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Congenital myopathies – Clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom

L. Maggi [a,b], M. Scoto [a], S. Cirak [a], S.A. Robb [a], A. Klein [a,c], S. Lillis [d], T. Cullup [d], L. Feng [a], A.Y. Manzur [a], C.A. Sewry [a,e], S. Abbs [d], H. Jungbluth [f,g,1], F. Muntoni [a,*,1]

[a] *Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital for Children Foundation Trust, London, UK*
[b] *Carlo Besta Neurological Institute, Neuromuscular Diseases Unit, Milan, Italy*
[c] *Paediatric Neurology, University Children's Hospital Zurich, Switzerland*
[d] *Diagnostics Genetics Laboratory, GSTS Pathology, Guy's Hospital, London, UK*
[e] *Centre for Inherited Neuromuscular Diseases, RJAH Orthopaedic NHS Foundation Trust, Oswestry, SY10 7AG, UK*
[f] *Clinical Neuroscience Division, IOP, King's College, London, UK*
[g] *Evelina Children Hospital, Department of Paediatric Neurology – Neuromuscular Service, London, UK*

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Abstract

The congenital myopathies are a group of inherited neuromuscular disorders mainly defined on the basis of characteristic histopathological features. We analysed 66 patients assessed at a single centre over a 5 year period. Of the 54 patients where muscle biopsy was available, 29 (54%) had a core myopathy (Central Core Disease, Multi-minicore Disease), 9 (17%) had Nemaline Myopathy, 7 (13%) had Myotubular/Centronuclear Myopathy, 2 (4%) had Congenital Fibre Type Disproportion, 6 (11%) had isolated type 1 predominance and 1 (2%) had a mixed Core–Rod Myopathy. Of the 44 patients with a genetic diagnosis, *RYR1* was mutated in 26 (59%), *ACTA1* in 7 (16%), *SEPN1* in 7 (16%), *MTM1* in 2 (5%), *NEB* in 1 (2%) and *TPM3* in 1 (2%). Clinically, 77% of patients older than 18 months could walk independently. 35% of all patients required ventilatory support and/or enteral feeding. Clinical course was stable or improved in 57/66 (86%) patients, whilst 4 (6%) got worse and 5 (8%) died. These findings indicate that core myopathies are the most common form of congenital myopathies and that more than half can be attributed to *RYR1* mutations. The underlying genetic defect remains to be identified in 1/3 of congenital myopathies cases.

Keywords: Congenital myopathies; RYR1; Core myopathy; Muscle ultrasound; NEB; MTM1; SEPN1; ACTA1; TPM3

1. Introduction

Congenital myopathies (CM) are a group of inherited neuromuscular diseases with early onset, mainly defined by the predominant histopathological features which include central cores, multiple minicores, nemaline rods and central nuclei [1,2]. Based on these features, individual congenital myopathies such as Central Core Disease (CCD) [3], Multi-minicore Disease (MmD) [4], Nemaline Myopathy (NM) [5] and Centronuclear Myopathy (CNM) [6] were reported in the 1950s and 1960s. However, with recent molecular genetic advances it has become increasingly obvious that different genetic CMs can share pathological findings, complicating the correlation between pathological diagnosis and genetic findings. Moreover, it has become equally clear that many individuals with a genetically confirmed CM have only non-specific histopathological features.

* Corresponding author. Address: Dubowitz Neuromuscular Centre, UCL Institute of Child Health, 30 Guilford St., London WC1N 1EH, England, UK.
E-mail address: f.muntoni@ucl.ac.uk (F. Muntoni).
[1] These authors contributed equally.

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The frequency of single CMs entities is not known. Epidemiological data in the literature are scarce and either focused on single CMs subgroups or limited to geographical regions [7–9]. Whilst some of these studies have suggested NM as the most frequent CM [10,11], two recent studies indicate CCD [12] and other forms related to mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene as the most common subgroup [9]. The true prevalence of CMs is likely to be underestimated, due to a substantial proportion of patients with mild clinical and/or non-specific histopathological features, or at the other end early fatal variants, and the complexity of systematically studying all CMs genes, which include some of the largest genes involved in neuromuscular disorders.

The primary goal of the present study was to establish relative frequencies of individual CMs variants, classified according to the predominant histopathological feature and, where available, genetic diagnosis. The secondary goal was to evaluate the clinical profiles of the CMs cases assessed at our centre.

2. Patients and methods

2.1. Patients

We studied retrospectively the clinical, histological and genetic data of 66 patients affected with CM who had been referred to the Dubowitz Neuromuscular Centre in London, UK, during the years 2005–2009. The Dubowitz Neuromuscular Centre is nationally commissioned by the United Kingdom National Health Service to assess and diagnose patients from England, Northern Ireland and Scotland affected by congenital muscular dystrophies and congenital myopathies. Patients can be referred for clinical assessment, or the referring clinician can forward muscle biopsies and/or DNA for further testing. The Diagnostic DNA Laboratory at Guy's Hospital, affiliated to the Centre, offers genetic screening of most of the currently known CMs genes.

We included only patients who had been clinically assessed at the Dubowitz Neuromuscular Centre and for whom a diagnosis of CM could be established, based on clinical features and the presence of suggestive histopathological features, an established genetic diagnosis or an affected relative. The clinical diagnosis of a congenital myopathy was made in individuals with essentially static weakness, affecting predominantly proximal and axial muscles, often of congenital or early childhood onset, with normal or mildly elevated serum CK, and in whom other conditions such as muscular dystrophies, myofibrillar myopathies, congenital myasthenic syndromes and neurogenic conditions had been excluded by the appropriate investigations. The pathological categories considered were those related to the predominance of specific structural changes according to criteria suggested by Dubowitz and Sewry [2] and included congenital myopathies (i) with cores (core myopathies) (Central Core Disease, CCD, and Multi-minicore Disease, MmD), (ii) with central nuclei (Centronuclear Myopathy, CNM), (iii) with nemaline rods (Nemaline Myopathy, NM), (iv) fibre type disproportion (Congenital Fibre Type Disproportion, CFTD). We also included patients with (v) type 1 fibre predominance or uniformity, as this abnormality has previously been associated with mutations in CMs genes, and (vi) mixed structural pathological features, for example a combination of cores and rods.

2.2. Muscle imaging

Muscle ultrasound was performed with a 7.5 MHz PVG 7205 transducer (Toshiba CAPASEE II) for qualitative assessment of the lower limb muscles, mainly the quadriceps, the calves, and in some cases the upper limb muscles, mainly the deltoid, biceps and triceps brachii muscles. The examination was considered abnormal in the presence of increased and/or reduced muscle volume and/or abnormal muscle echogenicity, according to criteria proposed by Heckmatt et al. [13,14].

2.3. Muscle biopsy

Skeletal muscle biopsies were investigated according to standard histopathological and immunohistochemical procedures and reviewed by one of the authors (CAS) [2]. Fibre typing was demonstrated by immunolabelling of fast and slow isoforms of myosin heavy chain. Analysis by electron microscopy was used in selected cases to characterize better certain structural abnormalities, in particular rods and cores [2].

2.4. Molecular genetic studies

Genomic DNA was extracted from peripheral blood leukocytes according to standard procedures and the PCR-amplified exons of the genes investigated were sequenced from genomic DNA. The following genes were analysed based on their recognised involvement in the CMs: skeletal muscle ryanodine receptor (RYR1) gene, selenoprotein N (SEPN1) gene, skeletal muscle alpha actin (ACTA1) gene, tropomyosin 2 (TPM2) gene, tropomyosin 3 (TPM3) gene, myotubularin (MTM1) gene, amphiphysin 2 (BIN1) gene and dynamin 2 (DNM2) gene. One patient had a deletion in MTM1 gene detected by MLPA (multiplex ligand-dependent probe amplification) (SALSA MLPA kit P309-A1 MTM1, MRC, Holland) not further investigated. Considering the large size of the gene, for nebulin (NEB) we screened only for the common c.7431+1916_7536+372del of intron 54 and exon 55. Analysis of the rest of the gene is not available as yet in an accredited UK laboratory. The choice of specific genetic tests was mainly informed by the presence of suggestive clinical and histopathological