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REVIEW

Mitochondrial DNA Depletion Syndromes: Review and Updates of Genetic Basis, Manifestations, and Therapeutic Options

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Abstract Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are a genetically and clinically heterogeneous group of autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs. MDS are due to defects in mtDNA maintenance caused by mutations in nuclear genes that function in either mitochondrial nucleotide synthesis (*TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, and *TYMP*) or mtDNA replication (*POLG* and *C10orf2*). MDS are phenotypically heterogeneous and usually classified as myopathic, encephalomyopathic, hepatocerebral or neurogastrointestinal. Myopathic MDS, caused by mutations in *TK2*, usually present before the age of 2 years with hypotonia and muscle weakness. Encephalomyopathic MDS, caused by mutations in *SUCLA2*, *SUCLG1*, or *RRM2B*, typically present during infancy with hypotonia and pronounced neurological features. Hepatocerebral MDS, caused by mutations in *DGUOK*, *MPV17*, *POLG*, or *C10orf2*, commonly have an early-onset liver dysfunction and neurological involvement. Finally, *TYMP* mutations have been associated with mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease that typically presents before the age of 20 years with progressive gastrointestinal dysmotility and peripheral neuropathy. Overall, MDS are severe disorders with poor prognosis in the majority of affected individuals. No efficacious therapy is available for any of these disorders. Affected individuals should have a comprehensive evaluation to assess the degree of involvement of different systems. Treatment is directed mainly toward providing symptomatic management. Nutritional modulation and cofactor supplementation may be beneficial. Liver transplantation remains controversial. Finally, stem cell transplantation in MNGIE disease shows promising results.

Keywords Mitochondrial myopathy · Mitochondrial encephalomyopathy · Hepatocerebral syndrome · Mitochondrial neurogastrointestinal (MNGIE) disease · Alpers-Huttenlocher syndrome

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Introduction

Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are autosomal recessive disorders with a broad genetic and clinical spectrum that are characterized by a severe reduction in mtDNA content in affected tissues and organs. An adequate amount of mtDNA is required for the production of key subunits of mitochondrial respiratory chain complexes and therefore for energy production. Therefore, mtDNA depletion results in organ dysfunction that is likely due to insufficient synthesis of respiratory chain components needed for adequate energy production [1–3].

MDS are associated with defects in mtDNA maintenance caused by mutations in nuclear genes that function in either mitochondrial deoxyribonucleoside triphosphate (dNTP) synthesis or mtDNA replication. *TK2* (thymidine kinase 2), *SUCLA2* [adenosine diphosphate (ADP)-forming succinyl CoA ligase beta subunit], *SUCLG1* [guanosine diphosphate

(GDP)-forming succinyl CoA ligase alpha subunit], *RRM2B* (ribonucleotide reductase M2 B subunit), *DGUOK* (deoxyguanosine kinase), and *TYMP* (thymidine phosphorylase) encode proteins that maintain the mitochondrial dNTP pool; therefore, mutations in any of these genes result in depleting the mitochondria from DNA building blocks and, subsequently, mtDNA depletion. *POLG* (DNA polymerase gamma) and *C10orf2* (Twinkle) are essential for mtDNA replication; therefore, mutations in these genes result in insufficient mtDNA synthesis to keep up with mtDNA turnover and segregation to daughter cells during cell divisions resulting in reduction of mtDNA content [4, 5].

MDS are phenotypically heterogeneous and may affect either a specific organ or a combination of organs, including muscle, liver, brain, and kidney. Clinically, MDS are usually classified as 1 of 4 forms: a myopathic form associated with mutations in *TK2*; an encephalomyopathic form associated with mutations in *SUCLA2*, *SUCLG1*, or *RRM2B*; a hepatocerebral form associated with mutations in *DGUOK*, *MPV17*, *POLG*, or *C10orf2*; and a neurogastrointestinal form associated with mutations in *TYMP* [4, 5].

In this review we discuss the genetic basis, clinical manifestations, and therapeutic options for MDS.

Genetic Basis of mtDNA Depletion Syndromes

MDS are due to defects in mtDNA maintenance caused by mutations in nuclear genes, which function in either maintaining the mitochondrial nucleotide pool (*TK2*, *DGUOK*, *SUCLA2*, *SUCLG1*, *RRM2B*, and *TYMP*) or by mutations in genes associated with mtDNA replication (*POLG* and *C10orf2*). The function of the *MPV17* gene remains unclear (Fig. 1).

Defects in Maintaining Mitochondrial Nucleotide Pool

Unlike nuclear DNA, which replicates with each cell division, mtDNA replicates continuously and independently of cell division. dNTPs can be synthesized via either the de novo pathway, which is cell cycle-regulated, thereby operative only in S-phase cells or the salvage pathway in which dNTPs are produced by utilizing preexisting deoxynucleosides to synthesize DNA precursors. As mtDNA synthesis is continuous throughout the cell cycle, the salvage pathway becomes essential for mtDNA maintenance. *TK2*, *DGUOK*, *SUCLA2*, *SUCLG1*, *RRM2B*, and *TYMP* encode proteins that maintain the mitochondrial dNTP pool mainly through salvage pathways; therefore, mutations in any of these genes result in depleting the mitochondria from DNA building blocks with subsequent mtDNA depletion.

Mitochondrial thymidine kinase 2 (TK2) is encoded by the nuclear gene *TK2* and plays an essential role in the pyrimidine nucleoside salvage pathway [6]. It mediates the first, and rate-limiting, step in the phosphorylation of pyrimidine nucleosides in the mitochondrial matrix. Mitochondrial deoxyguanosine kinase is encoded by the nuclear gene *DGUOK* and is

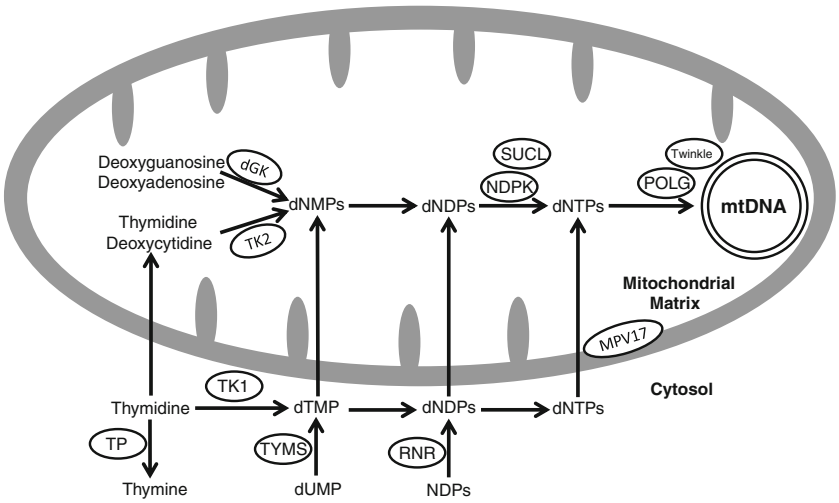

Fig. 1 Schematic presentation of protein involved in mitochondrial nucleotide pools maintenance and mitochondrial DNA replication. TK2 = mitochondrial thymidine kinase 2 (encoded by *TK2* gene); dGK = mitochondrial deoxyguanosine kinase (encoded by the *DGUOK* gene); SUCL = succinyl CoA ligase (SUCL is composed of an alpha subunit, encoded by *SUCLG1* and a beta subunit, encoded by either *SUCLA2* or *SUCLG2*); NDPK = nucleoside diphosphate kinase; POLG = DNA polymerase gamma (POLG is a heterotrimer enzyme composed of one catalytic subunit encoded by *POLG* and two accessory subunits encoded by *POLG2*); TP = thymidine phosphorylase (encoded by *TYMP* gene); RNR = ribonucleotide reductase (*RRM2B* encodes the p53-inducible small subunit (p53R2) of the RNR); dNMP = deoxynucleoside monophosphate; dNDP = deoxynucleoside diphosphate; dNTP = deoxynucleoside triphosphate; NDP = nucleoside diphosphate; dTMP = deoxythymidine monophosphate; TK1 = cytosolic thymidine kinase 1; TYMS = thymidylate synthase. The twinkle protein is encoded by *C10orf2* and the MPV17 by the *MPV17* gene

essential for the purine nucleoside salvage pathway as it mediates the first step in the phosphorylation of purine nucleosides in the mitochondrial matrix [7]. Mutations in *TK2* or *DGUOK* result in impaired synthesis of mitochondrial dNTPs, the building blocks for mtDNA, leading to decreased mtDNA amount and mtDNA depletion.

SUCLA2 and *SUCLG1* encode subunits of succinyl CoA ligase (SUCL). SUCL is a mitochondrial tricarboxylic acid cycle enzyme that catalyzes the reversible conversion of succinyl-CoA and ADP or GDP to succinate and adenosine triphosphate or guanosine triphosphate. SUCL is composed of an alpha subunit, encoded by *SUCLG1* and a beta subunit, encoded by either *SUCLA2* or *SUCLG2*. The alpha subunit forms a heterodimer with either of its beta subunits, resulting in an ADP-forming SUCL and a GDP-forming SUCL, respectively. SUCL also forms a complex with the mitochondrial nucleoside diphosphate kinase, and the lack of this complex formation in SUCL deficiency has been suggested to disturb the kinase function, resulting in decreased mtDNA synthesis leading to mtDNA depletion [8].

RRM2B encodes the p53-inducible small subunit (p53R2) of ribonucleotide reductase, a cytosolic enzyme that catalyzes the terminal step of de novo synthesis of deoxyribonucleoside by direct reduction of ribonucleoside diphosphates to their corresponding deoxyribonucleoside diphosphates. The p53R2 is expressed in post-mitotic cells and therefore has a key function in the maintenance of dNTP pools for mtDNA synthesis [9].

TYMP encodes thymidine phosphorylase (TP), which is a cytosolic enzyme that catalyzes the conversion of thymidine to thymine and deoxyuridine to uracil, and is therefore essential for the nucleotide salvage pathway. Low TP activity results in the accumulation of thymidine and deoxyuridine, leading to an imbalance of cytosolic dNTP pools. Because the mitochondrial dNTP pool relies, in part, on dNTP imported from the cytosol, an imbalanced cytosolic dNTP pool can lead to an imbalanced mitochondrial dNTP pool that can impair mtDNA synthesis [4].

Defects in mtDNA Replication

POLG encodes the catalytic subunit of DNA polymerase gamma, which is a heterotrimer enzyme composed of one catalytic subunit encoded by *POLG* and two accessory subunits encoded by *POLG2* that assist in binding and processing the synthesized DNA. DNA polymerase gamma is required for mtDNA synthesis as it is the only DNA polymerase in humans that allows for replication and repair of mtDNA [10]. The twinkle protein, encoded by *C10orf2*, serves the important function of a DNA helicase that is required for DNA replication [11]. Therefore, *POLG* and *C10orf2* are essential for mtDNA replication and mutations in these genes result in insufficient mtDNA synthesis to keep up with mtDNA turnover and segregation to daughter cells during cell divisions, resulting in a reduction of mtDNA content and mtDNA depletion.

mtDNA Depletion Caused by Defects in a Protein of Unknown Function

MPV17 encodes the MPV17 protein, an inner mitochondrial membrane protein whose function and role in the pathogenesis of mtDNA depletion are as yet unknown. It has been suggested that MPV17 plays a role in controlling mtDNA maintenance and oxidative phosphorylation activity in mammals and yeast [12]. A dysfunctional MPV17 protein caused by *MPV17* mutations impairs mtDNA maintenance and can cause mtDNA depletion.

Clinical Manifestations of MDS

MDS are classified as 1 of 4 clinical forms: a myopathic form associated with mutations in *TK2*, an encephalomyopathic form associated with mutations in *SUCLA2*, *SUCLG1*, or *RRM2B*, a hepatocerebral form associated with mutations in *DGUOK*, *MPV17*, *POLG*, or *C10orf2*, and a neurogastrointestinal form associated with mutations in *TYMP* (Table 1).

TK2-Related Myopathic MDS

To date, approximately 50 affected individuals have been reported with *TK2*-related MDS. The clinical presentation of *TK2*-related MDS is variable, with a broad phenotype. Initial development is typically normal and the majority of affected children present before the age of 2 years with gradual onset of hypotonia, generalized fatigue, decreased physical stamina, proximal muscle weakness, and feeding difficulty. Some patients develop facial weakness and bulbar weakness, including dysarthria and dysphagia. Hypotonia and weakness is observed in all patients and previously acquired motor skills are lost. However, cognitive function is typically spared [13–23].

Although *TK2*-related MDS has been thought to be associated with a purely myopathic form, other organ system involvements have been reported, including an encephalomyopathic presentation with hypotonia, weakness, epilepsy, and microcephaly [20], and hepatic involvement with hepatomegaly and elevated transaminases accompanied by mtDNA depletion in muscle and liver [19]. Other, less common, presentations include spinal muscular atrophy-like presentation [13] and chronic progressive external ophthalmoplegia with proximal muscle weakness [23]. Milder presentations have been reported and include late onset

Table 1 Clinical phenotypes of different mitochondrial DNA depletion syndromes

Mitochondrial DNA depletion syndromes	Age of onset	Common clinical features
Myopathic		
TK2-related	Infancy—early childhood	Hypotonia and muscle weakness, facial weakness, bulbar weakness (dysarthria and dysphagia), elevated serum creatine phosphokinase
Encephalomyopathic		
SUCLA2- and *SUCLG1*-related	Infancy	Hypotonia and muscle weakness, psychomotor delay, scoliosis/kyphosis, abnormal movement disorders (dystonia, athetoid, or choreiform), sensorineural hearing impairment, epilepsy, growth retardation, lactic acidosis, elevated methylmalonic acid in urine and plasma, cortical atrophy and basal ganglia involvement in neuroimaging
RRM2B-related	Neonatal—infancy	Hypotonia and muscle weakness, psychomotor delay, microcephaly, sensorineural hearing loss, failure to thrive, lactic acidosis
Hepatocerebral		
DGUOK-related	Neonatal	Hepatic dysfunction, psychomotor delay, hypotonia, rotary nystagmus developing into opsoclonus, lactic acidosis, hypoglycemia
MPV17-related	Infantile—childhood	Hepatic dysfunction, psychomotor delay, hypotonia, peripheral neuropathy, lactic acidosis, hypoglycemia, leukoencephalopathy in neuroimaging
POLG-related	Early childhood	Hepatic dysfunction, epilepsy, psychomotor delay, ataxia, neuropathy, hyporeflexia and hypotonia evolving into spastic paraparesis, stroke or stroke-like episodes, myoclonus, choreoathetosis, parkinsonism, nystagmus, somnolence, irritability, cortical visual loss, and sensorineural hearing impairment, generalized brain atrophy in neuroimaging
C10orf2-related	Neonatal—infancy	Hepatic dysfunction, psychomotor delay, epilepsy, peripheral neuropathy, hypotonia, ophthalmoplegia, nystagmus, athetosis, ataxia, sensorineural hearing impairment, lactic acidosis, cerebellar cortical atrophy in neuroimaging
Neurogastrointestinal		
TYMP-related	Late childhood—adolescence	Gastrointestinal dysmotility, weight loss, peripheral neuropathy, ptosis, ophthalmoplegia, elevated thymidine and deoxyuridine in plasma, leukoencephalopathy in neuroimaging

proximal muscle weakness [15], adult-onset progressive myopathy [22], and sensorineural hearing loss [21].

Serum creatine phosphokinase concentration is usually elevated and electromyography (EMG) usually shows non-specific myopathic changes. Histopathological findings on skeletal muscle include prominent variance in fiber size, sarcoplasmic vacuoles, and increased connective tissue. Ragged red fibers are present. Succinate dehydrogenase activity is increased, whereas cytochrome c oxidase activity is low, or absent. Electron microscopy shows abnormal mitochondria with circular cristae. mtDNA content is typically severely reduced in muscle tissue. Electron transport chain (ETC) activity assays in skeletal muscle typically show decreased activity of multiple complexes with complex I, I + III, and IV being the most affected [13–23].

Typically, muscle weakness rapidly progresses leading to respiratory failure and death within a few years of onset. The most common cause of death is pulmonary infection. Only a few patients have survived to late childhood and adolescence.

SUCLA2 and *SUCLG1*-Related Encephalomyopathic MDS

Nearly 20 individuals have been reported with *SUCLA2*-related MDS. Mutations in *SUCLG1* have been reported less frequently with a similar phenotype to that observed in *SUCLA2*-related MDS [4, 24–30]. Affected infants present with hypotonia typically before the age of 6 months. All affected children develop hypotonia, muscle atrophy, and psychomotor delay. Other frequent manifestations include progressive scoliosis or kyphosis, abnormal movements, including dystonia and athetoid or choreiform movements, feeding difficulty, gastroesophageal reflux, sensorineural hearing impairment, postnatal growth retardation, and respiratory insufficiency that can result in frequent pulmonary infections. Other, less common, manifestations include hyperhidrosis, strabismus, ptosis, and epilepsy presenting with either infantile spasms or generalized convulsions. Urine organic acids analysis consistently shows elevated methylmalonic acid. Similarly, plasma methylmalonic acid concentration is elevated. Lactate is elevated in both plasma and cerebrospinal fluid (CSF) in most affected individuals.

EMG may reveal findings suggestive of motor neuron involvement, whereas neuroimaging may show cortical atrophy, bilateral basal ganglia involvement, and delayed myelination. Histopathological findings on skeletal muscle include increased fiber variability, increased number of mitochondria, and extensive intracellular fat accumulation. ETC activity assays in muscle typically show a combined deficiency of respiratory complex I, III, and IV, with normal complex II activity. Quantitation of mtDNA shows a decreased mtDNA content in muscle. Prognosis is poor, with most affected children dying in childhood, most commonly from an intercurrent infection [24–30].

RRM2B-Related Encephalomyopathic MDS

To date, *RRM2B* mutations have been reported in about 15 infants with severe encephalomyopathic MDS that is associated with early-onset (neonatal or infantile), multi-organ presentation, and mortality during infancy. Affected individuals typically present during the first months of life with hypotonia, lactic acidosis, failure to thrive, tubulopathy, microcephaly, psychomotor delay, sensorineural hearing loss, and profound mtDNA depletion in muscle. The disease progresses rapidly, leading to death in few months [4, 31–34].

RRM2B mutations have also been reported to cause a mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like phenotype with mtDNA depletion [35] and autosomal-dominant progressive external ophthalmoplegia (PEO) with multiple mtDNA deletions [36, 37].

DGUOK-Related Hepatocerebral MDS

Approximately 100 individuals have been reported with *DGUOK*-related MDS, which can present in two forms: multi-organ disease in neonates and isolated hepatic disease later in infancy or childhood [38]. The majority of affected individuals have a neonatal-onset multi-organ illness that presents with lactic acidosis and hypoglycemia in the first week of life. Within weeks of birth, all infants develop hepatic disease and neurologic dysfunction. Severe myopathy, developmental regression, and typical rotary nystagmus developing into opsoclonus are also seen. Cholestasis is prominent early in the clinical course. Liver involvement may cause neonatal- or infantile-onset liver failure that is generally progressive with ascites, edema, and coagulopathy. A minority of affected individuals present initially in infancy or childhood with isolated hepatic disease, occasionally following a viral illness. Affected individuals with this form may develop mild hypotonia and renal involvement manifesting as proteinuria and aminoaciduria [2, 38–55]. More recently, *DGUOK* mutations have been reported in a neonate with clinical and autopsy findings consistent with neonatal hemochromatosis and mtDNA depletion [56], and in individuals with adult-onset mitochondrial myopathy and mtDNA multiple deletions in skeletal muscle [57].

The majority of affected newborns with the multi-organ form of the disease show elevated serum concentration of tyrosine or phenylalanine on newborn screening [54, 55]. Findings of intrahepatic cholestasis typically include elevations in serum concentrations of liver transaminases, gamma-glutamyltransferase (GGT), and conjugated hyperbilirubinemia. Increased serum concentration of ferritin is observed in a large number of affected infants. mtDNA content is reduced in liver and muscle [54, 55]. ETC activity in liver typically shows a combined deficiency of complexes I, III, and IV [49]. Liver histopathology typically reveals microvesicular cholestasis, but may show bridging fibrosis, giant cell hepatitis, or cirrhosis. Liver electron microscopy may reveal an increase in the number of mitochondria and is commonly associated with abnormal cristae [40, 45, 54, 55, 58].

Hepatic dysfunction is progressive in the majority of individuals with both forms of *DGUOK*-related MDS and is the most common cause of death. Hepatocellular carcinoma has also been reported in 1 patient. For children with the multi-organ form, liver transplantation provides no survival benefit [53].

MPV17-Related Hepatocerebral MDS

MPV17-related hepatocerebral MDS, an infantile-onset disorder, can present with a spectrum of combined hepatic, neurologic, and metabolic manifestations. Approximately 30 affected individuals have been reported with *MPV17*-related hepatocerebral MDS [59–68]. Of note, among those confirmed cases are individuals with Navajo neurohepatopathy who were found to have homozygous p.Arg50Gln mutations in *MPV17*. Navajo neurohepatopathy, a disorder prevalent in the Native American Navajo population, has the manifestations of *MPV17*-related hepatocerebral MDS, as well as painless fractures, acral mutilation, and corneal anesthesia, ulceration, and scarring [60].

Affected individuals typically present with manifestations of liver dysfunction, including jaundice, cholestasis, and coagulopathy. Infancy is the typical age of onset; however, individuals homozygous for the p.Arg50Gln mutation may present later in childhood [60]. In the vast majority of affected individuals, liver disease progresses to liver failure typically during infancy or early childhood. Hepatomegaly and liver cirrhosis occur in some affected individuals. Hepatocellular carcinoma has also been reported in 2 affected individuals. The vast majority of affected individuals exhibited neurologic manifestations, including developmental delay, hypotonia, muscle weakness, and motor and sensory peripheral neuropathy. Some affected individuals presented with psychomotor delays during early infancy,

while others had normal development early in life followed by loss of motor and cognitive abilities later in infancy or early childhood. Less frequent neurologic manifestations include epilepsy, ataxia, dystonia, microcephaly, cerebrovascular infarction, and subdural hematoma. Failure to thrive is one of the common manifestations, although some children have normal growth, especially early in the course of the disease. The vast majority of affected individuals have metabolic derangements, including lactic acidosis and hypoglycemia, which typically presents during the first 6 months of life. Less frequent manifestations include renal tubulopathy, hypoparathyroidism, and gastrointestinal dysmotility that manifests as gastroesophageal reflux, cyclic vomiting, and diarrhea. Corneal anesthesia and ulcers were reported in individuals homozygous for the mutation p.Arg50Gln [59–68].

More recently, *MPV17* mutations have been reported in adult presentation of neuropathy and leukoencephalopathy with multiple mtDNA deletions in muscle indicating that *MPV17* mutations are associated with an evolving broader phenotype [69]

Affected infants demonstrate elevated transaminases and GGT, and hyperbilirubinemia. Liver histopathology may show cholestasis and cirrhosis. Neuroimaging may show white matter abnormalities (leukoencephalopathy). mtDNA content is severely and consistently reduced in liver tissue, and can also be reduced in muscle tissue. ETC activity assays in liver and muscle tissue typically show decreased activity of multiple complexes with complex I or I + III being the most affected [66].

Liver disease typically progresses to liver failure in affected children and liver transplantation remains the only treatment option for liver failure. Approximately half of affected children reported did not undergo liver transplantation and died because of progressive liver failure—the majority during infancy or early childhood. A few children were reported to survive without liver transplantation [66].

POLG-Related Hepatocerebral MDS

POLG-related disorders present a continuum of broad and overlapping phenotypes presenting from early childhood to late adulthood. The clinical phenotypes of *POLG*-related disorders include autosomal recessive and dominant adult-onset PEO [70–73], myoclonic epilepsy, myopathy, sensory ataxia (MEMSA) syndrome [74, 75], ataxia-neuropathy spectrum including mitochondrial recessive ataxia syndrome (MIRAS), and sensory ataxia, neuropathy, dysarthria, ophthalmoplegia (SANDO) syndrome [76–79], and hepatocerebral MDS (Alpers-Huttenlocher syndrome) [80–90]. More recently, *POLG* mutations were identified in individuals with clinical features of MNGIE, but no leukoencephalopathy [91].

The incidence of Alpers-Huttenlocher syndrome has been estimated to be ~1:50,000 [92]. It is the most severe phenotype associated with *POLG* mutations and characterized by a progressive encephalopathy with intractable epilepsy and psychomotor delay, neuropathy, and hepatic failure. Affected individuals usually present between the age of 2 and 4 years with seizures (focal, generalized, myoclonic, epilepsia partialis continua, or status epilepticus), headaches that are typically associated with visual sensations or visual auras, hypotonia, and psychomotor regression. Early in the disease course areflexia and hypotonia are present and later followed by spastic paraparesis that evolves over months to years, leading to psychomotor regression. All affected individuals develop neuropathy, ataxia, and loss of cognitive function, including concentration, language skills, and memory. Affected individuals may also develop stroke and stroke-like episodes, myoclonus, choreoathetosis, parkinsonism, nystagmus, somnolence, irritability, loss of normal emotional responses, depression, cortical visual loss, and sensorineural hearing loss. Neurologic signs and symptoms may worsen during infections or other stressful situations. Affected individuals develop liver dysfunction with elevated transaminases, hypoalbuminemia, coagulopathy, hypoglycemia, and hyperammonemia. Liver involvement can progress rapidly to end-stage liver failure within a few months. CSF protein is generally elevated. Neuroimaging may show gliosis and generalized brain atrophy. Liver histology may demonstrate macro- and microvesicular steatosis, centrilobular necrosis, fibrosis, cirrhosis, bile duct proliferation, and mitochondrial proliferation. mtDNA content is reduced in liver. Disease progression is variable, with life expectancy from onset of symptoms ranging from 3 months to 12 years [80–90].

C10orf2-Related Hepatocerebral MDS

Mutations in *C10orf2* have been associated with variable phenotypes, including infantile-onset spinocerebellar ataxia [11, 93–97], autosomal dominant PEO [98–100], and hepatocerebral MDS [101, 102]. Mutations in *C10orf2* are a rare cause of early-onset hepatocerebral MDS that has been reported in 5 children from 2 unrelated families. Affected individuals typically present in the neonatal or infantile period with lactic acidosis, hepatomegaly, hypotonia, and psychomotor delay. The neurologic involvement progresses to include hyporeflexia, muscular atrophy, ophthalmoplegia, nystagmus, athetosis, ataxia, epilepsy, sensory neuropathy, sensorineural hearing impairment, psychomotor regression. Liver involvement includes cholestasis, increased transaminases, and coagulopathy. Affected infants may also have feeding difficulties and growth retardation. Lactate is increased in plasma and CSF. Neuroimaging can show cerebellar cortical atrophy. ETC activity assays show reduced activities of complexes I, III, and IV. mtDNA content is severely reduced in liver tissue. Prognosis is poor with 3

of the reported affected children dying between 2 and 3 years of age [101, 102].

MNGIE Disease

Mutations in *TYMP* have been reported in about 70 individuals with MNGIE disease [103]. Affected individuals usually present clinical manifestations between the first and fifth decades with the majority starting with symptoms before age 20 years. All affected individuals develop weight loss and progressive gastrointestinal dysmotility manifesting as early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain and distention, and diarrhea. In addition, all affected individuals have peripheral demyelinating motor and sensory neuropathy that may be accompanied by axonal neuropathy in some cases. The neuropathy typically presents with distal weakness and paresthesias occurring in a symmetric stocking-glove distribution. Ptosis and ophthalmoplegia are common findings. Intellectual disability occurs in some individuals. Other variable manifestations include hepatic cirrhosis with increased liver enzymes and macrovesicular steatosis, anemia, sensorineural hearing loss, short stature, autonomic nervous system dysfunction (usually orthostatic hypotension), bladder dysfunction, ventricular hypertrophy, and diverticulosis [103–119].

Affected individuals can have elevated CSF protein and plasma lactate. Thymidine and deoxyuridine are increased in plasma. In affected individuals, thymidine phosphorylase enzyme activity in leukocytes is usually less than 10 % of the control mean [107, 112]. EMG and nerve conduction velocity show decreased motor and sensory nerve conduction velocities, and myopathic changes. Neuroimaging typically demonstrates diffuse white matter abnormalities (leukoencephalopathy) [103, 117]. mtDNA depletion, mitochondrial proliferation, and smooth cell atrophy are observed in the external layer of the muscularis propria in the stomach and in the small intestine. Skeletal muscle generally shows histologic abnormalities of a mitochondrial myopathy including ragged-red fibers and defects in single or multiple ETC complexes with the most common defect in complex IV. However, MNGIE has been reported without skeletal muscle involvement at the morphological, enzymatic, or mtDNA content level [120].

MNGIE is a progressive disease with mean age of death is approximately 40 years (ranging from 25–60 years) [108].

Therapeutic Options for MDS

Although MDS are severe disorders with poor prognosis in the majority of affected individuals, no curative therapy is available for any of these disorders. MDS are multi-organ disorders; therefore, affected individuals should have a comprehensive evaluation to assess the degree of involvement of different systems. Management of MDS should involve a multidisciplinary team, including different specialists and aims to provide supportive care and symptomatic treatment for complications associated with these disorders. Other treatment options for some MDS include dietary modulation, cofactor supplementation, liver transplantation, and stem cell transplantation.

Assessment of the Extent of MDS

Affected individuals with MDS should have an extensive evaluation to understand the involvement of different organs, including the neuromuscular, hepatic, gastrointestinal, cardiac, and renal systems.

Almost all affected individuals with MSD show neuromuscular manifestations; therefore, a neurology consultation with comprehensive neurologic examination and developmental/cognitive assessment are mandatory. The following diagnostic modalities can be used to assess the degree of neurological involvement: neuroimaging (mainly brain magnetic resonance imaging) to establish the degree of central nervous system, nerve conduction velocity to establish the degree of the peripheral nervous system involvement, EMG to assess myopathy, and electroencecephalography if seizures are suspected. A thorough ophthalmologic and hearing evaluation is also required.

The degree of liver involvement in the hepatocerebral forms of MDS can be assessed by liver function tests, including liver transaminases, GGT, albumin, fasting blood glucose, ammonia, and coagulation profile; ultrasound examination to assess liver size and texture, and for the presence of masses; alpha fetoprotein (AFP) to screen for hepatocellular carcinoma; and hepatology/liver transplantation consultation.

Gastrointestinal evaluation in MNGIE disease may depend on the symptoms and can include the following: gastrointestinal consultation, abdominal imaging (X-ray and computed tomography), upper gastrointestinal contrast radiography, esophagogastroduodenoscopy, sigmoidoscopy, liquid phase scintigraphy, and antroduodenal manometry. These studies may show hypoperistalsis, gastroparesis, dilated duodenum, and diverticulosis. Small bowel manometry shows reduced amplitude of contractions [103].

Echocardiogram and electrocardiogram are needed to determine cardiac involvement. Pulmonary function tests and assessment of blood gases are needed for patients with myopathy to assess for respiratory insufficiency. Nutritional evaluation and swallowing assessment are needed in those with feeding difficulty and growth retardation. Urine analysis, urine electrolytes, and urine amino acids can be performed to assess renal tubulopathy.

Symptomatic Management for MDS

Seizures are common features in MDS with neurological involvement. Seizure control with antiepileptic medications is the goal of treatment; however, refractory epilepsy may be very difficult to control. The use of high-dose anticonvulsants and/or treatment with more than 1 medication often becomes necessary to control refractory seizures. It is very important to avoid valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) in treating seizures in MDS, particularly *POLG*-related disorders, because of the risk of precipitating and/or accelerating liver disease [121, 122].

Physical therapy can help maintain muscle function and prevent joint contractures. Feeding difficulties and failure to thrive may require nutritional support by experienced dietitian, occupational therapy to improve oromotor functions, and the use of a nasogastric tube or gastrostomy tube feedings.

Respiratory insufficiency can benefit from chest physiotherapy, aggressive antibiotic treatment of chest infections, and artificial ventilation that could include assisted nasal ventilation or intubation, and the use of a tracheostomy and ventilator.

Other treatment options include bracing to treat scoliosis or kyphosis, surgery for ptosis, and cochlear implantation for sensorineural hearing loss.

Nutritional Modulation in MDS

Formulas with an enriched medium-chain triglyceride content may provide better nutritional support for infants with cholestasis than formulas with predominantly long-chain triglycerides [123].

Prevention of hypoglycemia requires avoidance of fasting by frequent or continuous feeding. In addition, uncooked cornstarch may reduce symptomatic hypoglycemia in individuals with *DGUOK* and *MPV17*-related hepatocerebral MDS [54, 65]. Furthermore, cornstarch use may slow the progression of the liver disease in *MPV17*-related hepatocerebral MDS [63, 65].

Cofactor Use in MDS

Succinate and ubiquinone were reported to slow the progression of liver impairment in *MPV17*-related MDS [64].

Elevated CSF inflammatory cytokines and blocking folate receptor autoantibodies associated with reduced CSF folate were reported in a child with Alpers-Huttenlocher syndrome. Treatment with oral folinic acid (leucovorine) resulted in improvement of CSF folate level and seizure frequency, and communicative abilities improved [124]. Therefore, CSF folate may be deficient in disorders that lead to mtDNA depletion. It has been suggested that testing for CSF folate deficiency with treatment offered to those with deficiency can be one option; the other option can be empiric therapy with folinic acid [90].

Levocarnitine, creatine monohydrate, coenzyme Q10, B vitamins, and antioxidants, such as alpha lipoic acid, vitamin E, and vitamin C, have been used as mitochondrial supplements. These cofactors have been used in MDS; however, there is very limited evidence for their effectiveness [125, 126].

More recently, enteral administration of sodium pyruvate to a child with myopathic MDS has been reported to improve muscle strength and quality of life score using used the Newcastle Pediatric Mitochondrial Disease Scale. No significant change of the blood lactate level or lactate-to-pyruvate ratio were noticed [127]. Further evaluation is need before reaching conclusions about the effectiveness of such therapy.

Studying myotube cells of individuals with MDS have demonstrated that the application of variable combinations of deoxynucleoside monophosphates in different types of MDS result in near normalization of mtDNA content in many cases. Therefore, the use of deoxynucleoside monophosphate combinations may be a possible therapeutic approach for individuals with MDS [128]. Further clinical investigation is needed to investigate this approach.

Liver Transplantation in MDS

Although liver transplantation remains the only treatment option for liver failure in hepatocerebral MDS, liver transplantation in mitochondrial hepatopathy is controversial, largely because of the multi-organ involvement.

Liver transplantation has been performed in about a third of affected individuals with *MPV17*-related MDS; the outcome has not been satisfactory, with half of the transplanted children dying in the post-transplantation period because of multi-organ failure and/or sepsis [66].

For children with multi-organ *DGUOK*-related MDS, liver transplantation provides no survival benefit. However, several children with isolated hepatic disease have had excellent 10-year survival with liver transplantation and, thus, it is a potential therapeutic option. However, this option warrants careful discussion with parents because at least 1 child with isolated liver disease developed neurologic features after liver transplantation [53].

Liver transplantation is not advised in children with Alpers-Huttenlocher syndrome because transplanting the liver does not alter the rapid progression of the neurological complications [129]. However, liver transplantation in adults who have an acceptable quality of life may be of benefit. Two affected individuals with *POLG*-related disorders were reported to survive after liver transplantation [79, 88].

Thymidine Reduction in MNGIE Disease

In MNGIE, a correlation between plasma thymidine levels and the severity of the phenotype has been observed [130]. Therefore, it has been proposed that the reduction in circulating thymidine levels can result in disease improvement. Peritoneal dialysis has been used to reduce the thymidine levels leading to an improvement of the symptoms in affected individuals with MNGIE disease [131]. Enzyme replacement therapy via infusion of platelets from healthy donors to individuals with MNGIE resulted in reduction of circulating thymidine and partially restored TP activity [132].

Allogeneic hematopoietic stem cell transplantation (HSCT) offers the possibility of sustained correction of enzyme deficiency and has become an established treatment for many different storage diseases. More than 10 individuals with MNGIE disease have so far been treated with allogeneic HSCT [133–136]. Allogeneic HSCT has been shown to restore TP activity, lowering thymidine levels and improving the gastrointestinal dysmotility [132–135]. However, neurological assessments remained unchanged [136]. Although HSCT corrects biochemical abnormalities and improves gastrointestinal symptoms, the procedure can be risky in patients already in poor medical condition, as are many MNGIE patients and several affected patients were reported to die in the post-transplantation period [136]. As transplant-related morbidity and mortality increase with the progression of the disease and the number of associated comorbidities, it has been suggested that individuals with MNGIE should be referred to HSCT when they are still relatively healthy in order to minimize the complications of the procedure [136].

Conclusion

MDS are a genetically and clinically heterogeneous group characterized by a severe reduction in mtDNA content in affected tissues. MDS are due to a defect in mtDNA maintenance caused by mutations in nuclear genes which function in either mitochondrial dNTP synthesis (*TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, and *TYMP*) or mtDNA replication (*POLG* and *C10orf2*). The function of *MPV17* is not yet known. According to the organ majorly involved, MDS are classified as the myopathic form associated with mutations in *TK2*, the encephalomyopathic form associated with mutations in *SUCLA2*, *SUCLG1*, or *RRM2B*, the hepatocerebral form associated with mutations in *DGUOK*, *MPV17*, *POLG*, or *C10orf2*, and the neurogastrointestinal form associated with mutations in *TYMP*. Although mutations in these different genes have been traditionally assigned to these phenotypes, the phenotypic associations have been expanding with the current advancement in the molecular testing. Although MDS are severe disorders with poor prognosis in the majority of affected individuals, no curative therapy is available for any of these disorders. Affected individuals should have a comprehensive evaluation to assess the degree of involvement of different systems. Treatment is directed mainly toward providing symptomatic management. Nutritional modulation and cofactor supplementation may be beneficial. Liver transplantation remains controversial. Finally, stem cell transplantation in MNGIE disease shows promising results.

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

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