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Mitochondrial Disease in Childhood: Nuclear Encoded

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Abstract Primary mitochondrial disorders are clinically and genetically heterogeneous, caused by an alteration(s) in either mitochondrial DNA or nuclear DNA, and affect the respiratory chain's ability to undergo oxidative phosphorylation, leading to decreased production of adenosine triphosphophate and subsequent energy failure. These disorders may present at any age, but children tend to have an acute onset of disease compared with subacute or slowly progressive presentation in adults. Varying organ involvement also contributes to the phenotypic spectrum seen in these disorders. The childhood presentation of primary mitochondrial disease is mainly due to nuclear DNA mutations, with mitochondrial DNA mutations being less frequent in childhood and more prominent in adulthood disease. The clinician should be aware of the pediatric presentation of mitochondrial disease and have an understanding of the myriad of nuclear genes responsible for these disorders. The nuclear genes can be best understood by utilizing a classification system of location and function within the mitochondria.

Keywords Mitochondrial · Encephalomyopathy · Developmental regression · Leigh syndrome · Alpers syndrome · POLG

Introduction

Primary mitochondrial diseases can present at any age with a diverse range of symptoms affecting any organ in the body. Being clinically and genetically heterogeneous, these disorders are caused by mutations in either mitochondrial (mt)DNA or nuclear (n)DNA, and result in decreased adenosine triphosphate (ATP) production [1]. Therefore, the organs most reliant on mitochondrial energy production will be the most symptomatic to such defects, and these include the central nervous system, skeletal muscle, heart, endocrine organs, and kidney [2]. Once considered rare, the prevalence of primary mitochondrial disease is approximately 1:5000 [3]. Though the phenotypes are highly variable, many of these conditions are severe and progressive, and remain without proven effective therapies.

Primary mitochondrial disease is caused by a defect in the respiratory chain (RC)—a series of 5 multimeric enzyme complexes embedded in the inner mitochondrial membrane. The complexes are composed of structural subunits and ancillary proteins that must be assembled together into their final structure to promote normal functioning. Some of the complexes form into supercomplexes—a group of several complexes and other factors that are closely associated for efficient energy production [4]. Some of the assembly factors may have dual roles in metabolism. For example, acyl-Coenzyme A dehydrogenase family, member 9 (*ACAD9*) has been identified in complex I deficiency, and also plays a role in fatty acid oxidation, providing a possible explanation for the overlapping phenotypes of primary mitochondrial disease and fatty acid oxidation disorders [5, 6].

mtDNA contains 37 genes, which encode for 13 protein subunits, 22 transfer ribonucleic acid and 2 ribosomal ribonucleic acid. The nDNA is therefore responsible for the remainder of the proteins needed for normal mitochondrial functioning. There are estimated to be 1500 nuclear-encoded proteins targeted to the mitochondria, catalogued in the MitoCarta human inventory [7]. Alterations in mtDNA are responsible for approximately 15–30 % of childhood mitochondrial disease; therefore, most primary mitochondrial disease is caused by a defect in a nuclear gene [8–10]. For example, in a series of children with a RC defect detected on biochemical testing of skeletal muscle, 12 % of them had a mtDNA mutation or deletion; the remainder was assumed to

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be nuclear in origin [11]. More than 200 nuclear-encoded genes have been linked to human disease [12]. The known nDNA mutations, as shown in Table 1, can be classified by location and function as occurring in a structural subunit protein, an assembly protein in one of the complexes; a protein that directly affects mtDNA replication, maintenance, and repair; mtDNA protein synthesis (transcription and translation); mitochondrial dynamics; stability of the phospholipid membrane creating the lipid milieu of the inner mitochondrial membrane (IMM); and the solute carrier importation transport system across the IMM [13, 14].

Classification of primary mitochondrial disease can be based on molecular defect, biochemical or enzymology abnormalities, and/or by clinical symptoms or phenotype. Further complicating classification is the overlap between clinical phenotypes and a highly variable genotype–phenotype correlation. Frequently, patients may have a similar clinical phenotype, yet have different molecular genotypes. In addition, the same genetic mutation can cause vastly different symptoms, even within a family harboring the same molecular defect. The diagnostic approach must use a combination of clinical, biochemical, neuroradiological, pathologic, and molecular information. Careful interpretation of laboratory results is needed as enzyme deficiencies found on RC testing may be indicative of the primary disease or be secondary to other primary pathological conditions. Enzymology testing results can vary from tissue to tissue and depend on individual laboratory analysis. Molecular diagnosis is becoming more prevalent with rapidly evolving next generation genetic testing. Current technology allows for massive parallel sequencing of hundreds of nuclear mitochondrial genes. The current mutation detection rate is a definite diagnosis in about 25 % of patients, with an additional 30 % of patients having a candidate gene detected in a carefully selected pediatric population [15]. Since 2009, more than 200 nuclear genes have been implicated in mitochondrial disease and an average of 10 new disease-causing genes are discovered per year [15]. The purpose of this article is not to review an exhaustive list of currently known nuclear genes causing primary mitochondrial disease, but to review the molecular classification scheme, as well as the associated phenotypes of these disorders in childhood. Identifying the molecular basis of disease will help us not only understand the pathophysiology of the disease, but also give insight to their clinical and genetic heterogeneity, allow for genetic counseling and prenatal diagnosis, guide management and prognosis, and, eventually, lead to more specific directed therapies for mitochondrial disease [16]. The current available testing has taken us from the ability of single gene testing to targeted panels to concurrent next generation sequencing of the mtDNA and hundreds of nuclear mitochondrial genes.

Genetic Classification of the Nuclear Genes Involved in Mitochondrial Disease

Most inherited mitochondrial disease is nuclear-encoded and follows Mendelian inheritance patterns (autosomal dominant, autosomal recessive, or X-linked) [17, 18]. Testing can be performed on blood for nuclear DNA studies, and can be limited to a single gene, a panel of genes that cause a single RC defect (e.g., complex I deficiency panel) or phenotypic spectrum (mtDNA depletion disorders), or next generation sequencing of hundreds of nuclear mitochondrial genes. Commercial testing is available for known pathogenic mutations, and testing variants of unknown significance for pathogenicity is occurring on a research basis as new gene discoveries are being made. Nuclear mutations have been found in up to 25 % of selected infants with probable mitochondrial disease [15].

The genes encoded by nuclear DNA must undergo transcription, translation, and importation into the mitochondria. As outlined in Table 1, these nuclear genes can be classified by their function to better understand their pathological implications.

Disorders of mtDNA maintenance caused by mutations in nuclear genes can, in turn, cause changes in the mtDNA, such as deletions or depletion, and lead to the syndromes known as mitochondrial DNA depletion syndromes (MDS). A single nuclear gene mutation can lead to single or multiple respiratory chain defects. Up to 25 % of children with mitochondrial disease have multiple RC defects, caused by polymerase gamma 1 (*POLG*) mutations, mtDNA deletions, mitochondrial translation defects, or a defect in coenzyme Q10 (CoQ10)biosynthesis [19].

Mutations in Genes Encoding RC Subunit Structural Proteins or Ancillary Proteins (Subunit Assembly Factors, Biosynthetic Enzymes)

The nuclear genome encodes the majority of proteins needed for the structural subunits of each of the complexes in the respiratory chain. In addition, each complex has ancillary proteins which act as assembly genes. These assembly genes are needed to synthesize and orchestrate the proper assembly of the various subunits. Mutations in the structural protein or an assembly protein may lead to a complex deficiency. Table 2 provides an overview of some of the more common nuclear genes and reported disease phenotypes.

Complex I

Complex I (nicotinamide adenine dinucleotide-ubiquinone reductase) deficiency (Online Mendelian Inheritance in Man #252010) has been described in 25–30 % of all pediatric mitochondrial disease patients [23, 24]. Complex I is the

Table 1 Functional classification of nuclear (n)DNA alterations

- Mutations in genes encoding respiratory chain subunit structural proteins.
- Mutations in genes encoding respiratory chain subunit ancillary proteins (subunit assembly factors, biosynthetic enzymes).
- Defects of intergenomic communication: nDNA genes that control mitochondrial (mt)DNA replication, maintenance, repair; multiple mtDNA deletions and mtDNA depletion syndromes.
- Defects of mtDNA protein synthesis (includes defects of transcription and translation).
- Defects in mitochondrial dynamics: fission and fusion.
- Mutations affecting the lipid milieu of the inner mitochondrial membrane (IMM).
- Defects in solute transporter carriers across the IMM.

largest complex of the RC, as it is comprised of approximately 46 subunits. Thirty-nine of these are nuclear-encoded, and at least 13 mutations in these genes have been reported to cause complex I deficiency [25]. The most common neurologic manifestation is Leigh syndrome [26]; other manifestations include cardiomyopathy, hepatopathy, myopathy, encephalomyopathy, tubulopathy, hypotonia, and some forms of Parkinson disease [27, 28]. Neuroimaging findings in complex I deficiency includes brainstem lesions with associated basal ganglia lesions, which are hyperintense on T2-weighted images and hypointense on T1-weighted images; leukoencephalopathy; stroke-like lesions; cerebellar hyperintensities [29]; and increased lactate on magnetic resonance spectroscopy. Mutations in the complex I assembly gene *NDUFA12L* (*B17.2L*) result in a failure to assemble the holoenzyme complex and has been associated with a cavitating leukoencephalopathy [30].

Complex II

Complex II (succinate dehydrogenase) consists of only 4 subunits and 2 assembly factors, which are all nuclear-encoded. The first identified nuclear gene mutation responsible for mitochondrial disease was a subunit of complex II, succinate dehydrogenase complex, subunit A (*SDHA*), in siblings with Leigh syndrome [31], but only mutations in *SDHA* are implicated in primary mitochondrial disease, and these are inherited in an autosomal recessive manner

Table 2 Overview of the relevant nuclear mitochondrial genes involved with respiratory chain assembly and function [20–22]

	Genes	Clinical
Complex I	*C20ORF7, FOXRED1, NDUFA1, NDUFA2, NDUFA7, NDUFA8 , NDUFA10, NDUFA11, NDUFA13, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4 (HRPAP20), NDUFB6, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV3, NUBPL, ACAD9*	Leigh syndrome, cardiomyopathy, hepatopathy, myopathy, encephalomyopathy, tubulopathy, hypotonia, Parkinson disease, and leukoencephalopathy
Complex II	*SDHA, SDHAF1 SDHB, SDHC, SDHD, SDH5, (SDHAF2)*	Leigh syndrome, epilepsy, optic atrophy, ataxia, myopathy with exercise intolerance, cardiomyopathy, and leukoencephalopathy Hereditary paraganglioma and pheochromocytoma syndromes
Complex III	*BCS1L, TTC19, UQCRB, UQCRQ*	Epilepsy, severe psychomotor retardation, movement disorder, ataxia, hypotonia, and global developmental delay, lactic acidosis, hypoglycemia, magnetic resonance imaging abnormalities involving the deep gray nuclei, hepatopathy, renal tubulopathy, *BCS1L*: GRACILE and Bjornstad syndromes
Complex IV	*COX10, COX15, COX4I1, COX4I2, COX6B1, COX7A1, FASTKD2, LRPPRC, SCO1, SCO2, SURF1, TACO1*	Leigh syndrome; encephalocardiomyopathy; hypotonia; lactic acidosis
Complex V	*ATPAF2 (ATP12), ATP5E, TMEM70*	Hypertrophic cardiomyopathy, epilepsy
Coenzyme Q10	*PDSS1, PDSS2, CoQ2, CoQ3, CoQ6, CoQ7, CoQ9, ADCK3, ETFDH, APTX, BRAF, CABC1*	Encephalomyopathy, seizures, and ataxia; infantile encephalopathy, cardiomyopathy, and renal failure; cerebellar syndrome with ataxia and atrophy; Leigh syndrome; isolated myopathy; and steroid-resistant nephrotic syndrome

[32–34]. Complex II deficiency due to *SDHA* mutations can cause Leigh syndrome, epilepsy, optic atrophy, ataxia, myopathy with exercise intolerance, cardiomyopathy, and leukoencephalopathy [32–34]. *SDHAF1* is the first complex II assembly factor reported to cause a leukoencephalopathy [35]. The other subunits (*SDHB, SDHC, SDHD, SDH5*) have been reported in pathogenic associations of hereditary paraganglioma–pheochromocytoma syndrome. These are inherited in an autosomal dominant manner. Of note, muscle biopsies are stained routinely for SDH; SDH-positive fibers are abnormal and are a sign of mitochondrial dysfunction, but not specific of complex II deficiency.

Complex III

Complex III (ubiquinol-cytochrome c reductase) deficiency is caused by known mutations in the 10 nuclear-encoded genes, which include *BCS1L, TTC19, UQCRB*, and *UQCRQ* [36, 37, 38]. Manifestations of complex III deficiency include a triad of tubulopathy, encephalopathy, and liver failure [39]. Neurologic manifestations include epilepsy, severe psychomotor retardation, movement disorder, ataxia, hypotonia, global developmental delay, lactic acidosis, hypoglycemia, and abnormalities on brain magnetic resonance imaging (MRI) involving the deep gray nuclei. Systemic symptoms include hepatopathy and renal tubulopathy. Mutations in the complex III assembly factor *BCS1L* cause GRACILE syndrome (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, early death) and Bjornstad syndrome (sensorineural hearing loss with pili torti) [40–42].

Complex IV

Complex IV [cytochrome C oxidase (COX)] deficiency has been associated with mutations in 10 of the 13 nuclear-encoded genes [25]. These disorders are also quite common, being responsible for 25 % of all pediatric mitochondrial disease; Leigh syndrome is the most common clinical manifestation [43]. These disorders have included clinical manifestations of neonatal-onset hepatic failure (*SCO1*), cardioencephalomyopathy (*SCO2*), hypertrophic cardiomyopathy (*COX15*), and encephalomyopathy (*COX6B1*) [44]. COX is another routine stain in muscle histology, and COX deficient fibers are abnormal, but not specific, for complex IV deficiency.

Complex V

Complex V (ATP synthase) deficiency can be hard to measure biochemically, as it requires fresh muscle biopsy and specialized testing that is available at few centers. Genetic mutations are found in mtDNA or nuclear DNA. The nuclear mutations can cause hypertrophic cardiomyopathy, hypotonia, lactic acidosis, 3-methylglutaconic acid in urine, hyperammonemia, and epilepsy.

CoQ10 Deficiency

CoQ10 acts as an electron shuttle between complexes I and II to complex III, and is also an antioxidant. At least 12 genes are responsible for CoQ10 biosynthesis. Tissue biopsy may show deficiencies of complexes I and III or II and III [45, 46, 47]. There are 6 major phenotypes of CoQ10 deficiency [46, 47]: 1) encephalomyopathy, seizures and ataxia; 2) infantile encephalopathy, cardiomyopathy, and renal failure, 3) cerebellar syndrome with ataxia and atrophy; 4) Leigh syndrome; 5) isolated myopathy; and 6) steroid-resistant nephrotic syndrome.

CoQ10 deficiency *is amenable to treatment* and therefore identifying these disorders is imperative. The genes involved in CoQ10 deficiency include *PDSS1, PDSS2, COQ2, COQ6, COQ9, ADCK3 (CABC1; COQ8), ETFDH,* and *APTX*.

Defects of Intergenomic Communication: nDNA Genes that Control mtDNA Replication, Maintenance, and Repair

Proteins encoded by the nDNA are responsible for proper mtDNA replication, maintenance, and translation. Mutations in these genes may cause multiple mtDNA deletions or mtDNA depletion, or abnormal translation of the mitochondrial mRNA.

Multiple mtDNA Deletion Disorders

mtDNA replication depends on a nucleotide pool required to synthesize mtDNA and associated replication enzymes. The genes involved in mtDNA replication include *C10orf2, POLG, POLG2*, and *MPV17*. The mtDNA must be conserved by genes responsible for mtDNA maintenance: *DGUOK, RRM2B, SLC25A4, SUCLA2, SULG1, TYMP,* and *TK2*. Mutations in the mtDNA maintenance genes more typically cause mtDNA depletion syndromes, but mutations in any of these genes can lead to multiple mtDNA deletion disorders. Typical symptoms include progressive external ophthalmoplegia (PEO), ptosis, and proximal weakness, but can also involve other systemic symptoms, including peripheral neuropathy, ataxia, dementia, sensorineural hearing loss, and other ocular symptoms. Many of these are adult onset in nature [48–54].

Mitochondrial DNA Depletion Disorders

The mitochondrial DNA depletion (MDD) disorders are a group of autosomal recessive syndromes characterized by a quantitative reduction in the copy number of mtDNA,

defined as less than 35 % of the normal amount of mtDNA present in muscle or liver biopsy from affected patients [51]. These disorders were first described in 1991 [48], but have received tremendous attention since the discovery that mutations in *POLG* cause of one of the most devastating MDS disorders—Alpers-Huttenlocher syndrome (AHS). Infantile onset is common, with symptoms of epilepsy, hypotonia, developmental delay or regression, and hepatic failure that can be provoked by valproic acid [49]. Milder variants are associated with higher levels of mtDNA copy number, but can be slowly progressive and involve symptoms similar to the more severe phenotypes [50–52]. The nuclear genes involved in the MDD disorders are *DGUOK*, *MPV17*, *POLG*, *RRM2B*, *SUCLA2*, *SUCLG1*, *TK2*, *C10orf2* (*Twinkle*), and *TYMP*. Mutations in any of these genes leads to mtDNA depletion disorders, with quantitative reduction in mtDNA copy number by directly affecting mtDNA replication or in regulating the nucleotide pools needed for replication [53]. There are 3 main phenotypes within the MDS category that cover the most common presentations of these disorders with neurologic, muscular, and hepatic involvement: myopathic (*TK2*), encephalomyopathic (*SUCLA2, SUCLG1, RRM2B,* and *TYMP*) and hepatocerebral (*DGUOK, MPV17, POLG, C10orf2*). However, these categories tend to have symptom overlap, especially as the disease progresses. MDS is amongst the most common forms of mitochondrial disorders in childhood. Muscle or liver biopsy may show combined deficiencies of respiratory chain complexes I, III, IV, and the ATP synthase, or may be completely normal. The disease burden varies from tissue-specific mtDNA depletion (typically muscle or liver) to widespread multisystemic disorders. MDS can present at any age with a wide variety of symptoms. However, certain features appear to be age-related. For example, neonates and young infants tend to have more lactic acidosis, failure to thrive, and hypotonia. Children commonly present with encephalopathy and hepatic involvement. Muscle weakness is most prominent in children and adults; to a lesser degree in infants and adolescents. Adults have more ataxia, polyneuropathy, psychiatric symptoms with dementia, and gastrointestinal symptoms, although symptoms may start in adolescence. Migraine headaches seem to peak at adolescence [54]. Gene-specific symptomatic involvement in the MDS disorders is outlined in Table 3.

POLG-related Disorders

The nuclear gene *POLG* encodes mitochondrial DNA polymerase gamma 1, which is the only polymerase known to be involved in mtDNA replication and repair in eukaryotes [55]. *POLG* abnormalities result in mtDNA mutations and/or multiple deletions, and are responsible for the most common cause of inherited mitochondrial diseases in children and adults [56]. *POLG*-related disorders encompass a wide spectrum of disorders involving multiple organ systems, with variable severity and age of onset [56]. Younger patients mainly present with seizures, lactic acidosis, and hepatic failure; while myopathy, chronic progessive external ophthalmoplegia (CPEO), and sensory ataxia are the major presenting features when the disease manifests later in life [56]. More than 160 mutations have been identified in various domains of *POLG*. An updated map for these mutations is available at http://tools.niehs.nih.gov/polg/ [57]. *POLG*-related disorders are categorized into 6 recognizable phenotypes; however, the 2 PEO phenotypes are typically adult-onset disorders [58–60]. Childhood-onset manifestations of *POLG* include the following.

AHS

AHS is characterized by the clinical triad of refractory seizures, psychomotor regression, and hepatopathy. AHS is inherited in an autosomal recessive pattern, with the finding of 2 pathogenic mutations usually acquired in a compound heterozygote state [60, 61]. Infants usually develop normally until disease onset, which is typically before 4 years of age. The usual life expectancy ranges from 3 months to 12 years [56]. However, congenital static encephalopathy, as well as childhood- and juvenile-onset AHS are also known [56]. Hepatic dysfunction varies from early to late in the course of the disease, and could progress to fulminant end-stage liver disease in a few months—especially when exposed to certain anticonvulsants. Valproic acid must be used with extreme caution when the etiology of seizures is unknown, as it can precipitate liver dysfunction in AHS [61, 62]. Other neurologic symptoms include migraine with visual auras, cortical blindness, hypotonia, ataxia, extrapyramidal movements, peripheral neuropathy, and progressive spastic paraparesis [63]. Non-neurologic manifestations include renal tubular acidosis, hearing loss, cyclic vomiting, and pancreatitis [64].

Myoclonic Epilepsy Myopathy Sensory Ataxia

Myoclonic epilepsy myopathy sensory ataxia is characterized by epilepsy, myopathy, and ataxia without ophthalmoplegia, and has also been known as spinocerebellar ataxia with epilepsy. Typical disease onset occurs in adolescence with cerebellar and sensory ataxia. This is followed by the clinical manifestation of epilepsy. Refractory seizures lead to progressive encephalopathy similar to other *POLG*-related disorders. The lack of ragged red fibers from muscle biopsy helps distinguish this from the closely related clinical syndrome of myoclonic epilepsy with ragged red fibers [65].

Table 3 Select mitochondrial depletion genes by primary symptom

Genes	Other clinical features or associated phenotypes
Myopathic	
TK2	Muscle weakness, elevated creatine kinase, encephalopathy
ANT1 (SLC25A4)	adPEO, mild myopathy
RRM2B	Myopathy, renal tubulopathy
POLG	1) AHS; 2) MEMSA; 3) ANS; 4) MCHS; 5) arPEO; 6) adPEO
Hepatocerebral	
POLG	1) AHS; 2) MEMSA; 3) ANS; 4) MCHS; 5) arPEO; 6) adPEO
DGUOK	Hepatopathy; neurologic symptoms, severe failure to thrive, lactic acidosis, hypoglycemia
MPV17	Hypoglycemia, hepatopathy, neurologic symptoms; Navajo neurohepatopathy
C10orf2(Twinkle)	Infantile-onset spinocerebellar ataxia (ataxia, athetosis, areflexia, hypotonia, ophthalmoplegia, optic atrophy, seizures, sensory axonal neuropathy, progressive atrophy of cerebellum, brain stem and spinal cord); adPEO, myopathy, Parkinsonian features of rigidity, tremor, and bradykinesia
Encephalomyopathic	
SUCLA2	Early-onset severe hypotonia and muscle atrophy, dystonia/hyperkinetic movement disorder, severe developmental delay (nonambulatory), seizures (including infantile spasms), severe sensorineural hearing loss, methylmalonic aciduria, lactic acidosis, progressive scoliosis or kyphosis, postnatal growth retardation, MRI with bilateral basal ganglia involvement
SUCLG1	Hypotonia, lactic acidosis, hearing loss, MRI with bilateral symmetric basal ganglia lesions with methylmalonic aciduria
RRM2B	Hypotonia, developmental delay, develops renal tubulopathy

adPEO = autosomal dominant progressive external ophthalmoplegia; AHS = Alpers-Huttenlocher syndrome; MEMSA = myoclonic epilepsy myopathy sensory ataxia; ANS = ataxia neuropathy spectrum; MCHS = childhood myocerebrohepatopathy spectrum; arPEO = autosomal recessive progressive external ophthalmoplegia; MRI = magnetic resonance imaging

Ataxia Neuropathy Spectrum

Ataxia neuropathy spectrum includes ataxia, neuropathy, and, in most individuals, encephalopathy with seizures. The neuropathy may be sensory, motor, or mixed. The encephalopathy may be milder compared with AHS and is usually slowly progressive. This disorder was previously referred to as sensory ataxia, neuropathy, dysarthria and ophthalmoplegia. In contrast to myoclonic epilepsy myopathy sensory ataxia, it is characterized by the presence of PEO and absence of significant myopathy [66, 67]. Muscle pathology is often normal. The disease onset is usually in early teenage years to late third decade. Migraine headaches may precede other symptoms by many years. Psychiatric disturbance is a common feature. Other features include myoclonus, blindness, hearing loss, and a varying degree of liver failure [67].

Childhood Myocerebrohepatopathy Spectrum

Childhood myocerebrohepatopathy spectrum (MCHS) is a rapidly progressive disease with a fatal outcome that usually presents between the first few months of life and 3 years. It presents with developmental delay, encephalopathy, dementia, myopathy, and hypotonia. Other features include failure to thrive, lactic acidosis, liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss [67]. Similar to the presentation of AHS, MCHS presents early in life with hepatopathy, encephalopathy, and a fatal outcome. However, severe myopathy, specific liver pathology, and nonspecific MRI Brain findings of diffuse atrophy help differentiate MCHS from AHS.

Mitochondrial Neurogastrointestinal Encephalomyopathy

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disorder. Symptoms begin in childhood, but it is usually not diagnosed until adulthood. MNGIE is caused by mutations in *TYMP*, which encodes the enzyme thymidine phosphorylase, and leads to mtDNA deletions and mtDNA depletion. Clinical symptoms include gastrointestinal dysmotility and pseudo-obstruction, cachexia, ptosis and external ophthalmoplegia, peripheral sensorimotor neuropathy, and a diffuse leukoencephalopathy. Allogenic hematopoietic stem cell transplantation is in clinical trials and appears to be a promising cure for MNGIE; therefore, early recognition and diagnosis is important [68].

Defects of mtDNA Protein Synthesis (Including Defects of Transcription and Translation)

Translation of the 13 mtDNA-encoded subunits of the RC requires many factors, including intact mtDNA; functioning *POLG*; nucleotide building blocks; ribosomal proteins; tRNA modification enzymes; initiation, elongation, and termination factors; and aminoacyl-transfer RNA synthetases—all

encoded by nDNA. Defects in mtDNA translation result in severe combined RC defects [69, 70]. The defects include those encoding modifying enzymes, elongation factors, and tRNA synthetases (see Table 4).

Mutations of *MRPS16* have been reported with agenesis of corpus callosum, dysmorphic features, and fatal neonatal lactic acidosis [71]. Mutations in the *DARS2* gene causes multiple RC deficiencies, and a clinical syndrome of leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL), with cerebellar ataxia, spasticity, and dorsal column signs [72]. Mutations in *RARS2* cause pontocerebellar hypoplasia, epileptic encephalopathy, progressive microcephaly, developmental arrest, and feeding difficulties [73, 74]. Mutations in *YARS2* cause autosomal dominant intermediate Charcot-Marie-Tooth (CMT) neuropathy type C [75].

Defects in Mitochondrial Dynamics: Fission and Fusion

Mitochondria are not static organelles: their morphology is influenced by proteins that regulate motility [19]. Genes that encode these proteins are involved in mitochondrial dynamics and the processes of fusion and fission. The mitochondrial fusion genes are *optic atrophy 1 (autosomal dominant)* (*OPA1)* on the IMM and *mitofusin 2* (*MFN2*) on the outer mitochondrial membrane. The mitochondrial fission gene is *dynamin-like protein* (*DLP1*). Defects have been associated with human disease in the following genes: *KIF5A* causing hereditary spastic paraplegia (SPG10), *OPA1* causing autosomal dominant optic atrophy, *MFN2* causing CMT disease type 2A, and *Ganglioside-induced differentiation-associated protein 1* (*GDAP1*) also causing a CMT disease [76–78].

Mutations Affecting the Lipid Milieu of the IMM

The RC complexes are embedded in the IMM, and all membranes are composed of a lipid bilayer. However, cardiolipin is the major phospholipid in this unique membrane. Nuclear-encoded genes control the synthesis and composition of mitochondrial membrane phospholipids. Barth syndrome is an X-linked cardioskeletal myopathy and neutropenia with 3-methylglutaconic aciduria (Online Mendelian Inheritance in Man OMIM#302060). A mutation in the *TAZ* gene causes a change in the gene product, tafazzin. Tafazzin is a transacylase that catalyzes remodeling of immature cardiolipin to its mature composition, and the mutation in TAZ causes dysfunction of this protein [79]. 3-methylglutaconic aciduria with sensorineural deafness, encephalopathy, and Leigh-like syndrome is a recessive disorder characterized by dystonia and deafness with Leigh-like symptoms and 3-methylglutaconic aciduria caused by mutations in *SERAC1*, resulting in an altered cardiolipin [80]. Sengers syndrome consists of congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, and lactic acidosis, and is due to mutations in mitochondrial acylglycerol kinase (*AGK*), which has effects on phospholipid metabolism in mitochondria [81]. *AGK* mutations were also found in 2 out of 42 patients with infantile presentation of mitochondrial disease through targeted next generation sequencing [15].

Table 4 mtDNA translational defects

Function	Genes
tRNA modifying enzymes	*PUS1, TRMU*
Mitochondrial elongation factors	*TUFM, TSFM, GFM1, MRPS16*
Mitochondrial aminoacyl tRNA synthetases	*RARS2, DARS2, YARS2*

tRNA = transfer RNA; *PUS1* = pseudouridine synthase 1; *TRMU* = tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase; *TUFM* = mitochondrial translation elongation factor Tu; *TSFM* = mitochondrial translation elongation factor Ts; *GFM1* = mitochondrial elongation factor G1; *MRPS16* = mitochondrial ribosomal protein S16; *RARS2* = arginyl-tRNA synthetase, mitochondrial; *DARS2* = aspartyl-tRNA synthetase, mitochondrial; *YARS2* = Tyrosyl-tRNA synthetase, mitochondrial

Defects in Solute Transporter Carriers Across the IMM

A very important category of primary mitochondrial disease involves the transporter carrier proteins across the inner mitochondrial membrane. Metabolites, ions, metals, nucleotides, amino acids and coenzymes, the substrates of oxidative phosphorylation, inorganic phosphate, and adenosine diphosphate are transported across the IMM via secondary transport proteins called mitochondrial carriers, a nuclear-encoded superfamily, some of which are in the solute carrier group [82, 83]. Defects in the mitochondrial carriers are responsible for carnitine/acylcarnitine carrier deficiency, ornithine translocase deficiency (also called hyperornithinemia-hyperammonemia-homocitrullinuria syndrome owing to mutations in *SLC25A15*), aspartate/glutamate isoform 2 deficiency, Amish microcephaly, and neonatal myoclonic epilepsy. X-linked deafness dystonia (Mohr–Tranebjaerg syndrome) is due to mutations in *DDP1* (*TIMM8A*), a mitochondrial protein transporter [84].

Clinical Manifestations and Symptoms in Childhood

Mitochondrial disease is due to energy failure of the cell, and the organ systems that show the most symptoms are those requiring the most ATP to function properly. Clinical manifestations may involve a single organ or be multisystemic. Although symptoms can present at any age, the pediatric presentation differs from adults (see Table 5).

Even in childhood the spectrum can range from severe neonatal hypotonia, seizures and failure to thrive to older

children with sensorineural deafness and learning disabilities. Children have been noted to have progressive neurologic, cardiac, and hepatic dysfunction. Mitochondrial disease should be in the differential diagnosis for any multisystemic disease presentation. Mitochondrial disease can present with any symptom, any organ, any age, and any inheritance pattern [85]. Common presenting symptoms in childhood include stroke-like episodes, headache, seizures, psychomotor regression, ataxia, and encephalopathy [86]. Symptoms of mitochondrial disease may be progressive or recurrent, sometimes with partial recovery after a decline. Frequently, symptoms are precipitated by a metabolic stressor, such as infection, fasting, surgery, or medication. Mitochondrial disease should be considered when there is an unexplained association of neuromuscular and non-neuromuscular symptoms, when the course is rapidly progressive, and when symptoms involve unrelated organs. There are well-established red flag symptoms of mitochondrial disease, many of which affect the nervous system (Table 6) [20, 87].

Stroke-like Lesions in Nonvascular Distribution

Metabolic strokes differ from arterial ischemic strokes as they do not follow a vascular territory, and usually occur in children or young adults. These strokes are seen mostly in association with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, which is caused by mtDNA mutations. However, some nuclear gene mutations, such as *POLG* have been associated with a mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes-like presentation [88]. Neuroimaging shows a mixture of cytotoxic and vasogenic edema [89].

Leigh Syndrome (Bilateral Symmetric Basal Ganglia Lesions)

Denis Leigh, a British neuropathologist, first described this syndrome in 1951, in a 7-month-old patient with "subacute necrotizing encephalomyelopathy" [90]. Neuroimaging shows calcifications on computed tomography or MRI with bilateral and symmetric lesions of the basal ganglia, periaqueductal grey, pons, midbrain, brainstem, cerebellum, and, rarely, white matter [91, 92]. Leigh syndrome presents with global developmental delay, encephalopathy, epilepsy, movement disorder, risk of aspiration with feeds due to dysphagia and bulbar weakness, nystagmus, apnea, and ataxia. Choreathetosis and dystonia can cause constant movements, leading to muscle spasms, and pain, and contributes to failure-to-thrive. Other symptoms seen in Leigh syndrome include neuropathy, myopathy, optic atrophy, diabetes, short stature, cardiomyopathy, anemia, renal failure, vomiting, and diarrhea [93]. Leigh syndrome is a progressive disease, although patients may be misdiagnosed with "cerebral palsy" or "hypoxic-ischemic encephalopathy" [94]. Leigh syndrome has been reported in some adults, although it is a diagnosis made much more typically in children and usually carries a poor prognosis [47, 95, 96]. Leigh syndrome has many causes, mainly nuclear-encoded genes, including pyruvate dehydrogenase complex (*PDHC*) deficiency, deficiencies in complex I subunits and assembly factors, COX subunits, and assembly factors *SURF1* and *PDSS2* causing primary CoQ10 deficiency [97–101].

Encephalopathy with Hepatopathy

The mtDNA depletion syndromes are a common cause of encephalopathy with hepatopathy in children, accompanied by hypoglycemia and lactic acidosis [102]. The most common MDD syndrome is AHS, caused by nuclear gene mutations in *POLG*. The encephalopathy–hepatopathy phenotype of early onset neurologic abnormalities and progressive liver failure can also be caused by nuclear gene mutations in *DGUOK, MPV17, C10orf2 (Twinkle), SUCLG1, SCO1, and BCS1L* [103, 104].

Cognitive Decline (Mitochondrial Dementia)

A red flag sign of childhood neurodegenerative disease is regression or loss of previously achieved milestones. When

Table 5 Pediatric presentations of mitochondrial disease by age of symptom onset

Antenatal	Intra-uterine growth retardation, birth anomalies (20 %): poly-/oligohydramnios, arthrogryposis, ventricular septal defect, hypertrophic cardiomyopathy, VACTERL (vertebral and limb defects)
Neonates	Keto/lactic acidotic coma: apnea, seizures, severe hypotonia; hepatomegaly or hepatic failure; severe sideroblastic anemia; concentric hypertrophic cardiomyopathy; proximal tubulopathy (Fanconi syndrome); myopathy
Infants	Failure to thrive, chronic diarrhea, recurrent acute myoglobinuria, proximal tubulopathy, nephrotic syndrome, liver failure, Leigh syndrome
Childhood	Multisystemic disease, brain (seizure, regression, dystonia, ataxia, encephalopathy, stroke-like episodes), progressive myopathy, myalgia, exercise intolerance; hypertrophic or dilated cardiomyopathy, heart block; multiple endocrinopathies, CPEO/ptosis, retinopathy, cataracts, Sensorineural hearing loss

VACTERL = OMIM#192350 (also known as VATER): vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheoesophageal fistula with esophageal atresia (TE), and radial or renal dysplasia R), limb anomalies (L)

Table 6 Red flag symptoms related to primary mitochondrial disease

Symptom	Red flag signs
Stroke	Located in a nonvascular distribution
Basal ganglia lesions	Bilateral symmetric (characteristic of Leigh syndrome); also with brainstem lesions
Encephalopathy–hepatopathy	Precipitated by valproic acid exposure; associated hepatic failure
Epilepsy	Epilepsia partialis continua, myoclonus, status epilepticus
Cognitive decline	Regression with illness
Ataxia	Associated with epilepsy or other systemic symptoms; neuroimaging may show cerebellar atrophy, white matter lesions, basal ganglia lesion
Ocular signs	Optic nerve atrophy, ophthalmoplegia, ptosis; retinopathy
Sensorineural hearing loss	At early age, accompanied by other systemic symptoms
Cardiac conduction disorders	Wolff–Parkinson–White, heart block
Cardiomyopathy	Accompanied by skeletal myopathy
Glomerulopathy	Steroid-resistant nephropathy
Proximal tubulopathy; Fanconi's syndrome	Renal tubular acidosis; tubulointerstitial nephritis
Pancreatic dysfunction	Diabetes mellitus
Thyroid dysfunction	Hypothyroidism
Gastrointestinal dysmotility	Chronic intestinal pseudo-obstruction
Hepatopathy	With encephalopathy

regression is triggered by illness, surgery, stroke or epilepsy, mitochondrial disease—especially *POLG* or Leigh syndrome—may be the cause. Neuropsychological testing may help in determining the degree of cognitive impairment. Children may have frank behavioral changes, or the cognitive decline may be similar to that seen in Alzheimer or Parkinson disease [105]. The cognitive decline is often seen in a setting of epilepsy, stroke-like episodes, weakness, spasticity, movement disorders, ataxia, weakness, and migraine headache. Neuroimaging may reveal global cerebral atrophy, basal ganglia calcifications or areas of hyperintensity in the basal ganglia or white matter [106]. Cognitive decline may be seen in MNGIE; *POLG*-related disorders; PEO owing to mutations in *Twinkle, TK2,* or *ANT1*; LBSL; CMT type 2; Leigh syndrome (*SURF1*); diabetes insipidus, diabetes mellitus, optic atrophy, deafness (Wolfram syndrome); and Mohr–Tranebjaerg (*DDP1*: deafness and dystonia syndrome) [107]. Leigh syndrome is the most frequent mitochondrial phenotype seen in childhood mitochondrial syndromes that involve regression. A trial of CoQ10 should be given as CoQ10 deficiency could explain the phenotype and lead to clinical improvement [107].

Epilepsy

Epilepsy is seen frequently in children with mitochondrial encephalopathy, often among other multisystemic symptoms. Epilepsia partialis continua, myoclonic epilepsy, and status epilepticus are more suspicious forms of seizure presentation in mitochondrial disease. Other systemic symptoms include sensorineural hearing loss, retinopathy, cardiomyopathy or conduction defect, diabetes mellitus, hepatopathy, and renal tubulopathy. Seizures are seen in 35–60 % in patients with mitochondrial disease [22]. In a retrospective study of patients in the pediatric epilepsy monitoring unit, 28–75 % had biochemical abnormalities suggestive of mitochondrial dysfunction [108]. Seizure types are mixed, ranging from generalized to partial. Seizure onset is typical in young childhood with most patients having abnormal neuroimaging [109]. Seizures are preceded by multisystemic symptoms, such as global delay, failure to thrive, or ataxia in the majority of patients, although mitochondrial disease may not be suspected until seizure onset. Epilepsy has been reported as a poor prognostic sign in one population studied, with half of patients dying within 9 months of the onset of their epilepsy, and a 45 % mortality rate [110]. Nuclear mitochondrial genes that have been associated with epilepsy include *POLG* and other mtDNA depletion syndromes, complex I deficiency, complex II deficiency (*SDHA*), complex III deficiency (*BCS1L*), complex IV deficiency, *FOXRED1, SCO2, TMEM70, MTATP6*, CoQ10 deficiency, *RARS2, TFSM*, and *SLC25A22*. *SLC25A22* is the solute transporter for glutamate and mutations in this gene have been associated with neonatal/early infantile epileptic encephalopathy with burst suppression electroencephalography (Otohara syndrome) [111]. From the first few days of life, infants have myoclonic and focal seizures, followed by microcephaly, hypotonia, and global developmental delay. Neuroimaging abnormalities include hypoplasia

of the cerebellum and corpus callosum, and temporoparietal dysgenesis with hypomyelination.

Myoclonic epilepsy can be caused by mutations in *POLG* or complex I, mimic a progressive myoclonic epilepsy syndrome, and be very difficult to treat, especially when caused by *POLG* mutations. Treatment may require multiple antiseizure medications. The ketogenic diet has been used, but with significant side effects, such as metabolic acidosis and persistent hypoglycemia [112–115].

The ketogenic diet is specifically contraindicated in pyruvate carboxylase deficiency [116]. Valproic acid has been avoided in young children with idiopathic epilepsy owing to the risk of valproic acid -induced hepatoxicity and concern for AHS, with gene testing of *POLG* recommended prior to its use [61, 117].

Ataxia

Ataxia presents with a full cerebellar syndrome that also includes ataxic dysarthria and nystagmus. Neuroimaging may be normal or show cerebellar atrophy, involvement of the basal ganglia and white matter, or increased signal in the cerebellum. Other symptoms include encephalomyopathy, epilepsy, muscle weakness, regression, hearing loss, ophthalmoplegia, short stature, ataxia, optic atrophy, increased muscle tone, and stroke-like episodes [118]. The nuclear mitochondrial genes responsible for ataxia include causes of Leigh syndrome; *POLG*-related disorders; X-linked sideroblastic anemia with ataxia; infantile-onset spinocerebellar ataxia; LBSL; CoQ10 deficiency; and pyruvate dehydrogenase complex deficiency [119]. Friedreich ataxia is a due to mutations in frataxin, which leads to RC deficiencies and causes cerebellar ataxia, spasticity, cardiomyopathy, dysarthria, and diabetes [120].

Ocular Symptoms

Optic neuropathy and pigmentary retinopathy are symptoms seen in mitochondrial disease [121–123]. Ptosis and ophthalmoplegia can be seen in chronic PEO due *to POLG, POLG2, (SLC25A4) ANT1, C10orf2 (Twinkle),* or *OPA1* mutations [54, 124]. Visual evoked potentials and electroretinography can be abnormal in some nuclear mitochondrial diseases, and fundoscopy examination may reveal pigmentary retinopathy, and can be seen with ptosis or progressive external ophthalmoplegia [121, 125].

Sensorineural Hearing Loss

Hearing loss is usually seen with other multisystem symptoms, and may be missed as a result of more obvious clinical symptoms; routine screening is therefore recommended. Treatment with hearing aids or cochlear implantation is helpful. The nuclear mitochondrial gene mutations that are associated with hearing loss include the mtDNA depletion syndromes involving *SUCLA2, SUCLG1*, and *C10orf2 (Twinkle)* [54].

Heart

The major cardiac manifestations of mitochondrial disease are divided into two main categories: myopathic heart disease and arrhythmias. The myopathic heart disease presents as hypertrophic or dilated cardiomyopathy, and left ventricular noncompaction syndrome or histiocytoid cardiomyopathy [126–129]. The prevalence of cardiomyopathy has been found in 40 % of children with mitochondrial disease, with an earlier age of onset (33 months *vs* 40 months) and a substantially increased morbidity (82 % *vs* 5 %) compared with those without cardiac manifestations [126]. The nuclear genes most associated with an encephalocardiomyopathy are *SCO2* and *TAZ* (Barth syndrome). The cardiomyopathy may remain subclinical for years and therefore routine assessment is recommended. Neonatal presentations include hypertrophic or dilated cardiomyopathy, accompanying lactic acidosis, sometimes in the setting of multi-systemic disease [130]. Recently, dilation of the aortic root has been reported in 10 patients with mitochondrial disease [131]. Secondary defects of fatty acid oxidation, which have been reported in association with primary mitochondrial disease [6, 132, 133] can lead to development of a cardiomyopathy similar to those seen in primary fatty acid oxidation disorders [134]. Cardiac arrhythmias, such as heart block and Wolff–Parkinson–White syndrome, have been found more predominantly in mtDNA disorders [127]. Autonomic dysfunction may be the cause of bradycardia or tachycardia, and may be diagnosed as postural orthostatic tachycardia syndrome [135, 136].

Kidney

Renal involvement in mitochondrial disorders is more common in children than adults, with the majority of severe renal manifestations present by the age of 2 years [137]. The most common renal manifestation seen in primary mitochondrial disease is a renal tubular defect, so affected owing to the mitochondria-rich tubules, which have a high metabolic rate [138]. Debré-Toni-Fanconi's syndrome has been associated with hepatopathy in complex III deficiency due to mutations in *BCSL1*, a complex III subunit [41]. Another renal manifestation associated with mitochondrial disease is renal tubular acidosis with hypercalcinuria, which has been reported in a patient with short stature and found to have a partial complex IV deficiency [139]. Chronic tubulo-interstitial nephritis can lead to chronic renal failure, and has been found in patients with mtDNA mutations more than nuclear mutations. Other

genes that cause an encephalo-nephropathy phenotype include *BCS1L, COX10, PDSS2, COQ2,* and *RRM2B* [140]. Renal manifestations of mitochondrial disease may be subclinical or overshadowed by other systemic symptoms, and therefore requires routine monitoring in patients with mitochondrial disease. In a review of 42 children with primary mitochondrial disease in 1 series, only 8 of them had overt symptoms of renal dysfunction, although a mild tubular disorder was present in 50 % of this population [141]. At the same time, patients with unexplained renal manifestations should have a mitochondrial evaluation, especially if there is other organ involvement. Finally, CoQ10 biosynthesis disorders are a treatable form of mitochondrial disease, and have been noted to cause glomerulopathy or steroid-resistant nephrotic syndrome as one of its several phenotypes [142, 143].

Endocrine

Endocrinopathies may present in childhood or may develop over time and present in adulthood. Diabetes mellitus can be difficult to treat and can have features of both type I and type II. Hypothyroidism, adrenal insufficiency, and short stature are often seen in pediatric mitochondrial disorders as well.

Gastrointestinal

Gastrointestinal symptoms are very common in mitochondrial disorders and range from treatable condition, such as reflux and constipation, to severe dysmotility and pseudo-obstruction leading to dependency on total parenteral nutrition [144]. The gut is rich in mitochondria and requires energy for the smooth muscle and the autonomic nervous system for proper motility and peristalsis. Symptoms of dysfunction include cyclic vomiting, delayed gastric emptying, nausea, constipation, diarrhea, and severe dysmotility.

Conclusions

Nuclear mitochondrial disease in childhood should be suspected when there is multisystem involvement of unknown etiology. Nuclear genetic etiologies are much more prevalent in the pediatric population compared with the mtDNA alterations that comprise the majority of adult mitochondrial disease. Diagnostic testing in children should be directed by clinical symptoms, biochemical testing and findings on neuroimaging. Many laboratories are now offering nuclear mitochondrial gene testing, ranging from a few hundred to more than 1000 mtDNA and nDNA genes. Though there is a vast number of nuclear mitochondrial genes described, our understanding of clinical significance and prognosis may be limited owing to a small number of described patients with mutations. Additionally, clinicians are often faced with molecular results of uncertain significance. In these circumstances, clinical classification will remain very important for accurate diagnosis and prognostic counseling. Clinicians must still correlate these results with the patient's history, family history, physical examination, metabolic and biochemical testing, neuroradiological findings, and pathologic evaluations. Evolving genetic testing is leading to improved diagnoses, which will allow clinicians to understand the phenotypic variability, natural history, and provide the child's family with accurate genetic counseling. In time, this process will continue to evolve with the expansion of genomic testing technology and improved interpretation of molecular results to allow more personalized diagnosis, counseling, and management of patients with mitochondrial disease.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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