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Neurogenetic and inborn errors of metabolism in pediatrics: A case series highlighting phenotypic diversity and treatable presentations

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Abstract
Background: Neurogenetic and inborn errors of metabolism (IEMs) are rare but treatable causes of childhood neuroregression, seizures, and movement disorders. Timely diagnosis using metabolic and genetic tools can reverse or mitigate progression.
Methods: We present four pediatric cases with varied neurogenetic and metabolic disorders: Glutaric Aciduria Type I, Biotinidase Deficiency, KCTD7-related Progressive Myoclonus Epilepsy, and Lesch-Nyhan Syndrome.
Results: Despite overlapping neurological phenotypes, distinct biochemical and genetic profiles were observed. Early initiation of targeted therapy led to significant clinical improvement in all cases.
Conclusion: These cases emphasize the need for early suspicion and investigation of neurogenetic disorders in children with unexplained regression, seizures, or movement abnormalities. Early diagnosis can dramatically alter outcomes in these otherwise devastating conditions.

Keywords: Neurogenetics, inborn errors of metabolism (IEM), pediatric neurology, treatable neurodevelopmental disorders, glutaric aciduria type I, biotinidase deficiency, progressive myoclonus epilepsy, lesch-nyhan syndrome, whole exome sequencing, developmental regression

Introduction

Neurogenetic disorders and inborn errors of metabolism (IEMs) represent a critical but underrecognized category of pediatric neurologic conditions. These disorders often present during infancy or early childhood with a constellation of symptoms including global developmental delay, seizures, episodic encephalopathy, hypotonia, extrapyramidal features, or regression following infections or stressors [1, 2]. Though individually rare, collectively they represent a significant cause of pediatric neurologic disability. The recent availability of expanded newborn screening and next-generation sequencing has revolutionized diagnosis, yet in low-resource settings, many treatable cases remain undetected [3, 4].

Importantly, several IEMs and neurogenetic disorders are treatable with targeted interventions, including dietary modifications, vitamin or cofactor supplementation, enzyme replacement, and symptomatic control of seizures and movement disorders [5, 6]. Recognizing subtle clinical cues and promptly initiating investigations including neuroimaging, metabolic panels, EEG, and genetic testing can transform clinical outcomes. In this series, we describe four pediatric cases where early diagnosis and appropriate therapy altered the disease trajectory. These cases serve as exemplars of how meticulous clinical evaluation coupled with genetic confirmation can save children from irreversible neurodegeneration.

Case Summaries

Case 1: Glutaric Aciduria Type I

A 3-year-old male presented with bilateral progressive sensorineural hearing loss, gait unsteadiness, and abnormal involuntary limb movements. Development until age two was normal. Examination revealed hypotonia in lower limbs, power 4/5, and choreiform movements. MRI brain and EEG were normal. Elevated lactate levels prompted a metabolic workup, and genetic testing confirmed a heterozygous pathogenic variant in the GCDH gene.

He was initiated on L-carnitine, coenzyme Q10, B-complex vitamins, and dietary protein restriction. Notably, his involuntary movements subsided and gait stabilized after three months. He also underwent cochlear implantation. GA1 typically presents with macrocephaly and striatal necrosis; however, this patient had an atypical, non-encephalopathic presentation without neuroimaging findings

Case 2: Biotinidase Deficiency

A 2-year-old boy presented with drug-refractory seizures and failure to attain milestones. He had not achieved neck holding by 6 months and was unable to sit independently at age 2. Neurological exam showed generalized hypotonia and neck drop. Multiple antiepileptic drugs had minimal effect. MRI brain was normal while EEG showed generalized slowing. Tandem mass spectrometry and enzymatic assays revealed profound biotinidase deficiency. Biotin 10 mg twice daily was started along with mitochondrial supplements. Within weeks, the child demonstrated improved alertness, gained head control, and had a significant (>80%) reduction in seizure frequency. Biotinidase deficiency remains a treatable IEM that is often missed unless specifically tested for

Case 3: Progressive Myoclonus Epilepsy (KCTD7-related)

A 3-year-old girl, previously normal, developed motor and cognitive regression after a febrile illness. Over 6 months, she became nonverbal, wheelchair-bound, and developed dancing-like limb movements (chorea) along with brief jerky episodes consistent with myoclonus. Examination revealed quadriparesis, chorea-myoclonus, and neck drop. EEG revealed a high-frequency generalized spike-and-wave pattern resembling hypsarrhythmia; MRI showed mild periventricular enlargement. Whole exome sequencing identified a homozygous missense mutation in KCTD7, consistent with neuronal ceroid lipofuscinosis subtype of PME. She was treated with valproate, levetiracetam, coenzyme Q10, and L-carnitine. While myoclonus reduced, she remained dependent for mobility. This case exemplifies the importance of differentiating PME subtypes genetically for prognosis and future therapies

Case 4: Lesch-Nyhan Syndrome

A 4-year-old boy presented with developmental regression, frequent falls, and joint swellings. History was notable for cognitive decline since age 2 and recurrent bruises. Examination showed hypotonia, joint contractures, and poor sitting balance. Serum uric acid was elevated. MRI, EEG, CSF, and autoimmune panels were normal. Genetic analysis confirmed a pathogenic mutation in the HPRT1 gene. He was started on allopurinol and supportive therapies including coenzyme Q10 and B-complex. Joint swellings subsided, and mobility improved. While classical LNS includes self-injurious behavior, this patient had a milder neuro-behavioral phenotype. Genetic confirmation in such cases helps guide prognosis, avoids unnecessary immunological workup, and allows targeted therapy

Discussion

The above cases illustrate the diagnostic heterogeneity and therapeutic possibilities in pediatric neurogenetic and metabolic disorders. Despite overlapping symptoms such as developmental regression, seizures, hypotonia, or movement abnormalities, each case had a distinct biochemical or genetic etiology. Importantly, three of the four conditions were partially or largely reversible upon targeted therapy.

GA1 is typically diagnosed after an encephalopathic crisis in infancy; however, variant forms with normal MRI and late onset chorea are increasingly recognized [6, 7]. Biotinidase deficiency, though rare, is included in newborn screening in many countries due to its dramatic response to biotin therapy [8]. KCTD7-PME has no definitive cure but symptomatic control and genetic diagnosis enable appropriate counseling and differentiation from non-progressive epileptic encephalopathies [11]. LNS requires lifelong uric acid control and neurodevelopmental monitoring; early therapy can reduce complications such as gouty arthritis and nephropathy [13-15].

From a practical standpoint, clinicians should maintain a high index of suspicion for IEMs in children with unexplained regression, especially when standard imaging and EEG are inconclusive. Tandem mass spectrometry, lactate profiles, and increasingly accessible exome sequencing provide definitive answers [3, 4, 5, 16].

Early diagnosis prevents unnecessary treatments, reduces healthcare burden, and opens the possibility of rehabilitation in many cases. This is especially crucial in resource-constrained settings where timely therapy can be life-saving. Studies suggest that nearly 50% of treatable IEMs may be missed without a systematic approach [2, 4, 17].

Table 1: Neurological Examination Findings

Case	Tone	Power	Reflexes	Involuntary Movements	Cognitive/Speech
GA1	↓ LL tone	4/5 all limbs	DTRs present, plantars flexor	Chorea	Normal interaction
Biotinidase Deficiency	Hypotonia all limbs	Neck drop, unable to sit	Normal	None	Delayed milestones
KCTD7-related PME	Hypotonia	2/5 in all limbs	Normal	Chorea, Myoclonus	Regression, non-verbal
Lesch-Nyhan Syndrome	Normal	Normal	Diminished DTRs	None	Cognitive decline

Table 2: Investigations including EEG and MRI

Case	MRI Findings	EEG Findings	Metabolic Workup	Additional Tests
GA1	Normal	Normal	↑ Lactate	BERA: SNHL
Biotinidase Deficiency	Normal	Generalized slowing	↓ Biotinidase activity	TMS: Biotinidase deficient
KCTD7-related PME	Mild periventricular enlargement	Hypsarrhythmia-like pattern	Normal	TMS normal
Lesch-Nyhan Syndrome	Normal	Normal	↑ Uric Acid	CSF/Autoimmune panel: Normal

Table 3: Genetic Mutations and Confirmation

Case	Gene Involved	Mutation Identified	Inheritance	Method of Confirmation
GA1	GCDH	c.394C>T; p.Arg132Trp (heterozygous)	Autosomal Recessive	Clinical Exome
Biotinidase Deficiency	BTD	Likely pathogenic homozygous mutation	Autosomal Recessive	TMS + WES
KCTD7-related PME	KCTD7	c.602C>G; p.Pro201Arg (homozygous)	Autosomal Recessive	Whole Exome Sequencing
Lesch-Nyhan Syndrome	HPRT1	Pathogenic HPRT1 mutation	X-linked Recessive	Whole Exome Sequencing

Conclusion
This case series reinforces the critical need for awareness, early identification, and intervention in pediatric neurogenetic and metabolic disorders. With advancements in diagnostics and availability of disease-specific therapies, many of these conditions are no longer inevitably progressive. A child with regression or intractable seizures today could have a treatable IEM. A proactive, multidisciplinary approach can make a profound difference.

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Conflict of Interest
The authors declare no conflict of interest.

Ethical Approval
This case series was conducted in accordance with institutional ethical standards. Consent for publication was obtained from the parents/guardians of all included children.

Informed Consent
Written informed consent was obtained from the legal guardians of all patients for publication of this case series and accompanying images.

Author Contributions
Dr. Akshay Bhutada: Conceptualization, patient management, manuscript drafting, and final editing
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Dr. Marami Das: EEG and radiological correlation, critical manuscript review
Dr. Munindra Goswami: Overall guidance, manuscript approval, and senior authorship

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