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Movement disorders

Movement disorders in mitochondrial diseases

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INFO ARTICLE

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ABSTRACT

Mitochondrial diseases (MIDs) are a large group of heterogeneous disorders due to mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) genes, the latter encoding proteins involved in mitochondrial function. A multisystem clinical picture that involves several organs, including both the peripheral and central nervous systems, is a common presentation of MID. Movement disorders, even isolated ones, are not rare. Cerebellar ataxia is common in myoclonic epilepsy with ragged red fibers (MERFF) due to mutations in the mitochondrial transfer RNA (tRNA) lysine gene, in Kearns–Sayre syndrome due to mtDNA deletions, in sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO) due to nuclear *POLG1* gene mutations, and also in ARCA2, Friedreich's ataxia, SPG7, SCA28 and autosomal-recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) due to mutations in nuclear genes involved in mitochondrial morphology or function. Myoclonus is a key feature of MERFF, but may also be encountered in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), ARCA2, *POLG1* mutations and Leigh syndrome. Dystonia is common in Leigh syndrome (which may be caused by 75 different genes) and in Leber hereditary ocular neuropathy (LHON) plus disease, due to mutations in mtDNA genes that encode subunits of NADH dehydrogenase, as well as in ARCA2, pantothenate kinase-associated neurodegeneration (PKAN), mitochondrial membrane protein-associated neurodegeneration (MPAN) and *POLG1* mutations. Other movement disorders are rarer (such as parkinsonism, tremor, chorea). Although parkinsonism is more frequent in *POLG1* mutations, and myoclonus in MERFF, most movement disorders are found either isolated or combined in numerous MIDs. The presence of associated neurological signs, whether central or peripheral, or of evocative magnetic resonance imaging (MRI) abnormalities (striatal necrosis) should prompt a search for MID. In cases of a particular clinical spectrum (LHON, MERFF, Kearns–Sayre, SANDO, SPG7, ARCA2, ARSACS), a search for the most frequently implicated mutation(s) is recommended. In other cases, muscle biopsies followed by metabolic and genetic studies may be useful for arriving at a diagnosis.

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1. Introduction

Mitochondrial diseases (MIDs) are a group of heterogeneous disorders caused by dysfunction of the mitochondria. Most of them are associated with a primary defect of the mitochondrial electron transport chain (METC), which allows mitochondrial oxidative phosphorylation and also the main production of cellular adenosine triphosphate (ATP) [1,2]. The METC is composed of five complexes and two electron carriers (ubiquinone and cytochrome C). In the METC, mitochondrial DNA (mtDNA) encodes for only 13 protein genes, 22 transfer RNA (tRNA) and two ribosomal RNA (rRNA). Nuclear DNA (nDNA) encodes the remaining METC proteins and also numerous mitochondrial proteins, some of which are involved in the maintenance and expression of mtDNA, and others with mitochondrial morphology or cellular mitochondrial trafficking regulation [1,2]. Thus, over the past few years, numerous mitochondrial and nuclear gene mutations have been implicated in MIDs, thereby expanding the MID spectrum.

Mutations in mtDNA can be point mutations, single or multiple large-scale deletions or mtDNA depletions [3,4]. Point mutations are of maternal inheritance (as mitochondria are inherited only from mothers). Single large-scale deletions are often sporadic, but may be transmitted by women to their children. Multiple deletions and depletions are due to mutations of nuclear genes involved in the expression or maintenance of mtDNA (for example, *POLG1, POLG2, PEO1* [the *Twinkle helicase* or *C10orf2* gene], *RRM2B, SLC25A4 [ANT1], TK2, OPA1, MPV17, TYMP*); they display a classical pattern of inheritance (autosomal-recessive in most cases and sometimes autosomal-dominant) in the same way that other nDNA gene mutations involved in MIDs.

It is still not known why some tissues are more specifically involved in MIDs. Sensitivity of the nervous system and muscles could be due to their high-energy dependence and vulnerability. Indeed, neurological signs such as epilepsy, cerebellar ataxia, dystonia, myoclonus, diplopia, sensory neuropathy and myopathy are frequently seen. Nevertheless, there is, for a single mutation, a marked clinical heterogeneity from one patient to another, which may be explained in part by two mitochondrial peculiarities: heteroplasmy (a mix of mutated and wild-type mtDNA in each cell or tissue) and mitotic segregation (random distribution of mitochondria during cellular division) [1,2]. Nevertheless, associated genetic or environmental factors could also play a role in such phenotypic heterogeneity.

Given this wide phenotypic and genotypic heterogeneity, a new genetic classification that includes the mutated gene would appear to be more useful than the old phenotypic one [5]. Also, the suspected MID can be strongly supported by careful analysis of the clinical and radiological data. A multisystem clinical picture that involves several organs, including both the peripheral and central nervous systems, is a common presentation of MIDs [1,2,5]. Movement disorders such as cerebellar ataxia and dystonia are also very common. Even when isolated, these should in some cases (defined below) prompt a search for an MID. Indeed, the diagnosis of MID is crucial for genetic counseling, and should lead to care for any associated multisystemic disorders.

2. Cerebellar ataxia

This movement disorder should never be ignored, as it is responsible for abnormal movement and gait, and characterized by hyperkinesia and sometimes tremor. It is also well established that the cerebellum is closely connected to the basal ganglia. Cerebellar ataxia is one of the most prevalent neurological mitochondrial signs [6] and MIDs should be included in the classification of inherited ataxias [7].

In a few classical mitochondrial syndromes, including myoclonic epilepsy with ragged red fibers (MERFF), Leigh, neuropathy, ataxia and retinitis pigmentosa (NARP) and Kearns–Sayre, cerebellar ataxia is often seen, but rarely prominent. NARP syndrome, first described as a combination of developmental delay, retinitis pigmentosa, dementia, seizures, ataxia, proximal neurogenic weakness and sensory neuropathy, is due to point mtDNA mutations in the *ATP6* gene, encoding mitochondrial ATPase [2]. Kearns–Sayre syndrome is characterized by progressive external ophthalmoplegia, cardiac conduction defects, pigmentary retinal degeneration and a variable number of red ragged fibers on muscle biopsy. It starts before age of 20 and patients may present additional neurological features such as ataxia, dystonia, bulbar symptoms, dementia and, as seen in numerous MIDs, myopathy, sensorineural deafness, endocrine abnormalities, cataracts and renal failure. Kearns–Sayre syndrome is usually due to sporadic large-scale single deletions of mtDNA [2].

In other syndromes caused by mutations of nuclear genes involved in the expression or maintenance of mtDNA, cerebellar or mixed ataxia (with both cerebellar and proprioceptive ataxia) may reveal the disease or dominate the phenotype [8,9]. Mitochondrial recessive ataxia syndrome (MIRAS), mitochondrial spinocerebellar ataxia with epilepsy (MSCAE) and sensory ataxic neuropathy with dysarthria and ophthalmoplegia (SANDO) refer to very close phenotypes with ataxia and various associations of peripheral neuropathy, epilepsy, headache, cognitive impairment, psychiatric disturbances, movement disorders, ptosis and ophthalmoplegia. All three disorders have also been associated with homozygous or composite heterozygous mutations in the nuclear *POLG1* gene, which encodes the catalytic subunit of mtDNA polymerase-gamma, while *POLG1* mutations are associated, in most cases, with multiple mtDNA deletions [9]. Infantile-onset spinocerebellar ataxia (IOSCA) begins before age 18 months with ataxia, hypotonia and axonal sensory neuropathy, followed in some cases by ophthalmoparesis, sensorineural hearing loss and epilepsy; it is due to mutations in the *C10orf2* (or *PEO1*) gene, which encodes mitochondrial Twinkle helicase. Mutations in this gene lead to multiple mtDNA deletions in affected tissues [10,11]. *RRM2B* and *OPA1* genes mutations both also cause multiple mtDNA deletions, and are responsible for progressive external ophthalmoplegia (PEO) and ptosis (*RRM2B*), dominant optic atrophy (*OPA1*) and, sometimes, ataxia [12,13].