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CLINICAL AND LABORATORY PROFILE OF CHILDREN WITH MITOCHONDRIAL DISORDERS

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Abstract

Introduction: Mitochondrial disorders are a diverse group of inborn errors of metabolism caused by dysfunction of mitochondrial oxidative phosphorylation. They commonly present in children with non-specific neurological and systemic features, making early diagnosis challenging. This study aimed to characterize the clinical, biochemical, radiological, histopathological, and molecular profiles of pediatric mitochondrial disorders to improve early recognition and management.

Materials and Methods: A prospective observational study was conducted over one year at Indira Gandhi Institute of Child Health, Bengaluru, enrolling 67 children aged 1 month to 18 years with probable or definite mitochondrial disorders. Diagnosis was based on a composite scoring system integrating clinical, biochemical, radiological, and histopathological parameters. Investigations included blood tests, CSF analysis, tandem mass spectrometry, neuroimaging, muscle biopsy, and next-generation genetic sequencing where feasible.

Results: Leigh syndrome was the predominant phenotype (n=58). Neurological features such as seizures (78.2%), hypotonia (85.5%), dystonia (72.7%), and neuroregression (81.8%) were significantly more common in Leigh syndrome compared to other mitochondrial disorders. Elevated serum lactate was observed in 94.5% of Leigh syndrome cases. MRI revealed classic Leigh pattern lesions in 80% of affected patients. Genetic mutations were identified in all 17 cases where sequencing was performed, with a predominance of nuclear gene mutations. A high consanguinity rate (55.2%) was noted, correlating with the autosomal recessive inheritance pattern.

Conclusion: Pediatric mitochondrial disorders exhibit broad clinical heterogeneity, with Leigh syndrome being the most frequent presentation. A multimodal diagnostic approach combining clinical evaluation, biochemical testing, imaging, histopathology, and genetic analysis enhances diagnostic yield. Early suspicion, particularly in consanguineous populations, coupled with comprehensive evaluation, is crucial for timely intervention and genetic counseling.

Keywords: Mitochondrial diseases; genetic mutations; neuroregression; spectrometry

Introduction

Mitochondrial diseases represent one of the most common groups of inborn errors of metabolism, with an estimated prevalence of 1 in 5,000 individuals [1]. These disorders are caused by dysfunction in mitochondrial oxidative phosphorylation, affecting cellular energy production. Mitochondria are unique organelles, both structurally and genetically, possessing their genome (mitochondrial DNA, or mtDNA) while being under the dual control of both mtDNA and nuclear DNA (nDNA) [2]. Mutations in either genome can disrupt the intricate machinery responsible for ATP synthesis and lead to multisystem involvement [1]. The clinical and genetic heterogeneity of mitochondrial disorders is profound, making them a diagnostic challenge, especially in the pediatric population.

Pediatric mitochondrial diseases frequently present with non-specific signs such as developmental delay, hypotonia, poor weight gain, seizures, altered sensorium, and in some cases, clinical features that mimic sepsis or pneumonia [3]. The phenotypic overlap with more common pediatric conditions often leads to delayed or missed diagnoses. Complicating this further is the lack of universally accepted diagnostic criteria, and the current diagnostic framework requires a multimodal approach integrating clinical evaluation, biochemical assays, neuroimaging, histopathology, and molecular genetic testing [3]. However, even with this arsenal of tools, the confirmatory diagnosis often remains elusive in cases with vague or evolving phenotypes.

The term “mitochondrion” was coined in 1898, though the organelle had been visualized earlier by Altmann in 1890. It has long been recognized as the cell’s powerhouse, yet it is now understood to perform diverse functions beyond ATP production, including regulation of calcium homeostasis, apoptosis, redox signaling, and biosynthesis of macromolecules [4]. The first association between mitochondria and human disease was reported in 1962 by Rolf Luft, who described a case of childhood-onset hypermetabolism linked to mitochondrial dysfunction—now referred to as Luft disease [5]. Since then, over 200 nDNA genes and all 13 protein-coding mtDNA genes have been implicated in primary mitochondrial pathologies.

Children with mitochondrial disorders frequently have central nervous system involvement, reflecting the high energy demands of neuronal tissue. The resulting encephalopathy may follow a devastating and rapidly progressive course [6]. Despite advances in molecular diagnostics, the genetic basis remains unknown in a significant proportion of patients. In many low- and middle-income countries, limited access to comprehensive testing further hampers early diagnosis and management. This underscores the urgent need for well-characterized cohorts that examine both phenotypic and genotypic spectra, particularly in pediatric populations.

Current literature lacks large, integrative pediatric cohorts that correlate genotype with phenotype in mitochondrial disorders using a unified diagnostic approach [7]. There is limited region-specific data that describes the molecular landscape of these diseases, particularly in non-Western populations. Furthermore, diagnostic algorithms that effectively combine clinical, radiological, histopathological, and genetic data are either insufficiently validated or not routinely applied in clinical settings. The study explores the genotypic and phenotypic spectrum of childhood-onset mitochondrial diseases. The objectives are a) to characterize mitochondrial disorders in children using clinical, biochemical, radiological, molecular, and histopathological findings, b) to enhance early recognition and diagnosis of mitochondrial diseases in pediatric populations, and c) to inform early therapeutic interventions and provide timely genetic counselling aimed at preventing recurrence within affected families.

Materials and methods

This prospective observational study was conducted over a period of one year, including time allotted for data analysis, at the Indira Gandhi Institute of Child Health, Bengaluru. The study enrolled children aged between 1 month and 18 years who presented to the outpatient department or were admitted with a probable or definite diagnosis of mitochondrial disorder.

Given the low incidence of mitochondrial diseases, estimated at 1 in 5,000 live births, a formal sample size calculation was not deemed appropriate. Instead, patient recruitment was based on prior hospital records, with 55 cases documented in the preceding year. A total of 67 cases were included during the study period.

A structured proforma was used for data collection. Informed consent was obtained from the parent or legal guardian of each child. Detailed clinical history was taken, including perinatal events, developmental milestones, family history, and sociodemographic details. Thorough systemic examination findings were recorded. Suspected cases underwent targeted investigations based on clinical indications and financial feasibility.

Children aged 1 month to 18 years with either a probable or definite diagnosis of mitochondrial disorder, as defined by the modified mitochondrial disease criteria and an informed consent obtained from parent or guardian were included in the study. Children with other confirmed inborn errors of metabolism, nutritional deficiency disorders such as thiamine deficiency, and central nervous system infections were excluded from the study.

Diagnosis was made using a comprehensive scoring system comprising clinical, metabolic/imaging, and morphological parameters. Points were allocated across domains including muscular, central nervous system, and multisystem involvement (maximum 4 points). Biochemical and radiological investigations contributed an additional 4 points, and morphological criteria (e.g., muscle biopsy findings) contributed up to 4 points. Final scores were used to classify patients into one of four categories: mitochondrial disorder unlikely (score = 1), possible (score 2–4), probable (score 5–7), or definite (score 8–12).

Investigations included: complete blood count, arterial blood gas, serum electrolytes, creatine phosphokinase, lactate, cerebrospinal fluid (CSF) analysis (protein, lactate, alanine), tandem mass spectrometry, neuroimaging (CT/MRI), and muscle biopsy. Genetic testing, including targeted nuclear/mitochondrial gene panels or exome sequencing, were performed when indicated and feasible.

Results

Neurological Manifestations

In the Leigh Syndrome (LS) group, seizures were noted in 78.2% (43/55) of patients versus 44.4% (4/9) in the Other Mitochondrial Disorders (OMD) group (chi-square (χ^2)=4.35, p=0.037; Table 1, Figure 1). Hypotonia occurred in 85.5% (47/55) of LS compared with 55.6% (5/9) of OMD (Fisher's Exact test, p=0.045). Dystonia was present in 72.7% (40/55) of LS versus 22.2% (2/9) of OMD (Fisher's Exact test, p=0.008). Neuroregression affected 81.8% (45/55) of LS and 33.3% (3/9) of OMD (Fisher's Exact test, p=0.006). Myoclonic jerks were observed in 69.1% (38/55) of LS compared with 33.3% (3/9) of OMD (Fisher's Exact test, p=0.045). Developmental delay did not differ significantly between groups (81.8% [45/55] vs 55.6% [5/9]; χ^2=3.09, p=0.078; Table 1, Figure 1).

Table 1: Neurological Symptoms Comparison

Feature	LS_pct	OMD_pct	Test Used	Test Statistic	p-value	Significant
Seizures	78.2	44.4	Chi-square	Ï‡Â² = 4.35	0.037	Yes
Hypotonia	85.5	55.6	Fisherâ€™s Exact		0.045	Yes
Dystonia	72.7	22.2	Fisherâ€™s Exact		0.008	Yes
Neuroregression	81.8	33.3	Fisherâ€™s Exact		0.006	Yes
Myoclonic Jerks	69.1	33.3	Fisherâ€™s Exact		0.045	Yes
Developmental Delay	81.8	55.6	Chi-square	Ï‡Â² = 3.09	0.078	No

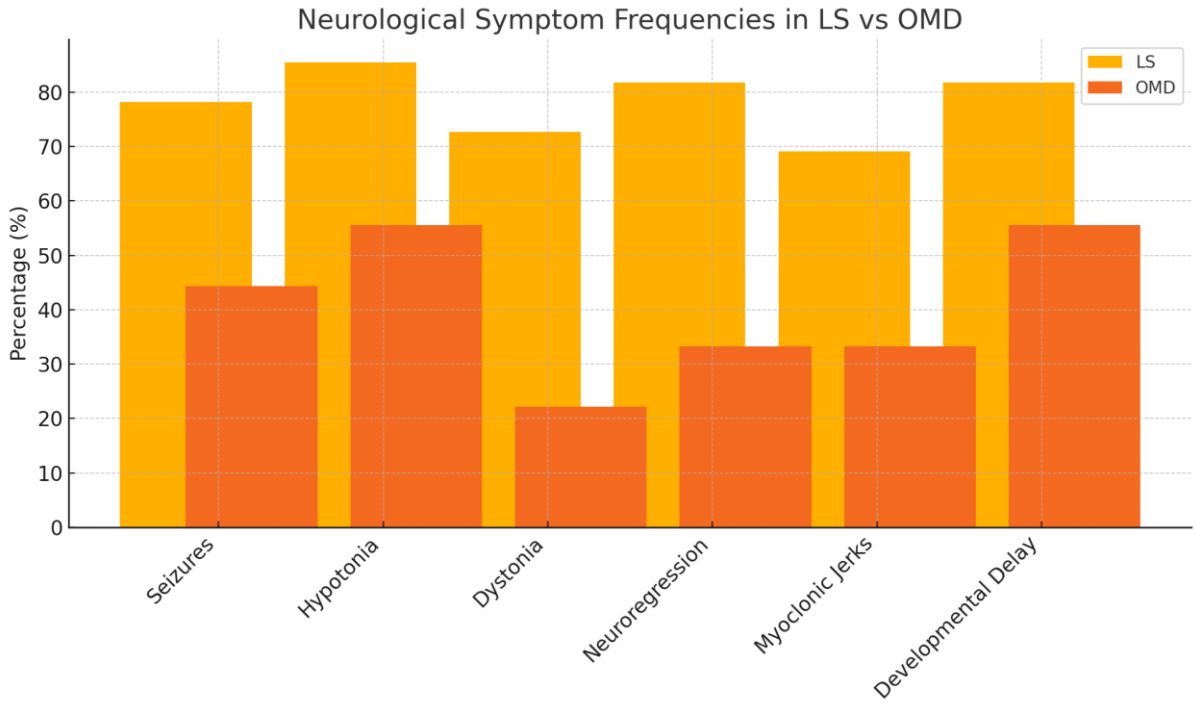

Figure 1: Neurological Symptom Frequencies in LSVs OMD

Systemic Features

Ophthalmological signs were significantly more frequent in LS (90.9%, 50/55) than OMD (66.7%, 6/9; Fisher's Exact test, p=0.049; Table 2, Figure 2). Hearing impairment occurred in 65.5% (36/55) of LS and 55.6% (5/9) of OMD (χ^2=0.35, p=0.554). Gastrointestinal symptoms or failure to thrive were documented in 87.3% (48/55) of LS compared with 77.8% (7/9) of OMD (χ^2=0.68, p=0.408). Syndromic features appeared in 87.3% (48/55) of LS versus 55.6% (5/9) of OMD (Fisher's Exact test, p=0.023; Table 2, Figure 2).

Table 2: Systemic Features Comparison

Feature	LS_pct	OMD_pct	Test Used	Test Statistic	p-value	Significant
Ophthalmological Signs	90.9	66.7	Fisher's Exact		0.049	Yes
Hearing Impairment	65.5	55.6	Chi-square	χ^2 = 0.35	0.554	No
GI Symptoms/FTT	87.3	77.8	Chi-square	χ^2 = 0.68	0.408	No
Syndromic Features	87.3	55.6	Fisher's Exact		0.023	Yes

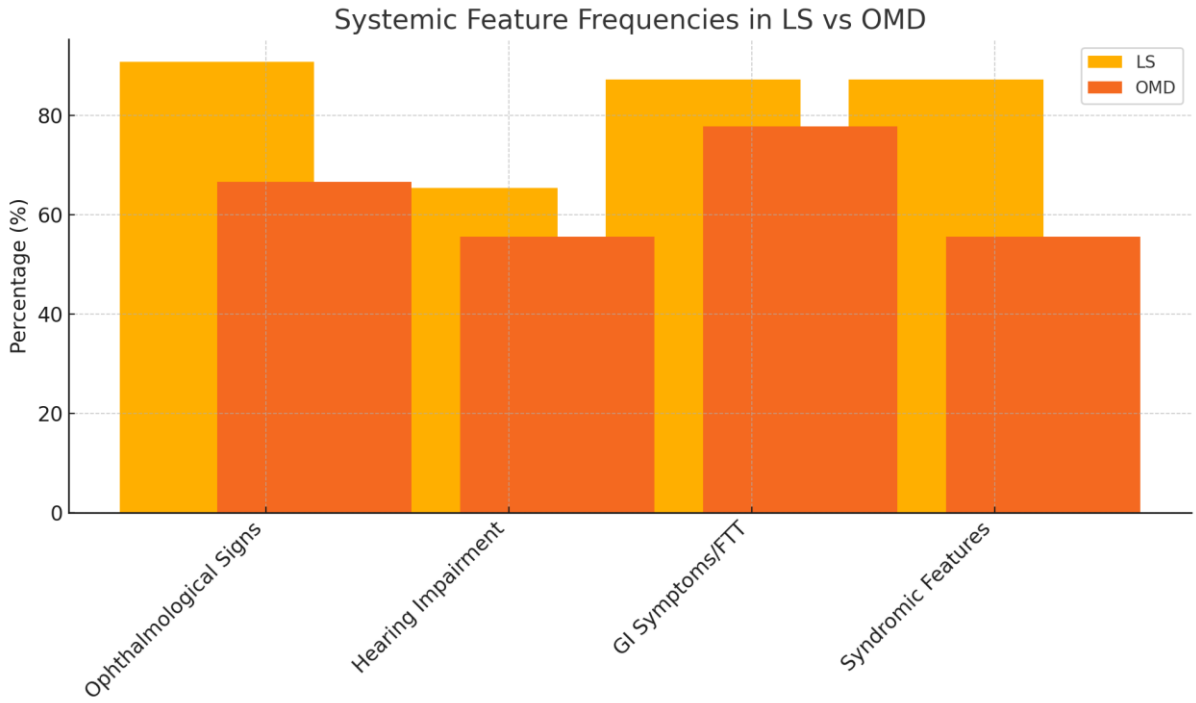

Figure 2: Systemic Feature Frequencies in LS vs OMD

Biochemical Profile

Elevated serum lactate was observed in 94.5% (52/55) of LS and 77.8% (7/9) of OMD (Fisher's Exact test, p=0.097; Table 3). Metabolic acidosis on arterial blood gas occurred in 78.2% (43/55) of LS versus 66.7% (6/9) of OMD (χ^2=0.59, p=0.444). Tandem mass spectrometry abnormalities were rare in both groups (9.1% [5/55] vs 11.1% [1/9]; Fisher's Exact test, p=0.855; Table 3).

Table 3. Biochemical Profile Comparison

Test	LS (%) (n)	OMD (%) (n)	Test Used	Test Statistic	p-value	Significant
Serum Lactate ↑	94.5% (52/55)	77.8% (7/9)	Fisher's Exact	—	0.097	No
Metabolic Acidosis	78.2% (43/55)	66.7% (6/9)	Chi-square	$\chi^2 = 0.59$	0.444	No
TMS Abnormal	9.1% (5/55)	11.1% (1/9)	Fisher's Exact	—	0.855	No

Consanguinity

A history of consanguineous parentage was significantly more common in LS (72.7%, 40/55) than OMD (33.3%, 3/9; χ^2=4.57, p=0.033) (Table 4).

Table 4. Consanguinity Rates

Group	Consanguinity (%) (n)	Test Used	Test Statistic	p-value	Significant
LS	72.7% (40/55)	Chi-square	$\chi^2 = 4.57$	0.033	Yes
OMD	33.3% (3/9)				

MDC Score

Mean mitochondrial disease criteria (MDC) composite scores were 6.89 ± 1.06 in LS and 6.44 ± 0.73 in OMD. This difference did not reach statistical significance (independent t-test: t=1.34, df=62, p=0.185) (Table 5).

Table 5. MDC Score Comparison

Group	Mean ± SD	Test Used	Test Statistic	df	p-value	Significant
LS	6.89 ± 1.06	t-test	t = 1.34	62	0.185	No
OMD	6.44 ± 0.73					

Neuroimaging

Classic "Leigh pattern" lesions in basal ganglia or brainstem on MRI were identified in 80.0% (44/55) of LS and 33.3% (3/9) of OMD (χ^2=8.63, p=0.003) (Table 6), confirming its diagnostic specificity.

Table 6. Classic Leigh MRI Pattern Frequency

Group	Leigh Pattern (%) (n)	Test Used	Test Statistic	p-value	Significant
LS	80.0% (44/55)	Chi-square	χ^2 = 8.63	0.003	Yes
OMD	33.3% (3/9)				

Discussion

This prospective observational study was conducted over a period of one year at the Indira Gandhi Institute of Child Health, Bengaluru, to evaluate the clinical, biochemical, radiological, histopathological, and molecular characteristics of childhood-onset mitochondrial disorders. The study cohort comprised 67 children aged 1 month to 18 years with a probable or definite diagnosis of mitochondrial disease, predominantly Leigh syndrome (n = 58), with the remaining presenting other mitochondrial phenotypes.

Epidemiological and Demographic Profile

The mean age at presentation was 34.81 ± 41.32 months, indicating that most children presented during early infancy or early childhood. This is consistent with findings by Hu et al. from the Children's Hospital of Fudan University, where the mean age at onset was approximately 3 years, further emphasizing the early life onset of mitochondrial pathology that often affects neurodevelopmental milestones [8].

A male predominance (67.2%) was noted in the cohort, aligning with previously published data from Sofou et al., who described a similar trend in a European multicenter cohort of 130 children with mitochondrial diseases. Although mitochondrial disorders are not known to follow a strict sex-linked inheritance pattern in most cases, subtle sex-related differences in disease expression have been reported and may reflect a diagnostic bias or differential disease penetrance [9].

A notable 55.2% of the participants were born to consanguineous parents. This high rate underscores the autosomal recessive nature of many mitochondrial disorders, particularly those resulting from nuclear gene mutations. It also highlights the significance of targeted genetic counseling and reproductive planning in populations where consanguineous marriages are prevalent.

Clinical Manifestations

The clinical phenotype of mitochondrial disorders in this study was broad and heterogeneous, reflecting the systemic involvement that characterizes these diseases. Developmental delay was the most prevalent presenting complaint, observed in 71.6% of cases. This reinforces existing literature that identifies global developmental delay—spanning motor, cognitive, and speech domains—as a cardinal early manifestation of mitochondrial dysfunction. Mitochondrial disorders often lead to a varied neurocognitive trajectory, ranging from mild learning delays to profound intellectual disability, without a clearly delineated cognitive profile [10].

Seizures were reported in 59.7% of participants, further supporting the central nervous system's vulnerability in mitochondrial disease. Epilepsy in mitochondrial disorders is typically multifocal, refractory, and of mixed semiology, including myoclonic, focal, and generalized tonic-clonic seizures. These findings align with the European cohort study by Sofou et al., where epilepsy was a predominant neurological manifestation [9].

Involuntary movements were documented in 40.3% of children, including choreoathetoid and dystonic features [11]. While this proportion appears higher than the 20%–40% reported in earlier literature, it underscores the broad phenotypic variability of extrapyramidal involvement in mitochondrial pathology, particularly in disorders such as Leigh syndrome.

Tone abnormalities were another consistent finding. Hypotonia was present in 20.9% and hypertonia in 38.8%. This trend is partly comparable with the findings of Sofou et al., where hypotonia was a dominant feature (74.6%), and hypertonia/dystonia was reported in about 40% of children [10]. The variation in our cohort might reflect disease stage at presentation or differing diagnostic criteria thresholds.

Microcephaly was observed in nearly half the cohort (44.8%), and failure to thrive (FTT) was a strikingly prevalent feature, seen in 88.1% of children. FTT may result from increased metabolic demands, feeding difficulties, and multiorgan dysfunction, and is often a subtle early indicator of mitochondrial cytopathy [12].

Cardiac manifestations, although less common in our cohort (8.6%), included both hypertrophic and dilated cardiomyopathies confirmed via echocardiography. These findings are consistent with those reported by Sofou et al., where 17.7% of patients exhibited cardiomyopathy [9]. Importantly, the presence of cardiac involvement is considered a negative prognostic factor in mitochondrial disorders [13].

Biochemical and Metabolic Investigations

Serum lactate was elevated in 83.6% of the cohort, a finding consistent with previous studies that identify lactic acidosis as a key though non-specific biochemical hallmark of mitochondrial dysfunction. As noted in both Hu et al.[8] and Sofou et al.[9], elevated lactate levels—particularly when sustained in the CSF—can support a diagnosis of respiratory chain defects, although they may also appear in other metabolic or hypoxic conditions.

ABG abnormalities were detected in 29.9% of children, indicating the presence of systemic acidosis in a subset of patients. While not universal, this further reinforces the importance of ABG screening as part of the initial workup in suspected cases.

Tandem mass spectrometry (TMS) yielded abnormal results in 9% of patients, indicating perturbations in organic acid metabolism. While a small fraction, these findings are valuable adjuncts when interpreted alongside other metabolic parameters.

Serum creatine phosphokinase (CPK) was elevated in 22.4% of patients. This aligns with the broader literature suggesting that mitochondrial myopathies can occasionally result in muscle fiber breakdown and increased enzyme leakage, especially in cases with prominent myopathic features.

Neurophysiological and Radiological Findings

EEG revealed epileptiform discharges or background slowing in 26.9% of the cohort. While this rate is modest, it is clinically significant, as a normal EEG does not exclude seizure risk in mitochondrial disease due to its paroxysmal nature.

MRI brain imaging was pivotal in diagnosis, with basal ganglia involvement identified in 70.1% of children—particularly among those with Leigh syndrome, where symmetrical necrotic lesions in the putamen and globus pallidus are classic. Cortex abnormalities and multistructural involvement were more frequent in non-Leigh phenotypes [14]. The role of MRI, particularly when interpreted alongside magnetic resonance spectroscopy (MRS), remains invaluable in guiding further investigations and reinforcing clinical suspicion.

Histopathology and Genetic Findings

Muscle biopsy was conducted in 10 selected patients. Of these, 90% showed abnormalities on mitochondrial enzyme assay via spectrophotometry, with complex I deficiency being the most common (40%). These results mirror those of Danhelovska et al., who also reported a predominance of complex I defects in pediatric mitochondrial disease cohorts [15].

Genetic analysis using next-generation sequencing (NGS) was performed in 17 cases and yielded definitive mutations in all. Nuclear gene mutations were more prevalent (82.35%) than mitochondrial gene mutations (17.6%). Identified mutations included *SURF1*, *MED17*, *POLG*, *ECH1*, *COX15*, *FBXL4*, *NDUFV2*, and *NDUFS6*. These findings echo those from Theunissen et al., who emphasized the expanding role of nuclear gene defects in pediatric mitochondrial encephalopathies [16]. The predominance of nuclear mutations further supports the need for comprehensive exome-based panels rather than targeted mtDNA testing alone.

Diagnostic Classification

Using the modified mitochondrial disease criteria, 61.2% of children were classified as having a probable mitochondrial disorder, and 37.3% as having a definite disorder. Only one child (1.5%) was classified as having a possible disorder. This underscores the diagnostic value of integrating clinical, biochemical, radiological, histological, and molecular data to achieve diagnostic confidence

Conclusion

Mitochondrial disorders in children exhibit significant clinical diversity and present considerable diagnostic challenges. Leigh syndrome was the most frequent phenotype identified, yet a wide array of non-Leigh presentations also emerged. Employing a comprehensive diagnostic approach—integrating biochemical testing, neuroimaging, muscle biopsy, and next-generation sequencing (NGS)—proved to be highly effective. The results underscore the critical role of early clinical suspicion, timely diagnostic evaluation, and genetic counseling, especially in settings with high consanguinity, early age of onset, and multisystem involvement, to improve patient outcomes and assist in family planning.

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