Available online at www.sciencedirect.com

SciVerse ScienceDirect

Neuromuscular Disorders 23 (2013) 160–164

www.elsevier.com/locate/nmd

Case report

Congenital myopathy with focal loss of cross-striations revisited

N.C. Voermans [a,*], H. Jungbluth [b,c], E. Aronica [d], N. Monnier [e], J. Lunardi [e], M. Swash [f], M. de Visser [g]

[a] Department of Neurology, Radboud University Nijmegen Medical Centre, The Netherlands
[b] Department of Pediatric Neurology, Evelina's Children Hospital, London, United Kingdom
[c] Clinical Neuroscience Division, IOP, London, United Kingdom
[d] Department of (Neuro) Pathology, Academic Medical Centre Amsterdam, The Netherlands
[e] Laboratoire de Biochimie Génétique et Moléculaire and Centre de Référence des Maladies Neuro-Musculaires, CHU Grenoble, Grenoble, France
[f] Department of Neurology, Royal London Hospital, London, United Kingdom
[g] Department of Neurology, Academic Medical Centre Amsterdam, The Netherlands

Received 16 March 2012; received in revised form 11 August 2012; accepted 28 August 2012

Abstract

In 1977 Wijngaarden et al. reported a Dutch family with a congenital myopathy characterized by external ophthalmoplegia and a remarkable histological feature, focal loss of cross-striations. A small number of other families with similar clinical and pathological features led to the consideration of this congenital myopathy as a distinct entity. Here we present more than 30 years of follow-up from the Dutch family and report recently identified compound heterozygous mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene, c.10627-2A>G and p.Arg3539His (c.10616G>A). Focal loss of cross-striations on muscle biopsy is another histopathological feature that should raise the possibility of *RYR1* involvement.

Keywords: Congenital myopathy; Focal loss of cross striations; *RYR1*; Skeletal muscle ryanodine receptor; Central Core Disease (CCD); Multi-minicore Disease (MmD)

1. Introduction

The structural congenital myopathies are a genetically heterogeneous group of inherited neuromuscular disorders defined by distinct but non-specific structural abnormalities on muscle biopsy. Recent years have seen emerging evidence for remarkable overlap between entities previously considered distinct. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene in particular have recently emerged as one of the most common causes of structural congenital myopathies and have now been implicated in most major forms [1–4]. The spectrum of structural changes associated with *RYR1* mutations, especially those associated with recessive inheritance, is extremely wide and may comprise central cores, Multi-minicores, fibre type disproportion, central nuclei, and nemaline rods, either coexisting in the same muscle biopsy or sequentially evolving over time [3–9].

In addition to the major structural congenital myopathies – Central Core Disease (CCD), Multi-minicore Disease (MmD), Centronuclear Myopathy (CNM) and Nemaline Myopathy (NM) – a number of much rarer entities have been reported often concerning a limited number of families. In 1977 van Wijngaarden et al. reported a brother and a sister from a Dutch family with a congenital myopathy characterized by "focal loss of cross-striations" on muscle biopsy and external ophthalmoplegia as the

* Corresponding author. Address: Department of Neurology, 943, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243665094; fax: +31 243541122.
E-mail address: n.voermans@neuro.umcn.nl (N.C. Voermans).

0960-8966/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.nmd.2012.08.010

Table 1
Clinical and histological features.

	Patient 1	Patient 2
Pregnancy	Normal	Normal
Postnatal period	Floppy; normal feeding	Weak cry, difficulty raising the head; normal feeding
Motor development	Delayed; waddling gait; never been able to stand up from a supine position without the support of his hands; never been able to run. Intelligence normal	Slightly delayed: standing at 15 months and walking at 21 months. Intelligence normal
Physical examination in childhood	Age 6 years: • Reduced facial expression and mild nasal dysarthria • Severe paresis of the extraocular muscles • No ptosis • Generalized muscle weakness and atrophy (neck flexors, proximal limb muscles and the dorsal flexors of the feet) • Bell-shaped thorax and a marked lumbar hyperlordosis	Age 22 months: • Facial weakness • High-arched palate • No obvious paresis of the extraocular muscles • No ptosis • Great difficulty in standing up from a supine or sitting position • Marked weakness atrophy and of the shoulder and pelvic girdle muscles (at age of 3 years)
Follow-up in adulthood	Age 39 years: • Sedentary life and a job as a civil servant • Functional abilities: unable to climb stairs, walking limited to 10 m, not able to rise from a chair without support • Tall and slender, but well-developed calf muscles • Scoliosis with lumbar hyperlordosis and some rigidity of the cervical spine • Mild long finger flexion contractures • Pes cavus deformity with some Achilles tendon shortening • Elongated, myopathic face • High arched palate • Nearly complete external ophthalmoplegia with only little residual abduction • No ptosis • Neck flexors weakness (MRC 2) • Scapular winging • Proximal muscle weakness (MRC 2) • Distal muscle weakness (MRC 4)	Age 28 years (Fig. 1): • Desktop publisher • Functional abilities; able to ride a bike, walking limited to 100 m, difficulty rising from a chair • Very thin but well-developed calf muscles • Increased lumbar lordosis, pronounced thoracic kyphosis and generalized spinal rigidity • Hypermobility of elbow • Contracture of long finger flexors, Achilles tendon and of jaw muscles • Elongated, myopathic face • Nearly complete external ophthalmoplegia with only little residual abduction • No ptosis • Weakness and atrophy of sternocleidomastoid muscle • Scapular winging • Proximal muscle weakness (MRC 2) • Distal muscle weakness (MRC 4)
Lung function test	• Weak cough, but lung function test not performed recently	Age 29 and 36 years: • Vital capacity 2.07 L/min (58%)
Muscle biopsy (Light microscopy)	Age 6 years; (Fig. 2): • Increased variability in fibre size • Increase of internal nuclei • A moderate increase in endomysial fat but no proliferation of connective tissue • Fibre type 1 predominance • Central and peripheral areas with reduced oxidative activity; on longitudinal sections they often occupied the complete fibre diameter with an abrupt transition from the normal to the abnormal parts	Age 2 years: • Similar but less severe features as in her brother Age 34 years (Fig. 3): • Increase in connective and adipose tissue • Prominent diameter variability and increase in number of internal nuclei • Type 1 predominance • Unevenness of the staining with oxidative enzymes

most prominent clinical feature [10,11]. The main histopathological abnormality in this family was characterized by areas with reduced or absent oxidative stains often stretching the entire fibre diameter on longitudinal sections. On electron microscopy, oxidative stain abnormalities corresponded to areas with complete loss of normal sarcomeric organization clearly demarcated from the normal sarcomere. In 1981, Swash et al. reported a British family with identical clinical and pathological features, and suggested that these families, together with others previously reported, may represent a genetically distinct subgroup of congenital myopathy [2,10–13], although some overlap