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Mitochondrial diseases

An overview of neurological and neuromuscular signs in mitochondrial diseases

Diversité des atteintes neurologiques et neuromusculaires dans les maladies mitochondriales héréditaires

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ABSTRACT

Mitochondrial disorders have a broad clinical spectrum and are genetically heterogeneous, involving two genomes. These disorders may be develop at any age, with isolated or multiple system involvement, and any pattern of inheritance. Neurological involvement is the most frequent, and concerns muscular, peripheral and central nervous system. Among these diverse signs, some are suggestive of mitochondrial disease, such as progressive external ophthalmoplegia, exercise intolerance, psychomotor regression, stroke-like episodes, refractory epilepsy and Epilepsia Partialis Continua. Others are less specific and mitochondrial hypothesis may be evocated because of either association of different neuromuscular signs or a multisystemic involvement. This review describes the wealth of this neurological and neuromuscular symptomatology through different syndromes reported in the literature, according to preponderant signs and to modes of inheritance, as key elements to guide genetics testing.

RÉSUMÉ

Les maladies mitochondriales présentent un large spectre clinique et une grande hétérogénéité génétique liée au double contrôle génétique, rendant ainsi leur diagnostic difficile.

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Abbreviations: ANS, ataxia neuropathy spectrum disorders; arPEO, autosomal recessive progressive external ophthalmoplegia; CK, creatine kinase; CNS, central nervous system; CoQ10, coenzyme Q10; COX, cytochrome oxidase negative; CSF, cerebrospinal fluid; IOSCA, infantile-onset spinocerebellar atrophy; KSS, Kearns-Sayre syndrome; LBSL, leukencephalopathy with brainstem and spinal cord involvement, and lactate elevation; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactacidosis, stroke-like episodes; MEMSA, myoclonus epilepsy, myopathy and sensory ataxia syndrome; MERRF, myoclonic epilepsy and ragged red fibers; MiDs, mitochondrial diseases; MIRAS, mitochondrial recessive ataxia syndrome; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NARP, neurogenic muscle weakness, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PNS, peripheral nervous system; RC, respiratory chain; RRF, ragged red fibers; SANDO, sensory ataxic neuropathy, dysarthria, ophthalmoplegia syndrome.

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ADNmt
Génome nucléaire
Ophtalmoplégie progressive externe
Intolérance à l'effort
Ataxie cérébelleuse
Épilepsie pharmaco-résistante
Mouvements anormaux

Elles peuvent se manifester à tout âge, sous la forme d'une atteinte isolée ou le plus souvent d'atteintes associées de tissus ou organes, et tous les modes de transmissions sont possibles. L'atteinte neurologique est la plus fréquente. Elle concerne le système musculaire, nerveux périphérique et nerveux central, engendrant ainsi une grande diversité de signes. Certains sont très évocateurs de maladie mitochondriale, comme l'ophtalmoplégie progressive externe, l'intolérance à l'effort, la régression psychomotrice, les « pseudo-stroke », l'épilepsie réfractaire ou l'épilepsie partielle continue. D'autres sont moins spécifiques et c'est l'association de différents signes neurologiques, musculaires ou systémiques qui vont faire suggérer une hypothèse mitochondriale. Dans cette revue, nous présentons un aperçu de la richesse de cette symptomatologie à travers les différents syndromes décrits dans la littérature, en fonction du signe prépondérant et du mode de transmission, ainsi que des éléments clefs permettant d'orienter les analyses génétiques.

Since the first reports of human disease due to defects in mitochondrial DNA (mtDNA) in 1988 [1,2], the number of disease-associated mtDNA mutations has expanded rapidly with identification of classic mitochondrial syndromes such as MELAS, MERRF, NARP, Kearns-Sayre syndrome and maternally inherited Leigh syndrome. Subsequently, the past decade has seen a clear expansion in the involvement of mutations in nuclear genes. In addition to being genetically heterogeneous with all possible patterns of inheritance, mitochondrial diseases (MiDs) are also clinically heterogeneous with multisystemic manifestations and an onset at any age. Many tissues and organs can be affected. However, post-mitotic tissues that are highly dependent on oxidative metabolism, such as neurons, muscle, and cardiac cells, seem to be preferentially vulnerable to energy depletion [3]. Muscular, peripheral and central nervous systems are frequently involved in MiDs. Myopathy, ocular myopathy, peripheral neuropathy, seizures, ataxia, stroke-like episodes, psychomotor retardation, migraine-like headaches, encephalopathy, cognitive regression and movement disorders are neurological manifestations commonly found in these diseases [4]. These neurological and neuromuscular manifestations can be isolated or associated, but often evolve into multisystem disease, a clue to the diagnosis of MiDs. In this review, we present an overview of large spectrum of MiDs through different neurological aspects.

1. Muscular manifestations of MiDs

The most evocative signs of MiDs remain the muscular signs, particularly ocular myopathy and exercise intolerance. Progressive external ophthalmoplegia (PEO) is characterized by progressive weakness or paresis of the extraocular eye muscles leading to bilateral gaze limited in all directions, usually without diplopia, and associated with ptosis. Ptosis may be also isolated. Myopathy begins usually in the teens or during adulthood and can occasionally be congenital. The weakness is slowly progressive, symmetric, and more often proximal than distal. The severity of myopathy varies from mild to severe forms that can lead to respiratory failure. Exercise intolerance is a failure to maintain an expected level of force during sustained or repeated muscle contraction linked to a reduction in maximal oxygen consumption with an excessive carbon dioxide production, increasing hyperdynamic circulatory response. It appears progressively with cramps, myalgias or fatigue, and may occasionally be combined with nausea, shortness of breath and dizziness or may occur even after normal daily activities. Each sign can be either isolated or associated with other neurological symptoms and/or systemic manifestations, such as growth retardation, diabetes, deafness, optic atrophy, retinitis pigmentosa, cataracts, and cardiomyopathy. Creatine kinase (CK) and lactate may be high in serum at rest or after exercise, and the association of both is suggestive of MiDs. EMG is normal or myopathic. A respiratory chain (RC) defect is sometimes identified by muscle spectrophotometry. Muscle histology usually shows ragged red (RRF) and/or cytochrome oxidase negative (COX−) fibers, sometimes with SDH-positive fibers or lipid accumulation in type I fibers. Abnormal mitochondrial morphology and presence of paracrystalline inclusions can be observed at electron microscopy. These phenotypes have been associated with either mtDNA mutations (Table 1) or mutations in nuclear genes (Table 2).

1.1. *Muscular syndromes related to mtDNA mutations (sporadic or maternally inherited)*

Large single mtDNA deletions, but also large-scale tandem mtDNA duplications are involved in a clinical spectrum including Kearns-Sayre syndrome, PEO or isolated ptosis (Table 1). Usually found in sporadic cases, large mtDNA mutations, when inherited, are maternally transmitted.

Kearns-Sayre syndrome (KSS) is a multisystem disorder characterized by childhood-onset PEO and pigmentary retinopathy (< 20 years of age), associated with at least one of the following signs: cardiac conduction block, hyperproteinorachia or cerebellar ataxia [5,6]. Other manifestations are frequent including limb weakness, hearing loss, dementia, diabetes, hypoparathyroidism and short stature (growth hormone deficiency). Muscle biopsy shows RRF, SDH+ and COX− fibers with defect of RC complexes containing mtDNA-encoded subunits. Nearly 90% of individuals with KSS have a large-scale mtDNA deletion that is usually present in muscle, but undetectable in blood cells, necessitating muscle biopsy.