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Case report

Adult course in dynamin 2 dominant centronuclear myopathy with neonatal onset

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ABSTRACT

We report a family with autosomal dominant centronuclear (myotubular) myopathy caused by a novel mutation, p.A618D, in dynamin 2 (*DNM2*). The 64-year-old mother and 26-year-old daughter had neonatal onset with hypotonia and weak suckling, followed by improvement, then slowly progressive muscle weakness and respiratory restriction. Muscle biopsy showed radial sarcoplasmic strands around the frequent central nuclei. Electrophysiology revealed predominantly myopathic patterns without peripheral nerve involvement. Centronuclear myopathy with neonatal onset caused by a DNM2 mutation in the C-terminal part of the pleckstrin homology domain may have a favorable prognosis and follow a course similar to adult-onset centronuclear myopathy. We advise respiratory follow-up in these patients.

1. Introduction

Centronuclear (myotubular) myopathy (CNM) is genetically and clinically heterogeneous [1]; X-linked inheritance is caused by myotubularin (*MTM1*) gene mutations [2–4], autosomal dominant inheritance is caused by heterozygous dynamin 2 (*DNM2*) gene mutations [5], and some cases with autosomal recessive inheritance are caused by amphiphysin 2 (*BINI*) gene mutations [6]. A *de novo* dominant mutation has been reported in the ryanodine receptor gene (*RYR1*) in one patient [7] and an inactivating variant in the hJUMPY phosphatase (*MTMR14*) gene has been characterized in another patient [8].

Mild and slowly progressive late-onset CNM is associated with mutations affecting the middle domain of *DNM2* [1,5,9,10] and more recently in the GTPase effector domain [11]. Heterozygous *de novo* mutations affecting the C-terminal part of the pleckstrin homology (PH) domain of *DNM2* have been associated with sporadic, more severe CNM with neonatal onset [12], while a mutation affecting the N-terminal part of the PH domain has been associated with CNM of intermediate severity [13]. Besides CNM, different mutations affecting the N-terminal part of the PH domain result in dominant intermediate Charcot-Marie-Tooth (CMT) type B and CMT2 [14–16].

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Here we present a mother and daughter with autosomal dominant CNM caused by a novel *DNM2* mutation in the C-terminal part of the PH domain. Although onset was in the neonatal period, the patients' condition improved and the course of the disease was mild with slowly progressive muscle weakness, indicating that autosomal dominant CNM may have neonatal onset and follow a course similar to that of the mainstream forms of congenital myopathies.

2. Case reports

The patients are of Swedish descent. The mother and one of her three daughters were affected. The clinical data are presented in Table 1. An asymptomatic daughter was examined and found to be healthy. There was no history of neuromuscular disease in the mother's parents, who were not available for study.

2.1. The mother

The mother was born at term. She gave a history of neonatal hypotonia, weak cry and suckling, and physical inactivity. She became cyanotic on suckling. Old hospital records were not available. The patient improved spontaneously and early psychomotor development was normal. She had congenital ptosis, for which she underwent repeated surgery from the age of 7 years. She was the slowest runner in her class. Progression of muscle weakness was slow and weakness was generalized; at the age of 64 years muscle strength was MRC grade 4 in limb muscles and grade 3 for foot extension. Ptosis and ophthalmoplegia were manifest. Dysarthria and dysphagia were not present. Tendon reflexes were absent. There were no sensory deficits. The patient had a jaw contracture, similar to that reported in another CNM patient [17]. She had a restrictive ventilatory defect and nocturnal assisted ventilation since the age of 64 years. Psychometric test results were normal. She has university education.

In the neurophysiological studies at the age of 44 years, neurography of motor and sensory nerves showed normal results, and compound muscle action potential (CMAP) amplitudes were just below the lower limits (1.5–2.7 mV). Sural nerve amplitudes were normal. EMG from the extensor digitorum communis, first dorsal interosseus, anterior tibial, and extensor digitorum brevis muscles showed fibrillation potentials and positive sharp waves, particularly in the leg muscles. Motor unit potentials (MUPs) were polyphasic and unstable and showed increased amplitudes in leg muscles. Interference pattern, quantified with the so-called turns/amplitude analysis at 20 different recording sites, gave normal results in the right anterior tibial muscle, but showed myopathic pattern in the extensor digitorum muscle. Overall, the EMG was interpreted as myopathic pattern in arm muscles, but normal or neurogenic in leg muscles.

Table 1
Summary of clinical data.

Characteristics	Mother	Daughter
DNM2 mutation, exon 16	p.A618D	p.A618D
Age at last examination	64 years	26 years
Neonatal period	Hypotonic, inactive Weak cry and suckling Congenital ptosis	Hypotonic, inactive Weak cry and suckling Nasogastric feed16 days
Psychomotor development	Normal	Normal
Ambulation	At 14–15 months, unaided	At 14–15 months, unaided
Course of weakness	Slowly progressive Ptosis, ophthalmoplegia Facial weakness Weak neck, trunk	Slowly progressive Asymptomatic ptosis Facial weakness Mildly weak neck, trunk
Muscle strength, MRC	Grade 3, foot extension Grade 4, otherwise Walks with aid, wheel-chair	Grade 4, proximal and distal limbs Walks unaided
Deep tendon reflexes	Absent	Absent
Sensation	Normal	Normal
Cataracts	No	No
Skeletal	Mild pes cavus Restricted jaw opening	Mild pes cavus
Ventilatory function	Age 44: FEV_1 61%, FVC 60% Restrictive defect Since age 64 Nocturnal CPAP	No respiratory symptoms FEV_1 41%, FVC 40% Restrictive defect
Electrocardiogram	Normal	Normal
EMG	Myopathic at age 44	Myopathic at age 24
Neurography	Normal	Normal
Serum CK (normal < 35 μkat/L)	0.4	0.7
Neutrophils (normal 1.3–5.4 × 10^9)	4.2	4.3
Lymphocytes (normal 0.7–3.9 × 10^9)	1.6	1.9
Erythrocytes (normal 3.9–5.1 × 10^{12})	4.95	4.57
Platelets (normal 150–350 × 10^9)	153	297

CPAP = continuous positive airway pressure, FEV = forced expiratory volume, FVC = forced vital capacity, % of normal value.

2.2. The daughter

The daughter was delivered at 39 weeks gestation after induction of labour, allegedly because of intrauterine growth retardation. Her Apgar scores were 9 at 1 min. and 10 at 5 min., birth weight 2.570 g, length 45 cm, and head circumference 33 cm. She had neonatal hypotonia, weak cry and suckling, and was physically inactive. Nasogastric feeding was necessary for 16 days and hospitalisation for 4 weeks. She improved spontaneously and early psychomotor development was normal. She was the slowest runner in her class. At the age of 26 years she had slight ptosis and muscle weakness of MRC grade 4 in proximal and distal limbs. Dysarthria and dysphagia were not present. Tendon reflexes were absent. There were no sensory deficits. There was a restrictive ventilatory defect. Psychometric test results were normal. The patient is a secondary school teacher.

In the neurophysiological studies at the age of 24 years, neurography of motor and sensory nerves was normal, but CMAP amplitudes were low in the tibial and peroneal nerves. Sensory amplitudes were normal. EMG showed increased numbers of short-duration low-amplitude MUPS, and spontaneous activity in distal muscles. The EMG showed myopathic patterns in arm and leg muscles, more evident in the lower limbs.

2.3. Muscle biopsies

Muscle biopsy specimens were obtained from the anterior tibial muscle in connection with neurophysiological studies. The specimens of both patients revealed predominance of type 1 fibers as common in anterior tibialis muscle (Fig. 1A). The fiber size variation was markedly increased with hypotrophic/atrophic and hypertrophic fibers of both fibers types (Fig. 1A–D). The nuclei were centrally placed in a great majority of both type 1 and 2 fibers (Fig. 1A–D). Several nuclei were enlarged with blurred borders (Fig. 1B). In many fibers the central nuclei were surrounded by accentuated nicotinamide adenine dinucleotide dehydrogenase–tetrazolium reductase (NADH–TR) staining with radially oriented sarcoplasmic strands (Fig. 1C and D). There was mild endomysial fibrosis and accumulation of fat (Fig. 1A and B).