

Review

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Spectrum of movement disorders in mitochondrial diseases

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Abstract

Mitochondrial disorders (MD) include a large group of maternally inherited, autosomal dominant, or recessive genetic syndromes caused by mitochondrial dysfunction. MD can be diagnosed at any age and many of them show a multisystem presentation with variable combinations of symptoms. Given the important role of mitochondria in neuronal homeostasis, neurological manifestations, including movement disorders, can accompany MD. Movement disorders (MoD), either hypo- or hyperkinetic type, are reported in MD, but the real incidence and a detailed characterization of these features are not addressed in population-based studies. Dystonia, usually in the context of Leigh syndrome, is the main extrapyramidal movement disorder in pediatric MD patients; whereas parkinsonism is the most prevalent hypokinetic disorder in adult MD patients. Ataxia is a common feature in MD, in both the pediatric and adult MD populations. Other MoD, such as myoclonus, chorea, or tremor, may also occur in MD. MoD manifest more frequently in the context of a complex phenotype but rarely can be isolated. From a genetic point of view, MoD are described in patients with either mutations in mtDNA or in nuclear genes related to mitochondria, and the same gene can be associated with different types of MoD. Recent studies demonstrate that the dopaminergic nigrostriatal system is very vulnerable to mitochondrial dysfunction and defects of mtDNA maintenance are frequently associated with a nigrostriatal degeneration, which may explain the pathophysiological mechanism. Therapeutic interventions for MoD in MD do not differ from treatment options used for MoD with different etiopathological background. Some forms benefit from specific treatments, e.g., primary Coenzyme Q10 deficiencies. Newer therapeutic strategies have been pursued which act on different mechanisms of mitochondrial dysfunction, but clinical trials are warranted to improve the management of MD patients.

Keywords: Mitochondrial diseases, dystonia, tremor, parkinsonism, myoclonus, basal ganglia, mtDNA mutations, multiple deletions



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INTRODUCTION

Mitochondrial diseases (MD) are the most common inherited metabolic disorders due to mitochondrial dysfunction^[1].

Mitochondria harbor their own DNA (mtDNA), which is a 16.6-kb double-stranded circular DNA encoding for 13 subunits of respiratory chain (RC), whereas the nuclear DNA (nDNA) identifies about 79 subunits of RC and several other proteins involved in the synthesis of cofactors (e.g., iron-sulfur proteins, hemes, and copper) as well as in the assembly of the five RC complexes.

In MD, the structure and function of mitochondria are impaired due to mutations in genes encoded by mtDNA or nDNA; for this reason, the genetics of MD is quite complex and in continuous evolution^[2]. A genetic classification of MD distinguishes two main categories: (1) MD caused by primary mtDNA mutations; and (2) MD due to mutations in several nDNA genes, related to mitochondria. Defects involving these nuclear genes can be divided into five subcategories: (1) genes encoding subunits of the five complexes of respiratory chain; (2) genes encoding assembly factors of the complexes; (3) genes responsible for mtDNA maintenance (replication, maintenance of nucleotide pools, and mtDNA quality control); (4) genes encoding for biosynthetic enzymes for lipids, amino acids, and cofactors; and (5) genes encoding for other proteins that influence secondarily oxidative phosphorylation.

The oxidative phosphorylation (OXPHOS) dysfunction results in an impairment of oxidative energy metabolism, with defective utilization of nutrients to generate energy (ATP), thereby causing an accumulation of metabolic intermediates, increased oxidative stress, and decreased energy production. Consequently, tissues highly energy-dependent such as skeletal muscle, central and peripheral nervous system, heart, and liver can be affected by the bioenergetics deficiency in the same individual, explaining the multi-organ failure that is typical of these disorders.

MD may appear at any age with a wide clinical spectrum, although some clinical syndromes have typical infantile onset, whereas others occur later and usually have a milder course^[3].

The nervous system and skeletal muscle, because of their high-energy dependence and susceptibility, are invariably involved in most MD. Neurological features include epilepsy, psychomotor retardation, migraine, stroke-like episodes, dementia, peripheral neuropathy, and sensitive and cerebellar ataxia^[4]. Movement disorders (MoD) are defined as neurological features due to dysfunction of basal ganglia and their connections and are common in MD, as either hyper- or hypokinetic form^[5]. Among them, dystonia, parkinsonism, myoclonus, tremor, and chorea are more frequently reported^[6,7]. In pediatric MD patients, dystonia and chorea are often reported, whereas parkinsonism is commonly described in adults^[8].

Clinical presentation of movement disorders is variable; some studies report on the occurrence of either a single type of extrapyramidal sign or a combination of two or more MoD in the same patient, usually in the context of a multisystem disorder but rarely as an isolated manifestation of MD^[7-9].

Diagnosis of MD is quite challenging because of the variability of the clinical presentation as well as the presence of symptoms overlapping with other neuromuscular or neurodegenerative disorders; however, recurrent clinical findings usually in classical syndromes associated with specific mtDNA mutations strongly suggest the diagnosis. Laboratory investigations can help to address the diagnosis, being the main findings that lead to the diagnosis: elevated lactate levels; the presence of some morphological findings on muscle biopsy as “ragged red fibers (RRF)” on Gomori trichrome stain and/or cytochrome oxidase negative fibers (COX-ve fibers); detection of defect of mitochondrial respiratory chain enzyme activities or CoQ levels; and the identification of pathogenic mutations in either mtDNA or nDNA.

Table 1. Main studies reporting on frequency of movement disorders associated with mitochondrial diseases

Author	Patients cohort	No. of MD patients with MoD (%)	Spectrum of movement disorders No. of MD patients (%)	Neuroradiological findings
Schreglmann <i>et al.</i> ^[14] 2018	50 pts with MD ¹	15 (30%)	5 (10%) dystonia; 3 (6%) parkinsonism; 2 (4%) myoclonus, 2 (4%) chorea; 3 (6%) ataxia	Brain MRI showed cerebellar atrophy mainly lobule VI and VII in all MD pts. with MoD
Martikainen <i>et al.</i> ^[8] 2016	678 pts with MD ¹ (87% adults)	42 (6.1%): 12 pediatric pts and 30 adults	11/12 (92%) dystonia 13/30 (43%) parkinsonism 11/30 (37%) multifocal or generalized dystonia in mtDNA mutations	Brain MRI revealed symmetric basal ganglia lesions (putamen and globus pallidus), in 16 pts; cerebellar atrophy in 6 pts No calcifications were detected DAT-SPECT abnormal in 9/12 pts
Mancuso <i>et al.</i> ^[90] 2014	1086 pts with MD ¹	39 (3.6%)	39 (3.6%) myoclonus (study focused only on myoclonus)	Brain MRI showed variably cortical/subcortical atrophy, white matter abnormalities, cerebellar atrophy
Sofou <i>et al.</i> ^[20] 2014	130 children with LS (73 genetically defined)	-	58 (44%) dystonia 45 (34%) ataxia 27 (20%) other dyskinesias 25 (19%) chorea/athetosis 9 (7%) myoclonus	n.r.
Piekutowska-Abramczuk <i>et al.</i> ^[23] 2009	41 pts with LS ¹	31 (75%)	17 (41%) tremor 14 (34%) dystonic movements, ataxia, extrapyramidal syndrome	n.r.
Zhang <i>et al.</i> ^[21] 2007	124 pts with LS, LLS (26% genetically defined)	12 (10%)	12 (10%) dystonia	n.r.
Finsterer <i>et al.</i> ^[50] 2002	76 pts with MD ¹	9 (12%)	9 (12%) parkinsonism (study focused only on parkinsonism)	n.r.
Macaya <i>et al.</i> ^[12] 1993	34 pts with LS	22 (65%)	19 (86%) dystonia 4 (18%) rigidity 2 (9%) tremor 2 (9%) chorea	n.r.

¹All patients genetically defined. MD: mitochondrial disorders; LLS: Leigh-like syndrome; MoD: movement disorders; LS: Leigh syndrome; n.r.: not reported

The frequency of MoD in MD patients has only been reported in single-center studies, from small series of patients, and for specific forms of MD^[8-14]. Few population-based, cross-sectional studies have assessed the clinical and genetic characteristics of MoD in large MD cohorts [Table 1].

In the present review, we highlight the clinical spectrum of MoD in mitochondrial encephalomyopathies, discussing separately each movement disorder which has been reported in the literature in MD patients with MoD, carrying either mtDNA or nuclear genes mutations. We focus on dystonia and parkinsonism with some recent developments on the pathophysiological mechanisms of extrapyramidal features in MD and their management.

DYSTONIA

Dystonia is a neurological movement disorder characterized by sustained or prolonged muscle contractions that result in twisting and repetitive movements or abnormal fixed postures^[15]. According to body distribution, it is classified as generalized, focal, or segmental. The genetics of dystonia is quite complex and several genes have been discovered, although the genetic underpinnings of several adult onset forms are still undefined^[16].

An international expert panel classified three main types of dystonia: isolated dystonia that is referred to as primary dystonia; combined dystonia when additional movement disorders are present; and complex dystonia,

Table 2. Main mtDNA mutations associated with dystonia and chorea

Gene	Mutation	Clinical features	Other clinical features	Ref.
<i>MtDNA</i>	Large single deletion	Segmental dystonia	KSS	Marie <i>et al.</i> ^[42] , 1999
<i>MT-TL1</i>	m.3243G > A	Writer's cramp Choreic movements	MELAS MELAS	Sudarsky <i>et al.</i> ^[43] , 1999 Nakagaki <i>et al.</i> ^[47] , 2005, Kang <i>et al.</i> ^[48] , 2005
<i>MT-TK</i>	m.3251G > A	Chorea-ballism	MELAS	Lahiri <i>et al.</i> ^[49] , 2019
<i>MT-ATP6</i>	m.8344G > A	Spasmodic dysphonia	MERRF	Peng <i>et al.</i> ^[44] , 2003
<i>MT-ATP6</i>	m.9176T > C	Generalized dystonia/chorea	LS	Martikainen <i>et al.</i> ^[8] , 2016
<i>MT-ND1</i>	m.3460G > A	Dystonia	LHON	Meire <i>et al.</i> ^[37] , 1995
<i>MT-ND1</i>	m.3796G > A	Adult onset dystonia	Spasticity, and core-type myopathy.	Simon <i>et al.</i> ^[39] , 2003
<i>MT-ND3</i>	m.10197G > A	Dystonia	LS/LLS, vertebral and arterial malformations	Tolomeo <i>et al.</i> ^[24] , 2019
<i>MT-ND4</i>	m.11178G > A	Dystonia	LHON	Wang <i>et al.</i> ^[26] , 2009
<i>MT-ND4</i>	m.11178G > A	Chorea	LHON	Nikoskelainen <i>et al.</i> ^[38] , 1995
<i>MT-ND6</i>	m.14459G > A	Dystonia	LHON	Morimoto <i>et al.</i> ^[46] , 2004
<i>MT-ND6</i>	m.14487T > C	Generalized dystonia	LS	Gropman <i>et al.</i> ^[27] , 2004 Ugalde <i>et al.</i> ^[25] , 2003

KSS: Kearns-Sayre syndrome; MELAS: mitochondrial encephalomyopathy and lactic acidosis and stroke-like episodes; LHON: Leber hereditary optic neuropathy; MERRF: mitochondrial encephalomyopathy with ragged red fibers

Table 3. Selected nDNA mitochondrial-related genes associated with dystonia and chorea

Gene	Defect on mitochondrial function	MoD clinical features	Other clinical features	Ref.
<i>SURF1</i>	Complex IV assembly	Dystonia, ataxia, athetoid movements	Developmental delay, ophthalmoplegia, feeding problems	Wedatilake <i>et al.</i> ^[29] , 2013
<i>NDUFA6</i>	Complex I assembly	Dystonia with childhood onset	LS	Baide-Mairena <i>et al.</i> ^[30] , 2019
<i>SUCLA2</i>	mtDNA depletion	Dystonia/Chorea	LS	Carrozzo <i>et al.</i> ^[31] , 2007
<i>ATAD3</i>	mtDNA depletion	Dystonia	Encephalopathy with cerebellar atrophy	Desai <i>et al.</i> ^[32] , 2017
<i>MTFMT</i>	Combined ox-phos deficiency	Multifocal dystonia with childhood onset	LS	Martikainen <i>et al.</i> ^[8] , 2016
<i>FARS2</i>	Combined ox-phos deficiency	Generalized dystonia with childhood onset	Seizures, learning disability	Martikainen <i>et al.</i> ^[8] , 2016
<i>PDHX</i>	PDH deficiency	Generalized dystonia with childhood onset	Seizures, learning disability, deafness	Martikainen <i>et al.</i> ^[8] , 2016
<i>TIMM8a</i>	Defect of mitochondrial protein import	Dystonia with childhood onset	Early deafness, optic neuropathy	Aguirre <i>et al.</i> ^[36] , 2006
<i>SERAC1</i>	Defect of ox-phos and cholesterol trafficking	Dystonia with infantile onset	3-Methylglutaconic aciduria, deafness, hepatopathy, Leigh-like syndrome (MEGDHEL)	Maas <i>et al.</i> ^[33] , 2017
<i>MECR</i>	Defect of ox-phos and cholesterol trafficking	Dystonia with childhood onset		Heimer <i>et al.</i> ^[34] , 2016
<i>POLG1</i>	mtDNA replication	Torticollis, focal eyelid dystonia, and limb dystonia with adult onset	Ataxia, seizures, neuropathy, PEO	Hinnell <i>et al.</i> ^[45] , 2012

LS: Leigh syndrome; ox-phos: oxidative phosphorylation; PDH: pyruvate dehydrogenase; PEO: progressive external ophthalmoplegia

referring to secondary forms when it occurs in the context of a complex phenotype^[17]. In the majority of MD cases, we are faced with complex dystonia type.

Dystonia has been described both in mtDNA mutations and in several nuclear genes related to mitochondria [Tables 2 and 3].

Dystonia in pediatric MD

Dystonia is the most common movement disorder in the pediatric population with MD, mainly in the context of a Leigh syndrome (LS)^[8].

LS is a devastating disorder, occurring in infants or children characterized by a severe encephalopathy with bilateral basal ganglia lesions in whom dystonia is part of a complex phenotype including developmental delay, hypotonia, ataxia, optic atrophy, and seizures. This syndrome is genetically quite heterogeneous and several genes, either mitochondrial or nuclear, have been involved. Leigh-like syndrome (LLS) is considered a variant of LS when features suggest a Leigh syndrome but some atypical clinical and neuroimaging are present.

A recent meta-analysis including five studies with 385 Leigh syndrome patients showed that 32% of the patients carried mtDNA mutations, whereas 38% had nDNA mutations^[18].

In a retrospective study on 34 patients with LS, dystonia was found in 59% and was present usually as generalized or multifocal form^[19]. In other studies, the recurrence was variable usually because of the retrospective nature of the studies and also the small number of patients included^[20-23].

Different mtDNA mutations are reported in patients with dystonia and LS or LLS including mainly mtDNA encoded complex subunits such as ATP6, ND3, or ND6^[8,24,25].

Interestingly, the 10197G > A in ND3 shows a quite variable phenotype ranging from LS to LHON. Recently, a review of published data on patients harboring the m.10197G > A mutation showed that 38% of patients had a stable dystonia associated with ataxia, seizures, and dysarthria. The same mutation was also described in a single large family with LHON and dystonia^[26]. Neuroimaging findings were consistent with LS. Dystonic postures appeared early and sometimes had a remitting-relapsing course^[24].

The m.14459G > A mutation in ND6 has been described in pediatric patients with generalized dystonia (also named as DYT-mt-ND6) with heterogeneous clinical manifestations, ranging from isolated dystonia with no cognitive involvement to encephalopathy with dystonia, dysphagia, pyramidal tracts dysfunction, and cognitive impairment^[27].

Variants in several nDNA genes are reported in patients with LS^[28]. We can distinguish nuclear genes encoding OXPHOS enzymes and their assembly factors, defects of mitochondrial DNA maintenance and translation, mitochondrial membrane lipid remodeling, and pyruvate dehydrogenase.

Among LS patients due to nDNA genes, SURF1 gene is one of the most frequently involved genes. SURF1 is a cytochrome c assembly factor and related mutations cause an isolated complex IV deficiency. Clinical symptoms begin in late infancy with gastro-intestinal symptoms, developmental delay, ophthalmoplegia, ataxia, seizures, dystonia, and respiratory failure^[29].

Recently, a mutation in NDUFAF6, a complex I assembly factor, has been described in three siblings with childhood onset dystonia associated with bilateral striatal necrosis, neurological regression, and long survival^[30].

Among mtDNA depletion syndromes, mutations in SUCLA2 gene, leading to succinyl-CoA synthase deficiency, have been reported in patients with neonatal onset encephalomyopathy, deafness, dystonia, and MRI abnormalities of putamen and caudate nuclei. As another nuclear gene causing mtDNA depletion, ATAD3 gene has been associated with a severe encephalopathy with generalized dystonia, ataxia, and brainstem and cerebellar hypoplasia^[31].

Mutations of MECR or SERAC1, genes involved in the mitochondrial lipid metabolism and transport, are associated with severe Leigh-like syndromes with early onset dystonia^[32,33].

Dystonia with childhood onset has been reported in complex phenotypes causing by combined oxidative phosphorylation deficiencies due to different mitochondrial genes, such as MTFMT and FARS2 involved in mtDNA translation^[8].

Of interest is a well-defined syndrome characterized by deafness, dystonia, and optic neuropathy previously called Mohr-Tranebjaerg syndrome (MTS) due to mutations in TIMM8A. The gene is located on

chromosome X and encodes for a protein (deafness dystonia protein 1) located in the inner mitochondrial membrane and implicated in the mitochondrial protein transport system^[34,35]. Dystonia is the second major feature of MTS and is usually generalized, affecting more cranio-cervical muscles, and slowly progressive. Age of onset is significantly variable, ranging from the first to the fourth decade. Interestingly, adult-onset focal dystonia (torticollis and writer's cramp) with no evidence of hearing impairment has been reported in female carriers^[35]. Brain MRI in this condition do not show the basal ganglia lesions that are usually evident in the majority of MD patients with dystonia.

Dystonia in MD adults

Dystonia is a MoD reported also in adult MD cases. The association of Leber hereditary optic neuropathy (LHON) with variable combination of progressive generalized dystonia and visual loss is well known, and is occasionally accompanied by pyramidal tract signs and intellectual impairment^[36]. Dystonia can precede ocular abnormalities by several years. LHON is due to homoplasmic mtDNA mutations in MT-ND1, MT-ND4, and MT-ND6; the three primary mutations are m.3460G > A, m.11778G > A, and m.14484T > C, which are all described in combination with generalized dystonia^[37,38]. Less common mutations in different mtDNA ND genes are described in patients with generalized dystonia^[39,40]. In the presence of dystonia, brain MRI shows frequently bilateral putamen and caudate nuclei lesions that have rarely been described in patients carrying MT-ND6 mutations without dystonia^[41].

Dystonia has sporadically been reported in some classical mtDNA-related syndromes such as Kearns-Sayre Syndrome (KSS), a sporadic condition due to large single deletions and characterized by progressive external ophthalmoplegia, cardiac conduction block, and pigmentary retinal degeneration in combination with other symptoms, e.g., ataxia, dystonia, and extraneurological signs^[42]. Focal dystonia has been described in single case reports of MELAS (mitochondrial encephalomyopathy with stroke-like episodes) and MERRF (myoclonus epilepsy with ragged-red fibers)^[43,44].

Dystonia is also rarely reported in MD patients harboring mutations in POLG (mitochondrial DNA polymerase γ), which is considered one of the most mutated nuclear genes in MD and is associated with a very heterogeneous phenotype characterized by progressive external ophthalmoplegia, myoclonic epilepsy, parkinsonism, and ataxia. In some POLG cases, the phenotype also includes cervical dystonia, focal eyelid dystonia, and limb dystonia but not as a prominent feature^[45].

CHOREA/CHOREOATETOSIS

Choreic or choreathetic movements have been described in children with LS. In the study by Martikainen *et al.*^[8], 6/42 MD patients with movement disorders (14%) presented with chorea or complex hyperkinetic movement disorders.

Choreic movements are rarely reported in adult-onset MD. Among mtDNA mutations, chorea has been described in a single case associated with the G11778A mutation. The patient presented at age 24 with involuntary movements that initially involved both hands and further became generalized; by the age of 37, she also developed severe dementia^[46]. Few MELAS cases are described with acute-onset chorea often triggered by hyperglycemia^[47-49].

PARKINSONISM

Parkinsonism is the most frequent hypokinetic disorder in adult MD patients. It has been associated with mtDNA and nDNA gene variants^[50]. In a study focused on the evaluation of cardinal features of parkinsonism such as bradykinesia, tremor, and rigidity, the prevalence of parkinsonism was calculated at 12%^[51]; although a possible incidental association was supposed, the complexity of the phenotype does not support this concern.

Table 4. Parkinsonism associated with mtDNA mutations

Gene	Mutation	Clinical features of parkinsonism	Other clinical features	Ref.
<i>MtDNA</i>	Large single deletions	Asymmetrical or symmetrical parkinsonism	PEO	Schreglmann et al. ^[14] , 2018
<i>MT-ND4</i>	m.11778G > A	Asymmetrical akinesia, rigidity Bilateral akinesia, rigidity	LHON LHON	Vital et al. ^[58] , 2015 Simon et al. ^[57] , 1999
<i>MT-TI</i>	m.4296G > A	Bilateral akinesia, rigidity	LS, hypogonadism	Martikainen et al. ^[54] , 2013
<i>MT-TK</i>	m.8344A > G	Asymmetrical akinesia, rigidity, tremor	MERRF	Horvath et al. ^[53] , 2007
<i>MT-RNR1</i>	m.1095T > C	Hemiparkinsonism with akinesia, rigidity, tremor	Hypoaacusia, neuropathy	Thyagarajan et al. ^[52] , 2000
<i>MT-CYB</i>	4 bp deletion	Symmetrical akinesia, rigidity, tremor	Stroke-like episodes	De Coo et al. ^[55] , 1999

PEO: progressive external ophthalmoplegia; LHON: Leber hereditary optic neuropathy; MERRF: mitochondrial encephalomyopathy with ragged red fibers

The majority of reports describing a Parkinson-like phenotype in the context of a mitochondrial syndrome are associated with mutation in nDNA genes but more rarely extrapyramidal features have been described in few cases of mtDNA-related syndromes, such as MERRF, MELAS, and LHON^[52-54]. De Coo et al.^[55] reported on a patient with a MELAS-like syndrome with parkinsonism due to a 4-bp deletion in the mitochondrial cytochrome B gene (*MTCYB*)^[55,56]. Similarly, bradykinesia and rigidity were reported in LHON cases with mutation in *ND4* gene^[57,58]. The main reports on mtDNA mutations associated with parkinsonism are summarized in [Table 4](#).

Recent studies have demonstrated that the nigrostriatal system is very vulnerable to mitochondrial dysfunction^[59], and conditions characterized by an impairment of mtDNA maintenance and consequently accumulation of somatic mtDNA damage are frequently associated with a nigrostriatal degeneration with or without clinical signs of parkinsonism^[14]. In the last two decades, several reports have described MD cases with a complicated phenotype, including parkinsonian features such as akinesia, resting tremor, and rigidity due to mutations in nuclear genes involved in mtDNA maintenance such as *POLG*, *TWINK*^[60,61], and, more rarely, *OPA1*, *MPV17*, and *POLG2*^[62-64]. *POLG1*-related syndromes are the most common forms, either dominant or recessive, associated with levodopa responsive parkinsonism with a variable onset of the parkinsonism from early to advanced age^[65-73]. Nevertheless, parkinsonism has been reported in few pathogenic *TWINK* mutations. *TWINK* (named also C10orf2) is a gene encoding the Twinkle protein, an adenine nucleotide-dependent DNA helicase that is involved in the maintenance of mtDNA integrity.

Patients showed an asymmetrical parkinsonism with progressive external opthalmoplegia (PEO) and myopathy and a wide range of disease onset from juvenile to adult forms^[74-77].

In recent years, it has been demonstrated that genes involved in mitochondrial dynamics have impaired mtDNA maintenance; among them, mutations in *OPA1*, but also in *AFG3L2* and *SPG7*, have been related to nigrostriatal dysfunction. Some years ago, we described two unrelated families harboring a heterozygous dominant *OPA1* mutation with a clinical picture characterized by PEO, parkinsonism, cognitive impairment, and nigrostriatal dysfunction at DAT-SCAN. Functional studies revealed an imbalance of autophagy and mitophagy^[62].

Recently, among 35 *SPG7* patients, parkinsonism was observed in 21% of cases. mtDNA copy number quantification in blood revealed significantly lower mtDNA levels in either patients or carriers than controls^[78].

An overview of clinical, genetic, and neuroradiological findings in MD cases with parkinsonism due to mitochondrial-related nDNA genes reported in the literature is summarized in [Table 5](#)^[79-84].

Clinical presentation of mitochondrial parkinsonism (MP) seems not different from idiopathic Parkinson disease and for this reason MP can be overlooked. For instance, parkinsonism related to *POLG* mutations

Table 5. Parkinsonism associated with mutations in mitochondrial-related nDNA genes

Gene	Mutation	Protein change	Clinical features of parkinsonism	Other clinical aspects	Ref.
POLG	c.2693T > C	I898T	Early onset rigidity, akinesia	PEO, optic atrophy	Ma <i>et al.</i> ^[84] 2019
	c.2993C > T	S998L			
	c.830A > T	H277L	Asymmetrical akinesia, rigidity	PEO	Sato <i>et al.</i> ^[73] 2011
	c.2827C > T	R943C	Bilateral akinesia, rigidity	PEO, myopathy	Synofzik <i>et al.</i> ^[71] 2010
	c.2864A > G	Y955C	Asymmetrical tremor	PEO, myopathy, neuropathy, hypogonadism	
	c.3311C > G		Akinesia, rigidity, tremor	PEO, myopathy	Betts-Henderson <i>et al.</i> ^[67] 2009
	c.2542G > A	G848S			
	c.1288A > T	M430L	Bilateral tremor, rigidity	PEO, myopathy	Invernizzi <i>et al.</i> ^[68] 2008
	c.2752T > C	W918L			
	c.2243G > C	W748S	Bilateral akinesia, rigidity, tremor	PEO, sensory and cerebellar ataxia	Remes <i>et al.</i> ^[69] 2008
	c.1389G > T	S511N	Bilateral akinesia, rigidity	PEO, myopathy, neuropathy	Hudson <i>et al.</i> ^[70] 2007
	c.1532G > A				
	c.2839C > T	R853N	Bilateral akinesia, rigidity	PEO, myopathy, dystonia	Davidzon <i>et al.</i> ^[66] 2006
c.2491G > C	G737R				
c.2492A > G	Y831C	Symmetrical akinesia, rigidity, tremor	PEO, myopathy	Mancuso M <i>et al.</i> ^[65] 2004	
c.2864A > G	Y955C	Tremor and/or akinesia, rigidity	PEO	Luoma <i>et al.</i> 2004 ^[60] 2004	
c.1402A > G	N468D				
c.313G > A					
ANT1	c.865G > A	A467T	Bilateral akinesia, rigidity	PEO, myopathy, neuropathy	Galassi <i>et al.</i> ^[72] 2008
POLG	c.1399G > A				
POLG2	c.970-1G > C	-	Asymmetrical tremor and bradykinesia	Sensory and cerebellar ataxia, dementia, PEO	Van Maldergem <i>et al.</i> ^[64] 2016
TWNK	c.1192-8_1207dup24	-	Camptocormia		Lehmann Urban <i>et al.</i> ^[83] 2020
	c.907C > T	R3030W	Asymmetrical tremor and akinesia, rigidity	PEO, myopathy	Brandon <i>et al.</i> ^[77] 2013
	c.1750G > A	A359T	Asymmetrical tremor and akinesia, rigidity	PEO, neuropathy	Kiferle <i>et al.</i> ^[76] 2013
	c.1031G > A	R334Q	Asymmetrical tremor, akinesia, rigidity	PEO, neuropathy	Vandenbergh <i>et al.</i> ^[75] 2009
	c.1121G > A	R374Q	Asymmetrical akinesia, rigidity, tremor	PEO	Baloh <i>et al.</i> ^[61] 2007
OPA1	c.1462G > A	G488R	Akinesia, rigidity, tremor	PEO, myopathy, neuropathy, dementia	Carelli <i>et al.</i> ^[62] 2015
	c.1484C > T	A495V			
MPV17	c.428T > G	L143*	Akinesia, rigidity, tremor	PEO, myopathy, neuropathy	Garone <i>et al.</i> ^[63] 2012
	c.263A > T	K88M			
	c.265A > T	M89L			
SPG7	c.1529C > T	A510V	bradykinesia, rest tremor, and rigidity	Ataxia, PEO	De la Casa-Fages <i>et al.</i> ^[78] 2019
n.a.	mtDNA MDels	-	Tremor, moderate bradykinesia	PEO, neuropathy	Wilcox <i>et al.</i> ^[79] 2007
n.a.	mtDNA MDels	-	Asymmetrical akinesia, rigidity, rest tremor	-	Siciliano <i>et al.</i> ^[81] 2001
n.a.	mtDNA MDels	-	Asymmetrical akinesia, rigidity	PEO, myopathy	Casali <i>et al.</i> ^[82] 2001
n.a.	mtDNA MDels	-	asymmetric rest tremor	PEO, myopathy, neuropathy	Chalmers <i>et al.</i> ^[80] 1996
			akinesia, rigidity		

PEO: progressive external ophthalmoplegia; mtDNA MDels: mitochondrial DNA multiple deletions; n.a.: not available

can mimic very well an idiopathic Parkinson disease (IPD) because age of onset, the asymmetric distribution of motor symptoms, the efficacy of dopaminergic drugs, and the support of the imaging studies showing nigrostriatal dysfunction are not dissimilar in these conditions. Nevertheless, reviewing the MP cases reported thus far, it appears evident that MP may manifest earlier than IPD, and some additional clinical features, rarely reported in IP, are indeed recurrent in MP. In fact, considering the reported cases with MP due to mutations in mitochondrial-related nuclear genes impairing mtDNA maintenance [Table 5], it is quite clear that external ophthalmoplegia is a common feature with frequent association with proximal myopathy and less commonly neuropathy and ataxia.

According to these considerations, MP should be suspected in patients manifesting an akinetic syndrome with PEO and myopathic signs.

The role of mitochondria in idiopathic and familiar Parkinson has been studied for several years and discussing this issue is beyond the scope of the present review. PD was for a long time considered a non-genetic disorder, but, in the last twenty years, several genes have been associated with familial PD. Many genes associated to familial PD are strictly related to mitochondrial function, and different studies have demonstrated that mitochondrial dysfunction has a major role in the pathogenesis of both sporadic and familial PD^[85,86]. For instance, two PD-related proteins, PTEN-induced serine/threonine kinase 1 encoded by PINK1 and E3 ubiquitin ligase Parkin encoded by PRKN, regulate mitochondrial quality control, modulating mitochondrial biogenesis via PGC1 α . However, it has been shown that LRRK2 interacts with several key regulators of mitochondrial fission/fusion^[87]. Progress on the pathogenesis of PD led to the development of therapeutic strategies targeting mitochondrial dysfunction in PD. Some agents were evaluated in clinical trials to act on neurodegeneration and disease progression but most of them failed to show any efficacy on PD^[88].

MYOCLONUS

Myoclonus is a well-known symptom of MD and its presence is traditionally considered in association with MERRF. Myoclonus in MD is due to a cortical involvement, mainly affects face and distal upper extremities, and is classified as focal, multifocal, or generalized^[89].

In a study on a large group of mitochondrial patients listed in the database of the “Nation-wide Italian Collaborative Network of Mitochondrial Diseases”, we evaluated the relevance of myoclonus. Data analysis revealed that myoclonus is rather infrequent in MD; in fact, it was reported in only 3.6% of patients (39 of 1,086)^[90]. In 7 of 24 MERRF patients (29%), myoclonus was the presenting clinical sign at onset.

Myoclonus has also been described in other classical mitochondrial encephalopathies due to mtDNA mutations, such as MELAS and LHON^[91-93]. More rarely, it has been reported in patients with LS^[94]. Among MD defects due to nDNA mutations, myoclonus is part of the complex phenotype of Alpers syndrome (hepatocerebral syndrome and mtDNA depletion) and MEMSA (myoclonus epilepsy, myopathy, and sensory ataxia), both associated with mutations in POLG^[95,96].

Subcortical myoclonus has also rarely been described in CoQ10 deficiency due ADCK3 mutations in association with dystonia (see in Section Ataxia)^[97].

ATAXIA

Although ataxia is not considered, *strictu sensu*, a movement disorder, it seems worth considering this clinical feature in the present review because it is one of the main and debilitating symptoms among MD. Pure cerebellar ataxia or spinocerebellar forms but also sensitive ataxia due to a sensory system involvement are reported, sometimes in combination, in MD patients^[98].

The genetic spectrum of mitochondrial ataxias is quite heterogeneous: it is encountered in several mtDNA mutations, such as large rearrangements or point mutations, but is included in many variants of different nDNA genes as well.

In the last few years, the development of exome-based technologies increased consistently the number of mitochondrial-related genes recognized as responsible for complex encephalopathies with ataxia, making it difficult to deal with this issue. Moreover, variants in the same gene can be associated with a clinical continuum of heterogeneous syndromes, ranging from infantile to late-onset forms (e.g., POLG-related disorders).

In this section, we first describe the most common phenotypes associated with mtDNA mutations with early or adult onset, and then we describe the main types of mitochondrial ataxias involving nuclear genes.

Considering primary mtDNA mutations, cerebellar ataxia is part of the phenotypic spectrum of KSS, usually in the context of a quite heterogeneous phenotype including neurological and extraneurological symptoms^[99].

Early onset sensory ataxia due to a sensitive axonal neuropathy is a prominent feature of NARP (neuropathy, ataxia, retinitis pigmentosa syndrome), a very severe syndrome characterized also by psychomotor retardation, retinitis pigmentosa, dementia, seizures, ataxia, and proximal weakness and due to point mtDNA mutations in the *ATP6* gene, one of the two mitochondrial-encoded subunits of ATPase.

Ataxia is also a common symptom in MERRF syndrome that manifests in juveniles or adults with myoclonus, seizures, muscle weakness, and cognitive decline. MtDNA mutation 8344A > G is the most common genetic variant reported in MERRF and represents about 4% of all reported mtDNA mutations^[100]. A review of the clinical phenotype in a large cohort of MERRF patients revealed “myoclonus” was more frequently linked to “ataxia” than to “generalized seizures”^[101].

Ataxia occurs in a consistent number of patients with MELAS and is associated with cortical atrophy^[102].

Pure cerebellar ataxia is one of the common features in Coenzyme Q10 (CoQ10) deficiency syndromes caused by different defects in biosynthetic cascade of CoQ10. This cofactor has a major role in the electron transport from complexes I and II to complex III in the respiratory chain. CoQ10 deficiency has shown a broad spectrum of clinical manifestations ranging from severe infantile multisystemic disease with nephrotic syndrome and encephalomyopathy to juvenile or adult cerebellar ataxia or even isolated myopathy^[103]. Several genes involved in the biosynthesis of *CoQ10* are known to be responsible for primary CoQ10 deficiency; among them, mutations in *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ7*, and *COQ9* are associated with different phenotypes. For example, mutations in *COQ2*, encoding para-hydroxybenzoate-polyprenyl transferase, a key enzyme in the CoQ10 biosynthetic pathway, are responsible for a multisystemic picture with muscle weakness and myoglobinuria, seizures, mental retardation, spasticity, ataxia, and ophthalmoparesis^[104]. Brain MRI usually reveals a pure cerebellar atrophy as a prominent feature^[105].

Mutations in *ADCK3*, an ancestral kinase with a regulatory role in ubiquinone biosynthesis, are responsible for the most common autosomal recessive ataxia with CoQ10 deficiency (ARCA2). The main clinical features are exercise intolerance, seizures, and mild cognitive impairment with either childhood or juvenile onset^[106]. However, some adult onset cases have also been reported with a slowly progressive cerebellar ataxia and no additional features. A prompt diagnosis of these forms is essential because patients greatly benefit from oral CoQ10 supplementation^[107].

Different mutations in nDNA genes controlling different mitochondrial pathways, such as *TWINK*, *COX20*, *OPA1*, *RR2MB*, *TTC19*, and *MSTO1* involved in mtDNA maintenance or *POLG* responsible of mtDNA replication, or genes encoding some amino acyl tRNA synthetase, involved in mtDNA translation, have been reported in MD patients with cerebellar or sensory ataxia usually as part of a complex phenotype^[108-116].

A distinctive clinical entity is infantile-onset spinocerebellar ataxia, which is frequently due to mutations in *TWINK* that encodes the Twinkle mitochondrial protein, a helicase that co-localizes with mtDNA in mitochondrial nucleoids, and causes multiple mtDNA deletions. The main clinical features are onset of ataxia before age of 18, deafness, epilepsy, and sensory axonal neuropathy^[112].

Recently, a complex phenotype with myopathy, cerebellar atrophy and ataxia, motor developmental delay, and pigmentary retinopathy has been associated with mutations in *MSTO1*, a cytoplasmic protein required for mitochondrial fusion and network formation^[114].

Mutations in *POLG1* gene encoding the catalytic subunit of mtDNA polymerase can cause either mtDNA depletion with early childhood syndromes or mtDNA multiple deletions leading to later onset syndromes. A wide spectrum of *POLG1* mutations is reported in the literature and it is considered the main gene responsible for inherited mitochondrial disorders; indeed, about 2% of the MD population carries these mutations. Among *POLG*-related disorders, cerebellar and sensory ataxia are prominent clinical features. Different abbreviations have been coined to distinguish *POLG1*-related ataxia in the context of a sensory neuropathy: MIRAS has been used to define a mitochondrial recessive ataxia syndrome; SANDO for sensory ataxia neuropathy, dysarthria, and ophthalmoplegia; and MEMSA for myoclonic epilepsy, myopathy, and sensory ataxia. A different form characterized by spinocerebellar ataxia with epilepsy is known as SCAE^[115]. More than 100 mutations in *POLG* have been described but four common mutations (*A467T*, *W748S*, *G848S*, and *T251I-P587L*) are frequently reported^[115,116].

Mutations in *SPG7* encoding paraplegin, a component of the mitochondrial AAA protease, have been reported both in patients with recessive hereditary spastic paraplegia and in patients with a predominant ataxic presentation^[117]. A strictly related gene to paraplegin is *AFG3L2* that is highly expressed in Purkinje neurons and is responsible of spinocerebellar ataxia type 28 (SCA28); the role of these proteins may explain the involvement of the cerebellum in both conditions.

Finally, it is worth mentioning some rare complex forms due to mitochondrial enzymes deficiencies, such as Aconitase 2 (*ACO2*) deficiency reported in severe encephalopathy with hypotonia, athetosis, seizures, optic atrophy, and retinal and cerebellar degeneration or defect of the epimerase encoded by *NAXE* that results in children with ataxia, cerebellar edema, spinal myelopathy, and skin lesions^[118,119].

A description of all genes will never be complete but the examples selected above, although arbitrary, reinforce the concept that MoD are often combined and manifest in variable clinical scenarios that imply diagnostic and management challenges even for physicians expert in the field.

Therapeutic interventions for MoD in MD

Over the last decades, significant progress has been achieved to improve the diagnosis of MD and to better understand the pathogenic mechanisms underlying these disorders, but thus far therapeutic options are very limited and mostly not specific^[120].

Among MD, some treatable disorders have to be considered and their diagnosis is critical to start early a specific treatment. In CoQ10 deficiency syndromes, oral supplementation with high-dose CoQ10 ameliorates the clinical condition and changes the disease progression.

Besides primary CoQ10 deficiencies, CoQ10 is largely used in combination with a variety of vitamins and cofactors such as L-carnitine, creatine, and riboflavin, a so-called “mitochondrial cocktail”, in all patients with MD. Although these treatments are based on the current knowledge of MD pathomechanisms, their use is not standardized and data on clinical efficacy are quite poor.

About the management of MoD, supportive treatment of the different features (e.g., myoclonus, parkinsonism, and dystonia) in subjects with MD is not dissimilar from the treatment of the same symptoms in the general population but physicians should take into account some cautions because of the well-known mitochondrial toxicity of some drugs, e.g., valproate, aminoglycosides, *etc.*

Levodopa and oral baclofen are the most common reported medications to treat dystonia, both drugs being well tolerated but the efficacy is variable. Treatments with intrathecal baclofen or deep brain stimulation are not yet reported in the literature^[120].

Botulinum neurotoxin injections are useful to treat focal or multifocal dystonia. Other medications such as oral baclofen, tizanidine, or trihexyphenidyl have been reported in few patients and data on their efficacy are inconsistent^[8]. A positive response for myoclonus may be seen with levetiracetam, clonazepam, or valproate, although for the latter particular attention should be paid in patients with MD because of its possible toxicity^[121].

MP patients benefit from dopaminergic treatment, although few cases have not had an optimal response to L-DOPA and early onset dyskinesia has also been reported. It is evidenced that symmetrical nigrostriatal degeneration at DAT-SCAN predicts a better response to treatment^[14].

From a perspective point of view, several attempts have been made to counteract mitochondrial dysfunctions. Many compounds active in mitochondrial biogenesis by activation of the pathway peroxisome proliferator-activated receptor γ , as well as its coactivator 1 α (PGC1 α), have been tested in patients with PD but most of them fail to produce a real benefit. Among them, some antidiabetic drugs acting on these mechanisms, such as pioglitazone and exenatide, have been tested in preclinical studies as well as clinical trials on PD patients, but their efficacy is uncertain^[88].

Preclinical studies have shown benefit to boosting mitochondrial function but translation in humans is still far from being a reality.

CONCLUSION

Movement disorders are part of the clinical spectrum of MD among both pediatric and adult patients usually in the context of a mitochondrial multisystem presentation. Data on the true incidence of MoD are quite limited because no population-based studies are available. In children, dystonia and ataxia are the most common MoD, more frequently associated with mtDNA mutations. In adults, myoclonus, ataxia, and parkinsonism are reported either in mtDNA mutations syndromes or in nDNA mutations, causing alterations of mtDNA maintenance. Basal ganglia and cerebellum degeneration appear to be the neuropathological substrate of MoD but the pathological mechanisms need still to be clarified. “Mitochondrial parkinsonism” is an emerging topic and should be suspected in patients manifesting an akinetic syndrome with PEO and myopathic signs. Treatment of these disorders is largely empirical and large cohort studies are necessary to improve the management of MD patients with MoD.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Musumeci O, Toscano A

Performed data acquisition, technical, and material support: Oteri R

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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