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Review Article

Inherited mitochondrial neuropathies

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ABSTRACT

Mitochondrial disorders (MIDs) occasionally manifest as polyneuropathy either as the dominant feature or as one of many other manifestations (inherited mitochondrial neuropathy). MIDs in which polyneuropathy is the dominant feature, include NARP syndrome due to the transition m.8993T>, CMT2A due to MFN2 mutations, CMT2K and CMT4A due to GDAP1 mutations, and axonal/demyelinating neuropathy with external ophthalmoplegia due to POLG1 mutations. MIDs in which polyneuropathy is an inconstant feature among others is the MELAS syndrome, MERRF syndrome, LHON, Mendelian PEO, KSS, Leigh syndrome, MNGIE, SANDO; MIRAS, MEMSA, AHS, MDS (hepato-cerebral form), IOSCA, and ADOA syndrome. In the majority of the cases polyneuropathy presents in a multiplex neuropathy distribution. Nerve conduction studies may reveal either axonal or demyelinated or mixed types of neuropathies. If a hereditary neuropathy is due to mitochondrial dysfunction, the management of these patients is at variance from non-mitochondrial hereditary neuropathies. Patients with mitochondrial hereditary neuropathy need to be carefully investigated for clinical or subclinical involvement of other organs or systems. Supportive treatment with co-factors, antioxidants, alternative energy sources, or lactate lowering agents can be tried. Involvement of other organs may require specific treatment. Mitochondrial neuropathies should be included in the differential diagnosis of hereditary neuropathies.

Contents

1. Introduction

Hereditary polyneuropathies (PNPs) are commonly classified according to a mixture of different criteria such as the type of nerve fiber affected (sensory-motor, sensory-autonomic, and pure motor), the type of lesion (axonal and demyelinating), the trait of inheritance (autosomal dominant, autosomal recessive and X-linked), and the mutated gene [1]. Following these criteria hereditary neuropathies are classified as hereditary sensori-motor neuropathies (HSMN), hereditary sensory-autonomic neuropathies (HSAN), hereditary motor neuropathies (HMN), and as hereditary neuralgic amyotrophy (HNA) (Table 1). In the majority of the cases tissues other than the peripheral nerves are additionally

Abbreviations: ADOA, Autosomal dominant optic atrophy; ADOAD, Autosomal dominant optic atrophy and deafness; AHS, Alpers–Huttenlocher disease; ATP, Adenosin triphosphate; CIDP, Chronic inflammatory demyelinating polyneuropathy; CMAP, Compound muscle action potential; CMT, Charcot–Marie–Tooth; DNA, Desoxy-nucleic acid; HMN, Hereditary motor neuropathies; HSAN, Hereditary sensory-autonomic neuropathies; HSMN, Hereditary sensori-motor neuropathies; IOSCA, Infantile-onset spinocerebellar ataxia; KSS, Kearns-Sayre syndrome; MDS, Mitochondrial depletion syndrome; MELAS, Mitochondrial encephalomyopathy, lactacidosis, and stroke-like-episodes; MEMSA, Myoclonic epilepsy, myopathy, and sensory ataxia; MERRF, Myoclonus epilepsy with ragged-red fibers; MID, Mitochondrial disorder; MIDD, Mitochondrial deafness dystonia syndrome; MILS, Maternally inherited Leigh syndrome; MIRAS, Mitochondrial autosomal recessive ataxia syndrome; MNGIE, Mitochondrial neuro-gastrointestinal encephalopathy; NARP, Neuropathy, ataxia, and retinitis pigmentosa syndrome; NCV, Nerve conduction studies; PNP, Polyneuropathy; PEO, Progressive external ophthalmoplegia; SANDO, Sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia syndrome; SNAP, Sensory nerve action potential; tRNA, Transfer ribonucleic acid.

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Table 1
Classification of hereditary polyneuropathies.

CMT (=HMSN)
CMT3 (AD, demyelinating, Dejerine-Sottas, early onset)
CMT1 (AD, demyelinating, NCV <38 m/s)
A (*PMP22*), B (*MPZ*), C (*LITAF*), D (*EGR2*), F (*NEFL*)
CMT2 (AD, axonal)
A (*MFN2*), E (*NEFL*)
CMT4 (AR, demyelinating, NCV <38 m/s)
A (*GDAP1*), C (*SH3TC2*), E (*EGR2*), F (*PRX*)
HNPP (*PMP22*)
CMTX (*GJB1*, X-linked)
HSAN (NCV <38 m/s)
AD: HSAN1 (*SPTCL1*)
AR: HSAN2 (*HSN2*), HSAN3 (*IKBKAP* (Riley-Day), *SCN9A*, Tangier), HSAN4 (*NTRK1*), HSAN5 (*NGF-β, ATM, FRDA* (Friedreich ataxia), Fabry, DHH)
HMN *HSPB8, GARS, BSCL2, DCTN1, SETX, PLEKHG5, HSBP1, IGHMBP2, seipin* (distal HMN)
HNA (familial brachial plexus neuropathy)

CMT: Charcot–Marie–Tooth, HMSN: hereditary motor and sensory neuropathies, HSAN: hereditary sensory-autonomic neuropathies, HMN: hereditary motor neuropathies, HNA: hereditary neuralgic amyotrophy, AD: autosomal dominant, AR: autosomal recessive, NCV: nerve conduction velocity, gene names are in italic.

affected, clinically manifesting as tremor, cataract, deafness, or cardiomyopathy (Table 2) [2]. One disadvantage of this classification is that PNPs as manifestations of mitochondrial disorders (MIDs) (mitochondrial PNPs) are not duly included and not explicitly mentioned as such.

MIDs constitute a group of increasingly recognized conditions, which share abnormalities in the oxidative metabolism or increased oxidative stress [3]. MIDs are multisystem disorders already at onset or become multisystem conditions during the progressive course of the disease (Table 2). One of the systems commonly affected is the peripheral nerves [4–7]. Affection of the peripheral nerves may occur in syndromic as well as non-syndromic MIDs and may be the dominant clinical feature or a collateral feature of the phenotype. Affection of the peripheral nerves in MIDs may be a direct consequence of the genetic defect (primary mitochondrial PNPs) or may be secondary to manifestations of the underlying MID, which are well known as risk factors for secondary PNPs, such as diabetes, renal insufficiency, hypothyroidism, hyperthyroidism, or hypoparathyroidism (secondary mitochondrial PNPs). This minireview aims to highlight and discuss recent findings concerning the presentation, cause, pathogenesis, and diagnosis of hereditary mitochondrial PNPs and their significance in relation to the classical hereditary PNPs (Table 3).

Table 2
Genetic causes of syndromic and non-syndromic MIDs.

mtDNA mutations
Point mutations
tRNAs (MELAS, MERRF, MIDD)
rRNA (aminoglycosid-induced deafness)
Protein-encoding (LHON, NARP)
Deletions/duplications
Pearson-syndrome, mtPEO, KSS
nDNA mutations affecting
Subunits or assembly factors of RCCs
Leigh syndrome, Leigh-like syndrome, GRACILE syndrome
Machinery for mtDNA maintenance
Breakage syndromes (multiple deletions): adPEO, arPEO, MNGIE, ANS (SANDO, MIRAS), MEMSA, AHS, MCHS
Depletion syndromes: myopathic MDS (myopathy), encephalomyopathic MDS (Leigh syndrome, Leigh-like syndrome, IOSCA), encephalo-hepatic MDS
Translation defects (protein synthesis machinery): PCH, LBSL, MLASA
Coenzyme-Q metabolism
Pure ataxia, pure myopathy, Leigh syndrome, cardio-facio-cutaneous syndrome
Lipid milieu
Barth syndrome
Mitochondrial transport machinery
DDS/Mohr–Tranebjaerg syndrome, XLASA/A
Mitochondrial biogenesis (fusion/fission)
ADOA/ADOAD, CMT2A, DIDMOAD

Table 3
Primary and secondary PNPs in syndromic as well as non-syndromic MIDs due to mtDNA or nDNA mutations.

Primary PNP
PNP predominates
Syndromic MIDs with PNP
NARP
Non-syndromic MIDs with PNP
CMT2A, CMT2K, CMT4A, severe mixed axonal/demyelinating sensori-motor neuropathy with PEO
PNP is a collateral feature
Syndromic MIDs with PNP
MELAS, MERRF, LHON, KSS, Mendelian PEO, Leigh syndrome, MNGIE, SANDO, MIRAS, MEMSA, AHS, IOSCA, ADOA
Non-syndromic MIDs with PNP
MIDs without acronyms but PNP as one among other manifestations
Secondary PNP
PNP is secondary to diabetes, renal insufficiency, hypothyroidism, hyperthyroidism, hypoparathyroidism, or paraneoplastic

2. Classification of MIDs

In addition to the differentiation into mono- and multi-organ diseases, inherited MIDs can be classified as syndromic or non-syndromic conditions (Table 2) [8–10]. The underlying genetic defect in syndromic as well as non-syndromic MIDs may be located in genes on the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA) [9,10]. MIDs may be further classified according to the affected structure or pathway within the mitochondrion (Table 2). In the vast majority of the inherited MIDs the oxidative metabolism (respiratory chain or oxidative phosphorylation) is impaired but also maintenance of mtDNA, the mitochondrial lipid milieu, or mitochondrial dynamics may be disturbed. Though syndromic MIDs are well known for their acronyms and important for the understanding of mitochondrial medicine, they represent only a small portion of the phenotypes. Non-syndromic forms, which do not fit into one of the established entities, are much more prevalent and frequently overlooked due to their atypical, often non-spectacular presentation. Since they are often a diagnostic challenge and often present with PNP as a collateral feature, more attention needs to be paid to these conditions. In a study on 27 pediatric patients with MIDs the prevalence of PNP was 37% [5]. In a retrospective study on 108 MID patients PNP was attributed to the mitochondrial defect in 35% of the cases [6].

2.1. Primary mitochondrial PNP

2.1.1. PNP as the dominant feature

Primary mitochondrial PNP as a dominant feature of the phenotype occurs in syndromic MIDs, such as neurogenic weakness, ataxia, and retinitis pigmentosa (NARP) syndrome or non-syndromic MIDs such as CMT2A, CMT2K, CMT4A, or mixed, sensori-motor neuropathy with progressive external ophthalmoplegia (PEO).

2.1.1.1. NARP (m.8993T>G). The clinical presentation of NARP is dominated by proximal muscle weakness due to sensori-motor PNP, ataxia due to cerebellar atrophy, and visual impairment either due to optic atrophy or due to salt and pepper retinopathy, bull's eye maculopathy, or retinitis pigmentosa [11]. Variable manifestations include short stature, ophthalmoplegia, learning difficulties, dementia, sleep apnea, seizures, or cardiac arrhythmias [12]. The course is slowly progressive but patients may experience episodic deterioration during infections. NARP follows a maternal trait of inheritance and is due to the heteroplasmic transversion m.8993T>G or the transition m.8993T>C in the *ATP6* gene [13]. A NARP phenotype was also caused by the transition m.9185T>C in the *ATP6* gene [14]. PNP is usually sensori-motor and often more motor than sensory. Nerve conduction studies may show length-dependent sensori-motor, axonal PNP [15]. Sural nerve biopsy may show reduced number of predominantly myelinated fibers.