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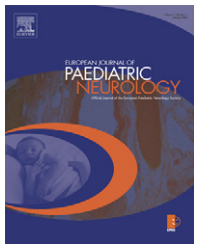

Original article

Differential diagnosis of congenital muscular dystrophies

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ABSTRACT

Congenital muscular dystrophies (CMDs) are defined by signs of muscle weakness in the first 6 months of life with myopathic changes in muscle biopsy. The progress in the last decade has helped to make molecular and genetic diagnoses in the majority of patients fulfilling these criteria. In a number of patients a definite diagnosis cannot be reached and these individuals are often grouped together as "merosin positive" congenital muscular dystrophy. In the last 5 years, 25 patients referred for assessment as possible congenital muscular dystrophy have been found to have alternative diagnoses. This paper aims to highlight these conditions as the common differentials or more difficult to diagnoses to consider in patients presenting as CMD.

1. Introduction

Congenital muscular dystrophies (CMD) are a heterogeneous group of disorders characterised by muscle weakness in the first months of life and muscle biopsy changes that range from myopathic to overtly dystrophic depending on the muscle biopsied and the age at biopsy.

Distinctive clinical features and immunohistochemical studies can often help to direct genetic testing and to diagnose a specific form of CMD but despite the molecular advances that have allowed the identification of 13 genetically distinct forms of CMD[1–3] there remain a number of patients that fulfill the criteria for CMD in whom all known variants can be excluded. In some of these cases, a definitive diagnosis may not be reached and the question arises as to whether, despite the early weakness and pathological changes on muscle biopsy, they might be affected by a condition other than CMD.

Muscle biopsy may help in such cases; histological findings such as cores or rods may indicate a diagnosis of congenital myopathy rather than CMD. In other cases however, early clinical and biopsy findings may not be indicative of a specific alternative diagnosis.

Hammersmith Hospital is commissioned by the National Commissioning Group (NCG) for the diagnosis and management of CMD and congenital myopathies in the UK. In the last 5 years, in excess of 400 patients were referred to this quaternary service with the possible diagnosis of CMD. In the majority of these cases, an integrated approach combining clinical and pathological findings and screening of the known CMD genes has enabled a precise diagnosis to be reached. In a number of other cases, review of the clinical and

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pathological findings has suggested alternative diagnoses that clinically overlap with CMDs. In this paper, we want to draw attention to these cases discussing the more common conditions that mimic CMD but also highlighting the rarer diagnoses that were more difficult to make.

2. Methods

This was a retrospective study of patients reviewed by Hammersmith NCG CMD service in the last 5 years. Criteria for inclusion in this review were either (1) new referrals of 'possible CMD' with myopathic or dystrophic features on muscle biopsy and no specific findings suggesting a structural congenital myopathy or (2) follow-up patients with a diagnosis of "merosin positive" CMD in whom the genetically known forms of CMD had been excluded.

From this cohort, we selected the patients in whom a diagnosis other than CMD was reached. Patients with congenital myotonic dystrophy were not included in this study.

The clinical notes of these patients were reviewed to obtain a clear picture of presentation, muscle biopsy findings, evolution and complications.

3. Results

In the past 5 years, in excess of 400 patients had been referred or were followed at the Hammersmith as part of the NCG service. Of this group, 25 patients were found to have diagnosis other than CMD. A total of 13 different diagnoses were reached in those 25 patients. The largest groups consist of early and severe presentation of known muscular dystrophies ($n = 5$) or congenital myopathies with atypical pathological features ($n = 3$), neurogenic disorders ($n = 5$) and metabolic ($n = 5$) or syndromic disorders ($n = 7$).

Ten of these patients had concomitant CNS involvement and/or multisystemic involvement.

Table 1 summarises the clinical details of all patients, including presentation and additional features that helped to make the diagnosis. Table 2 describes the evolution of clinical signs and complications.

Muscle biopsy findings ranged from unspecific myopathic changes to overtly dystrophic. In the few cases where specific features led to the diagnosis, more details will be provided in the text.

3.1. *Other muscular dystrophies with early onset*

Four patients were found to have a de novo mutation in the Lamin A/C gene.

They presented between the ages of 4 weeks and 5 months with axial weakness, lack of head control, proximal weakness affecting the arms more than the legs and bilateral talipes in one case. In some there was a reduced muscle bulk predominantly affecting the biceps and the calf muscles. They did not have prominent facial weakness and feeding difficulties were not a presenting feature. Their CK was between 600 and 1291 U/l.

On follow-up they all developed early flexion contractures, rigidity of the spine and scoliosis. Respiratory involvement led to early nocturnal hypoventilation and one patient presented with cardiac arrhythmia at age 3 years during general anaesthesia. None had a cardiomyopathy in infancy. All had progressive weakness, one child died suddenly at the age of 3 years during a respiratory tract infection and only one child achieved independent walking with knee–ankle–foot orthosis (KAFOs), but lost it at age 4 years. One patient has been previously reported.[4]

One child was diagnosed with de novo Facio Scapulo Humeral (FSH) muscular dystrophy. He presented at birth with facial weakness and feeding difficulties. At the age of 3 months, he had lack of head control, marked shoulder weakness, absent facial expression and absent tendon reflexes.

On follow-up he had achieved independent walking, subsequently lost at the age of 5 years, required a gastrostomy at age 4 years, and noninvasive nocturnal ventilation at age 6 years. Contractures other than TA tightness were not a feature. In addition to his muscular weakness he had learning difficulties, hearing impairment and myopia.

3.2. *Congenital myopathies*

Three patients were diagnosed as affected by core myopathies and were found to have a de novo mutation of the muscle Ryanodine Receptor gene (*RYR1*). They presented at birth with proximal weakness, contractures, normal CK and absent tendon reflexes. They had a clearly dystrophic pattern on muscle biopsy; in two patients occasional cores were seen. Weakness was more predominant in the lower limbs and there was mild facial weakness in one. On follow-up one died in the first 3 weeks of life, the others achieved walking in KAFOs one independently, one with the help of a walker. These two patients had predominant weakness of the lower legs and developed a scoliosis at the age of 3 years.

3.3. *Congenital spinal muscular atrophy (SMA) with predominant lower limb involvement*

Four patients had congenital SMA with predominant lower limb involvement. They all presented arthrogryposis at birth with a distinctive pattern of joint involvement, which was restricted to the lower limbs, short legs and weakness of the lower limbs. They had normal CK. In these patients early muscle biopsies of the quadriceps showed a marked increase of fat, reduced variability in fiber size and predominance of type I fibers that were reported as indicative of a myopathic pattern. On review of the muscle biopsy there was a suggestion of fibre grouping although this was difficult to appreciate because of the type I fibre predominance. Two of the four had neurogenic electro myography findings (EMG) later in life. One of them had a positive family history suggesting a dominant disorder with foot deformities, distal weakness with peroneal wasting and a relatively stable course, myopathic changes in muscle biopsy but a neurogenic pattern in EMG with normal nerve conduction studies (NCV and CMAP). The index patient also had a congenital onset with talipes and dislocated hips but had more severe