delayed acquisition of

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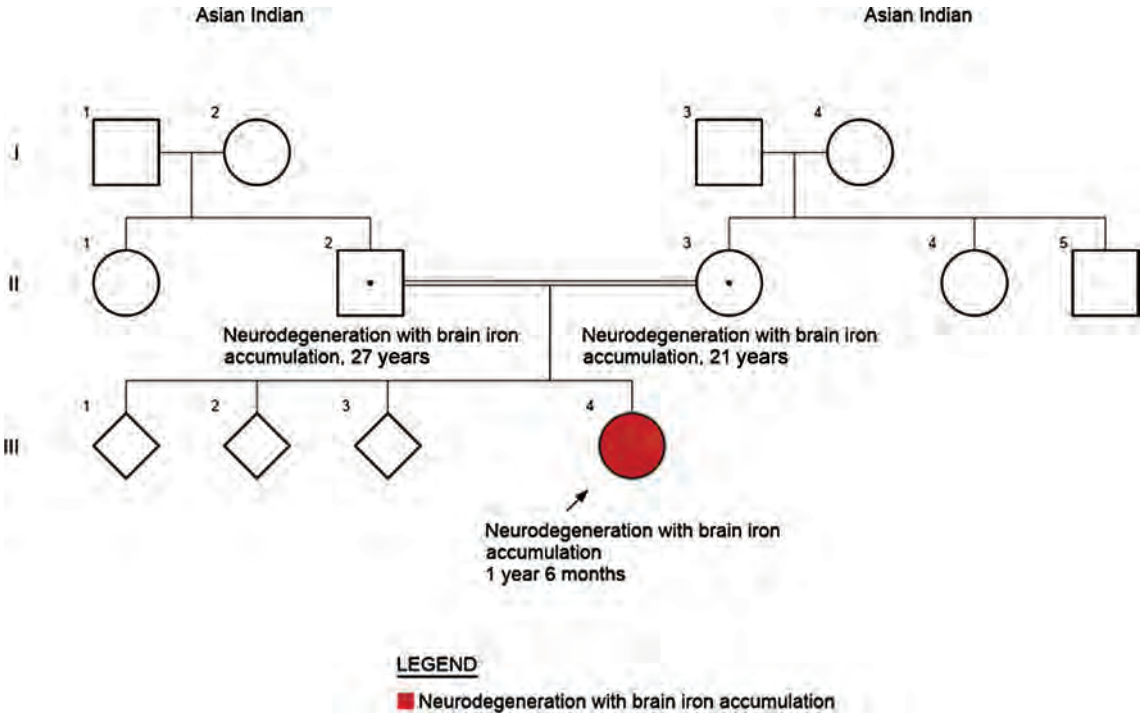


Fig. 1: Showing the three-generation family pedigree of case 1

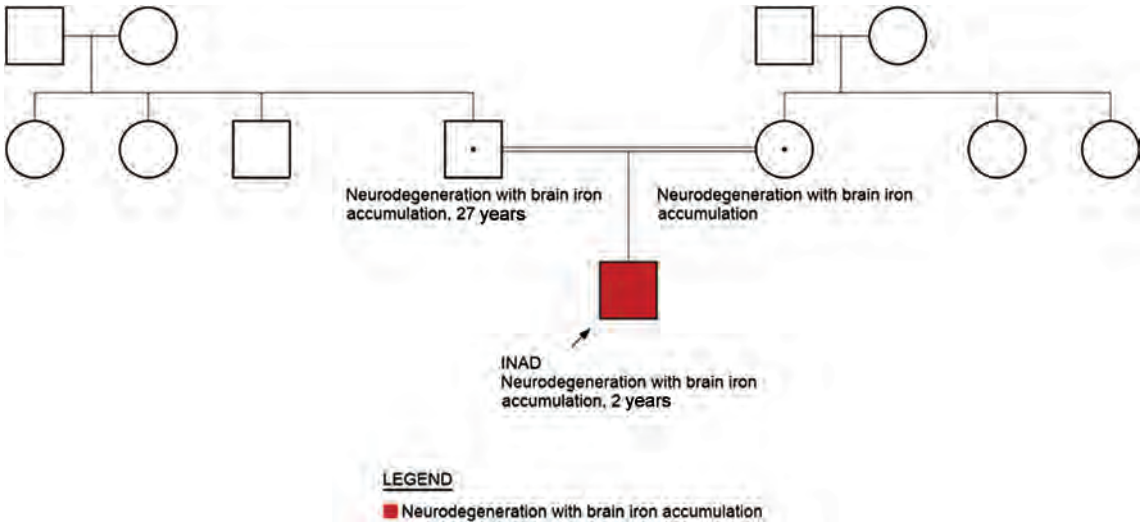


Fig. 2: Showing the three-generation family pedigree of case 2

both motor and language milestones. Neuroimaging with brain magnetic resonance Imaging (MRI) showed mild cerebellar atrophy but lacked evidence of iron deposition in the basal ganglia. Given the presence of clinical history and consanguinity, a genetic etiology was suspected (Fig. 1). Whole-exome sequencing identified a homozygous pathogenic *PLA2G6* splice-site mutation (c.1427+1G>A), which has been previously associated with NBIA-2A.[6] Segregation analysis confirmed that both parents were heterozygous carriers of this variant. Although NBIA-2A is often characterized by radiological evidence of basal ganglia iron accumulation, early-stage disease may not exhibit these findings, highlighting the necessity of genetic confirmation for accurate diagnosis.[7]

Case 2

A 2-year-old male, born to consanguineous parents, was referred to the pediatric neurology department due to developmental regression, seizures, and hypotonia (Fig. 2). The child had previously attained gross motor milestones, including independent sitting and standing, but had lost these abilities over a period of 6 months. Neurological examination revealed cerebellar signs such as ataxia and tremors. Brain MRI demonstrated cerebellar atrophy, white matter changes, and hypoplasia of the inferior vermis, suggestive of a Dandy–Walker variant. Given the consanguineous background and progressive neurological decline, genetic testing was pursued. WES revealed a homozygous likely pathogenic *PLA2G6* missense mutation

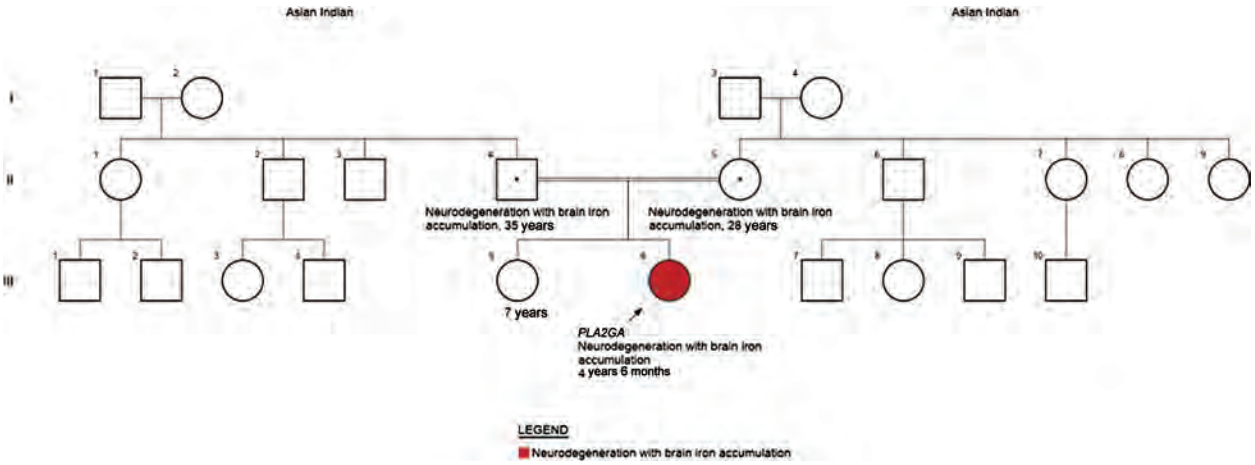


Fig. 3: Showing the three-generation family pedigree of case 3

(c.985C>T), consistent with INAD.[8] Segregation analysis confirmed that both parents were heterozygous carriers of this variant.

Case 3

A 4-year-6-month-old female, born to non-consanguineous parents, presented with clinical features of neuroregression (Fig. 3), frequent falls, lumbar lordosis, saccadic slouching, pyramidal signs, imbalance while walking, difficulty in squatting, pseudohypertrophy of calf muscles, toe walking, waddling gait, and a positive Gower sign. On observation, she exhibited mild tremors, gait abnormality, and suspected lordosis, with no gross dysmorphism. Birth history was uneventful. Magnetic resonance Imaging brain was reported as normal, and biochemical evaluation, including acylcarnitine and amino acid profiles, was within normal limits. However, serum creatine phosphokinase (CPK) was mildly elevated (311 IU/L). Whole-exome sequencing revealed compound heterozygous variants in the *PLA2G6* gene: One pathogenic variant (c.2222G>A) and one variant of uncertain significance (c.221T>C). Mutations in *PLA2G6* are associated with NBIA2B or INAD. Although the MRI was normal, the clinical phenotype strongly correlated with *PLA2G6*-related neurodegeneration, particularly given the genetic findings. Parental segregation was performed, and the pathogenic heterozygous variant (c.2222G>A) was detected in the father, and a heterozygous variant of uncertain (c.221T>C) was detected in the mother in the *PLA2G6* gene.

Management and Outcome

Across all three cases, the establishment of a genetic diagnosis played an important role in guiding clinical management, anticipatory care, and family counseling. In each scenario, confirmation of *PLA2G6*-associated neurodegeneration enabled early initiation of supportive therapies and long-term monitoring. Management was largely symptomatic and multidisciplinary, including physiotherapy to maintain mobility, occupational therapy for motor skills and daily functioning, speech and communication therapy where indicated, and regular neurological assessments to monitor progression. Seizure management, nutritional support, orthopedic evaluation for gait abnormalities or contractures, and palliative care planning were incorporated based on individual clinical needs.

Genetic counseling formed the cornerstone of family support in all cases. Families were counseled regarding the autosomal recessive inheritance pattern, the 25% recurrence risk for future pregnancies, and the implications of confirmed variants. Parental segregation analysis was important to clarify variant interpretation and enable accurate reproductive risk assessment. All families were informed about available reproductive options, including targeted prenatal diagnosis [chorionic villus sampling (CVS) or amniocentesis] and preimplantation genetic testing (PGT-M) for future pregnancies. The progressive and neurodegenerative nature of *PLA2G6*-associated disorders was discussed sensitively, ensuring parents understood the expected clinical course and the importance of early supportive interventions.

Discussion

The cases presented in this report emphasize the pivotal role of genetic testing in diagnosing rare pediatric neurodegenerative disorders. The clinical heterogeneity of *PLA2G6*-associated conditions necessitates molecular confirmation to achieve an accurate diagnosis and optimize patient care (Table 1). Traditional diagnostic methods, including neuroimaging and biochemical studies, may provide supportive evidence but often lack the specificity required for definitive diagnosis, particularly in early disease stages (Fig. 4).

Neurodegeneration with brain iron accumulation-2A and INAD represent two ends of the *PLA2G6*-associated neurodegenerative spectrum. Neurodegeneration with brain iron accumulation-2A typically manifests later in childhood with dystonia, Parkinsonism, and cognitive decline, often accompanied by radiological evidence of brain iron accumulation.[4,9] In contrast, INAD presents in infancy with developmental regression, hypotonia, and progressive cerebellar atrophy, leading to severe neurodegeneration.[10] The cases described in this report demonstrate that while neuroimaging findings can be helpful, genetic testing remains the gold standard for diagnosis.

The integration of NGS into pediatric neurology practice has significantly improved diagnostic accuracy, reduced diagnostic delays, and facilitated personalized management strategies. Beyond diagnosis, genetic testing also plays a critical role in reproductive counseling, allowing affected families to make informed decisions regarding future pregnancies. Emerging research into targeted therapies, including gene-editing techniques such as CRISPR-Cas9, RNA-based therapies, and treatments targeting mitochondrial dysfunction, may offer future therapeutic avenues for *PLA2G6*-associated disorders.[11] Genetic counseling

Table 1: Clinical, imaging, and genetic features of the three cases

Feature	*Case 1 (NBIA-2A)*	*Case 2 (INAD)*	*Case 3 (PLA2G6-related neurodegeneration)*
Age at presentation	1 year 6 months	2 years	4 years 6 months
Sex	Female	Male	Female
Consanguinity	Yes	Yes	No
Initial symptoms	Developmental delay, speech regression, hypotonia, irritability	Developmental regression, seizures, hypotonia, tremors	Neuroregression, falls, lordosis, waddling gait, calf pseudohypertrophy, Gower sign+
Neurological examination	Hypotonia, facial dysmorphism	Hypotonia, cerebellar dysfunction, ataxia	Pyramidal signs, tremors, abnormal gait, and posturing
MRI findings	Mild cerebellar atrophy, no iron deposition	Cerebellar atrophy, WM changes, vermis hypoplasia	Normal
Genetic findings	*PLA2G6* homozygous splice-site mutation (c.1427+1G>A)	*PLA2G6* homozygous missense mutation (c.985C>T)	*PLA2G6* compound heterozygous: c.2222G>A (pathogenic), c.221T>C (VUS)
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive
Disease category	NBIA-2A	INAD	*PLA2G6*-related neurodegeneration (spectrum)
Management approach	Supportive care, physiotherapy, and genetic counseling	Supportive care, seizure management, and genetic counseling	Supportive multidisciplinary care, physiotherapy, counseling, and reproductive planning
Prognosis	Progressive neurodegeneration, variable severity	Rapid progression, poor prognosis	Progressive, supportive management only

INAD, infantile neuroaxonal dystrophy; NBIA-2A, neurodegeneration with brain iron accumulation-2A

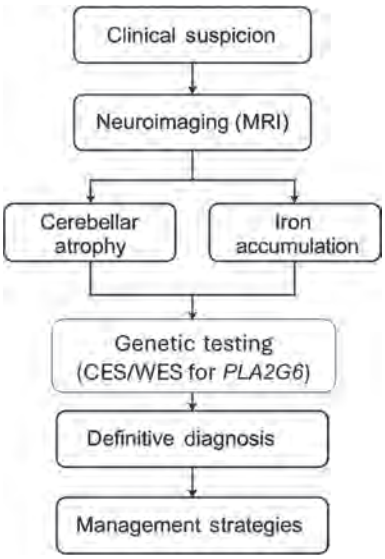


Fig. 4: Diagnostic algorithm for *PLA2G6*-associated neurodegeneration
CES, clinical exome sequencing; WES, whole exome sequencing

plays a crucial role in these cases by helping the families understand the diagnosis, inheritance pattern, recurrence risk, and potential outcomes associated with *PLA2G6*-related neurodegeneration. It also provides psychosocial support and guides informed decision-making regarding future pregnancies and available management strategies.[11,12]

Limitation(s) of the Study

This article is limited by the small sample size and lack of long-term clinical follow-up. Functional studies to assess the pathogenicity of the identified *PLA2G6* variants were not performed.

Conclusion

The cases presented in this report emphasize the pivotal role of genetic testing in diagnosing rare pediatric neurodegenerative disorders. We describe three cases of *PLA2G6*-associated neurodegeneration with variable clinical presentations. The use of WES facilitated accurate diagnosis, enabled targeted management strategies, and provided crucial genetic counseling for affected families. Given the growing recognition of genetic contributions to pediatric neurological conditions, routine integration of NGS-based diagnostic approaches is essential for improving patient outcomes. Further research into genotype-phenotype correlations and potential therapeutic interventions will be critical in advancing the field of pediatric neurogenetics. Genetic counseling is essential in these cases, as it enables the families to clearly understand the confirmed diagnosis, its mode of inheritance, the associated recurrence risks, and the likely clinical trajectory of *PLA2G6*-related neurodegeneration. It also offers important psychosocial support while helping the parents make informed choices about future pregnancies, reproductive options, and appropriate management options.

Clinical Significance

The study highlights the importance of early genetic testing in children with unexplained neurodevelopmental regression and movement disorders. Timely molecular diagnosis facilitates accurate disease classification, multidisciplinary management, prognostic assessment, and informed genetic counseling for affected families.

Lessons Learnt

- Genetic testing is essential in neurogenerative disorders – WES enables early and accurate diagnosis, especially when neuroimaging is inconclusive.

- Genetic counseling is critical – Early diagnosis supports better management, psychological and emotional support and informed reproductive decisions.
- Need for targeted therapies – Advancements in gene-editing and neuroprotective strategies hold future promise.

Declarations

Ethical Approval

Nil.

Data Availability Declaration

Available with correspondence author.

Artificial Intelligence (AI) Disclosure

No AI tools were used in the generation, analysis, or interpretation of the clinical data presented in this manuscript. Artificial intelligence-assisted language editing was used only for grammatical refinement and manuscript organization.

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Authors' Contributions

Prashant Utage: Concept of the study.
Nadir Aman: Manuscript draft, Manuscript editing.
Aparna Utage: Data collection, Drafting the manuscript.
Veeresh Maynal: Drafting the manuscript.
Vaibhav Utage: Data collection.

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CASE REPORT

Genetic Epilepsy in Twins: Early Infantile Developmental and Epileptic Encephalopathy Linked to Sodium Channel, Voltage-gated, Type VIII Alpha Subunit Mutation

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Abstract

Background: Developmental and epileptic encephalopathies are a group of early-onset epilepsies characterized by refractory seizures and progressive neurodevelopmental impairment. Among the monogenic causes, pathogenic variants in the sodium channel, voltage-gated, type VIII alpha subunit (*SCN8A*) gene have been increasingly recognized as an important etiology. Gain-of-function mutations in *SCN8A* result in neuronal hyperexcitability, early infantile onset seizures refractory to treatment, developmental delay. We report first case of monozygotic twins with early infantile developmental and epileptic encephalopathy due to a *de novo SCN8A* mutation from India.

Case description: Monozygotic female twins, born at term to nonconsanguineous parents, presented at 45 days of life with recurrent tonic seizures occurring multiple times daily. There was no history of fever or perinatal insult. Clinical examination revealed absence of social smile and poor visual tracking, with otherwise unremarkable systemic findings. Initial biochemical investigations, cerebrospinal fluid analysis, and neuroimaging were normal. Seizures were refractory to conventional antiepileptic drugs, including phenobarbitone and levetiracetam. Whole-exome sequencing identified an identical heterozygous pathogenic missense variant in the *SCN8A* gene (NM_001330260.2: c.4398C>A; p.Asn1466Lys) in both infants, consistent with a gain-of-function effect. Sodium channel blockers were subsequently introduced with only partial seizure control. Both infants developed persistent refractory seizures and succumbed to sudden unexpected death in epilepsy within the first 6 months of life. Parental testing confirmed the mutation to be *de novo*.

Conclusion: This report describes a rare and severe presentation of *SCN8A*-related developmental and epileptic encephalopathy in monozygotic twins with identical genetic and clinical profiles and a fatal outcome.

Keywords: Case report, Developmental and epileptic encephalopathy, Refractory seizures, Sodium channel, Voltage-gated, Type VIII alpha subunit, Twins, Whole exome sequencing.

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Introduction

Early infantile developmental epileptic encephalopathies present within the first few months of life with refractory seizures and progressive neurodevelopmental impairment. Among the recognized monogenic etiologies, sodium channel, voltage-gated, type VIII alpha subunit (*SCN8A*)-related developmental and epileptic encephalopathy has emerged as a notable cause owing to its distinct clinical features and underlying pathophysiology.[1,2]

The *SCN8A* gene encodes the Nav1.6 voltage-gated sodium channel, which is widely expressed throughout the central nervous system and plays a crucial role in regulating neuronal excitability. Pathogenic gain-of-function (GOF) variants in *SCN8A* have been implicated in severe infantile epileptic syndromes, which typically manifest as early onset tonic or multifocal seizures, developmental delay or regression, hypotonia, and frequent resistance to conventional antiepileptic therapies.[3,4]

Clinically, the phenotypic spectrum is highly variable. While some infants maintain relatively preserved milestones, many present with significant delays, hypotonia, and complex seizures. Since diagnosis is unclear in initial presentation, a high index of suspicion and early genetic evaluation and counseling are essential.

We describe a rare, documented instance of *SCN8A*-related developmental and epileptic encephalopathy in monozygotic twin girls, both presented in early infancy with refractory seizures. Whole-exome sequencing identified a pathogenic *SCN8A* variant.

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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.

While several cases of *SCN8A*-related developmental and epileptic encephalopathy have been described, only one report involving twins exists.[5] To our knowledge, no prior cases from India have been published, making this report a valuable addition to the limited global literature.

Case Description

A female twin pair, born to nonconsanguineous parents by an uneventful vaginal delivery at term. The birth weights were 2,010

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Table 1: Anthropometric profile of twin A and twin B

Parameter	*Twin A*	*Twin B*
Weight	2.8 kg (expected: 4.2 kg) *Z* score: –3 to –2 SD	2.5 kg (expected: 4.2 kg) *Z* score: < –3 SD
Length	50 cm (expected: 53.7 cm) *Z* score: –2 to –1 SD	48 cm (expected: 53.7 cm) *Z* score: –3 to –2 SD
Head circumference	34 cm (expected: 36.3 cm) *Z* score: –3 to –2 SD	34 cm (expected: 36.5 cm) *Z* score: –3 to –2 SD

Table 2: Laboratory profile of twin A and twin B

Investigation	*Twin A*	*Twin B*
Hemoglobin (gm/dL)	10.2	10.19
White blood cell count ($\times 10^3/\mu L$)	16.77	12.59
Platelet count ($\times 10^3/\mu L$)	770	634.5
MRI brain with contrast	No abnormality	No abnormality
Serum sodium (mEq/L)	135	138
Serum potassium (mEq/L)	5.37	5.59
Serum calcium (mg/dL)	10.13	10.24
Serum lactate (mmol/L)	1.15	0.98
Serum albumin (gm/dL)	4.23	4.08
Cerebrospinal fluid Gram stain	No pus cells; no organisms seen	No pus cells; no organisms seen
Cerebrospinal fluid culture	No growth after 48 hours	No growth after 48 hours
Whole exome sequencing	Heterozygous pathogenic *SCN8A* variant (c.4398C>A; p.Asn1466Lys)	Heterozygous pathogenic *SCN8A* variant (c.4398C>A; p.Asn1466Lys)

grams (Twin A) and 1,900 gm (Twin B), respectively. The immediate postnatal period was unremarkable.

At 45 days old, the twins presented to the emergency with a 3-day history of recurrent seizures. The events were characterized by sudden tonic posturing, stiffening of all four limbs, and upward gaze deviation, each lasting approximately 5 minutes and resolving spontaneously. Both infants experienced 3–5 episodes daily. There was no associated fever, feeding difficulties, excessive crying, or clinical signs suggestive of infection. On examination, both infants were hemodynamically stable and anthropometric assessment revealed evidence of growth faltering in both twins when compared with age-appropriate reference standards as summarized in Table 1. Initial clinical examination revealed normal tone and reflexes. No cranial nerve deficit was observed. The anterior fontanel was open and at level and no dysmorphic features or neurocutaneous markers were evident. Visual tracking was inconsistent, and social smiles were absent in both infants. Both infants had normal vital signs and no signs of systemic infection. There was no family history of seizures.

Blood glucose levels on admission were within the normal range. Intravenous phenobarbitone was administered as a loading dose, followed by maintenance doses. Initial laboratory investigations were unremarkable, as summarized in Table 2. Magnetic resonance imaging of the twins was normal for age. Empirical intravenous antibiotics were initiated and continued until blood and CSF cultures were reported to be sterile. Despite escalating dose, seizures persisted. Levetiracetam was added with only partial control of seizure activity. Given the clinical picture of refractory seizures, adjunctive therapy with biotin and pyridoxine was initiated. Considering the clinical profile suggestive of developmental and epileptic encephalopathy, whole exome sequencing (WES) was performed for genetic analysis which identified a heterozygous pathogenic missense variant in the *SCN8A* gene (NM_001330260.2: c.4398C>A; p. Asn1466Lys) in both patients, which was located within exon 24 and in a known mutational hotspot.

In follow-up at 3 months of age considering *SCN8A* mutation with partial response to initial antiepileptic therapy, phenobarbitone was stopped and oxcarbazepine was initiated given its sodium channel modulating properties. During follow-up, high dose phenytoin and clobazam were subsequently added as there was inadequate seizure control. Despite these interventions, seizure episodes persisted with only modest reduction in frequency. At 5 months of age, both twins succumbed to sudden unexpected death in epilepsy (SUDEP) within few days of each other. Parents were advised to undergo Sanger sequencing before planning further pregnancy. Parental sequencing analysis did not detect the *SCN8A* variant.

Discussion

Sodium channel, voltage-gated, type VIII alpha subunit encodes the Nav1.6 voltage-gated sodium channel alpha subunit, which is fundamental to neuronal excitability and signal propagation. Mutations in *SCN8A* have emerged as an important cause of developmental and epileptic encephalopathy (DEE), manifesting as early onset refractory seizures and neurodevelopmental impairment.[1] Our case of female twins presenting with early refractory seizures and a pathogenic *SCN8A* variant underscores the critical role of genetic testing in neonatal epilepsies.

Lin et al.[2] described a *de novo* heterozygous *SCN8A* mutation in a child with epileptic encephalopathy characterized by frequent tonic–clonic seizures and developmental delay, closely paralleling the phenotype in our twins. This supports the gain-of-function mechanism and drug resistance. Fan et al.[3] reviewed reported cases and highlighted that seizure onset usually occurs within the first year, and developmental outcomes are often poor despite treatment. These observations resonate with the clinical course in our twins—persistent seizures despite conventional therapy and delayed developmental milestones.

Keshri et al.[4] reported a novel *SCN8A* mutation in an infant with early-onset epileptic encephalopathy and resistant seizures, emphasizing phenotypic heterogeneity and the challenge of therapy. Our twins mirrored this, with partial response only after sodium channel blockers. Xiao et al.[6] described infants with *de novo* *SCN8A* mutations showing early seizures, EEG abnormalities, and developmental delay; some had normal neuroimaging, as seen in our cases. The treatment response in *SCN8A* encephalopathy is variable; sodium channel blockers such as phenytoin, carbamazepine, and oxcarbazepine have at times shown efficacy in channel dysfunction modulation, although full seizure control is often elusive.[7]

Hebbar et al.[8] expanded the known spectrum of *SCN8A* mutations, identifying both gain- and loss-of-function variants and correlating these with diverse clinical phenotypes ranging

from benign epilepsy with preserved milestones to severe developmental and epileptic encephalopathy. Their findings highlight that *SCN8A*-related disorders are best viewed as a continuum of neurodevelopmental syndromes, resonating with the severe, refractory phenotype seen in our twins. Meisler et al.[9] described *SCN8A*-related developmental and epileptic encephalopathy as being predominantly associated with gain-of-function variants that alter Nav1.6 channel function, leading to neuronal hyperexcitability, early-onset seizures, and varying degrees of developmental and intellectual impairment.

In our cases, oxcarbazepine produced only partial reduction, and seizures persisted despite adjunctive therapy. Mitsui et al.[10] described an infant with intractable *SCN8A*-related epilepsy effectively suppressed with high-dose phenytoin, illustrating an alternative therapeutic approach in select cases.

The absence of the *SCN8A* variant in both parents on next-generation sequencing suggests either germline mutation or *de novo* origin of the mutation in our patients. Our case is unique in that monozygotic twins possessing an identical pathogenic variant (c.4398C>A; p. Asn1466Lys) within a mutational hotspot developed mirror clinical features, suggesting the mutation likely arose in early embryogenesis. This twin presentation adds rarity and raises implications for genetic counseling and recurrence risk.

Limitations

- Limited longitudinal EEG and neurodevelopmental documentation.
- Single-family report with limited generalizability.
- Inability to assess mutation-specific targeted therapy and long-term outcomes.

Conclusion

This report describes a rare and first report from India, of monozygotic twins with early infantile developmental and epileptic encephalopathy due to a pathogenic *SCN8A* mutation. It underscores the critical importance of prompt early genetic evaluation in infants with refractory seizures is crucial for targeted management and timely genetic counseling. Recognition of such rare familial presentations has important implications for recurrence risk and family planning. Continued follow-up and further research are needed to refine therapeutic strategies and improve long-term outcomes.

Clinical Significance

Early genetic evaluation is crucial in infants with refractory seizures for etiological diagnosis, prognostication, therapeutic decision-making, and genetic counseling. This case expands the limited global literature on twin presentations of *SCN8A*-related encephalopathy and highlights the high risk of poor outcomes, including sudden unexpected death in epilepsy.

Declarations

Data Availability

All relevant data are included in the article. Additional details are available from the corresponding author on reasonable request, subject to ethical considerations.

Ethical Approval

Our Institute does not require ethical approval for publication of case report.

Artificial Intelligence (AI) Disclosure

No AI was used for the performed study.

Acknowledgment

None.

Authors' Contributions

Sharadraj Pillai: Data collection, writing-original draft preparation; Shubham Kamble: Conceptualization, data collection, writing-original draft preparation; Ruchika Kannake: Conceptualization, writing-reviewing and editing, validation; Smita Jategaonkar: Writing-review and editing, visualization, validation; Manish Jain: Review and editing, visualization, validation.

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CASE REPORT

All that Shakes is not Seizures: *ATP1A3*-related Alternating Hemiplegia Presenting as Oculogyric Crisis in an Infant

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Abstract

Aim and background: Paroxysmal events in infancy are frequently misdiagnosed as epileptic seizures. A significant proportion constitutes nonepileptic ocular or movement disorders. Here we report one such case of oculogyric crisis masquerading as a seizure.

Case description: A 1-year-old girl with global developmental delay and recurrent episodes of sustained upward eye deviation initially labeled as drug-refractory epilepsy. Home videos and prolonged video-electroencephalograph (EEG) demonstrated normal background activity without epileptiform discharges during events, confirming the non-epileptic nature of the spells. Metabolic and structural etiologies were excluded. The paroxysms ceased during sleep and were accompanied by fever-triggered episodic weakness, highly suggestive of alternating hemiplegia of childhood (AHC). A therapeutic trial of flunarizine significantly reduced episode frequency. Genetic testing revealed a pathogenic *ATP1A3* variant confirming AHC.

Conclusion: This underscores the importance of video-EEG in the evaluation of paroxysmal events. High clinical suspicion and early diagnosis help initiate prompt treatment.

Clinical significance: The early distinction of oculogyric crisis from epileptic seizures prevents misdiagnosis and enables initiation of targeted therapy.

Keywords: Alternating hemiplegia of childhood, *ATP1A3*, Case report, Oculogyric crisis.

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Introduction

Epileptic seizures are a common diagnostic consideration in infants presenting with recurrent paroxysmal events. However, several non-epileptic movements and ocular motor disorders may closely mimic seizures, leading to inappropriate treatment and diagnostic delays. Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder caused primarily by pathogenic variants in the *ATP1A3* gene, which encodes the α3 subunit of the Na^+/K^+-ATPase pump.[1,2] It is characterized by recurrent hemiplegic episodes, dystonia, abnormal ocular movements, autonomic spells, and paroxysmal events that uniquely stop during sleep and recur upon awakening.[3,4] Early recognition is essential, as prompt initiation of flunarizine and supportive therapies can significantly improve long-term outcomes. Misdiagnosis as epilepsy is common because of the striking paroxysmal nature of events. Here, we describe an infant with *ATP1A3*-related AHC presenting predominantly with oculogyric crisis, initially misinterpreted as epileptic seizures.

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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.

Case Description

A 1-year-old female child, born to a third-degree consanguineous couple with a history of two prior pregnancy losses and one sibling with anencephaly, had developmental concerns including global developmental delay, generalized hypotonia, microcephaly, irritability, and sleep disturbances. Parents reported recurrent episodes of sustained upward eye deviation, occurring mainly during wakefulness or crying and notably absent during sleep. Episodes initially brief, gradually increased in frequency and duration. Transient fever associated weakness episodes had also occurred earlier. She was started on multiple antiseizure medications and managed as drug-refractory epilepsy. There was no family history of similar events. Magnetic resonance imaging (MRI) brain performed at 5 months of age was normal. Home video recordings captured the child's typical paroxysmal episodes with persistent upgaze that settled during sleep, raising a suspicion of oculogyric crisis (Fig. 1). Video-electroencephalograph (EEG) monitoring demonstrated a normal background with appropriate sleep markers and no epileptiform discharges during the events, thereby effectively ruling out epilepsy. A thorough history ruled out any recent drug intake that could cause oculogyric crisis. A therapeutic trial of levodopa (1 mg/kg/day) was undertaken

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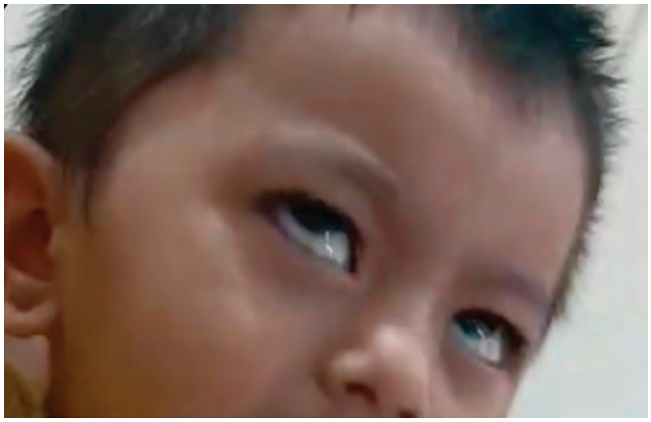


Fig. 1: Image showing persistent upward deviation of both eyes suggestive of oculogyric crisis

to evaluate the possibility of neurotransmitter disorders such as aromatic L-amino acid decarboxylase (AADC) deficiency or tyrosine hydroxylase deficiency, but no clinical improvement was observed. A comprehensive metabolic evaluation—including lactate, ammonia, creatine kinase (CK), prolactin, and blood gases were normal. The constellation of non-epileptic paroxysmal upward eye deviation, normal EEG during spells, cessation of events during sleep, fever-associated episodic weakness, and normal neuroimaging and metabolic workup strongly suggested a diagnosis of *ATP1A3*-related channelopathy with oculogyric crisis and AHC. The child was started on flunarizine, resulting in a substantial reduction in the frequency of paroxysmal ocular deviations. Subsequent genetic testing confirmed a pathogenic *ATP1A3* (c.2443G>A, heterozygous, autosomal dominant) variant, establishing the diagnosis.

Discussion

This case highlights the importance of distinguishing epileptic from non-epileptic paroxysmal events in infants. Misdiagnosis as epilepsy can lead to unnecessary antiseizure medications and delay targeted therapy. Whenever paroxysmal events occur, video-EEG is the gold standard.[5] Several clinical features in this child strongly favored an *ATP1A3*-related disorder rather than epilepsy. These included sustained upward ocular deviation resembling oculogyric crisis, preserved awareness during episodes, complete cessation of spells during sleep, and persistently normal video-EEG during events. Additional supportive features were a normal MRI and metabolic profile, fever-triggered transient weakness, and a clear therapeutic response to flunarizine. Collectively, these findings align closely with the classical phenotype of AHC, the most frequently encountered manifestation of *ATP1A3* variants.

ATP1A3 variants are known to produce a broad and heterogeneous phenotypic spectrum.[6,7] The most well-characterized presentation is AHC, typified by recurrent hemiplegic episodes, dystonia, autonomic disturbances, oculogyric crisis, and the hallmark resolution of symptoms during sleep.[6,7] Another phenotype, rapid-onset dystonia–parkinsonism (RDP), presents with abrupt-onset dystonia and prominent bulbar involvement.[6,7] CAPOS syndrome constitutes a distinct *ATP1A3*-related phenotype characterized by cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss.[6,7] Additional manifestations include fever-triggered exacerbations of movement disorder, relapsing encephalopathy with cerebellar ataxia, fever-induced paroxysmal weakness, and encephalopathy, childhood-onset schizophrenia, early-infantile neurodevelopmental syndromes featuring hypotonia, developmental delay, and oculomotor abnormalities.[6,7] This wide variability underscores the importance of maintaining a high index of suspicion when evaluating infants with complex paroxysmal events.

Management of *ATP1A3*-related AHC centers on reducing the frequency and severity of paroxysmal events and preventing triggers. Flunarizine remains the most effective preventive therapy and is known to significantly decrease the burden of hemiplegic and dystonic attacks.[8] Benzodiazepines may be beneficial during acute exacerbations, particularly for dystonic spells or oculogyric crises. Additional agents such as amantadine, topiramate, and trihexyphenidyl have been used with variable efficacy as adjunct therapies. Trigger avoidance—especially of fever, emotional stress, temperature extremes, and physical exertion—is an important component of long-term management. Supportive measures including physiotherapy, sleep regulation, and developmental interventions further enhance functional outcomes. Emerging therapeutic approaches such as the ketogenic diet, which has shown benefits in small case series, and oral adenosine triphosphate (ATP) supplementation, which remains experimental with preliminary supportive evidence, offer potential avenues for future treatment optimization.[9,10]

Limitations

This report represents a single-patient case study, which limits generalizability of the findings to the broader spectrum of *ATP1A3*-related disorders. Long-term follow-up data on neurodevelopmental outcomes, durability of response to flunarizine, and evolution of hemiplegic or dystonic episodes are not available. Functional validation of the identified *ATP1A3* variant (e.g., *in vitro* or electrophysiological studies) was not performed, and pathogenicity was inferred based on established genotype–phenotype correlations. These limitations are inherent to rare disease case reports but do not diminish the educational value of highlighting key clinical clues that help distinguish *ATP1A3*-related AHC from epileptic seizures.

Conclusion

Persistent upward eye deviation with normal EEG, normal neuroimaging, preserved awareness, and cessation of events during sleep are strong indicators of non-epileptic paroxysmal ocular motor disorders. *ATP1A3*-related AHC must be considered early to avoid mislabeling as refractory epilepsy. Timely initiation of flunarizine, trigger management and rehabilitative support significantly improve outcomes.

Clinical Significance

This report signifies the role of video-EEG in evaluating paroxysmal events. *ATP1A3*-related channelopathy can have various manifestations, including oculogyric crisis and AHC. Having a high clinical suspicion and conducting appropriate investigations will help in correct diagnosis and management.

Declarations

Ethics Statement

Institutional Ethics Committee (IEC) approval was not required for this case report, as it describes a single patient and involves no experimental intervention. Written informed consent was obtained from the child's parents/legal guardians for publication of the clinical details and accompanying images/videos. Patient confidentiality has been strictly maintained in accordance with the Declaration of Helsinki.

Artificial Intelligence (AI) disclosure

No AI was used on the performed study.

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Authors' Contributions

Shanthini Srinivasan: Conceptualization, Methodology, Data curation, Data analysis, Writing – original draft.
Aakash Mahesan: Formal analysis, Data curation, Writing – review and editing.
Suresh Chelliah: Project administration, Supervision, Writing – review and editing.
Meganathan Pachamuthu: Supervision, Writing – review and editing.
Senguttuvan Duraisamy: Supervision, Conceptualization, Methodology, Writing – review and editing.

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CASE REPORT

Concurrent 15q Duplication and 5p Deletion in a Child with Developmental Delay and Multiple Congenital Anomalies: A Case Report

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Abstract

Background: Children presenting with global developmental delay, dysmorphic facial features, and multiple congenital anomalies represent a genetically heterogeneous group. Chromosomal copy-number abnormalities are an important cause of syndromic neurodevelopmental disorders and may not be identified by sequencing-based testing alone.

Case presentation: We report a 19-month-old boy born to nonconsanguineous parents who presented with global developmental delay and absent speech. Clinical examination revealed facial dysmorphism and skeletal abnormalities. Brain magnetic resonance imaging showed a generalized reduction in cerebral white matter volume, hypoplastic cerebellum, and a trigonocephalic skull appearance. Cranial ultrasonography revealed bilateral grade I germinal matrix hemorrhages, while echocardiography identified small dysplastic atrioventricular and semilunar valves. Whole-exome sequencing (WES) was negative. Chromosomal microarray analysis (CMA), however, identified two pathogenic copy-number variants (CNVs) of 23.9-Mb duplication involving 15q25.1-q26.3 and a 1.19-Mb deletion involving 5p15.33.

Conclusion: The coexistence of pathogenic copy-number abnormalities involving chromosomes 15q and 5p provides a plausible genomic explanation for the child's complex phenotype. This case emphasizes the value of CMA as a complementary investigation in children with developmental delay, dysmorphism, and congenital anomalies, even when WES is nondiagnostic. The presence of abnormalities involving two chromosomes also raises the possibility of an underlying unbalanced chromosomal rearrangement, highlighting the importance of parental cytogenetic evaluation.

Keywords: 5p deletion, 15q duplication, Case report, Chromosomal microarray, Congenital anomalies, Copy-number variant, Developmental delay, Dysmorphism, Neurodevelopmental disorder.

Journal of Academy of Pediatric Neurology (2026): 10.5005/jaopn-11028-0042

Introduction

Global developmental delay associated with dysmorphic features and congenital anomalies is clinically and genetically heterogeneous. The underlying etiology may include single-gene disorders, chromosomal abnormalities, copy-number variants (CNVs), structural genomic rearrangements, metabolic disorders, and multifactorial causes. Identification of an underlying genetic diagnosis is important not only for establishing an etiological explanation but also for guiding clinical surveillance, management, and genetic counseling.

Exome and genome sequencing have substantially expanded the diagnostic evaluation of children with developmental disorders and congenital anomalies. Current evidence supports exome or genome sequencing as an important component of the diagnostic evaluation of pediatric patients with developmental delay, intellectual disability, and congenital anomalies.[1,2] However, sequence-based approaches and chromosomal microarray analysis (CMA) interrogate different types of genomic variation. Chromosomal microarray analysis remains particularly useful for detecting pathogenic deletions and duplications and can provide diagnostic information when exome sequencing is nondiagnostic.[2]

Duplications involving the distal long arm of chromosome 15 have been associated with variable neurodevelopmental, craniofacial, cardiac, and skeletal abnormalities. The region at 15q26.3 includes *IGF1R*, and alterations involving this region have been associated with variable effects on growth and development.[3,4] Similarly, deletions involving the distal short arm of chromosome 5 can produce features overlapping with 5p deletion syndrome, including developmental delay, microcephaly, and characteristic craniofacial findings.[4]

We describe a child with a complex neurodevelopmental phenotype in whom whole-exome sequencing (WES) was nondiagnostic, while CMA demonstrated simultaneous pathogenic CNVs involving 15q25.1-q26.3 and 5p15.33. The coexistence of these

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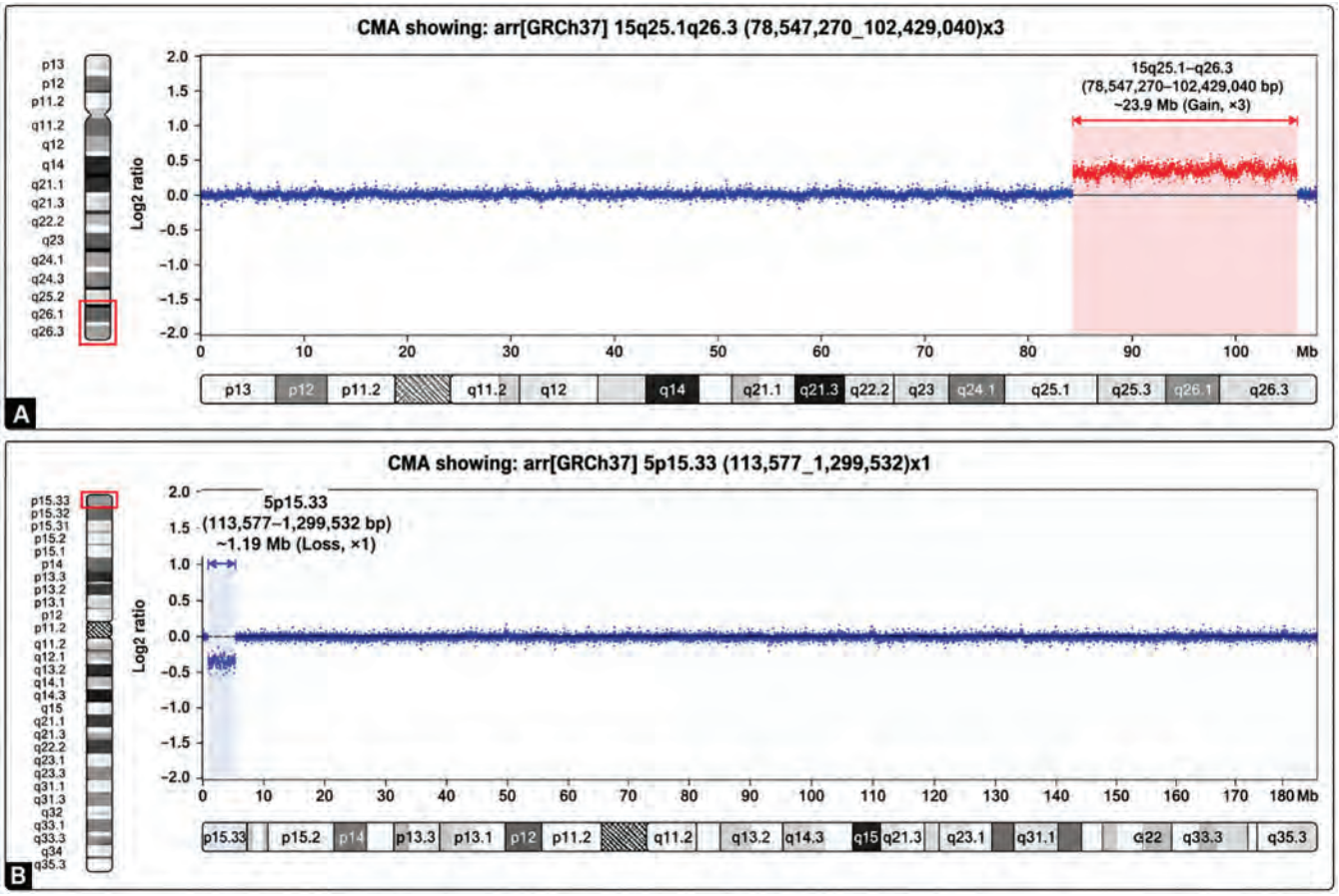
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Conflict of interest: None

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.

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Figs 1A and B: Chromosomal copy-number abnormalities identified by chromosomal microarray. (A) A 23.9-Mb duplication involving chromosome 15q25.1–q26.3 [arr(GRCh37) 15q25.1q26.3(78,547,270–102,429,040)×3]; (B) A 1.19-Mb deletion involving chromosome 5p15.33 [arr(GRCh37) 5p15.33(113,577–1,299,532)×1]

abnormalities is unusual and illustrates the diagnostic importance of complementary genomic testing.

Case Presentation

A 19-month-old boy was evaluated for global developmental delay and absent speech. He was born to nonconsanguineous parents following an uneventful pregnancy and birth history. There was no significant family history of developmental delay, intellectual disability, congenital anomalies, or a known genetic disorder.

Developmental assessment demonstrated significant global developmental impairment, with absence of meaningful speech at the time of evaluation. On clinical examination, the child had microcephaly and a distinctive craniofacial appearance. The observed features included trigonocephaly, a narrow forehead, hypertelorism, epicanthal folds, retrognathia, a long face, and a full chin. Skeletal examination revealed pectus excavatum and long fingers.

Brain magnetic resonance imaging demonstrated generalized reduction in cerebral white matter volume and a hypoplastic cerebellum and trigonocephalic appearance of the skull. Cranial ultrasonography demonstrated bilateral grade I germinal matrix hemorrhages. Cardiac evaluation by echocardiography identified small, dysplastic atrioventricular and semilunar valves. Considering the syndromic presentation, genetic testing was performed. Whole-exome sequencing did not identify any pathogenic or likely pathogenic sequence variant that could explain the clinical phenotype. In view of the persistent suspicion of a genomic disorder, CMA was subsequently performed. Chromosomal microarray analysis identified two pathogenic CNVs, comprising a 23.9-Mb duplication of 15q25.1-q26.3 [arr(GRCh37) 15q25.1q26.3(78,547,270_102,429,040)×3] and a 1.19-Mb deletion of 5p15.33 [arr(GRCh37) 5p15.33(113,577_1,299,532)×1] (Fig. 1). The 15q25.1-q26.3 duplication encompasses approximately 247 genes, including *IGF1R* at 15q26.3, whereas the 5p15.33 deletion encompasses approximately 29 genes, including *TERT*. The simultaneous presence of a deletion on chromosome 5p and a duplication on chromosome 15q may potentially result from an unbalanced chromosomal rearrangement. Parental cytogenetic evaluation was recommended. In particular, parental karyotyping was advised to determine whether either parent carries a balanced reciprocal translocation involving chromosomes 5 and 15. Such a finding would have important implications for recurrence-risk assessment and future reproductive counseling.

Genotype–Phenotype Correlation

The phenotype observed in this child showed overlap with clinical findings previously reported in individuals with distal 15q duplications and distal 5p deletions. The duplicated 15q25.1-q26.3 region is relatively large and contains numerous genes. Of particular interest is *IGF1R*, located at 15q26.3.

Table 1: Clinical features associated with the 15q duplication and 5p deletion

Finding	*15q duplication*	*5p deletion*	*Patient*
Developmental delay	+	+	+
Speech impairment	+	+	+
Microcephaly	Variable	+	+
Facial dysmorphism	+	+	+
Congenital heart disease	+	Variable	+
Long fingers/ arachnodactyly	+	–	+
Cerebellar hypoplasia	Unclear	Unclear	+

Structural abnormalities involving chromosome 15 and the *IGF1R* region have been associated with altered growth and variable developmental phenotypes.[4] Previous reports of individuals with 15q24-q26.3 duplication have described developmental delay, craniofacial dysmorphism, congenital heart disease, and skeletal abnormalities.[3] Features including micrognathia, arachnodactyly, and camptodactyly have also been reported in association with distal 15q duplication. The presence of developmental delay, facial dysmorphism, congenital cardiac abnormalities, and long fingers in the present child therefore demonstrates considerable phenotypic overlap.

The patient's growth and craniofacial phenotype may be influenced by the combined dosage effects of multiple genes within the duplicated interval rather than by a single gene alone.[5] Consequently, the contribution of *IGF1R* should be interpreted in the context of the entire duplicated region.

The second abnormality, a 1.19-Mb deletion involving 5p15.33, overlaps the distal region of chromosome 5 associated with 5p deletion syndrome. Individuals with distal 5p deletions may present with developmental delay, microcephaly, characteristic facial features, and variable congenital abnormalities.[6] In the present case, microcephaly, developmental delay, hypertelorism, and epicanthal folds demonstrate phenotypic overlap with reported features of distal 5p deletion.

The deleted region also includes *TERT*. Although this gene has recognized biological and clinical relevance, the contribution of individual genes within the relatively small deleted interval to the patient's specific phenotype cannot be established from the present case alone.

The clinical presentation is likely to reflect the combined effects of the two CNVs. Because both chromosomal abnormalities involve multiple genes, assigning individual clinical findings exclusively to either the 5p deletion or the 15q duplication would be inappropriate. The overlapping phenotypes provide biological support for the contribution of both genomic imbalances to the child's complex presentation (Table 1).

Discussion

This case highlights an important diagnostic consideration in children presenting with syndromic developmental delay. The WES did not identify any pathogenic or likely pathogenic variants, whereas CMA detected two pathogenic CNVs involving different chromosomes.

Whole-exome sequencing is primarily designed to identify sequence-level variation in coding regions, although CNV detection may be possible with some platforms and specialized bioinformatics pipelines. Its ability to detect CNVs depends on sequencing coverage, bioinformatic methodology, laboratory validation, and the characteristics of the genomic alteration. Therefore, a nondiagnostic WES result does not necessarily exclude clinically significant chromosomal copy-number abnormalities.

Chromosomal microarray analysis and sequencing-based approaches should consequently be considered complementary rather than mutually exclusive investigations. Studies evaluating combined genomic approaches have demonstrated that CMA and exome-based testing can provide additional diagnostic information when used appropriately in individuals with intellectual disability and developmental disorders.[7]

The present case is particularly notable because two pathogenic CNVs were identified simultaneously. The 15q25.1-q26.3 duplication is substantially larger than the 5p15.33 deletion and encompasses a large number of genes. Its association with developmental, craniofacial, cardiac, and skeletal abnormalities corresponds well with several features observed in this child. The 5p15.33 deletion provides additional phenotypic correlation for microcephaly, developmental delay, and characteristic facial features.[8]

The simultaneous occurrence of a deletion involving one chromosome and a duplication involving another chromosome also has cytogenetic implications. Such a pattern may occasionally arise as a consequence of an unbalanced structural rearrangement, including an unbalanced reciprocal translocation. Therefore, parental karyotyping is clinically relevant even in apparently unaffected parents. Identification of a balanced rearrangement in a parent would substantially alter recurrence-risk counseling and reproductive options.

An additional consideration is that the two CNVs may not necessarily have a single common mechanism. They could theoretically represent independent genomic events. Without parental cytogenetic or genomic studies, the mechanism underlying their coexistence cannot be established. Thus, the present case supports consideration of a possible chromosomal rearrangement rather than establishing one.

From a clinical perspective, identification of both pathogenic CNVs has several implications. It provides an etiological framework for the child's developmental and multisystem abnormalities, supports appropriate phenotype-informed surveillance, and enables more informed counseling of the family. Genetic counseling is particularly important when multiple genomic abnormalities are identified because families may require discussion of diagnostic certainty, prognosis, recurrence risk, parental testing, and reproductive implications.[9]

The rarity of the specific combination of 15q duplication and 5p deletion further emphasizes the value of detailed clinical and genomic characterization. To our knowledge, the concurrent involvement of these specific intervals appears to be rarely described. Further cases with similar genomic findings will be necessary to determine whether particular phenotypic features consistently result from the combined dosage imbalance.

Limitations of the Study

Parental karyotyping and additional cytogenetic studies were not available; therefore, the mechanism underlying the co-occurrence of the 15q duplication and 5p deletion could not be established.

Conclusion

This case demonstrates the diagnostic value of complementary genomic testing in a child with global developmental delay, dysmorphism, neuroimaging abnormalities, and congenital heart disease. Although WES was nondiagnostic, CMA identified two pathogenic CNVs involving 15q25.1-q26.3 and 5p15.33. The patient's phenotype showed overlapping features associated with both 15q duplication and 5p deletion.

The findings emphasize that a negative or nondiagnostic sequencing result should not preclude further evaluation for clinically significant chromosomal abnormalities. Chromosomal microarray analysis remains an important diagnostic modality for children with developmental delay and multiple congenital anomalies. The presence of CNVs involving two different chromosomes should prompt consideration of an underlying unbalanced chromosomal rearrangement and appropriate parental cytogenetic evaluation. Recognition of the combined genomic abnormalities provided a plausible molecular explanation for the child's complex phenotype and enabled more appropriate genetic counseling and management planning. This case highlights the value of complementary genomic testing and emphasizes the importance of parental chromosomal evaluation and genetic counseling for accurate recurrence-risk assessment and reproductive planning.

Clinical Significance

Identification of both pathogenic CNVs provided a molecular explanation for the patient's complex neurodevelopmental phenotype and supports phenotype-informed management, parental evaluation, and genetic counseling.

Declarations

Ethical Approval

Since this is a case report, there is no need for ethical approval.

Data Availability

The data are available from the corresponding author upon reasonable request.

Artificial Intelligence (AI) Disclosure

No AI was used in the preparation of this manuscript.

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Authors' Contributions

Prashant R Utage supervised and approved the manuscript; Falguni Dalal collected data, wrote and drafted the manuscript; Nadir Aman reviewed and conceptualized the manuscript; Aparna Utage collected data and conducted the literature review.

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CASE REPORT

A Case Report on Progress in a Child with Autism Spectrum Disorder Following Multidisciplinary Intervention

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social communication and interaction along with restricted and repetitive patterns of behavior. Early identification and intervention play a crucial role in improving developmental outcomes in children with ASD. The present case report describes the progress of a 9-year-old boy diagnosed with ASD who received multidisciplinary intervention. Developmental functioning was assessed using standardized tools including the Childhood Autism Rating Scale (CARS) and Vineland Adaptive Behavior Scales (VABS), along with clinical observations and caregiver interviews. The intervention program targeted speech development, sensory integration, attention enhancement, and behavioral regulation. In addition to the therapy, caregiver training and structured activities were implemented. After 1 year of consistent intervention, significant improvements were observed in communication skills, eye contact, sitting tolerance, attention span, sensory regulation, and social interaction. The case highlights the effectiveness of multidisciplinary intervention combined with caregiver involvement in supporting developmental progress among children with ASD.

Keywords: Autism spectrum disorder, Case report, Developmental rehabilitation, Early intervention, Multidisciplinary intervention, Speech and language development.

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Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and interaction, along with restricted, repetitive patterns of behavior, interests, or activities.[1] These core features often manifest early in childhood and can significantly impact a child's ability to function effectively in social, academic, and daily life contexts. Children with ASD commonly present with delayed speech and language development, reduced eye contact, impaired joint attention, sensory processing difficulties, and limited engagement in reciprocal social interactions.[2]

In addition to these core symptoms, individuals with ASD often exhibit a wide range of associated difficulties, including challenges in executive functioning, emotional regulation, and adaptive behavior. Sensory abnormalities, such as hypersensitivity or hyposensitivity to auditory, visual, or tactile stimuli, further complicate functional participation in everyday environments. These challenges not only affect the child's developmental trajectory but also place considerable emotional, social, and financial burdens on caregivers and families.

Over the past two decades, the global prevalence of ASD has increased substantially. Current epidemiological estimates indicate that approximately one in 36 children is diagnosed with ASD.[3] This rise can be attributed to improved awareness, expanded diagnostic criteria, and enhanced screening practices. Autism spectrum disorder is highly heterogeneous in nature, with considerable variability in cognitive abilities, language development, symptom severity, and adaptive functioning across individuals.[4] This heterogeneity necessitates individualized assessment and intervention approaches tailored to each child's unique needs.

Early diagnosis and timely intervention are widely recognized as critical factors in improving developmental outcomes for children with ASD. Evidence suggests that intervention during early developmental periods can significantly enhance neural plasticity, thereby improving communication skills, social functioning, and adaptive behavior.[5,6] Interventions that focus on structured teaching, behavioral modification, and skill development have demonstrated positive outcomes in reducing symptom severity and enhancing functional independence.

Multidisciplinary intervention approaches are considered the gold standard in autism management. These approaches integrate speech and language therapy, occupational therapy (including sensory integration), behavioral interventions, and caregiver training to address the multifaceted challenges associated with ASD.[7] Caregiver involvement, in particular, plays a crucial role in ensuring consistency of intervention across settings and promoting generalization of learned skills into daily life.

Despite growing awareness and advancements in intervention strategies, many families continue to face challenges in accessing appropriate and effective services. Inconsistent treatment

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approaches, lack of awareness, and financial constraints often delay intervention and limit optimal outcomes.

The present case report aims to document the developmental progress of a 9-year-old child with ASD who demonstrated significant improvement following structured multidisciplinary intervention combined with caregiver-supported strategies. The case highlights the importance of consistency, individualized planning, and active caregiver involvement in achieving meaningful developmental gains.

Review of Literature

A substantial body of research highlights the importance of early and structured intervention in improving outcomes for children with ASD. Developmental and behavioral intervention models, particularly those implemented during early childhood, have been shown to significantly enhance language development, social communication, and adaptive functioning.[8,9] These findings underscore the role of early neuroplasticity in facilitating learning and skill acquisition.

Speech and language impairments are among the most prominent and persistent challenges faced by children with ASD. Difficulties in expressive and receptive communication often hinder social interaction and limit participation in educational settings. Evidence suggests that targeted speech-language interventions can improve vocabulary acquisition, sentence formation, and pragmatic language skills.[10,11] Early and intensive communication-focused therapies are particularly effective in promoting meaningful language use and reducing reliance on nonverbal communication.

Sensory processing dysfunction is another critical area of concern in autism. Many children with ASD experience atypical responses to sensory stimuli, which may manifest as hypersensitivity or hyposensitivity to sounds, textures, lights, or movement. These sensory challenges can interfere with attention, learning, and daily functioning. Occupational therapy interventions incorporating sensory integration techniques have demonstrated effectiveness in reducing sensory-related difficulties and improving engagement in structured activities.[12]

In recent years, there has been increasing recognition of the role of caregiver involvement in intervention programs. Parent-mediated interventions empower caregivers to implement therapeutic strategies within natural environments, thereby enhancing consistency and promoting generalization of skills across contexts. Studies have shown that such interventions lead to improvements in communication, social engagement, and adaptive behavior.[13,14] Caregiver training also reduces parental stress and increases confidence in managing the child's needs.

Furthermore, contemporary research emphasizes the importance of individualized and multidisciplinary approaches in autism intervention. Given the heterogeneity of ASD, no single intervention is universally effective. Instead, tailored intervention plans that integrate multiple therapeutic modalities are recommended.[15] Multidisciplinary models that combine speech therapy, occupational therapy, behavioral strategies, and educational support have been found to produce more comprehensive and sustained outcomes.[16]

Recent advances also highlight the need for continuous monitoring and outcome-based evaluation of intervention programs. The use of standardized assessment tools, along with domain-specific progress tracking, enables clinicians to modify intervention strategies based on the child's evolving needs.

Overall, the literature strongly supports the effectiveness of early, intensive, multidisciplinary, and family-centered intervention models in improving developmental trajectories for children with ASD. The present case study builds upon this evidence by demonstrating practical application and outcomes within a real-world clinical context.

Materials and Methods

Study Design

This study employed a descriptive single-case report design to document the developmental progress of a child with ASD following multidisciplinary intervention.

Setting

The intervention was conducted by a group of rehabilitation experts who provide assessment, therapy, and caregiver training for children with developmental disorders.

Participant

The participant was a 9-year-old boy (client) diagnosed with ASD at the age of 5 years. He lives with his mother and grandparents. Following the death of his father in 2020, his mother became the primary caregiver.

Assessment Tools

Developmental functioning was evaluated using the following tools:

- Childhood Autism Rating Scale (CARS).
- Vineland Adaptive Behavior Scales (VABS).
- A clinical severity rating scale (1–4) was used to document functional changes across domains, where 1 indicates functional/near-normal performance and 4 indicates severe impairment.
- Parent interviews and therapy progress reports.

Intervention Program

A multidisciplinary intervention program was designed focusing on:

- Speech and language development
- Sensory integration therapy
- Attention enhancement
- Improvement in sitting tolerance
- Management of auditory avoidance behavior

Regular therapy sessions were conducted by experts. In addition, the caregiver received training sessions and a structured intervention plan to reinforce therapy outcomes.

Results (Case Report)

Background

The client is a 9-year-old child diagnosed with ASD at the age of 5 years. After the death of his father in 2020, his mother assumed full responsibility for his upbringing and developmental support.

Initial Concerns

During the coronavirus disease 2019 (COVID-19) lockdown period, the client's mother noticed several developmental concerns, including:

- Limited eye contact
- Unclear speech
- Repetition of words
- Sensory sensitivities
- Short attention span
- Poor sitting tolerance

Despite visiting multiple healthcare providers, the child did not show meaningful improvement.

Intervention

In 2024, the client's mother approached for a developmental assessment. Based on the evaluation, regular therapy sessions were initiated.

The intervention focused on improving communication skills, eye contact, sitting tolerance, attention span, sensory regulation, and social interaction.

Outcomes

After 1 year of consistent multidisciplinary intervention, significant improvements were observed across multiple developmental domains, as shown in Table 1 and graphically represented in Figure 1.

In terms of communication, the child initially demonstrated limited expressive abilities, restricted to a few words and naming familiar people or objects, and could only express basic needs. Receptive language was also limited, with the ability to follow only one-step instructions and inconsistent responses to questions. Following intervention, the child progressed to producing meaningful and simple sentences, with a noticeable reduction in echolalia and improved accuracy in responses.

Eye contact, which was initially minimal (score = 3), showed consistent improvement (score = 2).

A substantial improvement was observed in sitting tolerance, increasing from 1–3 minutes (score = 3–4) to approximately 2.5 hours (score = 1–2), indicating strong functional gains.

Attention span improved from poor engagement (score = 3) to better task participation (score = 2).

Sensory sensitivities, previously high (score = 3), reduced significantly (score = 2), allowing improved participation in therapeutic and daily activities.

Table 1: Developmental progress before and after intervention (with clinical scores)

Developmental domain	*Before intervention*	*Score*	*After 1 year of intervention*	*Score*
Expressive communication	Few words; naming people/objects; expresses only basic needs	3 (moderate)	Meaningful and simple sentences; reduced repetition	2 (mild)
Receptive communication	Understands 1-step instructions; limited response to questions	3 (moderate)	Improved comprehension; more accurate responses	2 (mild)
Eye contact	Limited	3	Improved and more consistent	2
Sitting tolerance	1–3 minutes only	3–4	Approximately 2.5 hr (functional improvement)	1–2
Attention	Poor task engagement	3	Better task participation and focus	2
Sensory response	High sensitivity	3	Reduced sensitivity	2
Social interaction	Limited engagement	3	Improved interaction and participation	2

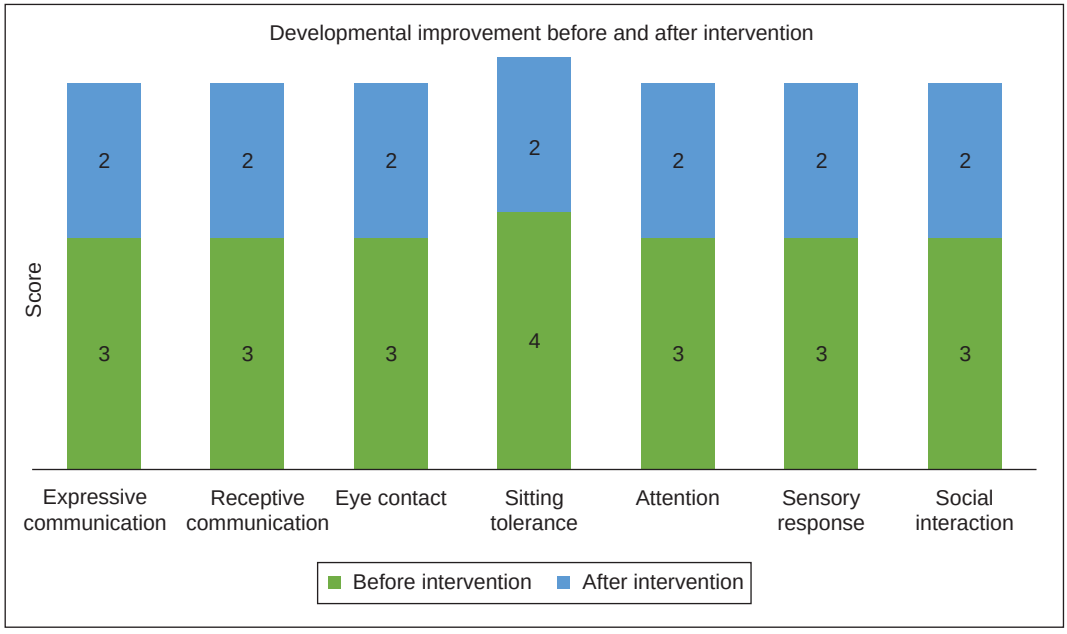


Fig. 1: Improvement in various domains following 1 year of multidisciplinary intervention

Similarly, social interaction improved from limited engagement (score = 3) to more active participation (score = 2).

Discussion

The present case study highlights the significant impact of structured multidisciplinary intervention on developmental outcomes in a child with ASD. Before intervention, the child exhibited several core characteristics associated with ASD, including deficits in communication, heightened sensory sensitivities, and limited attention span, all of which affected functional participation in daily activities.

Following 1 year of consistent intervention, notable improvements were observed across multiple developmental domains, particularly in communication, attention, sitting tolerance, and sensory regulation. These findings are consistent with existing literature demonstrating that early and sustained intervention can significantly enhance communication abilities and adaptive functioning in children with ASD.[5,17] The observed transition from limited verbal output to meaningful sentence formation reflects the effectiveness of targeted speech and language interventions.

Caregiver participation emerged as a critical factor contributing to the child's progress. The structured involvement of the mother in implementing strategies ensured continuity of intervention beyond the clinical setting. This aligns with evidence suggesting that parent-mediated interventions enhance treatment outcomes by promoting consistency, generalization of skills, and increased learning opportunities in natural environments.[14]

Improvements in sensory regulation and sitting tolerance played a pivotal role in enhancing the child's ability to engage in structured tasks. Reduced sensory sensitivities likely contributed to better attention and participation, thereby facilitating readiness for educational inclusion. These findings support the role of sensory integration-based approaches in improving functional engagement among children with ASD.

An important strength of the present case report is the use of a domain-wise clinical scoring system to systematically document developmental changes. The observed reduction from moderate impairment (score = 3) to mild levels (score = 2) across most domains, along with near-functional levels (score = 1–2) in sitting tolerance, reflects meaningful and measurable therapeutic gains. Such structured monitoring is consistent with recommendations for individualized, outcome-based intervention tracking in autism research.[16]

Despite these positive outcomes, it is important to interpret the findings within the context of a single-case design. Individual variability in ASD necessitates cautious generalization. Nevertheless, the case provides valuable insights into the effectiveness of multidisciplinary and family-centered intervention approaches in real-world clinical settings.

Limitations of the Study

This study has several limitations. First, it is based on a single clinical case; therefore, the findings cannot be generalized to all children with ASD, given the considerable heterogeneity in developmental profiles, symptom severity, and response to intervention. Second, the absence of a control or comparison group limits the ability to attribute the observed developmental improvements exclusively to the multidisciplinary intervention. Third, the assessment period was limited to one year, and long-term maintenance and generalization of the observed gains were not systematically evaluated. In addition, some outcome information was based on clinical observations, caregiver reports, and domain-wise clinical ratings, which may be subject to observer or reporting bias. Future studies involving larger samples, standardized outcome measures, comparison groups, and longer follow-up periods are recommended to establish the effectiveness and sustainability of multidisciplinary intervention approaches in children with ASD.

Conclusion

This case report demonstrates that structured multidisciplinary intervention, combined with active caregiver involvement, can lead to significant improvements in developmental functioning among children with ASD. Notable gains were observed in communication, attention, sensory regulation, and task engagement following 1 year of consistent therapy. The findings reinforce the importance of early identification, individualized intervention planning, and family-centered care models in supporting children with ASD. Caregiver training and reinforcement emerged as key factors in sustaining and generalizing therapeutic gains. With continued intervention, monitoring, and appropriate educational placement, children with ASD can achieve improved functional independence and enhanced quality of life. The present case underscores the need for accessible, consistent, and multidisciplinary intervention services to optimize developmental outcomes in children with ASD.

Clinical Significance

This case highlights the clinical importance of early identification, individualized multidisciplinary intervention, and active caregiver involvement in supporting developmental progress in children with ASD. Improvements were observed in expressive and receptive communication, eye contact, sitting tolerance, attention, sensory regulation, and social interaction following one year of consistent intervention. The case also demonstrates the practical value of integrating speech and language therapy, sensory-based intervention, attention and behavioral strategies, structured activities, and caregiver training within an individualized intervention plan. Regular monitoring of developmental domains can help clinicians identify progress, modify intervention strategies according to the child's evolving needs, and promote functional participation and greater independence in daily activities.

Declarations

Ethical Approval

This manuscript reports a single clinical case using anonymized information obtained during routine clinical care. According to the applicable institutional policy, formal approval from an Institutional Ethics Committee was not required for publication of this anonymized case report. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the child's legal guardian for participation in the intervention and publication of the case information.

Data Availability

The data supporting the findings of this case report are included within the manuscript. Additional anonymized clinical information may be made available by the corresponding author upon

reasonable request, subject to ethical, privacy, and confidentiality considerations.

Artificial Intelligence (AI) Disclosure

Artificial intelligence-assisted writing support was used to improve the clarity, grammar, language, and overall organization of the manuscript. Artificial intelligence assistance was limited to language and editorial support and was not used to independently generate or interpret clinical findings. All clinical information, interpretation of findings, scientific content, literature selection, and final editorial decisions were independently reviewed, verified, and approved by the author(s). The author(s) assume full responsibility for the accuracy, integrity, and originality of the submitted manuscript.

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Authors' Contribution

Subodh Kumar conceptualized the study and contributed to the overall development of the case report. Soumya S Samal performed the clinical assessment and contributed to the collection and interpretation of clinical data. Ramesh K Goyal designed and supervised the intervention plan. Priyanka Pandey conducted the literature review. Subodh Kumar drafted the manuscript, critically revised the content, and approved the final version of the manuscript. All authors reviewed and approved the final manuscript and agree to be accountable for the work.

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VIEWPOINT

Cross-border Gene Therapy in Spinal Muscular Atrophy and Duchenne Muscular Dystrophy: Ethical, Systemic, and Family Determinants of Outcomes

Vivek Mundada[1], Rahul Shukla[2]

Abstract

Aim and background: Gene therapies for spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) have transformed prognosis but exposed profound global inequities in access and post-treatment care. This narrative review and perspective examine the ethical, systemic, and family determinants that shape outcomes for children who travel across borders for these therapies.

Materials and methods: We draw on the clinical experience of a tertiary gene therapy hub in Dubai that treated 173 children (159 SMA and 14 DMD) from 17 nationalities between 2020 and 2025, and integrate these structured observations with the existing literature. The article does not present a formal statistical analysis of clinical outcomes; the cohort provides the real-world context from which our observations are drawn.

Results: Four interdependent determinants emerged as central to post-therapy trajectories: diagnostic access, parental awareness and health literacy, financial capacity, and continuity of multidisciplinary care. Cross-border care improved access but frequently disrupted post-return continuity, and unequal fundraising capacity raised distinct ethical tensions for families and clinicians.

Conclusion: Molecular efficacy alone does not guarantee durable benefit. Sustaining these therapies requires informed families, stable funding pathways, and cohesive global clinical networks supported by shared registries, standardized discharge, and capacity building.

Clinical significance: Recognizing and addressing the family, systemic, and ethical determinants of gene therapy outcomes, alongside the therapy itself, is essential to translating molecular success into equitable, real-world benefit for children with SMA and DMD.

Keywords: Cross-border care, Duchenne muscular dystrophy, Gene therapy, Health equity, Spinal muscular atrophy.

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Introduction

The past decade has marked an extraordinary shift in the management of inherited neuromuscular disorders. The first approvals of nusinersen in 2016, onasemnogene abeparvovec in 2019, and delandistrogene moxeparvovec in 2023, together with exon-skipping therapies and small-molecule treatments such as risdiplam, have redefined therapeutic possibilities for spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD), offering disease-modifying options once deemed unattainable.[1–5] Yet, these breakthroughs have also highlighted global inequities in access and post-treatment care.

Dubai has emerged as one of the leading destinations for children seeking gene therapy from regions where such treatments remain restricted or unavailable. Serving as a regional hub for these advanced therapies has provided a unique vantage point, revealing that scientific innovation alone does not guarantee equitable outcomes. Instead, family resources, health system readiness, and cross-border continuity of care often determine which children ultimately benefit.

This article explores the multidimensional determinants that shape outcomes for children traveling abroad for gene therapy and proposes collaborative solutions to ensure sustained post-therapy care.

This article is a narrative review and perspective piece. It draws on our clinical experience of managing a large cross-border gene therapy cohort and integrates these observations with existing literature; it does not present a formal statistical analysis of clinical outcomes. The cohort is described to provide the real-world context from which our observations and arguments are derived. Accordingly, the relationships we describe between family, systemic, and ethical factors and post-therapy trajectories represent structured clinical impressions rather than measured effect sizes and are intended to be hypothesis-generating. To our knowledge, this represents one of the largest real-world cross-border gene therapy cohorts reported from a single center.

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Real-world Experience

Between 2020 and 2025, 173 children (159 with SMA and 14 with DMD) representing 17 nationalities underwent gene therapy at our center in Dubai (Table 1). Families traveled from countries including Turkey, Russia, India, Iran, Kyrgyzstan, and Kazakhstan, and, in some cases, from European nations such as Hungary and the United Kingdom.

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Table 1: Demographic and clinical characteristics of children receiving gene therapy

Characteristic	*SMA (n = 159)*	*DMD (n = 14)*
Sex distribution	Male: 61 (45%); female: 74 (55%)	Male: 14 (100%)
Age at therapy (months)	14.9 ± 12.3 (range: 4–83)	98.8 ± 37.1 (range: 44–171)
Country distribution	Turkey: 69%; UAE: 3%; Iran: 3%; Russia: 3%; others: 22%	Russia: 36%; Turkey: 21%; Kazakhstan: 14%; Kyrgyzstan: 7%; India: 7%; Iran: 7%; Georgia: 7%
Ventilation status	Self-ventilating: 35%; NIV: 28%; tracheostomy: 47%	All self-ventilating
Feeding status	Oral: 33%; NG: 26%; gastrostomy: 40%	All oral feeding

DMD, Duchenne muscular dystrophy; NG, nasogastric; NIV, non-invasive ventilation; SMA, spinal muscular atrophy

Families sought treatment abroad due to restrictive drug labels or limited local availability.[6] For example, gene therapy for DMD was restricted to children under 9 years of age in Russia, while in Turkey, neither Zolgensma nor Elevidys was available during this period. In several regions, SMA gene therapy eligibility was confined by age limits, whereas in Dubai, treatment was offered to all children weighing under 21 kg in accordance with the European Medicines Agency (EMA) label, which defines dosing based on weight rather than age.[7,8] This flexibility contrasts with the Food and Drug Administration (FDA)-approved label, which is restricted to patients under 2 years of age. Many families raised funds through charitable foundations or crowdfunding, reflecting systemic disparities in access rather than elective preference.

At our center, a structured pre- and post-therapy framework was established encompassing patient readiness for travel, including logistical assistance, multidisciplinary evaluations including regular physiotherapy sessions, and continued teleconsultations after the family's return home. Most families remained in Dubai for an average of three months.[9] Structured questionnaires and family interviews captured demographic, psychosocial, and care-continuum data, providing a comprehensive overview of both clinical and social determinants of outcome.

To ensure smooth coordination, a dedicated gene therapy coordinator and multilingual translators (e.g., Turkish and Russian) facilitated communication between families and clinical teams. They also supported teleconsultations, travel logistics, and follow-up interactions with referring clinicians. Structured discharge summaries were routinely shared with home-country neurologists before the family's return with parental consent, ensuring continuity of care.

This diverse experience provided clinical insights into the multidimensional challenges that shape post-therapy trajectories. Beyond the technical success of vector infusion, family preparedness, socioeconomic context, and healthcare infrastructure collectively determine how well children integrate therapy into daily life. The following sections summarize the key domains that emerged from our observations.

This experience also positioned Dubai as a case study for how emerging healthcare hubs can contribute to global therapeutic equity by sharing expertise, infrastructure, and training with neighboring regions.

Family and Psychosocial Determinants of Outcomes

Analysis of this multinational cohort identified four interdependent domains influencing post-therapy outcomes: Diagnostic access, parental awareness, financial capacity, and continuity of multidisciplinary care.

Diagnostic Access

A noticeable shift was observed in the profile of children accessing gene therapy over the study period. Increasingly, families sought treatment soon after diagnosis, and a growing proportion of referrals involved children identified through newborn screening programs in their home countries.[10,11] These children typically presented with fewer comorbidities and greater physiological stability at the time of therapy.[12] While this analysis does not assess functional outcomes, prior studies have consistently shown that presymptomatic treatment is associated with superior motor trajectories and reduced need for ventilatory or orthopedic interventions. The emergence of such early diagnosed cases in cross-border settings reflects improving awareness and diagnostic readiness across regions, representing a positive evolution in the real-world delivery of gene therapy. Early detection remains pivotal even in the era of gene therapy.

Parental Awareness and Health Literacy

In our experience, families with higher disease literacy and access to reliable educational resources appeared more engaged with physiotherapy, nutritional monitoring, and orthopedic surveillance after gene therapy. Such families were often more vigilant for complications such as scoliosis, hip dislocation, and osteopenia. Conversely, we observed that a limited understanding of long-term rehabilitation could contribute to preventable functional decline despite adequate initial gene expression. These reflect clinical impressions rather than formally measured associations.

Financial Support

Timely access to insurance, charitable, or governmental funding strongly influenced both therapy initiation and sustained engagement with follow-up programs. In our experience, stable financial pathways facilitated regular physiotherapy and nutritional oversight, whereas interrupted support was frequently accompanied by irregular care schedules.

In addition to financial strain, families frequently encountered logistical and administrative challenges when seeking reimbursement across borders. Differences in insurance recognition, documentation requirements, and exchange-rate fluctuations often delayed therapy access, adding to parental anxiety. Charitable foundations and international advocacy networks played a crucial role in bridging these gaps and facilitating equitable access.

Continuity of Care

In our experience, families able to maintain regular physiotherapy and timely access to supportive services appeared to sustain better functional trajectories after therapy. This clinical impression is consistent with previously published quantitative data from

our center, which demonstrated that comprehensive post-gene therapy care, combined with the pharmacological effect of the vector, was associated with improvements in nutritional status, fewer contractures and fractures, lower hospitalization rates, and better motor function scores even in complex or advanced cases.[9] Families with stronger psychosocial support also more often described lower caregiver burden and better adherence. Although we did not formally analyze outcomes in the present cohort, these observations reinforce the view that consistent engagement across these domains supports more stable post-therapy trajectories.

Cross-border and Systemic Challenges

Cross-border gene therapy introduces both opportunities and complexities. Families traveled primarily because of therapy inaccessibility, restrictive local regulations, or the need for broader eligibility criteria. Some countries lacked newborn screening programs or had insufficient genetic diagnostic infrastructure, delaying treatment until after symptom onset.

While the therapeutic benefits were clear, post-return continuity often suffered. In several cases, families had no dedicated pediatric neurologist in their home country or relied solely on general pediatricians unfamiliar with post-gene therapy care protocols. Parents frequently withheld prior treatment reports, fearing ineligibility for add-on therapies such as nusinersen or risdiplam. This secrecy, while understandable, hampered clinician communication and continuity of care.

To support continuity, our team maintained regular contact with families through teleconsultations, during which parents shared clinical updates and laboratory results. Guidance was provided remotely on when to seek specific medical services or specialist input. Several families also returned to Dubai for scheduled follow-up assessments, which allowed in-person review and data verification, further strengthening the longitudinal understanding of post-gene therapy outcomes.

Such cross-border efforts underscored that gene therapy's real-world success relies not only on molecular efficacy but also on global clinical networks capable of sustaining long-term multidisciplinary care.

Collaborative Solutions and Capacity Building

Obtaining reliable post-therapy functional scores was also challenging in some cases, as local physiotherapists were unfamiliar with standardized neuromuscular assessment tools such as Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurological Examination, Section 2 (HINE-2), or North Star Ambulatory Assessment (NSAA).[13–15] To address these systemic gaps, several collaborative strategies were implemented. Dedicated preceptorship programs for pediatric neurologists and regional workshops supported by industry partners such as Novartis and Roche were organized, bringing together clinicians and physiotherapists from multiple countries. These initiatives enhanced shared understanding of post-gene therapy care standards, promoted consistency in functional assessments, and fostered cross-border professional networks.

Parent symposia were also conducted to increase disease awareness and encourage transparent sharing of prior treatment histories with home clinicians. A mapping project identified regional pediatric neurologists and rehabilitation specialists in their home countries, guiding families lacking established care providers toward appropriate follow-up. Direct outreach visits to Turkey, Kyrgyzstan, and Russia strengthened these collaborative ties and fostered trust among local teams.

These educational and networking efforts have shown that structured discharge, shared registries, and telecommunication can effectively bridge the post-treatment gap for internationally treated patients.

Future integration of telehealth platforms and artificial intelligence-based analytics within shared registries could further streamline follow-up, standardize data collection, and enhance real-time collaboration between centers.

Ethical Reflections on Cross-border Access and Responsibility

The rapid expansion of gene therapy has blurred traditional boundaries between innovation, equity, and ethics. For many low- and middle-income countries, the debate extends beyond affordability to questions of justice, prioritization, and informed consent.

The rise of crowdfunding for high-cost gene therapies has prompted debate about fairness, transparency, and resource allocation.[16,17] Critics argue that unequal fundraising capacity perpetuates global inequities. Yet for clinicians, the ethical duty is individual and immediate. When a child meets eligibility criteria, and therapy is both FDA-approved and consistent with international guidelines, refusal of treatment on grounds of geographic inequity would itself be unethical.

The physician's role is to deliver safe, evidence-based care while advocating for broader access frameworks. The proper response is ethical transparency, ensuring families understand the therapy, its follow-up needs, and the collaborative efforts underway to build capacity locally.

For families, the emotional weight of decision-making is profound since families must balance hope, financial burden, and uncertainty. Treating clinicians often face moral tension between acting as compassionate advocates for an individual child and recognizing the broader inequities of access that persist globally. Transparent communication, shared decision-making, and ethical oversight within institutions are therefore essential to ensure fairness and trust in the delivery of these transformative yet costly therapies.

Cross-border treatment, therefore, should not be viewed as opportunistic "medical tourism," but as a transitional mechanism, a bridge providing immediate access while health systems evolve toward equity and readiness.

Discussion and Future Directions

Our center's experience shows that real-world gene therapy outcomes are shaped by both individual and systemic determinants. Molecular success is sustained only when complemented by informed families, structured funding, and cohesive multidisciplinary care networks.

Future efforts should prioritize the following:

At the microlevel, empowerment should focus on areas within the clinician's influence: Enhancing family education, reinforcing adherence to standards of care, and ensuring that parents understand the importance of long-term rehabilitation well before gene therapy is initiated. While implementation of newborn screening depends largely on national policies and political

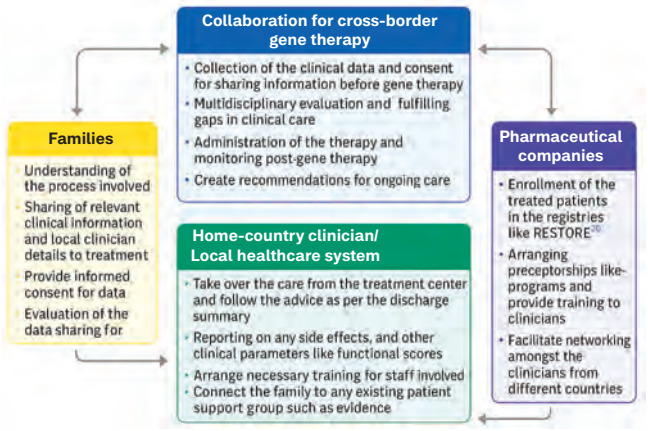


Fig. 1: Proposed framework for cross-border continuity of care in gene therapy

commitment, treating centers can advocate for its adoption and contribute to early diagnostic readiness through awareness campaigns and professional training.[18] Sustained rehabilitation, caregiver training, and structured follow-up remain essential to translate molecular correction into meaningful functional benefit.

At the macrolevel, harmonization requires the creation of shared registries, standardized discharge templates, and clinician exchange programs that connect treating and home-country specialists. Each center performing gene therapy should also encourage parental empowerment and professional collaboration, thereby building a distributed yet cohesive global network for post-gene therapy care (Fig. 1).

As newborn screening expands and more countries develop the regulatory and logistical capacity to deliver gene therapy locally, the need for cross-border treatment is likely to decline. Earlier diagnosis and domestic access will enable timely intervention within national healthcare systems, reducing the dependence on international centers for therapy delivery. Until then, international centers must ensure transparent documentation, bidirectional communication, and training collaborations that support global standards of care.

Gene therapy has expanded both scientific and ethical horizons.[19,20] The next frontier lies not only in viral vectors but also in building sustainable, equitable ecosystems for rare disease management across borders.

Limitation(s) of the Study

This article has several limitations inherent to its design. It is a single-center narrative review and perspective rather than a controlled study, and it does not present a formal statistical analysis of clinical outcomes. The determinants we describe are derived from structured clinical observation, questionnaires, and family interviews and are therefore subject to selection, recall, and observer bias; the associations we discuss should be regarded as hypothesis-generating rather than causal. The cohort reflects families able to travel to and fund treatment in Dubai and may not represent the wider population of children with SMA and DMD, and referral patterns may have shifted over the study period. Functional outcomes were not systematically collected within this cohort, and the quantitative results referenced here derive from our previously published work and other cited studies.[9] Finally, as a perspective grounded in a single regional hub, our ethical and systemic reflections may not generalize to all cross-border settings. These limitations notwithstanding, we believe the scale and diversity of the cohort offer a useful vantage point on the non-molecular determinants of gene therapy success.

Conclusion

Our experience with 173 children from 17 countries leads us to argue that outcomes in SMA and DMD depend not only on gene therapy alone but also on the family, systemic, and ethical environment surrounding it. Integrating family engagement, ethical responsibility, and clinician collaboration is, in our view, essential if the promise of gene therapy is to translate into durable and equitable benefit worldwide.

Ultimately, the sustainability of these therapies will depend not only on biological durability but also on the collective will of clinicians, policymakers, and communities to build a truly inclusive global model of rare disease care. Without such coordinated global efforts, the promise of gene therapy risks becoming a privilege rather than a standard of care.

Clinical Significance

The real-world success of gene therapy for SMA and DMD depends not only on the vector but also on the family, systemic, and ethical environment that surrounds it. Clinicians can materially influence outcomes by strengthening family education, adherence, and structured multidisciplinary follow-up, while advocating for newborn screening and local diagnostic capacity. Building shared registries, standardized discharge pathways, and cross-border clinical networks offers a practical route to more equitable and durable outcomes as access to these therapies expands.

Declarations

Ethical Approval

This article is a narrative review and perspective. It does not report a study involving human participants, identifiable patient data, or animal subjects, and all observations are presented in aggregate, non-identifiable form. Formal ethical approval and a specific approval number were therefore not required.

Data Availability Declaration

No new datasets were generated or analyzed for this article. Any relevant information is available from the corresponding author upon reasonable request.

Artificial Intelligence Disclosure

During revision of this manuscript, the authors used a generative artificial intelligence large language model to assist with language editing, restructuring, and formatting. The tool was not used to generate research data, clinical findings, or references. The authors reviewed and verified all content and take full responsibility for the integrity of the manuscript.

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Authors' Contributions

Vivek Mundada conceptualized the article and wrote the original draft; Rahul Shukla critically reviewed and edited the manuscript. Both authors approved the final version and agree to be accountable for all aspects of the work.

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