Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 24 (2014) 97–116

www.elsevier.com/locate/nmd

Approach to the diagnosis of congenital myopathies ☆

Kathryn N. North [a,b,*], Ching H. Wang [c], Nigel Clarke [b], Heinz Jungbluth [d,e,f], Mariz Vainzof [g], James J. Dowling [h], Kimberly Amburgey [h], Susana Quijano-Roy [i], Alan H. Beggs [j], Caroline Sewry [k,l], Nigel G. Laing [m], Carsten G. Bönnemann [n], Members of the International Standard of Care Committee for Congenital Myopathies

[a] *Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, Victoria 3052, Australia*
[b] *Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, University of Sydney, Sydney, Australia*
[c] *Driscoll Children's Hospital, Corpus Christi, TX, United States*
[d] *Evelina Children's Hospital, Department of Paediatric Neurology, London, United Kingdom*
[e] *Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, King's College, London, United Kingdom*
[f] *Clinical Neuroscience Division, IoP, London, United Kingdom*
[g] *Human Genome Research Center, University of Sao Paulo, Sao Paulo, Brazil*
[h] *Division of Neurology, Department of Paediatrics, Hospital for Sick Children, Toronto, ON, Canada*
[i] *Department of Pediatrics, Garches Neuromuscular Reference Center (GNMH), APHP Raymond Poincare University Hospital (UVSQ), Garches, France*
[j] *Children's Hospital Boston, Boston, MA, United States*
[k] *Dubowitz Neuromuscular Centre, London, United Kingdom*
[l] *Wolfson Centre of Inherited Neuromuscular Diseases, RJAH Orthopaedic Hospital, Oswestry, United Kingdom*
[m] *Centre for Medical Research, University of Western Australia and Harry Perkins Institute of Medical Research, QQ Building, QEII Medical Centre, Nedlands, Western Australia 6009, Australia*
[n] *Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD, United States*

Received 12 August 2013; received in revised form 6 November 2013; accepted 8 November 2013

Abstract

Over the past decade there have been major advances in defining the genetic basis of the majority of congenital myopathy subtypes. However the relationship between each congenital myopathy, defined on histological grounds, and the genetic cause is complex. Many of the congenital myopathies are due to mutations in more than one gene, and mutations in the same gene can cause different muscle pathologies. The International Standard of Care Committee for Congenital Myopathies performed a literature review and consulted a group of experts in the field to develop a summary of (1) the key features common to all forms of congenital myopathy and (2) the specific features that help to discriminate between the different genetic subtypes. The consensus statement was refined by two rounds of on-line survey, and a three-day workshop. This consensus statement provides guidelines to the physician assessing the infant or child with hypotonia and weakness. We summarise the clinical features that are most suggestive of a congenital myopathy, the major differential diagnoses and the features on clinical examination, investigations, muscle pathology and muscle imaging that are suggestive of a specific genetic diagnosis to assist in prioritisation of genetic testing of known genes. As next generation sequencing becomes increasingly used as a diagnostic tool in clinical practise, these guidelines will assist in determining which sequence variations are likely to be pathogenic.

Keywords: Congenital myopathy; Diagnosis; Guidelines

* Corresponding author at: Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, Victoria 3052, Australia. Tel.: +61 3 8341 6226; fax: +61 3 9348 1391.
E-mail address: kathryn.north@mcri.edu.au (K.N. North).

0960-8966/$ - see front matter © 2013 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.nmd.2013.11.003

1. Introduction

The congenital myopathies are a group of genetic muscle disorders characterised clinically by hypotonia and weakness, usually from birth, and a static or slowly progressive clinical course. Historically the congenital myopathies have been classified on the basis of the major morphological features seen on muscle biopsy – e.g., rods (nemaline myopathy), cores (central core disease and multiminicore disease), central nuclei (centronuclear/myotubular myopathy) and selective hypotrophy of type 1 fibres (congenital fibre type disproportion). Over the past 15 years, the genetic basis of many of the different forms of congenital myopathy has been identified – although it is evident that there are still many additional genes to be discovered. The relationship between each congenital myopathy, defined on histological grounds, and the genetic cause is complex for a number of reasons:

(1) Many of the congenital myopathies can be caused by mutations in more than one gene (genetic heterogeneity). For example, there are currently eight known genetic loci for nemaline myopathy.
(2) Mutations in the same gene can cause different muscle pathologies. For example, mutations in α-skeletal actin can result in nemaline myopathy [1,2], intranuclear rod myopathy [3], actin accumulations [4], congenital fibre type disproportion (CFTD) [5], cap disease [6], and zebra body myopathy [7].
(3) There are examples of the same genetic mutation leading to different pathological features in members of the same family or in the same individual at different ages. Notably, this has been demonstrated for mutations in the ryanodine receptor gene (*RYR1*) and has been reproduced in a mouse model of a *RYR1* mutation [8].

In this overview, we will provide an approach to the diagnosis of congenital myopathies and a guide to identifying the genetic basis for an individual patient based on clinical clues, muscle imaging (MRI) and histological features on muscle biopsy. It is acknowledged that the increasing use of exome, targeted sub-exomic and whole genome sequencing as a diagnostic tool in clinical practise is likely to reduce the need for muscle biopsy as a first line investigation. However a systematic approach to clinical diagnosis will remain essential in the initial assessment of patients and their families, and in the interpretation of sequencing results to determine which changes are likely to be pathogenic.

2. Approach to developing this consensus statement

We initially performed a literature review and consulted a group of experts in the field of congenital myopathies to describe:

(1) the key clinical features common to all forms of congenital myopathy that help to differentiate them from other causes of muscle hypotonia and weakness and
(2) the specific clinical features, muscle MRI findings and pathological changes that help to discriminate between the different genetic subtypes for each of the congenital myopathies that may assist in prioritizing diagnostic testing (a "syndromic approach" to diagnosis).

We divided the phenotypic descriptions into two age-groups to reflect the different combinations of signs the clinician is likely to be confronted with at the initial evaluation of an infant or an older patient.

To complement the "expert" opinion, we developed a questionnaire that was circulated to a wider group of clinicians who care for patients with neuromuscular disorders. The questionnaire focused on the features that clinicians consider specific to congenital myopathies (or were useful to exclude potential differential diagnoses), as well as the phenotypic features that distinguished the different subtypes. In addition, we surveyed current clinical practise and access to specific investigations e.g., electron microscopy, muscle MRI, genetic testing.

This final "consensus" document combines the information obtained by both approaches and will focus on the following major forms of congenital myopathy:

- Nemaline myopathy (including cap disease and zebra body myopathy and core-rod myopathy since these appear to be pathological variants of nemaline myopathy).
- Core myopathies (including central core disease and multi-minicore disease).
- Centronuclear myopathies.
- Myosin storage myopathy (also known as hyaline body myopathy).
- Congenital fibre type disproportion.

We have specifically excluded three disorders that have historically been grouped with the congenital myopathies but which we no longer consider appropriate to be classified in this way.

(1) Sporadic adult onset nemaline myopathy has a late onset and rapidly progressive course. It is unclear whether this entity has a genetic basis and some cases are associated with a monoclonal gammopathy.
(2) Spheroid body myopathy and sarcotubular myopathy due to mutations in *TRIM32* and myotilin (*MYOT*) should be classified with the limb girdle muscular dystrophies and myofibrillar myopathies respectively.
(3) Reducing body myopathy due to mutations in *FHL1* has a rapidly progressive, severe course that is atypical of a true congenital myopathy.