# Dystrophinopathies

# 17

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## 17.1 Introduction and Classification

Duchenne muscular dystrophy (DMD, OMIM #310200) and Becker muscular dystrophy (BMD, OMIM #300376) are also referred to as the dystrophinopathies and are among the most common and best characterized forms of muscular dystrophy worldwide, with DMD affecting one in 3,500 newborn males.

### 17.1.1 Synonyms, Abbreviations

Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD).

## 17.2 Genetics and Pathophysiology

Dystrophinopathies have an X-linked recessive mode of inheritance, distinguishing them from the large group of autosomal recessive and dominant limb girdle muscular dystrophies (LGMDs), which also present with progressive weakness and wasting of the pelvic and shoulder girdle muscles. Although the majority of DMD and BMD cases are transmitted in an X-linked manner, with a positive family history or a known carrier status in the mother, approximately 30 % result from a de novo mutation. The dystrophin protein is encoded by the largest gene described to date, spanning 2.5 million bp of genomic sequence on the X chromosome (Xp21.2-p21.1). Mutations that result in the absence or severe reduction of the dystrophin protein generally manifest as DMD, whereas a less severe reduction and/or expression of an internally truncated, semifunctional protein generally manifests as BMD. The size of the mutation is not the determining factor in severity, but the type of mutation and location can be. Deletions, duplications and missense mutations that interrupt the reading frame generally lead to DMD, whereas in-frame mutations generally lead to the less severe BMD phenotype. There are exceptions to these rules, however, and further research is ongoing to identify possible modifier genes. Dystrophin is organized into four domains: amino-terminal actin-binding domain; central rod domain; cysteine-rich domain; carboxyl-terminal domain. The localization of the deletions has shown that the amino-terminal, cysteine-rich and carboxyl terminal domains are essential for dystrophin function, whereas the central rod domain can accommodate large in-frame deletions.

Approximately 65 % of the mutations in the dystrophin gene are caused by intragenic deletions and

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the remaining 35 % of the mutations are caused by duplications and point mutations. Although deletions can occur anywhere in the dystrophin gene, deletion hotspots are located in the central part of the 79 exons comprising the gene.

In skeletal muscle tissue, the dystrophin protein is integral to the stability of the myofibers. Dystrophin is expressed as a 427-kDa protein that consists of two apposed globular heads with a flexible rod- shaped center. It forms part of the dystrophin glycoprotein complex (DGC), which works as a transmembrane linkage between the extracellular matrix and the cytoskeleton. Mutations of the dystrophin gene result in disruption of the normal stability of the DGC, resulting in increased susceptibility to loss of cytoskeletal and sarcolemmal integrity. It is believed that this structural defect gives rise to a further misregulation of mainly calcium ionsand increased production of reactive oxygen species (ROS), which can cause further protein and membrane damage. Increased ROS is also a sign of altered mitochondrial function which leads to reduced muscular energy production.

## 17.3 Clinical Presentation

Patients with DMD tend to show their first symptoms at 3–5 years of age (Fig. 17.1). The initial presentation may include signs of delayed motor milestones or even a global developmental delay, isolated speech delay, a waddling gait, calf hypertrophy and increased frequency of falling. Boys tend to run more slowly than their peers. Sometimes elevated liver enzymes are a first misleading finding. Hence the serum creatine kinase (CK) activity and the γ-glutamyl transferase level should therefore always be checked prior to a liver biopsy in a boy with developmental delay.

Generally young boys with DMD develop a waddling gait often accompanied by toe walking and tight Achilles tendons. Hypertrophy of the calf and other muscles can also be seen, including forearm muscles and less commonly the tongue. At first presentation, the serum CK is often elevated 10–100 times of the normal upper limit. As the disease progresses weakness increases in the proximal muscles, initially the lower limb muscles but eventually involving the neck flexors, shoulders and arms. Difficulty climbing stairs is often seen at 8–10 years of age, and loss of ambulation occurs between 10 and 15 years. The clinical course has become more variable since steroid treatment was introduced. Once ambulation has been lost there is often a steady decline in respiratory function with many of these boys requiring nocturnal ventilation in their late teens/early twenties. Scoliosis or kyphoscoliosis may progress or develop once a boy is non-ambulant and wheelchair-bound. This situation, in turn, contributes to further decline in respiratory function and compromised gastrointestinal function. Cardiomyopathy develops later in

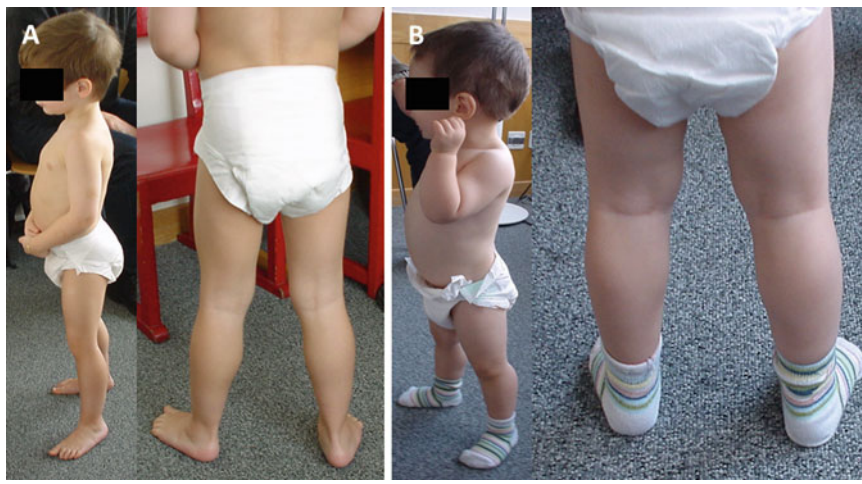


**Fig. 17.1** Clinical findings in Duchenne muscular dystrophy. (**a**) DMD patient at disease onset (age of 3.5 years) already showing slight hyperlordosis, a broad based stance, and pseudohypertrophy of calves. (**b**) similar findings in a patient in whom diagnosis was made at the age of 2 years. Courtesy of Dirk Fischer, Basel, Switzerland

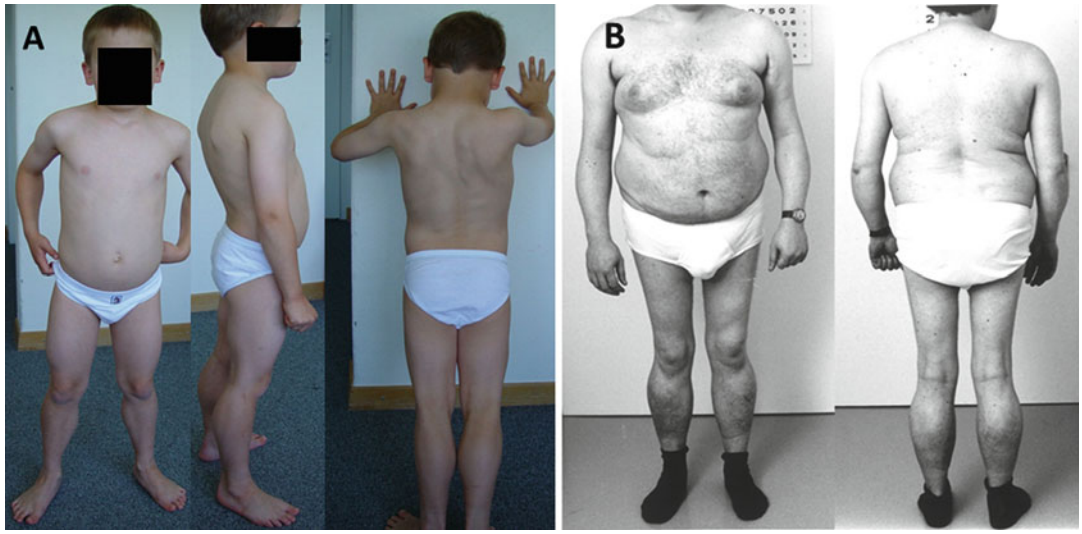


**Fig. 17.2** Clinical findings in BMD. The clinical presentation is often similar as in DMD with predominant limb girdle weakness, but age of onset is later. (**a**) BMD patient (9 years) at onset, and (**b**) BMD patient, 25 years (about 10 years after onset) with thigh atrophy, pseudohypertrophy of calves, but no scapular winging. Courtesy of Dirk Fischer, Basel, Switzerland. B with permission from Springer (Fischer D, et al. (2005) J Neurol. 252;538–547)

the disease course with the majority of the patients developing signs of cardiomyopathy in their late teens and early twenties. Nutrition plays a major role in the late stages of DMD, and poor nutrition can be a serious complication exacerbating weakness and respiratory function.

Approximately 30 % of patients with DMD and some with BMD have a low level of intellect and present with cognitive impairment involving several domains (e.g., learning difficulties). Children with DMD or BMD perform poorly at tests, particularly on verbal skills, but also have challenges processing complex verbal information. In addition, patients frequently present with an attention deficit hyperactivity disorder, autistic spectrum disorder, or obsessive-compulsive disorder.

The BMD phenotype manifests more slowly and evolves over a longer period of time. Patients typically present during late childhood or even adulthood (Fig. 17.2). In contrast to DMD patients who are wheelchair bound by their mid-teens, BMD patients are able to ambulate for a longer time, often into their fourth decade and in sometimes up to their seventh decade. Life expectancy in mild BMD, although diminished compared to that of the general population, may be into their seventh or eighth decade.

## 17.4 Histopathology

Histopathological changes in muscle biopsies of dystrophinopathy patients show dystrophic changes similar to those seen in other muscular dystrophies. Findings include increased variation in fiber size, fibrosis, degenerating fibers, regeneration, and in later stages variable replacement of muscle tissue by fat and connective tissue. Specific immunhistochemical (IHS) markers facilitate the diagnosis, using commercial antibodies directed toward three domains of the dystrophin protein usually allowing a reliable diagnosis of DMD and BMD. IHS is sometimes successful in identifying symptomatic female carriers (Fig. 17.3).

## 17.5 Imaging Findings

### 17.5.1 Skeletal Ultrasonography

Muscle US can be highly predictive for detecting a neuromuscular disorder in children from birth through their teenage years. The sensitivity of 78 % and specificity of 91 % reported is increased to a sensitivity of 81 % and a specificity of 96 % in

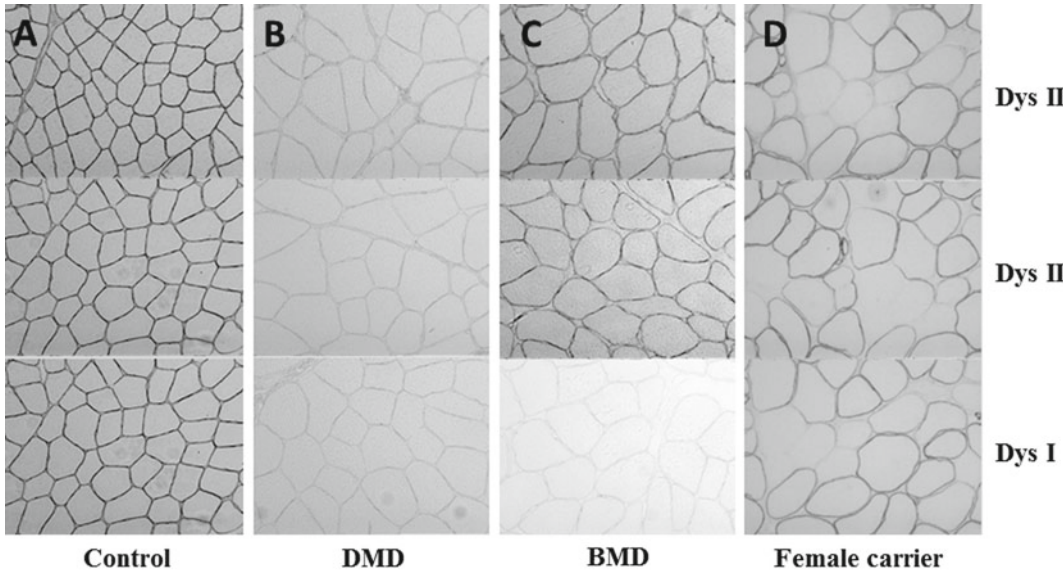


**Fig. 17.3** Immunhistochemistry using commercial antibodies (DYS I, DYS II, and DYS III) against three differential domains of the dystrophin protein: (**a**) normal sarcolemmal dystrophin staining in a control. (**b**) completely absent dystrophin staining using all three antibodies in a DMD patients. (**c**) normal sarcolemmal dystrophin staining using DYS III and DYSII antibody, but absent dystrophin staining using DYS I in a BMD patient indicating the presence of a partially present (shortened) dystrophin protein. (**d**) partially (mosaic) absent reaction in a female DMD carrier using all three antibodies. Courtesy of Dirk Fischer, Basel, Switzerland

children > 3 years of age. In children < 3 years, the sensitivity decreases because of structural changes in the muscle usually being minor at this early age. If an abnormality is detected, more-invasive tests are required. Muscle US is a suitable screening tool for detecting a neuromuscular condition in children (see Chap. 2). These sensitivities are different for specific neuromuscular diseases, approaching 100 % for clinically affected patients with DMD, but only 25–45 % for those with mitochondrial myopathies. Its diagnostic value for other specific neuromuscular diseases has not been studied, and only small series have been reported.

The pattern of muscle involvement can also be described with US. As with magnetic resonance imaging (MRI) and computed tomography (CT), US can help with the differential diagnosis. Muscle US can also detect suitable muscles to biopsy, thereby preventing biopsy of severely affected muscles. Those with pronounced fibrosis and atrophy may provide specimens that are not interpretable.

Changes in muscle in muscular dystrophies seen with US were first described for DMD. Preclinical cases of DMD can appear normal on US scans, unlike the changes seen by MRI. Once the first clinical signs manifest, however, muscle US reveals abnormalities in almost every patient. The proximal muscles have the highest echo intensities, and within the muscle there is a homogeneous, fine granular appearance.

The pattern of infiltration in the muscles in DMD shows sparing of the gracilis and sartorius muscles, even in patients with severe pathology. The selective involvement in "mid-stage" DMD has demonstrated sparing of the gracilis and sartorius muscles, the peroneus and tibialis anterior muscles, and the posterior muscles in the lower leg. The same pattern of sparing was also observed In BMD.

### 17.5.2 Skeletal CT

The use of CT in early-DMD patients has documented changes that are reflected in both US and MRI scans and are pattern-specific for DMD. In a recent study, DMD patients aged 6 months to 12 years, who were reported to be preclinical, with motor skills still continuing to develop, were

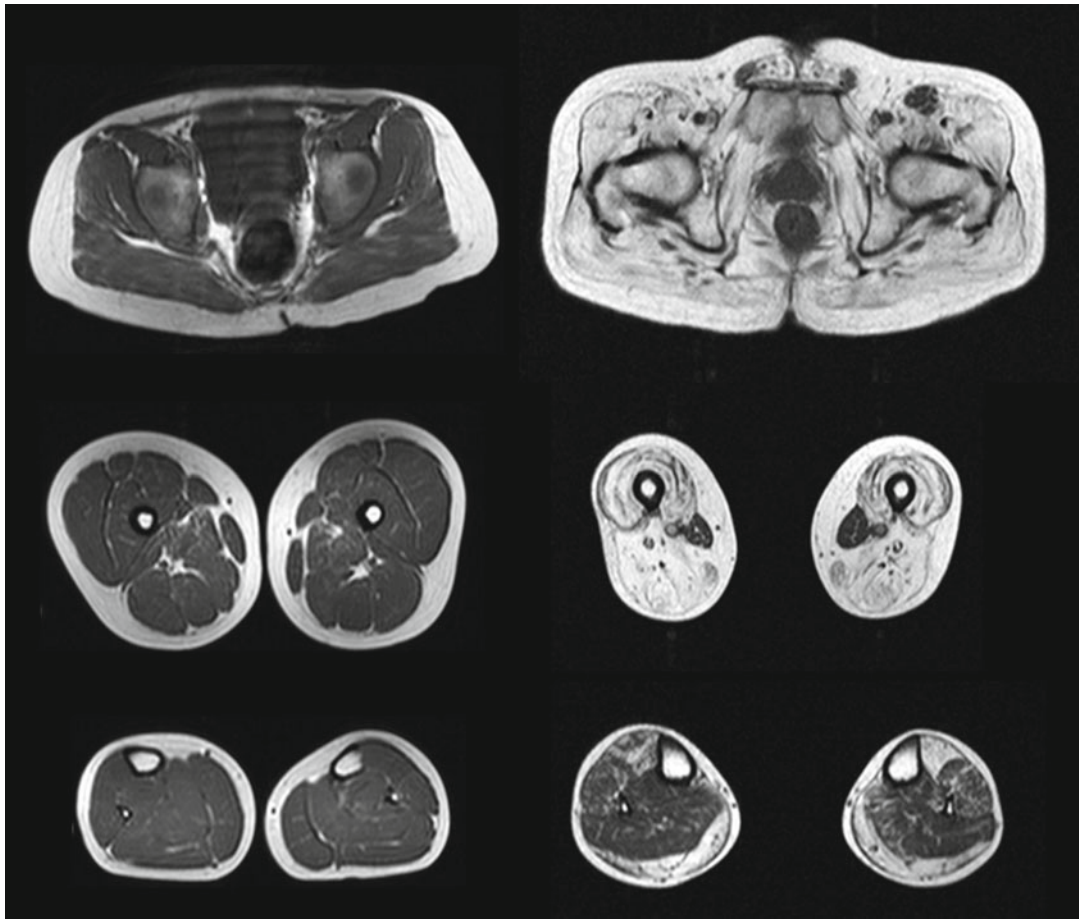

**Fig. 17.4** The T1-weighted axial MR images through the pelvic girdle and leg muscles of two ambulant patients with dystrophinopathies show the broad spectrum of muscle pathology. The images on the left are from an 8-year-old boy with DMD who clinically showed the typical symptoms of the disease, despite the fact that hardly any muscle pathology was detectable on MRI. The images on the right are from a 43-year-old patient with BMD, who despite severe muscle pathology in his thigh muscles was still ambulant

imaged using quantitative CT. Hounsfield units (HU) were used and correlated with the age of the patient. The HU refer to the density of the muscle seen on CT imaging. Changes in HU in individual muscles were demonstrated, particularly those that visually did not appear to be affected. Less-affected muscles that were generally well preserved, such as the anterior and posterior tibialis muscles, showed higher HUs. A slow, gradual regression rate was reported for the gracilis muscle, reflecting the so-called selective pattern of involvement seen in DMD even during the preclinical stage. This regression rate was analyzed cross sectionally, correlating the degree of disease severity seen in the boys clinically with the HU value obtained from the CT scans of the gracilis muscle. Although this study was important from a quantitative perspective and identified that gross visual inspection alone is insufficient, there were no longitudinal data and no age-matched controls.

### 17.5.3 Skeletal Muscle MRI

Because of the progressive nature of DMD, there has been a need to develop an objective, noninvasive measurement of disease progression. Muscle MRI allows evaluation of the muscles over time. Standard T1-weighted images are often normal during the early stages of DMD (Figs. 17.4, 17.5,

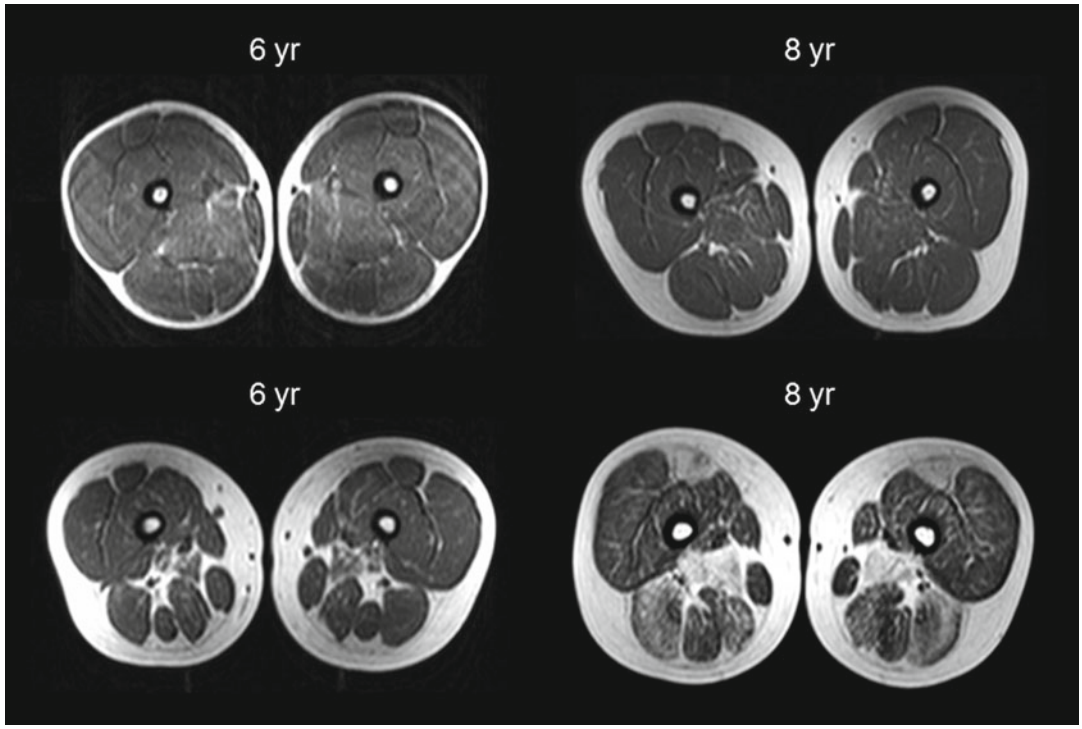


**Fig. 17.5** The panel shows axial T1-weighted MR images through the thighs of four different boys with a genetically confirmed diagnosis of DMD. The images illustrate that there can be differences in the degree of pathology and the amount of muscle mass between patients of the same age. The images also illustrate that boys of different ages and therefore different levels of clinical severity can show similar MRI features

and 17.6), but after 6–7 years progressive involvement is usually evident (Figs. 17.5 and 17.6). The degree of muscle pathology may vary among DMD boys of a specific age despite the fact that the overall pattern of involvement is fairly consistent in all patients (Figs. 17.5 and 17.6). Single muscles, such as the rectus femoris, are more severely affected in some patients, and the overall muscle mass also shows interindividual variation (Figs. 17.5 and 17.6).

The abnormal signals are initially confined to the gluteus maximus and adductor magnus, followed by involvement of the quadriceps, rectus femoris and biceps femoris (Figs. 17.5 and 17.6). There is relative sparing of the sartorius, gracilis, semimembranosus and semitendinosus muscles (Figs. 17.5 and 17.6). In the lower legs, the gastrocnemius muscles are affected earlier than the other muscle groups (Figs. 17.5 and 17.6), however on fat suppressed T2-weighted images (e.g. STIR), oedematous changes and possible signs of inflammation can be seen in the muscles not thought to be affected on the standard T1-weighted images. These findings are interesting as they do suggest an inflammatory element, or phase of necrosis associated with oedema, pre-dating the fibrotic/dystrophic change seen later (see Chap. 4).

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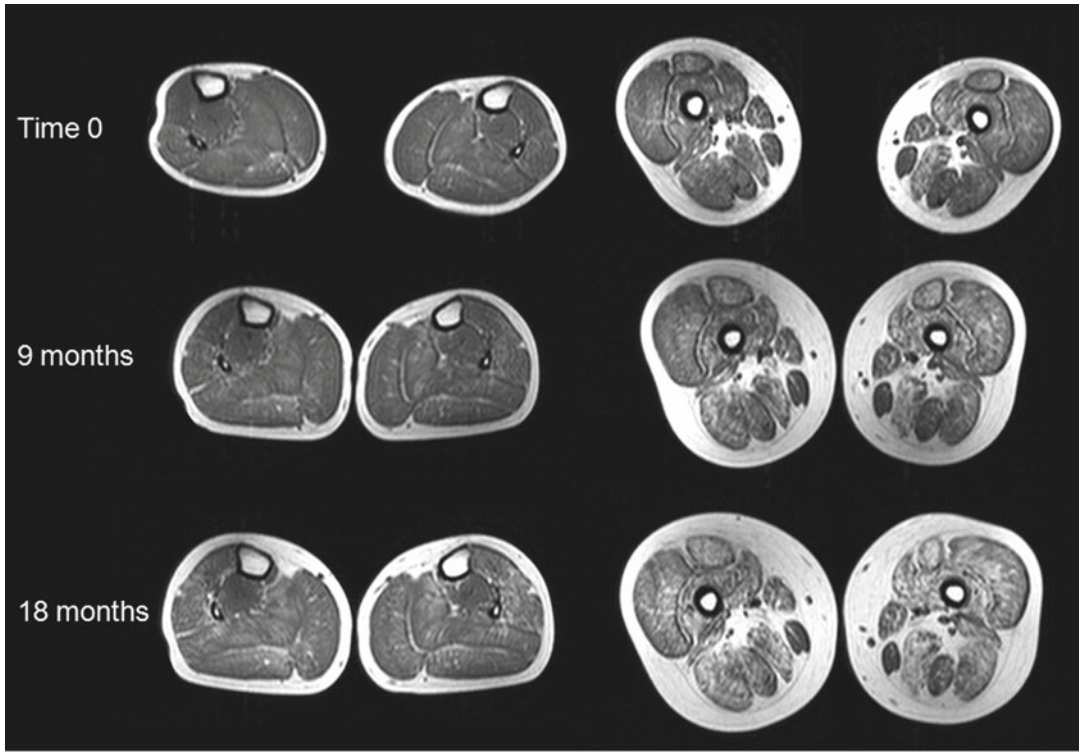


**Fig. 17.6** The axial T1-weighted MR images through the calves and thighs of a 6 years old (a) and an 8 years old (b) boy (age at time 0) with DMD show the progression of muscle pathology by MRI over a period of 18 months. The proximal muscles are much more severely affected than the lower leg muscles. In the thigh, the gracilis and the sartorius muscles were best preserved

thought not to be affected based on the standard T1-weighted images. These findings are interesting as they suggest an inflammatory element, or phase of necrosis associated with edema, predating the fibrotic/dystrophic changes seen later (see Chap. 4). Many studies have assessed the pattern of pathology and temporal changes in DMD using subjective, qualitative scoring or semi-quantitative rating scales (see Chap. 4). More recently, techniques such as the three-point Dixon imaging technique have been used to quantify the changes. The results can also be used on a longitudinal basis (see Chap. 5). Strong correlations with both the fat fractions on quantitative MRI and disease progression as indicated on functional testing have been documented. Manual muscle testing and myometry did not demonstrate the same strong correlation with the fat fractions analyzed with quantitative MRI. Quantitative MRI using the three-point Dixon technique is a potentially useful objective, noninvasive tool that correlates strongly with disease progression and particularly functional testing. It is not reliant on patient effort, which in a pediatric situaton is vitally important. The muscle involvement in patients with BMD overall shows a pattern similar to that described for patients with DMD. The sartorius and gracilis are often the most well preserved muscles. Even at a stage where muscles in the thigh are almost completely replaced by fat tissue, patients with BMD are still able to walk (Fig. 17.4).

## 17.6 Therapy

Currently no curative treatment is available for these conditions. However, the standards of care have been improving steadily over the last few decades and have been disseminated world-wide,

prolonging survival, improving quality of life and limiting morbidity from the complications associated with DMD and BMD. The only treatments we have currently are steroids and, cardiac, respiratory and scoliosis management offered in a timely fashion and the clinical management of symptoms and complications.

There have been a number of clinical trials testing new therapeutic strategies, which in itself is a positive development. One of the most promising approaches based on pre-clinical studies and proof of principal studies in humans is the application of antisense oligonucleotides (AONs) for DMD. Trials are ongoing based on AON-induced exon skipping of exon 51 using two different chemical backbones, 2-*0*-methyl AONs (PRO051) and morpholino AONs (AVI-4658).

## 17.7 Differential Diagnosis

A dystrophinopathy should always be considered in the differential diagnosis of male patients with progressive limb-girdle weakness and elevated serum CK activity. Patients with BMD or a female carrier of a dystrophin mutation may also present with dilated cardiomyopathy with or without muscle weakness as a first symptom.

As both DMD and BMD patients present with limb-girdle weakness, many of the LGMDs (see Chap. 19) fall into the differential diagnosis. Sarcoglycanopathies (see Sect. 19.4) can closely mimic DMD, although inheritance patterns and immunostaining of muscle tissue obtained by biopsy should point to the correct diagnosis. LGMD2I (see Sect. 16.5) may also present with features resembling DMD or BMD, including calf hypertrophy, markedly elevated CK levels, and respiratory and cardiac complications. Genetic analysis can confirm the diagnosis. The various forms of Emery–Dreifuss muscular dystrophy (see Chap. 18) and Pompe disease (see Sect. 14.2.1) are other genetic muscle diseases that can present with progressive limb-girdle weakness. They need to be included in the differential diagnoses of dystrophinopathies. Milder forms of congenital muscular dystrophies (see Chap. 16), particularly the dystroglycanopathies (see Sect. 16.5) and MDC1A (see Sect. 16.2), can also present with predominantly limb-girdle weakness and elevated serum CK and need to be distinguished from the dystrophinopathies. A flow chart demonstrating how muscle imaging and clinical findings may be used to differentiate the dystrophinopathies from other LGMDs is provided in Chap 25.

### Dystrophinopathies

#### Key Points

- The dystrophinopathies DMD and BMD are caused by mutations in the dystrophin gene.
- The dystrophin gene is located on the X chromosome and is the largest known gene to date.
- DMD presents with delayed motor milestones, calf hypertrophy and a raised CK from around 3 years of age, whereas onset of BMD is later and much more variable in childhood through to adulthood. BMD can also present with isolated cardiomyopathy and only minor muscle weakness.
- There is no cure for DMD; however supportive treatment is available including steroid treatment, scoliosis surgery, non-invasive ventilation and treatment of cardiomyopathy.
- Muscle imaging is less important for diagnostic purposes in the dystrophinopathies but might help to define objective measures of muscle pathology.

## Suggestions for Further Reading

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