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Mitochondrial neuropathy

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Abstract

Polyneuropathy is a frequent feature of mitochondriopathy (MCP). If and how often polyneuropathy in MCP is primarily due to the underlying disorder (mitochondrial neuropathy, MN) or due to other well-known causes is unknown. Retrospectively investigated were 108 MCP-patients with polyneuropathy. According to established diagnostic criteria 37 patients were classified as definite MCP, 56 as probable MCP and 15 as possible MCP. In 38 of the 108 MCP-patients with polyneuropathy (35%), no plausible cause for polyneuropathy other than MCP could be found. MN was characterized by weakness, muscle cramps, wasting, reduced tendon reflexes, muscle pain, ataxia, restless legs, hypesthesia, paresthesia, dysesthesia, and vegetative impairment. In 21 cases predominantly motor fibers, in 14 cases both motor and sensory fibers and in 3 cases predominantly sensory fibers were affected. Axonal degeneration was found in 19 cases, demyelination in 4 and mixed-type polyneuropathy in 15. On sural nerve biopsy axonal loss was the predominant finding. In a single case tomaculae and abnormally shaped and structured mitochondria were found. MN exists, occurs in one third of the MCP-patients with polyneuropathy, and is characterized by predominant affection of the motor and sensory fibers with diffuse, symmetric and equal distribution between upper and lower limbs and by axonal degeneration.

Keywords: Respiratory chain; Neuromuscular disorder; Encephalomyopathy; Metabolic disorder; Lactacidosis

1. Introduction

Mitochondriopathy (MCP) due to respiratory chain dysfunction is frequently a multi-system disorder that affects not only the central nervous system, endocrine system, heart, ears, eyes, intestines, kidneys, hematopoetic system, the dermis or the skeletal muscle, but also the peripheral nervous system (PNS) as polyneuropathy [1–17] or, in single cases, as motor neuron disease [18], Guillain-Barre syndrome [1], or chronic inflammatory, demyelinating polyneuropathy [19]. Whether and how often polyneuropathy in MCP is only secondary to simultaneously occurring diabetes, renal insufficiency, thyroid dysfunction, malignancy or alcoholism, or also a primary manifestation of MCP (MN), is so far unknown. The following study was thus conducted to find out (1) if MN is a feature of MCP, (2) what is the prevalence of MN, and (3) which are the clinical, electrophysiological and morphological characteristics of MN.

2. Materials and methods

We retrospectively evaluated the records of all MCP patients of the second Department of the Neurological Hospital Rosenhügel, Vienna, who additionally suffered from polyneuropathy.

MCP was diagnosed according to Walker's major and minor diagnostic criteria as definite, probable or possible MCP [20]. Major diagnostic criteria were: (1) clinical and instrumental findings indicative of a PNS, CNS, endocrine, cardiac, ocular, auditory, gastrointestinal, renal, dermal, or hematological abnormality alone or in combination, (2) >2% ragged red muscle fibers, (3) <20% activity of one or more of the respiratory chain complexes (NADH/UbQ-oxido-reductase, succinate-cytochrome-c oxido-reductase, cytochrome-c-oxidase), or >2% COX-negative fibers if <50 year of age, or >5% COX-negative fibers if >50 years of age, (4) mtDNA or nDNA mutation in genes encoding for respiratory chain enzyme complexes, tRNAs or rRNAs, polymerases, transport proteins, signaling proteins of undisputed pathogenicity [20]. Minor diagnostic criteria were: (1) PNS

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or CNS abnormalities without involvement of other organs, (2) 1–2% ragged-red fibers if 30–50 years of age, or any ragged red fibers if <30 years of age, or abnormal mitochondria on electron microscopy, like subsarcolemmal accumulation of abnormally shaped or structured mitochondria, or intra-mitochondrial paracristalline inclusions, (3) 20–30% activity of one or more of the respiratory chain complexes or reduced staining for NADH, SDH, or cytochrome-c oxidase, (4) MtDNA or nDNA mutation of disputed pathogenicity, (5) resting serum lactate >2 mmol/l, or CSF lactate >1.6 mmol/l, or abnormal lactate stress test (LST, >50% of the serum lactate values determined before, 5, 10, and 15 min after starting a standard workload of 30 W on a bicycle ergometer, and 15 min after finishing the exercise are increased >2.0, >2.0, >2.1, >2.0 and >1.7 mmol/l, respectively), or abnormal magnetic resonance spectrosocopy or PET [20,21]. Definite MCP was diagnosed if two major criteria or one major and two minor criteria were fulfilled. Probable MCP was diagnosed if one major and one minor criterion or if three minor criteria were fulfilled. Possible MCP was diagnosed if one major or one minor criterion was fulfilled.

Polyneuropathy was diagnosed if there was weakness, wasting, reduced tendon reflexes, muscle cramps, fasciculations, restless legs, glove-pattern or stocking-type sensory disturbances (hypesthesia, paresthesia, dysesthesia), or autonomic impairment, like pupillary disturbances, sicca-syndrome, reduced heart rate variability, acquired long-QT syndrome, anhidrosis, hyperhidrosis, dilated atonic colon or bladder, impotence, or reduced vaso-reactivity (orthostatic hypotension) alone or in combination, and if motor or sensory nerve conduction studies revealed slowing of the nerve conduction velocity or reduction of the compound muscle or nerve action potential, respectively [22,23]. According to the predominant affection of the impaired quality, polyneuropathy was classified as motor, sensory or autonomic polyneuropathy alone or in combination. According to the distribution, neuropathy was classified as focal (a single nerve or limb is predominantly affected) or polyneuropathy. Polyneuropathy was categorized as symmetrical, asymmetrical, diffuse, distally predominant or proximally predominant [17]. Polyneuropathy was classified as axonal if the compound muscle or nerve action potential was reduced and the conduction velocity was normal. Polyneuropathy was classified as demyelinating if nerve conduction velocity was reduced and the compound muscle or nerve action potential was normal. If both the conduction velocity and the compound muscle or nerve action potential were reduced, polyneuropathy was defined as mixed [22]. According to the histological findings, polyneuropathy was classified as axonal, demyelinating or tomaculous (myelin thickening due to reduplicative folding of the myelin lamellae) [23].

Muscle and nerve biopsies were either carried out by plastic surgeons or general surgeons. In all cases the material was immediately processed by experienced colleagues. The methods of fixation, embedding, slicing and staining were the same in all three laboratories involved in the diagnostic work-up of the biopsies.

3. Results

Altogether 108 MCP patients with polyneuropathy, 62 women, 46 men, aged 34–88 years, were included. According to the diagnostic criteria 37 patients were classified as definite MCP, 56 as probable MCP and 15 as possible MCP. Creatine-kinase was determined in 95 patients and was elevated in 43 of them (45%). Resting lactate was determined in 88 patients and elevated in 21 (24%) of them. Lactate stress testing was performed in 89 patients and was abnormal in 59 of them (66%). Biochemical investigations of the muscle homogenate were carried out in 11 cases and revealed reduced activity of oxidative enzymes in 4 of them. Eight patients underwent a screening for mtDNA mutations. MtDNA polymorphisms were found in four patients and silent mutations in three patients. In one patient the substitutions C10142T in the ND3 gene and C8684T in the ATPase6 gene were detected. In another patient the secondary LHON-mutation T4216C and the substitution T3394C in the ND1 gene were found. In a single patient a CMT1A duplication and deletion was excluded. In another patient a CTG-repeat expansion in the DMPK-gene was excluded.

Causes of polyneuropathy in the 108 MCP patients are given in Table 1. Polyneuropathy was due to a single cause in 89 cases, two causes in 15 patients, three causes in 3 patients and due to four causes in a single patient. In the 89 patients with a single cause, polyneuropathy was attributable to diabetes ($n = 22$), uremia ($n = 9$), hypothyroidism ($n = 6$), hyperthyroidism ($n = 5$), psoriasis ($n = 4$), paraproteinemia ($n = 2$), vitamin B6 deficiency ($n = 2$) vitamin B1 deficiency ($n = 1$) or remained unknown ($n = 38$). Altogether, at least one plausible cause for polyneuropathy could be detected in 70 patients (65%). In all these cases, however, it cannot be excluded that MCP was an additional causative factor. Among the 38 patients with polyneuropathy of unknown etiology step 1 of an

Table 1
Causes of polyneuropathy in 108 patients with MCP[a]

Cause	Number	Percent
Unknown	38	35
Diabetes	35	32
Uremia	20	19
Hypothyroidism	12	11
Hyperthyroidism	7	7
Psoriasis	5	5
Alcoholism	5	5
Vitamin B1 deficiency	3	3
Paraproteinemia	3	3
Vitamin B6 deficiency	2	2
Vasculitis	1	1
M. Crohn	1	1

[a] In 19 of the 108 patients more than a single cause for polyneuropathy was detected.