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Exercise Intolerance as a Clinical Red Flag For Childhood-Onset Mitochondrial Diseases : A Narrative Review

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Abstract

Background: Childhood-onset mitochondrial diseases comprise a clinically and genetically heterogeneous group of inherited disorders in which impaired oxidative phosphorylation predominantly affects tissues with high energy demands. Exercise intolerance is a common but nonspecific manifestation that may be overlooked or attributed to other conditions, contributing to delayed diagnosis. This narrative review aims to summarize the current evidence regarding exercise intolerance as a potential clinical red flag for childhood-onset mitochondrial diseases.

Methods: A narrative literature review was conducted using the PubMed/MEDLINE database. English-language articles published between 2010 and 2026 were identified using keywords related to mitochondrial diseases, exercise intolerance, diagnosis, and pediatric populations. Additional relevant studies were identified through backward citation searching.

Results: Current evidence suggests that exercise intolerance frequently represents one of the earliest manifestations of childhood-onset mitochondrial diseases. Its diagnostic significance increases when accompanied by neurological or multisystem manifestations together with supportive laboratory or neuroimaging abnormalities, warranting further metabolic and genetic evaluation.

Conclusions: Exercise intolerance should be recognized as an important clinical red flag for childhood-onset mitochondrial diseases, particularly when associated with additional neurological or multisystem features. Early clinical recognition followed by appropriate metabolic and genetic evaluation may reduce diagnostic delay, facilitate molecular diagnosis, and improve patient management.

Keywords: mitochondrial diseases, mitochondrial disorders, mitochondrial myopathies, exercise intolerance, physical activity, pediatric, childhood, diagnosis

1. Introduction

Mitochondrial diseases comprise a genetically and clinically heterogeneous group of inherited disorders caused by pathogenic variants affecting mitochondrial function and oxidative phosphorylation (OXPHOS). As a consequence of impaired ATP production, tissues with high

energy demands, including skeletal muscle, the central nervous system, and the myocardium, are particularly susceptible to dysfunction (Gorman et al., 2016).

Primary mitochondrial diseases are caused by pathogenic mutations affecting either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) leading to structural and/or functional impairment of mitochondria. Approximately 80% of childhood-onset mitochondrial disease cases are caused by pathogenic variants in nuclear DNA (Heath et al., 2025). Mutations in the same gene may cause different clinical phenotypes.

Mitochondrial diseases are one of the most common inborn errors of metabolism with the estimated prevalence of 1:5000 (Parikh et al., 2015). The reported prevalence of childhood-onset mitochondrial diseases (<16 years of age) is estimated to be approximately 5-15 cases per 100,000 individuals (Gorman et al., 2016). However, the actual prevalence is likely underestimated because a number of affected patients remain undiagnosed in clinical practice.

Mitochondrial diseases are characterized by remarkable clinical heterogeneity, with considerable variability in the age of onset, disease progression, and extent of organ involvement. This phenotypic diversity makes the diagnostic process particularly challenging. While the nonspecific nature of early manifestations may contribute to delayed recognition, premature attribution of unexplained symptoms to mitochondrial disease may also result in unnecessary, costly, and potentially invasive diagnostic investigations.

Exercise intolerance is one of the most frequently reported manifestations of mitochondrial dysfunction. It is generally characterized by reduced exercise capacity, premature fatigue, exercise-induced myalgia, or delayed recovery following physical activity, reflecting impaired oxidative energy metabolism within skeletal muscle. Beyond its impact on physical performance, exercise intolerance may substantially impair activities of daily living and quality of life, representing a significant source of disability in patients with mitochondrial diseases (Porcelli et al., 2019).

The aim of this narrative review is to summarize the current evidence regarding exercise intolerance as a potential clinical red flag for childhood-onset mitochondrial diseases. Particular emphasis is placed on the underlying pathophysiological mechanisms, associated clinical features, and the diagnostic approach that may facilitate earlier recognition of these disorders.

2. Methodology

This study was designed as a narrative literature review aimed at summarizing the current evidence on exercise intolerance as a potential clinical red flag for childhood-onset mitochondrial diseases, with particular emphasis on its pathophysiology, associated clinical features, and diagnostic evaluation.

A literature search was performed using the PubMed/MEDLINE database. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to mitochondrial diseases, exercise intolerance, exercise-induced fatigue, diagnosis, clinical recognition, diagnostic evaluation, and pediatric populations. The search was limited to English-language publications involving human subjects published between January 2010 and December 2026.

Original clinical studies, randomized controlled trials, clinical trials, systematic reviews, meta-analyses, and narrative reviews were considered eligible for inclusion. Case reports, conference abstracts, editorials, letters to the editor, and non-English publications were excluded. Titles and abstracts were screened for relevance, and studies not relevant to the objectives of this review were excluded. The remaining publications underwent full-text assessment. Additional relevant studies were identified through backward citation searching (snowballing) of the reference lists of eligible articles and review papers.

The included studies were qualitatively synthesized with a particular focus on the pathophysiological basis of exercise intolerance, associated clinical red flags, and the diagnostic approach to childhood-onset mitochondrial diseases. As this work represents a narrative review, no formal review protocol was registered, and a PRISMA-guided study selection process was not applied.

3. Pathophysiology of Exercise Intolerance

Continuous ATP production is essential for sustaining skeletal muscle contractions during exercise. As intramuscular ATP stores are limited, energy must be continuously regenerated, either through phosphocreatine and glycogen breakdown (anaerobic) or oxidative phosphorylation (aerobic) that takes place in mitochondria (Hargreaves & Spriet, 2020).

Because mitochondrial energy metabolism is essential for virtually all tissues, mitochondrial diseases may affect almost every organ system (Heath et al., 2025).

Mitochondria play a central role in cellular energy metabolism by generating adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS). During exercise, skeletal muscle ATP demand increases markedly and must be continuously regenerated to sustain muscle contraction. Consequently, efficient mitochondrial function is essential for maintaining exercise capacity, particularly during prolonged aerobic activity. Defects affecting the mitochondrial respiratory chain impair ATP synthesis and reduce the ability of skeletal muscle to meet the metabolic demands of exercise, providing the fundamental pathophysiological basis of exercise intolerance in mitochondrial diseases (Conley, 2016).

Impaired oxidative phosphorylation forces skeletal muscle to rely increasingly on anaerobic glycolysis to maintain ATP production during exercise. Although this compensatory mechanism temporarily supports energy generation, it is substantially less efficient and results in accelerated lactate accumulation, phosphocreatine depletion, intracellular acidosis, and earlier onset of muscle fatigue, leading to exercise intolerance, premature exhaustion and prolonged recovery following physical activity (Mancuso et al., 2012; Wen et al., 2025).

Importantly, exercise intolerance in mitochondrial disease primarily reflects impaired oxygen utilization rather than inadequate oxygen delivery. Although oxygen transport to skeletal muscle is usually preserved, dysfunctional mitochondria are unable to effectively utilize oxygen for ATP synthesis. This mismatch between oxygen delivery and oxygen consumption contributes to reduced aerobic capacity, diminished maximal oxygen uptake ($\text{VO}_{2\text{ max}}$), and exaggerated fatigue during exercise (Porcelli et al., 2019)(Taivassalo et al., 2003; Tarnopolsky, 2004). Patients with mitochondrial myopathies demonstrate reduced oxidative capacity due to impaired skeletal muscle oxygen extraction rather than inadequate oxygen delivery. Consequently, maximal oxygen uptake ($\text{VO}_{2\text{ max}}$) is reduced despite increased cardiac output and ventilation during exercise (Berardo et al., 2010).

Although exercise-induced lactate elevation represents a useful diagnostic clue, current evidence suggests that lactate itself is unlikely to be the primary mechanism responsible for exercise intolerance (Vissing et al., 2001).

The severity of exercise intolerance varies considerably among patients and depends on multiple factors, including the underlying genetic defect, mutation load, tissue-specific distribution of pathogenic variants, and the degree of residual mitochondrial function. Consequently, exercise intolerance may occur as an isolated manifestation or as part of a broader multisystem phenotype involving the nervous system, heart, endocrine organs, and other high-energy-demand tissues (Porcelli et al., 2019).

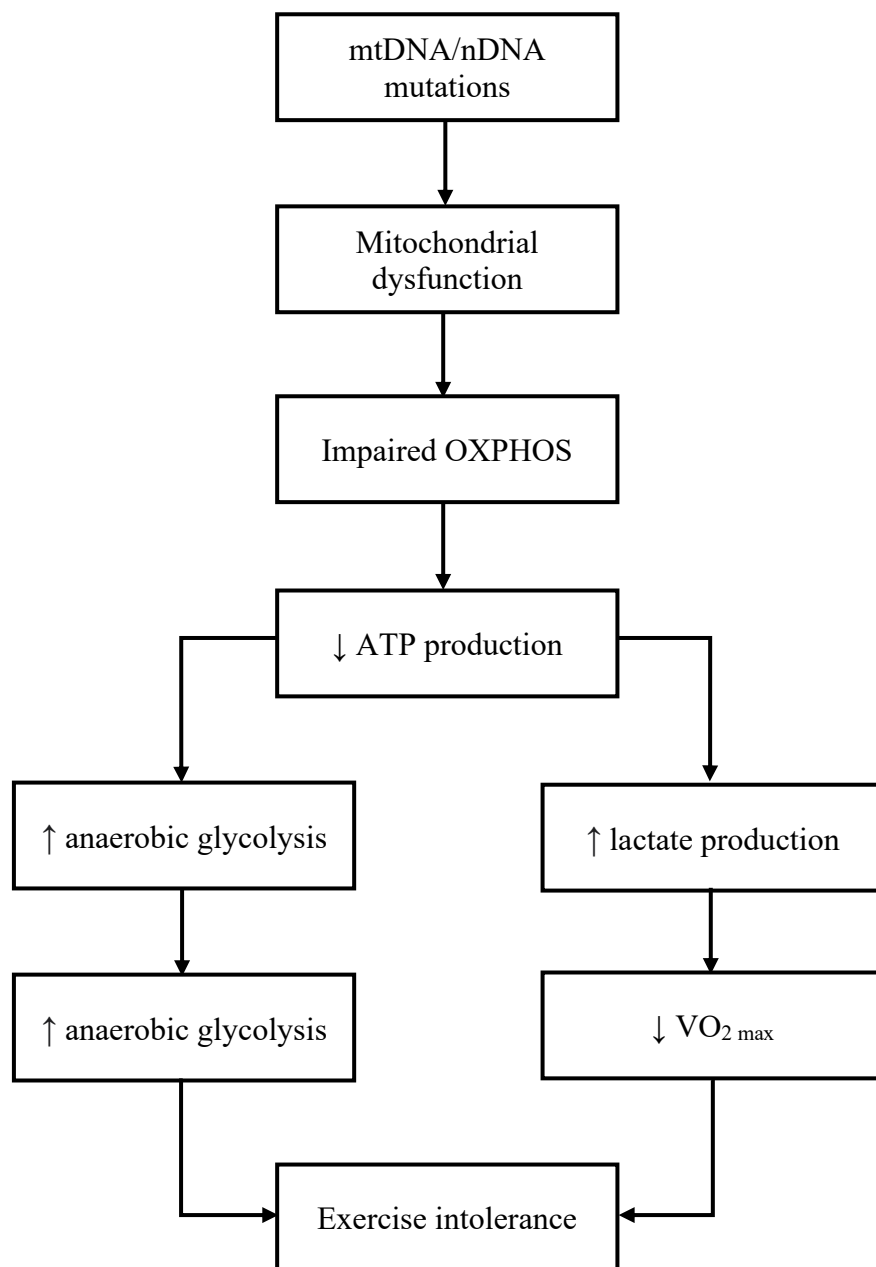


Figure 1. Pathophysiology of exercise intolerance in mitochondrial diseases

4. Clinical Presentation and Red Flags

Exercise intolerance in mitochondrial diseases may occur as an isolated manifestation or in combination with progressive muscle weakness and multisystem involvement, although in pediatric population it most commonly occurs as a part of multisystem mitochondrial disorder (Rahman, 2020). Exercise intolerance typically manifests as exertional fatigue and muscle cramps and may occasionally be accompanied by post-exercise vomiting due to lactic acidosis, whereas rhabdomyolysis is uncommon.

Patients often describe a subjective sensation of muscle heaviness or burning during exercise, occasionally accompanied by post-exercise vomiting due to lactic acidosis, whereas rhabdomyolysis is uncommon (Rahman, 2020). Symptoms such as muscle stiffness, painful cramps (especially during isometric exercise), or the "second-wind" phenomenon are typically absent, these clinical characteristics may help differentiate mitochondrial myopathies from other metabolic myopathies (Berardo et al., 2010). Mitochondrial myopathies typically present with recurrent exercise intolerance and premature fatigue, most commonly triggered by prolonged submaximal exercise. Symptoms may also be precipitated by fasting, intercurrent illness, or fever (Danti et al., 2021).

Although exercise intolerance itself is a nonspecific symptom, its diagnostic significance increases substantially when accompanied by additional neurological or multisystem manifestations. In pediatric patients, exercise intolerance and myopathy should prompt evaluation for multisystem involvement rather than being interpreted as isolated muscle manifestations. Clinical features such as ophthalmoplegia, stroke-like episodes, epilepsy, movement disorders, migraine, cognitive decline, pigmentary retinopathy and optic atrophy, sensorineural hearing loss, gastrointestinal symptoms, cardiomyopathies and arrhythmias, tubulopathies, diabetes mellitus and short stature should raise suspicion of an underlying mitochondrial disease and prompt further diagnostic evaluation. (Heath et al., 2025; Conti et al., 2023; Berardo et al., 2010; Mancuso et al., 2012). In patients presenting with clinically significant muscle weakness, unexpectedly normal CK concentrations and electromyographic findings should prompt consideration of a mitochondrial disorder (Koenig, 2008).

In children, exercise intolerance may present subtly as delayed motor development or reduced athletic performance compared with age-matched peers, contributing to delayed clinical recognition (Heath et al., 2025).

Data from the Italian Collaborative Network of Mitochondrial Diseases (Mancuso et al., 2012) demonstrated that exercise intolerance was present in 20,2% patients (222/1100) with the diagnosis of mitochondrial disease, making it the fourth most frequent clinical manifestation after ptosis/ophthalmoparesis, muscle weakness, and hearing loss. Importantly, nearly half of the patients with exercise intolerance presented with this symptom at disease onset, suggesting that reduced exercise capacity may represent an early manifestation of mitochondrial disease.

Exercise intolerance is frequently underrecognized in clinical practice and may initially be attributed to cardiopulmonary disorders, contributing to delayed diagnosis of mitochondrial disease (Conti et al., 2023).

According to (Danti et al., 2021), exercise intolerance in the absence of myoglobinuria, particularly when accompanied by multisystem involvement, an elevated lactate/pyruvate ratio, or lactic acidosis, should raise suspicion of a mitochondrial respiratory chain disorder.

Exercise intolerance is often difficult to assess and quantify on the basis of clinical history alone. Therefore, cardiopulmonary exercise testing (CPET) represents the most objective method for evaluating exercise intolerance in patients with suspected mitochondrial myopathy. It enables comprehensive assessment of aerobic capacity by measuring parameters including oxygen uptake (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio, heart rate, minute ventilation, cardiac output, and perceived exertion. Patients with mitochondrial myopathies typically demonstrate reduced peak VO_2 , impaired peripheral oxygen extraction, and an exaggerated cardiovascular response despite preserved oxygen delivery. Beyond quantifying functional impairment, CPET may support the differential diagnosis of metabolic myopathies and guide subsequent metabolic and genetic investigations (Jeppesen et al., 2021; Mancuso et al., 2012)

5. Diagnostic Approach

Evaluation of suspected mitochondrial disease should begin with careful assessment of the clinical phenotype, family history, and extent of organ involvement, followed by targeted biochemical investigations and molecular genetic testing. A detailed clinical history, including symptom evolution, triggering factors, and family history, remains essential in the evaluation of suspected mitochondrial disease (Heath et al., 2025).

Exercise intolerance alone has limited diagnostic specificity; however, its significance as a clinical red flag increases considerably when accompanied by additional neurological, muscular, or multisystem features. Careful assessment of the overall clinical phenotype is therefore essential to identify patients who warrant further metabolic and genetic evaluation for mitochondrial disease. Exercise testing may serve as a useful screening tool by demonstrating reduced exercise capacity and characteristic abnormalities in aerobic metabolism (Berardo et al., 2010). Although serum lactate remains the most widely used biochemical marker of mitochondrial dysfunction, it does not reliably predict the presence of exercise intolerance.

The characteristics of exercise intolerance may help distinguish the major groups of metabolic myopathies. Glycogen storage diseases typically manifest during brief, high-intensity exercise and are characterized by muscle pain, contractures, elevated CK (creatine kinase) level, and the "second-wind" phenomenon. In contrast, fatty acid oxidation disorders and mitochondrial diseases usually present during prolonged exercise; however, mitochondrial diseases are more often accompanied by multisystem involvement and elevated lactate levels, whereas fatty acid oxidation defects are frequently triggered by fasting or intercurrent illness ((Berardo et al., 2010; Danti et al., 2021).

The diagnosis of mitochondrial diseases remains challenging due to their marked clinical and genetic heterogeneity (Heath et al., 2025). Although some patients present with well-defined clinical phenotypes, such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) or myoclonic epilepsy with ragged-red fibers (MERRF), allowing a more targeted genetic evaluation, the majority exhibit nonspecific or incomplete clinical manifestations. Consequently, several clinical scoring systems have been developed as a bedside instrument for screening and to evaluate and quantify the probability of an underlying mitochondrial disorder. among which the Mitochondrial Disease Criteria (MDC) are the most widely used (Table 1, Table 2). The MDC scoring system has demonstrated high specificity for distinguishing mitochondrial diseases from other multisystem disorders (Morava et al., 2006; Witters et al., 2018; Heath et al., 2025). Despite the widespread implementation of next-generation sequencing (NGS), the MDC score continues to play an important role in clinical practice by supporting phenotype interpretation, facilitating the assessment of whole-exome sequencing findings, and helping identify patients who may benefit from muscle biopsy (Witters et al., 2018).

The diagnostic work-up of suspected mitochondrial myopathy should include biochemical evaluation with serum lactate, pyruvate, and creatine kinase measurements. An elevated lactate-to-pyruvate ratio may support the diagnosis, whereas creatine kinase levels are often normal or only mildly increased. When clinically indicated, muscle biopsy may provide additional diagnostic information through histopathological findings such as ragged red fibers (RRF) and COX-negative fibers, together with the assessment of activity of respiratory chain complexes (Toscano et al., 2017). In patients presenting with acute exercise intolerance triggered by prolonged exercise, fasting, infections, fever or stress, initial evaluation should include serum lactate measurement. Elevated lactate levels should prompt further investigation for mitochondrial disease, including molecular genetic testing and, in selected cases, muscle biopsy (Toscano et al., 2017). Although elevated lactate remains one of the most useful biochemical markers, normal lactate levels do not exclude mitochondrial disease and lactate does not correlate with disease severity (Heath et al., 2025), and its diagnostic utility is limited; up to 70% of children with mitochondrial disease may have normal venous lactate concentrations (Munnich et al., 1996), its elevated level is nonspecific and may occur in numerous non-mitochondrial conditions (e.g. venous stasis, seizure, sepsis etc.). Therefore, lactate should always be interpreted in the context of the overall clinical presentation. Cerebrospinal fluid (CSF) lactate may be more reliable marker than blood lactate (Munnich et al., 1996).

Although serum lactate, pyruvate, and creatine kinase remain widely used in the initial evaluation of suspected mitochondrial disease, their diagnostic sensitivity and specificity are limited. More recently, fibroblast growth factor 21 (FGF-21) and growth differentiation factor 15 (GDF-15) have emerged as promising biomarkers, particularly in patients with mitochondrial myopathies, although they should be interpreted within the overall clinical context (Davis et al., 2016; Ji et al., 2017; Lehtonen et al., 2016; Morovat et al., 2017; Suomalainen et al., 2011), and remain to have a limited role in clinical routine diagnostics (Heath et al., 2025). According to one study (Bermejo-Guerrero et al., 2023). GDF-15 may help differentiate mitochondrial myopathy from chronic fatigue syndrome in patients presenting with exercise intolerance and fatigue symptoms.

Neuroimaging, especially MRI and MR spectroscopy, are valuable supportive diagnostic tools in suspected mitochondrial disease, as they may reveal characteristic imaging patterns. However, neuroimaging findings are not disease-specific and do not correlate with disease

severity; therefore, MRI currently plays a complementary rather than primary diagnostic role and should always be interpreted alongside clinical and molecular findings (Heath et al., 2025).

Advances in next-generation sequencing (NGS), particularly targeted gene panels and whole-exome sequencing (WES), have fundamentally transformed the diagnostic pathway for suspected mitochondrial diseases (Wortmann et al., 2017). Current diagnostic strategies prioritize early molecular analysis of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA), with muscle biopsy now largely reserved for selected unresolved cases, e.g. to clarify a variant of unknown significance (VUS) or when the diagnosis is not established after NGS (Heath et al., 2025; Parikh et al., 2015; Wortmann et al., 2017). This molecular-first approach has significantly improved the diagnostic yield, especially in pediatric patients, while a confirmed genetic diagnosis provides important implications for genetic counseling and reproductive planning (Gorman et al., 2016). Despite advances in genomic testing, careful clinical assessment remains fundamental for recognizing children with suspected mitochondrial disease. A negative blood-based genomic test does not exclude mitochondrial disease, particularly when clinical suspicion remains high (Heath et al., 2025).

Table 1. Mitochondrial disease criteria (simplified version for bedside use) (Morava et al., 2006)

I. Clinical signs and symptoms (1 point/symptom, max 4 points)			II. Metabolic/imaging studies (max 4 points)	III. Morphology (max 4 points)
A. Muscular presentation (max 2 points)	B. CNS presentation (max 2 points)	C. Multisystem disease (max 3 points)		
Ophthalmoplegia (2 pt) Facies myopathica Exercise intolerance Muscle weakness Rhabdomyolysis Abnormal EMG	Developmental delay Loss of skills Stroke-like episode Migraine Seizures Myoclonus Cortical blindness Pyramidal signs Extrapyrarnidal signs Brainstem involvement	Hematology GI tract Endocrine/growth Heart Kidney Vision Hearing Neuropathy Recurrent/familial	Elevated lactate (2 pt) Elevated L/P ratio Elevated alanine (2 pt) Elevated CSF lactate (2pt) Elevated CSF protein Elevated CSF alanine (2pt) Krebs cycle intermediaries (2 pt) Ethylmalonic aciduria Stroke-like picture/MRI Leigh syndrome/MRI (2pt) Elevated lactate/MRS	Ragged red/blue fibers COX-negative fibers Reduced COX staining Reduced SDH staining SDH positive blood vessels (2pt) Abnormal mitochondria/EM (2pt)

*Score 1: mitochondrial disorder unlikely; score 2-4: possible mitochondrial disorder; score 5-7: probable mitochondrial disorder; score 8-12: definite mitochondrial disorder

*L/P = lactate/pyruvate; COX = cytochrome c oxidase; SDH = succinate dehydrogenase; EM = electron microscopy; EMG = electromyography; TA = tricarboxylic acid

Table 2. Mitochondrial disease criteria (simplified version by (Witters et al., 2018))

I. Clinical signs and symptoms (1 point/symptom, max 4 points)			II. Metabolic/imaging studies (max 4 points)
A. Muscular features (max 2 points)	B. Neurological features (max 2 points)	C. Multisystem features (max 3 points)	
Exercise intolerance	Developmental delay or ID	GI tract disease	Lactate high at least 2x (2 pt)

Myopathy	Speech delay	Growth delay	Alanine high at least 2x
Abnormal EMG	Dystonia	Endocrine	Krebs' cycle intermediates
Motor developmental delay	Ataxia	Immune	Ethylmalonic and methylmalonic acid
	Spasticity	Vision or hearing	3-methyl-glutatonic acid
	Neuropathy	Renal tubular acidosis	CSF lactate, alanine
	Seizures/encephalopathy	Cardiomyopathy	Leigh disease in MRI (2pt)
			Stroke-like episodes/MRI (2pt)
			Lactate peak on MRS
			Leukoencephalopathy with brainstem and spinal cord involvement
			Cavitating leukoencephalopathy
			Leukoencephalopathy with thalamus involvement
			Deep cerebral white matter involvement and corpus callosum agenesis

*Score 1: mitochondrial disorder unlikely; score 2-4: possible mitochondrial disorder; score 5-7: probable mitochondrial disorder; score 8: definite mitochondrial disorder

6. Conclusions

Exercise intolerance is a common but nonspecific manifestation of childhood-onset mitochondrial diseases. However, when unexplained and accompanied by additional neurological or multisystem features, together with supportive laboratory or neuroimaging abnormalities, it should be regarded as an important clinical red flag, should raise clinical suspicion and prompt further metabolic and genetic evaluation.

The diagnosis of mitochondrial diseases remains challenging because of their rare prevalence and clinical heterogeneity. Although advances in next-generation sequencing (NGS) have substantially transformed the diagnostic pathway, current diagnostic strategies combine careful and detailed clinical assessment with first-line genomic testing, highlighting the complementary roles of clinical phenotyping and molecular genetics in achieving an accurate diagnosis of mitochondrial disease.

Prompt identification of children in whom exercise intolerance reflects an underlying mitochondrial disorder may shorten the diagnostic delay, facilitate timely molecular diagnosis, and enable appropriate multidisciplinary management and genetic counseling.

Disclosure

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