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NEUROLOGICAL UPDATE

Movement disorders in mitochondrial disease

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Abstract
Mitochondrial disease presents with a wide spectrum of clinical manifestations that may appear at any age and cause multisystem dysfunction. A broad spectrum of movement disorders can manifest in mitochondrial diseases including ataxia, Parkinsonism, myoclonus, dystonia, choreoathetosis, spasticity, tremor, tic disorders and restless legs syndrome. There is marked heterogeneity of movement disorder phenotypes, even in patients with the same genetic mutation. Moreover, the advent of new technologies, such as next-generation sequencing, is likely to identify novel causative genes, expand the phenotype of known disease genes and improve the genetic diagnosis in these patients. Identification of the underlying genetic basis of the movement disorder is also a crucial step to allow for targeted therapies to be implemented as well as provide the basis for a better understanding of the molecular pathophysiology of the disease process. The aim of this review is to discuss the spectrum of movement disorders associated with mitochondrial disease.

Keywords Mitochondrial disease · Movement disorders · Ataxia · Parkinsonism · Myoclonus · Spasticity · Choreoathetosis · Tremor · Tic disorders · Restless leg syndrome

Abbreviations

mtDNA	Mitochondrial DNA
nDNA	Nuclear DNA
COX	Cytochrome c oxidase
CoQ10	Coenzyme Q10
MERRF	Myoclonus epilepsy with ragged-red fibers
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
PEO	Progressive external ophthalmoplegia
LS	Leigh syndrome
POLG	Polymeraseγ-1
KSS	Kearns–Sayre syndrome
NARP	Neuropathy, ataxia and retinitis pigmentosa
SANDO	Sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO)
DDP1	Deafness dystonia protein
AHS	Alpers–Huttenlocher syndrome
MEMSA	Myoclonic epilepsy myopathy sensory ataxia
ANS	Ataxia neuropathy spectrum disorders
LHON	Leber's hereditary optic neuropathy
IOSCA	Infantile-onset spinocerebellar ataxia
MEGDEL	3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome
SPAX3	Autosomal recessive spastic ataxia-3
ARSACS	Autosomal recessive spastic ataxia of the Charlevoix–Saguenay type
MIRAS	Mitochondrial inherited recessive ataxia syndrome
NBIA4	Neurodegeneration with brain iron accumulation-4
PKAN	Pantothenate kinase-associated degeneration

Introduction

Mitochondrial diseases are due to genetic mutations that impair the function of the mitochondrial respiratory chain [1]. Affected patients may present with a wide spectrum of clinical manifestations that can occur at any age, affecting one or more organs with varying severity. Common clinical features of mitochondrial disease include ptosis, external ophthalmoplegia, proximal myopathy, exercise intolerance, cardiomyopathy, sensorineural hearing loss, optic atrophy, retinal pigmentary changes and diabetes mellitus

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[2]. Neurological features that manifest with mitochondrial disease can involve the central or peripheral nervous system and often include seizures, encephalopathy, stroke-like episodes, migraine, dementia, spasticity, and peripheral neuropathy [3]. Movement disorders are common presentations of mitochondrial disease whether they manifest from mutations in the mitochondrial or nuclear encoded genes (Table 1).

Myoclonus and ataxia are the most frequently encountered movement disorders among patients with mitochondrial disease but parkinsonism, dystonia, chorea, spasticity, tremor, tics and restless leg syndrome have also been reported [4, 5].

There is marked heterogeneity of the movement disorder phenotype, even in patients with the same underlying genetic mutation [4]. In this review, we will discuss the movement disorders associated with mitochondrial disease. Because of wide phenotypic variability, identification of the underlying genetic basis of these movement disorders is crucial to aid in genetic counselling of families and to better understand the molecular pathophysiology of these diseases to consequently further the development of effective therapeutic targets.

Mitochondrial disorders and ataxia

Ataxia is the most frequently described movement disorder reported in patients with mitochondrial disorders and can present because of primary defects of mitochondrial DNA (mtDNA), such as point mutations or large-scale mtDNA deletions, or from nuclear genes involved in mtDNA maintenance [6, 7] that may cause secondary defects such as mtDNA depletion or deletions. Ataxia may indicate pure cerebellar, spinocerebellar, or sensory system involvement (that causes ataxia) and can present in isolation, but in most cases, features as part of a multisystem disorder.

Mitochondrial syndromes with ataxia as a major and/or early clinical manifestation

Ataxia is a major feature in some of the well-characterised mitochondrial syndromes, including Polymerase-1 (*POLG1*)-related ataxia neuropathy spectrum (ANS) and neuropathy, ataxia and retinitis pigmentosa (NARP).

The maintenance of mtDNA is critically dependent upon polymerase-gamma encoded by *POLG1*. Mutations in *POLG1* cause multiple mtDNA deletions in affected tissues. Syndromes that commonly manifest with ataxia secondary to *POLG* mutations include myoclonic epilepsy myopathy sensory ataxia (MEMSA), ataxia neuropathy spectrum disorders (ANS) that includes mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) [8, 9] and Alpers–Huttenlocher syndrome (AHS).

Mutations in *POLG1* are a cause of myoclonic epilepsy myopathy sensory ataxia (MEMSA), previously referred to as spinocerebellar ataxia with epilepsy (SCAE). MEMSA

Table 1 Genes associated with mitochondrial disease and each type of movement disorder

Myoclonus	Ataxia	Parkinson's disease	Dystonia	Spasticity	Other movement disorders
POLG	*POLG*	*POLG*	*POLG*	*POLG*	*POLG*
mtDNA mutations	mtDNA deletions	mtDNA mutations	mtDNA deletions	*ND6*	*ND4*
ND4	*MTFMT*	*MTTK*	*ND1*	*COQ2*	*MTTG*
ND6	*MTTK*	*ND4*	*ND3*	*NDUFV1*	*MICU1*
MTTK	*MTTH*	*C10orf2 (TWNK)*	*ND4*	*ECHS1*	*MRPL3*
MTTH	*MTTS1*	*MTCYB*	*ND6*	*SERAC1*	*SDHA*
MTTS1	*MTTF*		*MTFMT*	*LYRM7*	*COX20*
MTTF	*MTTP*		*ADCK3*	*BOLA3*	*HSD10*
MTTP	*MTTL1*		*NDUFS3*	*SLC25A12*	
MTTL1	*ADCK3*		*COQ9*	*MTO1*	
COQ2	*COQ2*		*ATP6*	*SPG7*	
ADCK3	*NDUFS8*		*NDUFAF6*		
PDHA1	*SURF1*		*SUCLA2*		
CARS2	*SPG7*		*FARS2*		
	ATP6		*PDHX*		
	C10orf2 (TWNK)		*MTO1*		
	TTC19		*C19orf12*		
	COX20		*PANK2*		
	OPA1		*TIMM8A*		
	RRM2B		*MR1*		
	AFG3L2				
	MARS2				
	SACS				
	SDHA				

mt.DNA mitochondrial DNA

may cause myopathy, epilepsy and ataxia without ophthalmoplegia. Cerebellar ataxia and sensory polyneuropathy begin in young adulthood. Epilepsy develops in later years, often beginning focally before becoming generalized. The seizures may be refractory to conventional therapy, including anaesthesia. The myopathy in MEMSA may be distal or proximal, and, as in the other *POLG* spectrum disorders, may also present with exercise intolerance [8].

Ataxia neuropathy spectrum (ANS) includes mitochondrial recessive ataxia syndrome (MIRAS) [9] and a separate entity known as sensory ataxia, neuropathy, dysarthria and ophthalmoplegia (SANDO). ANS is characterized by ataxia, neuropathy, and in most, an encephalopathy with seizures. The encephalopathy is similar to that seen in AHS, but tends to be slowly progressive. The neuropathy may be sensory, motor, or mixed and can be severe enough to contribute to a sensory ataxia. Other phenotypic features also vary widely, even within the same family, and can include myopathy, seizures, and hearing loss [10, 11].

Alpers–Huttenlocher syndrome (AHS) is a severe phenotype of *POLG*-related disorders. AHS is characterized by a progressive and life-threatening encephalopathy with intractable epilepsy, neuropathy and hepatic failure [12]. AHS is usually fatal, however, the age of onset, rate of neurologic degeneration and time of death may vary. Neurological symptoms including ataxia (cerebellar and/or sensory) and nystagmus which may worsen during infections or with other physiological stressors [13, 14].

Ataxia is also a common feature in NARP syndrome. NARP syndrome is characterized by proximal neurogenic muscle weakness with a sensory neuropathy, cerebellar ataxia, and pigmentary retinopathy and is due to mutations in *ATP6*. Onset of symptoms, particularly ataxia and learning difficulties, are often in early childhood [15].

Other mitochondrial syndromes with ataxia as part of a multisystem disorder

Cerebellar ataxia in Kearns–Sayre syndrome (KSS), myoclonus epilepsy with ragged-red fibers (MERRF) and in Leigh syndrome is often progressive and may be a major cause of disability [16].

KSS is a multisystem disorder typically caused by a sporadic mitochondrial deletion, but has also been reported in patients with *MTTL1* mutations [17]. KSS is defined by a triad of disease onset before age 20 years with a pigmentary retinopathy and progressive external ophthalmoplegia (PEO) [6]. Cerebellar ataxia has been reported in KSS [6, 18, 19]. Other clinical manifestations of KSS include short stature, hearing loss, dementia, limb weakness, diabetes mellitus and other endocrinopathies [20, 21].

Myoclonus epilepsy with ragged-red fibers (MERRF) syndrome is a multisystem disorder characterized by myoclonus (often the first symptom), generalized epilepsy, ataxia, weakness, and dementia. Other common findings include hearing loss, short stature, optic atrophy, and lipomatosis [22]. MERRF is associated with mutations in a number of mitochondrial genes including *MTTK*, *MTTL1*, *MTTH, MTTS1*, *MTTS2*, *MTTF, MTTP* and *MTND5*. Ataxia has been described in mutations associated with *MTTK*, *MTTH, MTTS1*, *MTTF* and *MTTP* [22–26].

Leigh syndrome (LS) or subacute necrotizing encephalopathy is a devastating neurodegenerative disease, typically manifesting in infancy or early childhood. However, late-onset cases have been reported. LS typically presents with hypotonia, developmental delay, cerebellar ataxia, dystonia and optic atrophy [27]. Magnetic resonance imaging (MRI) typically demonstrates focal or bilateral lesions in the brainstem, thalamus, basal ganglia, cerebellum or the spinal cord. The clinical course follows a rapid deterioration of cognitive and motor function [28, 29]. Ataxia with LS has been documented in patients with mutations in *NDUFS8*, *SURF1, SDHA* and *MTFMT* [30–33]. Mutations in *SURF1* cause COX IV deficiency and also manifest with ataxia, mild intellectual disability, short stature and facial dysmorphism, and thus diagnosed as a mild form of LS [32, 34]. Mutations in the *SDHA* gene encoding the flavoprotein subunit (SDHA) of complex II may cause truncal ataxia and cerebellar features [30]. Cerebellar and spinocerebellar ataxia has also been reported with the *MTFMT* gene mutations (on chromosome 15q22) associated with combined oxidative phosphorylation deficiency-15 (*COXPD15*). *MTFMT* encodes mitochondrial methionyl-tRNA formyltransferase, which is required for the initiation of translation in mitochondria. *MTFMT* mutations result in an encephalo-myopathic phenotype with onset in infancy or early childhood, delayed psychomotor development and subsequent retardation, gait ataxia, and hypotonia. Other features reported in some patients included nystagmus, microcephaly and spasticity [33].

Ataxia as part of a multisystem disorder associated with nuclear genes involved in the maintenance of mitochondrial DNA

Cerebellar or sensory ataxia can manifest with mutations in genes involved in mitochondrial DNA maintenance including *C10orf2* (*TWNK*), *TTC19*, *COX20*, *OPA1* and *RRMB*.

Mutations in *C10orf2* or *TWNK* cause multiple mtDNA deletions and manifest as a multisystem disorder known as infantile-onset spinocerebellar ataxia (IOSCA). Onset of ataxia is usually before the age of 18 and associated with axonal sensory neuropathy, sensorineural hearing loss and epilepsy [35].

Mitochondrial complex III deficiency nuclear type 2 (MC3DN2) is caused by mutations in *TTC19* located on chromosome 17p12. Mutations in *TTC19* manifest with

childhood-onset of a slowly progressive neurodegenerative disorder, mental retardation and ataxic gait. Clinical symptoms include nystagmus, diplopia, dysphagia, dysmetria, dysarthria, hyperreflexia, and dysphonia. Cerebral MRI shows progressive necrotic lesions in the caudate, olives, substantia nigra and putamen in addition to cerebral atrophy and severe cerebellar atrophy [36].

Mutations in *COX20,* a gene involved in the assembly of mitochondrial complex IV, are associated with childhood-onset cerebellar ataxia with intention tremor and pyramidal signs [37]. Other clinical features include hypotonia, developmental delay, choreoathetosis and dystonia. Affected patients may have cerebellar atrophy and complex IV and coenzyme Q10 deficiencies [38, 39].

OPA1 and *RRM2B* gene mutations cause multiple mtDNA deletions and ataxia. The *OPA*-related disorder typically presents with visual loss and optic atrophy in childhood, followed by PEO, cerebellar and sensory ataxia, deafness and a sensory-motor neuropathy in adult life [40]. The *RRM2B* gene is involved in the de novo conversion of ribonucleoside diphosphates into deoxyribonucleoside diphosphates essential for DNA synthesis [41]. Although PEO and ptosis are prominent features in affected individuals, additional features include fatigue, ataxia, proximal myopathy, dysphagia, and glaucoma [42].

Mutations in other mitochondrial targeted nuclear genes are associated with hereditary ataxias and include primary coenzyme Q10 deficiency (CoQ10D1), primary coenzyme Q10 deficiency-4 [(CoQ10D4)-also known as autosomal recessive spinocerebellar ataxia-9 (SCAR9)], spastic paraplegia (*SPG7*), autosomal recessive spastic ataxia-3 (SPAX3) and autosomal recessive spastic ataxia of the Charlevoix–Saguenay type (ARSACS).

Primary CoQ10 deficiency is a rare, clinically heterogeneous autosomal recessive disorder caused by mutations in genes directly involved in coenzyme Q10 (CoQ10), synthesis. CoQ10 or ubiquinone, is a mobile lipophilic electron carrier critical for electron transfer by the mitochondrial respiratory chain [43]. Mutations in *COQ2* are associated with type 1 CoQ10 deficiency (CoQ10D1). The disorder is clinically heterogeneous manifesting with myopathy, rhabdomyolysis, seizures, developmental delay, mental retardation, pyramidal signs, myoclonus, cardiomyopathy, renal failure and ophthalmoparesis [44–46]. However, cerebellar ataxia and cerebellar atrophy on MRI have been reported to be prominent features [47]. The correct diagnosis is important because some patients show a favourable response to CoQ10 treatment [46].

Primary coenzyme Q10 deficiency-4 (CoQ10D4) also known as autosomal recessive spinocerebellar ataxia-9 (SCAR9), is due to mutations in the *ADCK3* gene on chromosome 1q42. The disorder is characterized by the childhood-onset of a cerebellar ataxia and exercise intolerance [48]. Some affected individuals develop seizures and mild cognitive impairment [49].

Mutations in *SPG7*, are associated with hereditary spastic paraplegia (HSP-SPG7) although many patients may present with CPEO. SPG7 encodes paraplegin, a component of the m-AAA protease in an ATP-dependent proteolytic complex of the mitochondrial inner membrane that degrades misfolded proteins and regulates ribosome assembly [50]. HSP-SPG7 is characterized by an insidiously progressive bilateral lower limb weakness and spasticity. Additional features such as hyperreflexia in the arms, sphincter disturbances, spastic dysarthria, dysphagia, optic atrophy, spinocerebellar or cerebellar ataxia, nystagmus, ophthalmoplegia, hearing loss, scoliosis, pes cavus, neuropathy and amyotrophy may be observed [51, 52].

SCA28 is caused by a heterozygous mutation in *AFG3L2,* the catalytic subunit of the m-AAA protease, an ATP-dependent proteolytic complex of the mitochondrial inner membrane that degrades misfolded proteins and regulates ribosome assembly [50]. Onset is in mid-adulthood and most patients present with cerebellar ataxia. Overall, the disease is slowly progressive and other features included dysarthria, ophthalmoplegia and/or gaze-evoked nystagmus, slow saccades, ptosis and spasticity. Individuals may develop dystonia or Parkinsonism without major functional incapacity [53].

Autosomal recessive spastic ataxia-3 (SPAX3) is caused by mutations and complex genomic rearrangements involving the mitochondrial methionyl-tRNA synthetase (*MARS2*) gene. Mutations in *MARS2* cause multiple mitochondrial respiratory chain enzyme deficiencies, consistent with a mitochondrial translation defect [54]. Affected patients have ataxia, spasticity and hyperreflexia. Other features include urinary urgency, dysarthria, dystonic postures, nystagmus, scoliosis, and mild hearing impairment. Patients may also have cognitive impairment, cerebellar and cerebral atrophy [55].

Autosomal recessive spastic ataxia of the Charlevoix–Saguenay type (ARSACS) is caused by mutations in *SACS,* a gene encoding the sacsin protein on chromosome 13q12.12 [56, 57]. ARSACS is a neurodegenerative disorder usually manifesting in early childhood with cerebellar ataxia, pyramidal tract signs, and peripheral neuropathy. A distinctive reported feature is prominence of the myelinated retinal nerve fibers [58]. Other associated clinical features include myoclonic epilepsy with action myoclonus, absence epilepsy and mild learning disability [56, 59].

Mitochondrial disorders and Parkinson's disease (PD)

Parkinsonism can arise from mutations in either mtDNA genes or nDNA genes [60].

Parkinsonism responsive to levodopa therapy due to mtDNA mutations include MERRF syndrome, mitochondrial encephalomyopathy with stroke-like episodes (MELAS) and Leber's hereditary optic neuropathy (LHON) [61]. Other mutations described in patients with Parkinsonism include a 4-bp deletion in the mitochondrial cytochrome B gene (*MTCYB*) [62] and mitochondrial ND4 gene of complex I [63], previously only identified in families with LHON.

Mutations in *POLG1* are reported to be the most frequent nDNA defect causing either dominant or recessive associated levodopa responsive parkinsonism with an age of onset of the parkinsonism of between 26 and 75 years of age [12, 13, 64]. However, Parkinsonism can also be caused by nDNA mutations encoding other mitochondrial genes such as *C10orf2* (*TWNK*). *TWNK* encodes the twinkle mitochondrial protein, a helicase that co-localizes with mtDNA in mitochondrial nucleoids [65]. Pathogenic mutations in *TWNK* cause patients to develop symptoms as adults between 17 and 73 years of age. Only a minority of patients may develop Parkinsonism or tremors as the most common symptoms are PEO and ptosis. Other associated features include myopathy (usually limb-girdle), polyneuropathy, depression, diabetes, ataxia, cataracts, memory loss, hearing loss or cardiac problems.

Mitochondrial disorders and myoclonus

Myoclonus is defined as a sequence of brief jerking movements resulting from sudden involuntary contractions or relaxations of one or more muscles. Myoclonus can be focal, multifocal or generalised and defined on the presumed source of its generation (cortical, subcortical, spinal or peripheral) [66]. Cortical myoclonus is the commonest form of myoclonus in mitochondrial disease and can be confirmed by surface EMG (Fig. 1a), associated with giant SEPs (Fig. 1b) and positive C-reflexes [67].

Myoclonus is an important clinical feature in MERRF syndrome associated with various mtDNA point mutations, the most frequent being the m.8344A>G [68], however, other mtDNA mutations in addition to *POLG* mutations have also been associated with MERRF [69]. More rarely, myoclonus has also been observed in m.3243A>G MELAS mutations [70] and mtDNA mutations associated with Leigh syndrome [62, 71] and LHON [72]. Subcortical myoclonus with autosomal recessive spinocerebellar ataxia-9 (SCAR9) due to *ADCK3* mutations has also been described and in some cases associated with dystonia [73].

Other mitochondrial disorders associated with myoclonus include Alpers with *POLG*-related disease [14], Leigh syndrome due to *PDHA1* resulting in genetic defects in the pyruvate dehydrogenase complex [69] and *CARS*2, which encodes mitochondrial cysteinyl-tRNA synthetase 2 and associated with combined oxidative phosphorylation deficiency-27 (COXPD27) [74].

Mitochondrial disorders and dystonia

Dystonia is another common feature of mitochondrial disease and may present with other neurological features such as ptosis, seizures, visual loss, ataxia and neuropathy. Dystonia can manifest in mtDNA related disorders (e.g., MERRF, Fig. 2), Leigh Syndrome (described in the "Ataxia" section) and LHON. Dystonia is also associated with mitochondrial DNA depletion syndrome-5 (MTDPS5), combined oxidative phosphorylation deficiency-10 (COXPD10), X-linked dystonia-deafness syndrome, and with mitochondrial genes involved in brain iron accumulation.

The mitochondrial m.1178G>A mutation has also been reported as a common cause of generalised dystonia [5] and m.9176T>C in the mitochondrial ATP6 gene has been associated with dystonia in children [5]. Other genetic defects manifesting with dystonia include mutations in the mitochondrial ND4 gene (*ND4*) and the nuclear genes *SUCLA2* (described below), *NDUFAF6* (encodes a protein that plays an important role in the assembly of mitochondrial respiratory complex I) [75], *FARS2* (encodes phenylalanyl-tRNA synthetase and associated with combined oxidative phosphorylation deficiency-COXPD14) [5], *PDHX* [encodes component X of the pyruvate dehydrogenase (PDH) complex] [76] and *MTFMT* (described above).

LHON patients present with midlife, acute or subacute, painless, central vision loss leading to a central scotoma. Neuro-ophthalmologic examination can reveal peripapillary telangiectasia, microangiopathy, disc pseudoedema, and vascular tortuosity. Common mutations associated with LHON include m.3460G>A, m.11778G>A and m.14484T>C [77]. LHON Plus syndrome also known as LHON plus dystonia (designated as LDYT) is due to mutations in ND1 [78], ND3 [79], ND4 and ND6 genes [80] that encode subunits within Complex I [81, 82]. The clinical phenotype is variable and can manifest with a progressive generalized dystonia and visual loss accompanied by pyramidal tract signs, pseudobulbar signs and intellectual impairment [83]. Cerebral MRI shows caudate nuclei and putamenal lesions [84].

Mitochondrial DNA depletion syndrome-5 (MTDPS5) is an autosomal recessive disorder characterized by a hyperkinetic-dystonic movement disorder. MTDPS5 is caused by mutations in the beta subunit of the succinate-CoA ligase gene (*SUCLA2*). It is characterized by an infantile-onset of hypotonia, progressive neurological deterioration, external ophthalmoplegia, hearing loss, and renal tubular dysfunction [85].

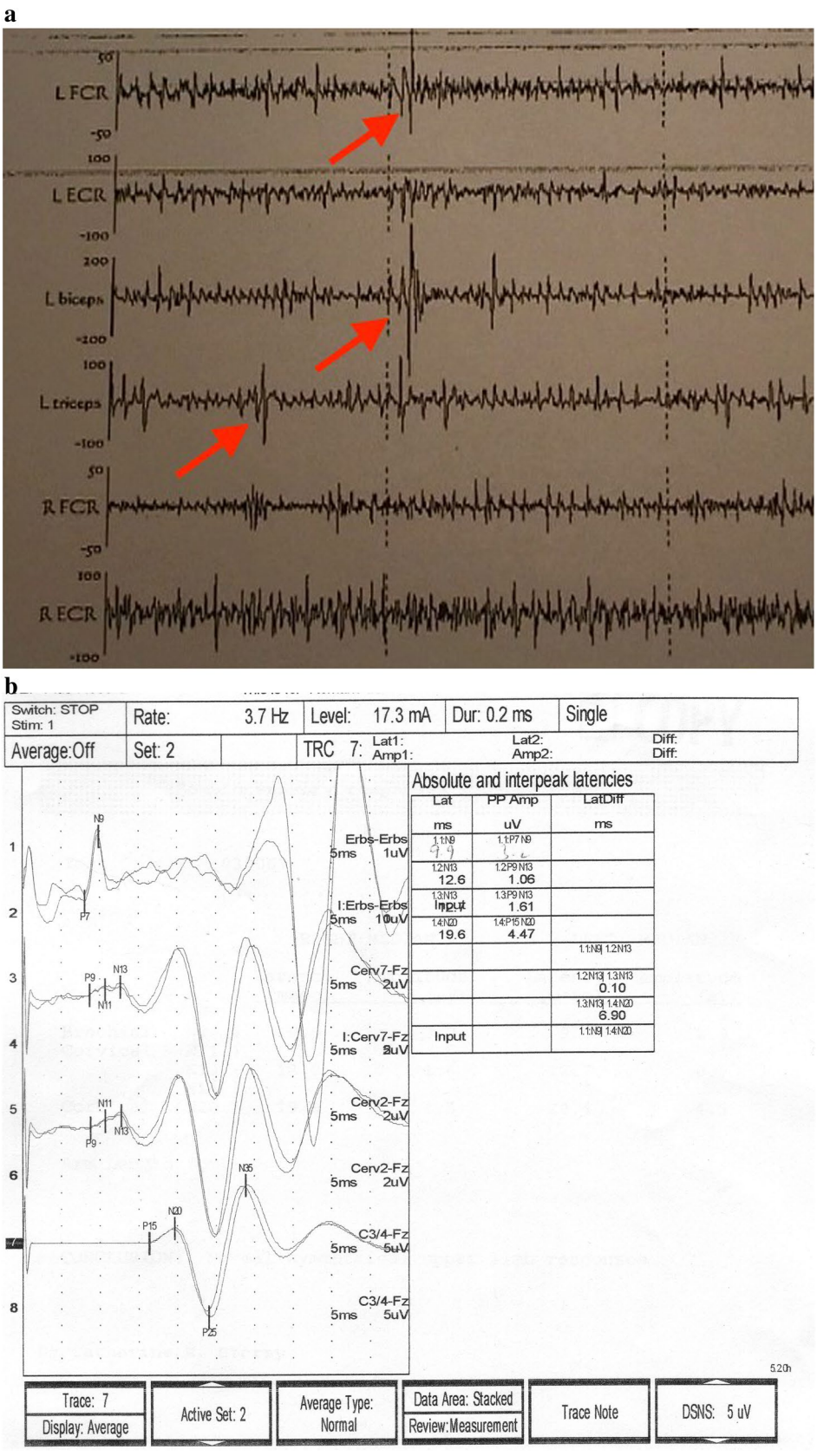

Fig. 1 **a** Surface EMG showing brief jerking movements of the left biceps, triceps and flexor carpi radialis muscles (FCR) in a patient with myoclonus and mitochondrial disease. **b** Median somatosensory evoked potential from a mitochondrial disease patient with cortical myoclonus showing a giant cortical response (amplitude 30–40 μV). The site of recording was the median nerve from the right wrist

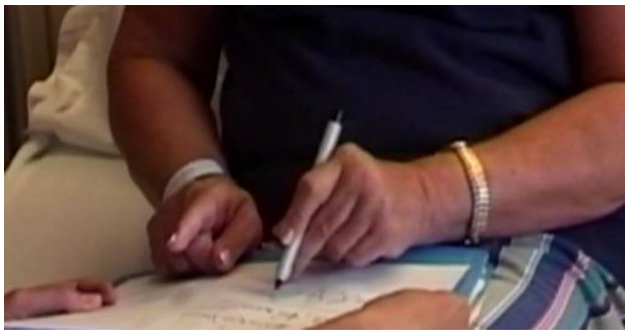

Fig. 2 Patient with MERRF syndrome who has dystonic posturing of the left hand during writing. Right hand demonstrates mirror movements with extension of the right index finger

Combined oxidative phosphorylation deficiency-10 (COXPD10) is an autosomal recessive disorder due to mutations in *MTO1* [86] resulting in variable defects of mitochondrial oxidative respiration. The disease course is highly variable, causing failure to thrive, psychomotor delay, hypertrophic cardiomyopathy and lactic acidosis with variable neurologic features including dystonia, spasticity, and seizures [87].

Mutations in *TIMM8A* are associated with sensorineural deafness and dystonia. This gene encodes deafness dystonia protein 1 (DDP1), part of a family of proteins that are organized in heterooligomeric complexes in the mitochondrial intermembrane space. These proteins mediate the import and insertion of hydrophobic membrane proteins into the mitochondrial inner membrane. Mutations in *TIMM8A* cause X-linked dystonia-deafness syndrome, also known as Mohr–Tranebjaerg syndrome. Deafness can present at an early age, followed by varying degrees of dystonia presenting at ages 15–30 years [88]. Mild mental deterioration has been reported without associated visual impairment (Ujike, 2001) [89].

Some mitochondrial genes involved in brain iron accumulation are also associated with dystonia. These include *PANK2* and *C19orf12* [90]. Pantothenate kinase-associated degeneration (PKAN) due to mutations in *PANK2* is characterized by progressive iron accumulation in the basal ganglia and other regions of the brain, resulting in Parkinsonism, chorea and dystonia [91]. Onset is in the first or second decade of life and death usually occurs before the age of 30 years. Dystonia may involve muscles supplied by cranial nerves, resulting in difficulties in articulation and swallowing. In all patients with PKAN, T2-weighted MRI of the brain shows a specific pattern of hyperintensity within the hypointense medial globus pallidus [92]. Neurodegeneration with brain iron accumulation-4 (NBIA4) also known as mitochondrial protein-associated neurodegeneration (MPAN) is an autosomal recessive neurodegenerative disorder due to *C19orf12* mutations. MPAN is characterized by a progressive spastic paraplegia, parkinsonism unresponsive to L-dopa treatment, and psychiatric or behavioural symptoms. Associated neurological features may include optic atrophy, ophthalmoplegia, dystonia, dysphagia, dysarthria, and a motor axonal neuropathy [90]. Cerebral MRI shows T2-weighted hypointensities in the globus pallidus and substantia nigra. Onset is usually in the first two decades of life, but later onset has also been reported [93]. Some patients may not have extrapyramidal signs and rather have muscle weakness and atrophy as well as cognitive impairment or developmental delay [94].

Dystonia has also been described with *POLG1*, *ADCK3*, Kearns–Sayre syndrome, myofibrillogenesis regulator-1 (MR1) gene associated with paroxysmal non-kinesigenic dyskinesia (PNKD) [95], *NDUFS3* (*NDUFS3* encodes one of the subunits of complex I) [96] and CoQ10 deficiency [43].

Other movement disorders associated with mitochondrial disease

Other movement disorders associated with mitochondrial disease include choreoathetosis, spasticity, tremor and restless leg syndrome.

Choreoathetosis is characterized by involuntary, irregular, purposeless, non-rhythmic, abrupt, rapid movements flowing from one part of the body to another (chorea) that blend with slow, writhing, continuous movements (athetosis) [97]. Choreic movements have been reported with *POLG* [9], *MTTG* and *MTND4* mutations [5]. It has also been described with HSD10 mitochondrial disease. This disorder most commonly presents as an X-linked neurodegenerative disorder with highly variable degree of severity and age at onset ranging from the neonatal period to early childhood. Clinical features associated with *HSD10*-related disorder may be multisystemic [98] and include mild mental retardation and abnormal behaviour [99] metabolic acidosis and refractory epilepsy [100].

Spasticity has been reported in patients with LHON and the m.14459G>A mutation of the ND6 gene [101]. Mutations in the ND6 gene also cause a broad spectrum of clinical manifestations as previously described including dystonia, anarthria, and mild encephalopathy. Complex I deficiency due to mutations in *NDUFV1* can also cause spasticity, infantile myoclonic epilepsy, psychomotor regression, and macrocephaly. Cerebral MRI scans demonstrate cerebral atrophy and a progressive leukodystrophy [102].

Spasticity has also been described in Leigh syndrome due to CoQ10 deficiency [103], and in Leigh syndrome with mutations in *ECHS1* causing mitochondrial short-chain enoyl-CoA hydratase-1 deficiency (ECHS1D) [104].

Mitochondrial complex III deficiency, nuclear type 8, is an autosomal recessive disorder due to mutations in *LYRM7* and is characterized by progressive neurodegeneration and spasticity with onset in childhood. Affected individuals may have delayed early development, and often have episodic acute neurological decompensations and regression associated with febrile illnesses. The developmental regression results in variable intellectual disability, hypotonia, axial hypertonia, with some patients losing the ability to walk independently [105].

3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL), also referred to as 3-methylglutaconic aciduria type VI (MGCA6) is an autosomal recessive disorder characterized by childhood-onset of delayed psychomotor development, sensorineural deafness, spasticity or dystonia, and increased excretion of 3-methylglutaconic acid. Brain imaging shows cerebral and cerebellar atrophy as well as lesions in the basal ganglia reminiscent of Leigh syndrome. MEGDEL is caused by mutations in *SERAC1* [106].

Multiple mitochondrial dysfunctions syndrome-2 (MMDS2) with hyperglycinemia due to mutations in *BOLA3* is a severe autosomal recessive disorder characterized by motor regression in infancy. Affected children have an encephalopathic disease course with seizures, spasticity, loss of head control, and abnormal movements. Additional but more variable features include optic atrophy, cardiomyopathy, and leukodystrophy [107].

SPG7 mutations (also described in above in the "Ataxia" section) result in progressive weakness and spasticity of the lower limbs, external ophthalmoplegia, sensory loss and urinary incontinence [52].

SLC25A12 encodes aralar, a protein that functions in the transport of aspartate from mitochondria to the cytosol in exchange for glutamate. Mutations in *SLC25A12* are associated with autosomal recessive infantile epileptic encephalopathy. Spasticity and hyperreflexia has also been described with other features including severe psychomotor retardation, hypotonia, seizures, episodic apnoea and hypomyelination of the central nervous system [108].

Tremor is a less frequent movement disorder associated with mitochondrial disease but has been described in LHON [83, 109] and in cytochrome c oxidase deficiency, due to *COX20* mutations. Intention tremor has also been described in combination with cerebellar ataxia (discussed in the "Ataxia" section) [38]. SANDO due to *POLG* mutations can manifest as resting tremor, pure progressive ataxia, palatal tremor [110] and facial dyskinesia [111].

There are a limited number of case reports describing tic disorders and restless leg syndrome as a result of mitochondrial disease and one case report of LHON with m.11778G>A that had a tic disorder and associated postural tremor [83]. Combined oxidative phosphorylation deficiency-9 (COXPD9) is associated with compound heterozygous mutations in the mitochondrial ribosomal protein L3 (*MRPL3*) gene. Variants within *MRPL3* were reported in one family to segregate with tics, but the disease mechanism remains unknown [112]. Restless leg syndrome was found in an adult mitochondrial cohort to be associated with *POLG* and *SDHA* mutations [5].

More recently, mutations in *MICU1* (a subunit of the mitochondrial uniporter, for the multisubunit calcium channel of the mitochondrial inner membrane) [113], have been shown to manifest with extrapyramidal features. Associated proximal myopathy and learning disabilities can occur in early childhood. While the muscle weakness is static, most patients develop progressive extrapyramidal signs that may become disabling. Most patients develop subtle extrapyramidal motor signs that progress over several years to a debilitating involuntary complex movement disorder including chorea, tremor, dystonic posturing, and orofacial dyskinesia. Additional clinical features found in only a few patients may include ataxia, microcephaly, ophthalmoplegia, ptosis, optic atrophy and an axonal peripheral neuropathy [114].

Conclusion

Movement disorders have become an increasingly recognized clinical manifestation of mitochondrial disorders. They can present clinically in isolation, simultaneously with other movement disorders or part of a multisystemic presentation [4]. Although myoclonus and ataxia are more frequently encountered among patients with mitochondrial disorders, Parkinsonism, dystonia, chorea, spasticity, tremor, tics and restless leg syndrome have also been reported. Parkinsonism due to *POLG1* has been reported to be common in adult mitochondrial patient cohorts while dystonia due to MT-ATP6 mutations is more common in paediatric cohorts of mitochondrial disease patients [4, 5].

There is, however, marked phenotypic variability with the same gene manifesting with different types of movement disorders. For example, *POLG1* may be associated with Parkinsonism, dystonia, myoclonus, chorea or ataxia. The phenotypic heterogeneity associated with mitochondrial disorders presents a challenge to the diagnostic process, but the advent of next-generation sequencing will likely improve the diagnostic yield in these patients. Identification of the genetic aetiology of the mitochondrial movement disorder is important as some conditions, such as CoQ10 deficiency, may be responsive to treatment. Understanding the genetic basis of movement disorders in mitochondrial disease is essential for improving our understanding of the physiological and molecular basis of these disorders and can be used to develop targeted therapies with mechanistic precision in the future.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

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