

EARLY ONSET AUTOSOMAL DOMINANT PROGRESSIVE MUSCULAR DYSTROPHY PRESENTING IN CHILDHOOD AS A BECKER PHENOTYPE—THE IMPORTANCE OF DYSTROPHIN AND MOLECULAR GENETIC ANALYSIS*

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Abstract—We present two cases of autosomal dominant limb girdle muscular dystrophy in a father and son. Both presented in childhood with a classical Becker muscular dystrophy phenotype. The father had initially been informed that he would not have affected children. After the diagnosis of muscular dystrophy in the son, immunoblot analysis was performed on muscle and revealed normal dystrophin. The polymerase chain reaction did not show any deletions in the dystrophin gene, and the father's dystrophin gene was not passed to his son. These cases demonstrate that autosomal dominant muscular dystrophy may present in childhood, and that dystrophin and molecular genetic analyses should be performed when considering the diagnosis of childhood muscular dystrophy, even in the presence of a classical phenotype.

Key words: Autosomal dominant muscular dystrophy, dystrophin.

INTRODUCTION

The limb girdle syndromes are a heterogeneous group of disorders characterized by muscle weakness, which predominantly affects proximal limb and girdle muscle. An autosomal dominant limb girdle muscular dystrophy has been described, but it is uncommon, and usually has an adult onset [1]. We report two cases in a father and son who presented in early childhood with a classical Becker muscular dystrophy (BMD) phenotype, including calf hypertrophy and grossly elevated creatine kinase (CK) levels, and demonstrate the importance of dystrophin and molecular genetic analyses in the differential diagnosis of childhood muscular dystrophy.

CASE REPORTS

The father presented at age 3 yr with difficulty with running. Subsequently he was reported to

have proximal muscle weakness, toe walking, heel cord contractures, prominent calves and wasting of pelvifemoral and scapular distribution. At age 13 yr, an EMG showed a myopathic pattern and the serum CK was 4400 iu (10–90). Muscle biopsy at age 18 yr from the left quadriceps muscle, revealed a wide variation in fiber size, degeneration and regeneration of muscle fibers, fiber splitting and interstitial fibrosis (Fig. 1). Routine histochemistry showed poor differentiation of fiber type, and no evidence of the defects found in the congenital structural myopathies. Family history was negative for neuromuscular disease and close female relatives had normal examinations and serum CK values. Muscle weakness progressed and he became wheelchair bound at age 30 yr. A diagnosis of BMD was made, and he was advised that he would not have clinically affected sons, although his daughters might be carriers. Neurological examination (GM) at age 34 yr showed normal higher mental functions, cranial nerves, eye movements, coordination and sensation. There was no facial weakness. Wasting was present in the shoulder and pelvic girdle, deltoid and quadriceps muscles. Muscle power was MRC grade 3 in the neck flexors and extensors; 2 in the

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Fig. 1. Muscle biopsy of father at age 18 yr showing wide variation in fiber size; internal nuclei, fiber splitting, myophagocytosis, and interstitial fibrosis. Hematoxylin and eosin stain $\times 125$.

trunk; and 2 or 3 in the scapular, pelvic and proximal limb muscles. Distal muscles were grade 3 or 4. Deep tendon reflexes were diminished, and greatest at the ankles. Contractures were absent (Achilles tendon lengthening had been performed). An electrocardiogram showed mild right ventricular hypertrophy, but there was no evidence of cardiomyopathy on the echocardiogram. It was uncertain whether the presence of the patient's extreme obesity contributed to his electrocardiographic change.

The son presented at age 6 yr with toe walking, a waddling run, and calf muscle cramps on exercise which were relieved by rest. Serum CK was 12,700 iu (20–180). Muscle biopsy from the right quadriceps revealed variation in fiber size, round atrophic fibers, occasional myophagocytosis, and mild interstitial fibrosis (Fig. 2). Routine histochemistry was normal. On neurologic examination there was mild proximal muscle weakness, heel cord contractures and enlarged calves. Otherwise the examination was normal. An electrocardiogram and echocardiogram were normal.

Neither muscle biopsy contained internalized capillaries, and examination of a blood smear did not demonstrate the Pelger–Huet anomaly.

Dystrophin analysis

Muscle dystrophin content was determined by

Western blot analysis followed by densitometry and expressed as a percentage of adjacent control samples. The antibodies used were affinity purified sheep anti-dystrophin antibodies derived from 60 kDa fusion proteins and used at a 1/1000 working dilution. Abundance of myosin was assessed by examining Coomassie blue stained post-transfer gels. Western blots were performed as described by Hoffman *et al.* [2]. The muscle biopsy from both father and son contained dystrophin indistinguishable from normal quantity (abundance) and quality (molecular weight).

Molecular genetic analysis

Deletion analysis of the dystrophin gene was performed by the polymerase chain reaction (PCR) on samples from the parents and child as described using the primers of Chamberlain *et al.* [3], and Beggs *et al.* [4]. In addition, new primers for exons 16, 32, 34, 41 and 42 were used. To ascertain whether there were any dystrophin gene abnormalities, PCR-based deletion analysis was performed using primers that amplified a total of 23 exons. No abnormalities were detected, which was consistent with the findings of normal sized dystrophin by Western blot analysis. This deletion analysis leaves open the possibility of a father-to-son transmission (e.g. by uniparental disomy for sex chromosomes) of a



Fig. 2. Muscle biopsy of son at age 6 yr showing mild variation in fiber size and mild interstitial fibrosis. Hematoxylin and eosin stain $\times 320$.

point mutation of the dystrophin gene that affects function without otherwise altering the size or quantity of the protein. Although this is an unlikely cause for father-to-son transmission of an X-linked disease, it has been reported for hemophilia A [5]. To rule this out, we examined the inheritance of a polymorphic CACA repeat in the 3' untranslated region of the dystrophin gene [6]. The father's dystrophin gene was not passed on to his son. There is the remote possibility that the mother was a Becker carrier of a point mutation which produced dystrophin of normal size and quality. There is no precedent for this in the literature, and its occurrence here is highly unlikely.

DISCUSSION

The findings in our cases are consistent with a clinical diagnosis of BMD. The onset was in early childhood and manifested by toe walking, heel cord contractures, progressive proximal muscle weakness, calf hypertrophy, a dystrophic myopathy, and grossly elevated CK levels more than 40 times the normal. An autosomal recessive limb-girdle muscular dystrophy might have been diagnosed in the father when he initially presented. However, we have demonstrated by dystrophin and molecular genetic analyses that

our patients do not have a dystrophinopathy and that the inheritance pattern and clinical features are consistent with an autosomal dominant progressive limb-girdle muscular dystrophy. Our patients' distribution of weakness, CK levels and electrical muscle activity, clearly differentiate them from other forms of autosomal dominant muscular dystrophy such as facioscapulo-humeral dystrophy, myotonic dystrophy and humeroperoneal myopathy with early elbow contractures. There is a remote possibility that the father has classical autosomal recessive limb-girdle muscular dystrophy, and the mother is a carrier, but this is unlikely.

Autosomal dominant limb-girdle muscular dystrophy is rare and usually has an adult onset. Gilchrist *et al.* [1] described 16 cases in a large multigeneration family, whose clinical onset was in the third decade. All affected members had absent ankle jerks, some had dysarthria, and 3 cases had facial weakness. The highest CK levels were less than 10 times normal. Other reports have described similar patients with normal or mild elevations of serum CK levels, and a slowly progressive proximal dystrophic myopathy of adult onset [7, 8]. In one of these reports an associated Pelger-Huet anomaly was described which was seen in 80% of the neutrophils of several of the affected patients in a large kindred

[6]. Our cases did not show this anomaly. Autosomal dominant limb-girdle muscular dystrophy presenting in childhood is even less common than the adult onset form, and can be easily mistaken for autosomal recessive limb-girdle or Becker muscular dystrophy. Only a few cases have been reported [9, 10] and these resemble our patients, as most presented in childhood with toe walking, calf hypertrophy and progressive proximal muscle weakness. None demonstrated the grossly elevated CK values we found, and in one report central cores and internalized capillaries were seen in type 1 fibers, which we did not observe.

Our findings support those of others [11] who report that manifesting carriers of Duchenne muscular dystrophy, limb-girdle muscular dystrophy, and BMD, cannot necessarily be differentiated on the basis of clinical and pathologic criteria, and that dystrophin and molecular genetic analyses are required. Furthermore, an early childhood onset does not distinguish between the autosomal dominant and recessive forms of limb-girdle muscular dystrophy.

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