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Original article

Clinical and allelic heterogeneity in a pediatric cohort of 11 patients carrying *MFN2* mutation

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Abstract

Introduction: The Mitofusin 2 gene (*MFN2*), which encodes a mitochondrial membrane protein, is known to be the first cause of autosomal dominant Charcot–Marie–Tooth disease type 2 (CMT2) with early onset. This gene is involved in typical CMT2A and in more atypical phenotypes as optic atrophy or spastic paraplegia. CMT2 refers to inherited axonal polyneuropathy, which associates progressive peripheral motor and sensory neuropathy, a family history consistent mainly with autosomal dominant inheritance, and normal nerve conduction velocities.

Subjects: Between 1999 and 2012, the genetic diagnosis of *MFN2* mutation was made in 11 children who were treated in our department for different neurological symptoms. All data including family and personal history data, results of standardized clinical and electrophysiology testing, brain magnetic resonance imaging (MRI), neuro-ophthalmic evaluation, muscle biopsy histopathology and molecular diagnosis were retrospectively analyzed.

Results: Five different mutations were found in 6 unrelated families. Three of them have previously been described; the two remaining are new mutations: one of them related a new phenotype.

Clinical signs appeared before the age of 6 years in more than half of the patients (54%). The motor deficit was predominant in 8 patients (72%). Two children presented an acute onset of disease that stabilized afterwards; the other children showed a more progressive deterioration that was managed symptomatically.

Conclusion: This large pediatric study describes a great interfamilial and intrafamilial phenotypic variability. We recommend screening this gene in pediatric patient with chronic neurologic symptoms such as motor deficit or optic atrophy but also in acute neurologic deficiencies such as subacute polyradiculoneuritis.

Keywords: Charcot–Marie–Tooth (CMT); Mitofusin 2 (MFN2); Neuropathy; Optic atrophy; White matter lesion; Subacute polyneuropathy; Respiratory chain deficiency

1. Introduction

The Mitofusin 2 gene (*MFN2*) encodes for a protein located on the outer membrane of mitochondria (Mitofusin 2) and involved in mitochondrial dynamics

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[1]. This protein has a dual activity with its functional domain dynamin-like GTPase. Furthermore MFN2 protein seems to play a role also in mitochondrial anterograde transport by binding the Miro 1-Milton complex [2]. Its principal function is to regulate the mitochondrial network architecture by mitochondrial fusion and to tether the endoplasmic reticulum and mitochondria to control the efficiency of mitochondrial uptake of Ca^{2+} ions [3]. Since 2004 *MFN2* mutations were commonly associated with an hereditary motor and sensory neuropathy also known as Charcot–Mari e–Tooth disease (CMT) type 2A (CMT2A) [1]. *MFN*2 mutations are associated with a wide phenotypic spectrum and may be responsible for CMT severe forms or more atypical signs such as optic atrophy, exceptionally spastic paraplegia, or alterations of the cerebral white matter too [4–6]. To date *MFN2* mutations account for 2–3% of CMT, and about 10–20% of patients with CMT2 [7].

CMT is the most common inherited polyneuropathy. Prevalence is estimated at 1 in 2500 individuals [8]. CMT2 is the axonal form and is rarer than the myelinic form. In Harding and Thomas' study [9], CMT2 patients represented about one third of all CMT cases. The diagnosis of CMT2 refers to a set of arguments: clinical findings, familial history and electrophysiological data. The phenotype is characterized by progressive peripheral motor and sensory neuropathy. Family history is mainly consistent with autosomal dominant [10] and, in few case, recessive inheritance. Electrophysiological studies [9] typically show axonal neuropathy and nerve conduction velocities within the normal range (>40–45 m/s) or at least greater than 38 m/s. Additional abnormalities can be observed on nerve conduction studies [11] such as polyphasic potentials, reduced amplitudes of evoked motor and sensory responses or greatly reduced compound motor action potentials and less frequently positive sharp waves and fibrillation potentials. CMT2 has been divided into many subtypes that are clinically similar but distinguished only by molecular genetics findings. Many genes among which *MFN*2 have been described on different loci associated with CMT2 (*GDAP*1, *PMZ*, *HSP27*...) [12].

Our study analyzes retrospectively 11 children from 6 families with *MFN*2 mutations associated to clinical different presentation.

2. Patients and methods

2.1. Patients

Between 1999 and 2012, the diagnosis of *MFN2* mutations was made in 11 children who were treated in our department. Most patients had chronic neurological symptoms but for 2 children the onset of disease was acute (cases D-II-1 and F-III-6). Five children, all from the same family previously described in Rouzier et al. [13], were originating from Tunisia (cases F-III-2, 3, 4, 5 and F-III-6). The others 6 children were from Caucasian origin.

2.2. Clinical assessment

Clinical data were collected by a pediatric neurologist or a specialist of physical and functional rehabilitation, who examined the children in the presence of their parents.

Neurological examination was standardized: it included analysis of deep tendon reflexes and sensory-motor skills. Muscle strength was assessed manually using a standard Medical Research Council scale. Severity of sensory-motor impairment was qualified using with the following score according and adapted from the CMT disease neuropathy score [14]. Because of the retrospective nature of the study, it was not possible to obtain all the information necessary to accurately calculate this composite score; furthermore for the same reason the CMT disease pediatric scale could not be used [15]. Motor parameters were evaluated at lower and upper limbs combining functional deficits and strength (abnormal foot conformation, manual dexterity, strength, vibration). Maximal score was 20; when orthopedic surgery or equipment was required, the motor impairment was noted as severe: 0 points patient was asymptomatic (0), from 1 to 5 points patient was mildly affected (1), from 6 to 10 points patients was moderately affected (2) and higher than 10 points patient presented severe symptoms (3). Sensory symptoms were evaluated in the same way.

2.3. Electrophysiological study

Compound muscle and sensory action potential amplitudes were obtained in the upper limbs. Testing was done outside the acute phase. The median nerve was explored, as our population was exclusively pediatric and because carpal tunnel syndrome is rare in children. Compound muscle and sensory action potential amplitudes were measured from the positive peak to the negative peak values: an amplitude below 3 mV was called "decreased". Three children (patients C-III-2, F-III-2 and F-III-5) did not have electrophysiological study performed.

2.4. Magnetic resonance imaging (MRI) study

Cerebral MRI was performed in 5 patients using a 1.5T system. For patient D-II-1 spinal MRI was performed in the same time. The imaging protocol consisted of T2-wheigted spin echo, diffusion tensor imaging, flair and fluid-attenuated inversion recovery.