
INVITED LECTURE

PROGRESSIVE MUSCULAR DYSTROPHIES IN CHILDREN

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In children, progressive muscular dystrophies (dystrophinopathies, limb girdle muscular dystrophies, facioscapulohumeral muscular dystrophy) are clinically and etiologically heterogeneous group of myopathies. Historically, the term muscular dystrophy was first introduced by Wilhelm Erb in 1891 for a progressive neuromuscular disease ("dystrophia muscularis progressiva"). The term dystrophy was intended to describe the clinical and histological coexistence of signs of muscular atrophy and hypertrophy. Various myopathological changes described in this disease constitute a criterion that is still valid today. The expanding identification of numerous etiologically different myopathies, however, makes it more difficult now to identify a progressive degenerative myopathy either as a muscular dystrophy or as a myopathy. Thus, the classification is made somewhat arbitrarily as, for example, various forms of distal myopathies are not progressive dystrophies. Conversely, oculopharyngeal muscular

dystrophy does not usually present with dystrophic histopathological changes. Still, progressive muscular dystrophies are clearly differentiated from congenital muscular dystrophies. This etiologically heterogeneous group of autosomal recessive disorders usually occurs at birth and leads to severe progressive disability.¹

DYSTROPHINOPATHIES

Dystrophinopathies are X-linked recessive hereditary muscular dystrophies with different phenotypes caused by mutations of the dystrophin gene in the skeletal muscle. Dystrophin is a subsarcolemmal cytoskeletal protein which is encoded by the biggest human gene on Xp21. Two major types of dystrophinopathies are the Duchenne (Duchenne muscular dystrophy, DMD) and the Becker (Becker muscular dystrophy, BMD) type. Dystrophin is usually absent or significantly reduced (<5%) in DMD, and is present in BMD and less reduced than in DMD.^{1,2}

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy is probably the best known myopathy in general, and this form of muscular progressive dystrophy is indeed most frequently associated with the term muscular dystrophy. The first detailed clinical description was given by a Frenchman Duchenne de Boulogne in 1868, after whom the disease was named, even though other authors (Meryon or Gaetano Conte, for example) described this dystrophy before him.

Epidemiology and pathogenesis. The incidence of the Duchenne muscular dystrophy (DMD) ranges between 1 to 3500 and 1 to 4215 in male infants born alive, while the prevalence ranges from 2 - 9.5 in 100 000 men.^{1,2} A higher incidence (1 to 3600 - 6000 in male infants born alive) has also been reported.⁴ It has been known for quite some time that this is a genetically conditioned recessive disease, linked to the X chromosome. The first detailed clinical description of the progressive muscular dystrophy was produced by Meryon in 1852, while Duchenne, whose name later on became associated with the severe form of muscu-

lar dystrophy, essentially added to the description of the disease, introducing in 1868 muscular biopsy into the diagnostics of the disease.³ In 1985, Kunkel and his associates^{4,5} located gene deletions for DMD and BMD in the Xp21 region, and two years later, Kunkel's colleague, Hoffman, identified a gene product - dystrophin, which is absent in DMD and reduced or damaged in BMD.⁶ As a result, the gene diagnostic testing for these two diseases became possible after 1987. The deletions can occur anywhere in the dystrophin gene with around 60-65% of mutations. Either partial gene deletion (60%) or gene duplication (5%) occurs in around 65% of DMD/BMD cases. Deletions are most common in the proximal part of the gene (exons 2-19) and in its center (exons 45-52).

Dystrophin is a huge subsarcolemmal protein weighing 427 kD, which together with other cytoskeletal proteins from the dystrophin - glycoprotein complex (DGC) provides mechanical support to the muscular membrane (of the skeletal and cardiac muscle) and normal contractility of the muscle fiber. The damage of the DGC leads to the damage of the myocytes; however, it is still unclear why weakness affects certain muscle groups more than others and why the muscle weakness manifests only after several years even though dystrophin had been altered already in the fetal muscle.

Clinical features. The main clinical presentation, described way back by Duchenne ("hypertrophic paraplegia of the early childhood"), includes: weakness originating in proximal muscles of the lower extremities and pelvic girdle; lumbar lordosis and waddle-like (duck-like) walk; hypertrophy of some muscle groups especially of the calf; progressive course (Figure 1).

Duchenne and Becker types of muscular dystrophy primarily affect boys. Girls can only be primary carrier of the disease or get the disease if the X - chromosome is inactive in the Turner syndrome, i.e. in case of structural changes or translocations of the X chromosome.⁷

The disease usually occurs before the age of three or when the child starts walking. The first symptoms are associated with the walk and occur due to the symmetric weakness of the muscles of the pelvic girdle, proximal muscles of the extremities.

The first signs can also be associated with hypertrophy of calves, which are of rubber-like consistency (so called pseudo-hypertrophy) (Figure 1b). Boys start walking either "on time" or a little later, with the early tendency to walk on toes. They usually do not significantly stick out in play with their peers by the age of three; but later, they start to manifest clumsiness, less speed in play, most of them never experience running, and in soccer, for example, they tend to play more in defense than forward. They start to walk and waddle (duck-like walk), it becomes harder and harder for them to walk up the stairs or up the slope, they fall

often and increasingly harder get off the floor, leaning on and crawling with assistance of own legs or nearby furniture (so called Gower's manoeuvre or sign) (Figure 2a,b/the same boy as in the Figure 1 and Figure 2b).



Figure 1. Lumbar hyperlordosis (a) and pseudo-hypertrophy of calves (b) in a boy with the Duchenne muscular dystrophy

Deep tendon reflexes tend to disappear early except Achilles, which can be present "until the end", and in fact more often can be intensified.⁸ At the age between 7 and 11, they are not able to get off the floor or walk up the stairs. The weakness spreads gradually from the lower to the upper extremities, neck and respiratory muscles. The so called scapulae alatae becomes visible, caused by the weak muscles of the shoulder girdle (Figure 3).

In most cases, boys stop walking between the age of 12 and 13 (Figure 4, showing the same boy from the figures 1, 2a and 3). Ceasing to walk increases the risk of developing contractures in ankle, knee and pelvic joints. The cardiac muscle is also affected, possibly causing sudden death due to cardiac arrest, while progressive heart diseases are rare.⁹⁻¹⁰ The cardiac muscle is affected in a form of cardiomyopathy, or a heart rhythm disorder. The cardiomyopathy can also be the most significant manifestation of the disease, more common in the Becker type of muscular dystrophy.⁷

The progressive weakness gives rise to the development of kyphoscoliosis, which furthermore facilitates the reduction of the vital capacity of the lungs and causes breathing difficulties, which occur already at the age of eight due to the development of the weakness of the respiratory muscles. The weakness of the

respiratory muscles and weak lung ventilation often cause lung inflammation, which can lead to progression, and represent the most common co-morbidity in these patients. Lethal outcome occurs between the age of 20 and 25 due to cardiac arrest⁹ or respiratory failure.¹¹⁻¹⁴ With the introduction of assisted ventilation, the life span can be extended by as many as ten years.¹⁵

In places with developed neurology around 95% of DMD patients are diagnosed before the age of six but we diagnose it somewhat later.



Figure 2B. *Gower's manoeuvre*



Figure 2A. *Gower's manoeuvre*



Figure 3. *Scapulae alatae in a boy with the Duchenne muscular dystrophy*

The Duchenne muscular dystrophy is essentially a multi-systemic disease which also affects the brain. The IQ in DMD averages around 85, and less than 50 in around 3% of cases. Mental inferiority manifests exceptionally rarely and the problems primarily relate

to memory and learning (stellar students are rare, but this, for example, is not true in case of spinal muscular atrophy). The slowing down of the mental development cannot be simply explained by the reduced expression of dystrophin in the brain, which was proven.⁷ There are probably some other factors, still to be sufficiently explained.



Figure 4. Boy with the advanced Duchenne dystrophy, non-ambulatory phase, weakness of the muscles of the shoulder girdle.

Diagnostics. In setting the diagnosis of DMD the primary tool is the clinical presentation; however, it is not sufficient. The values of the muscle enzymes are very high (10 to 200 times higher than the upper limit of the normal, especially at the early stages of the disease. The values increase during exertion (rhabdomyolysis) and reduce during the course of the

disease. In case of accidentally detected high values of creatine-kinase (CK) in newborns or somewhat later, while there are no clinical signs of the disease just yet, DMD or BMD should be suspected, as the values of CK are elevated immediately after birth in both types of dystrophinopathies. The values of alanine transaminase (ALT) and aspartate transaminase (AST) are also elevated in DMD patients.

The electromyoneurographic finding is a very important diagnostic procedure. The electromyogram is typically myopathic (fast recruitment of the interference innervation pattern with the potential of low amplitude and increased polyphasia). The conduction velocity through nerve fibers is normal.

It makes sense to perform the muscle biopsy if the analysis of dystrophin can be made. The quality of dystrophin is determined by the immunohistochemical analysis of a frozen biopsy sample using dystrophin antibodies. The quantity of dystrophin is determined with the Western-blot technique. The final confirmation of the DMD diagnosis cannot be set without this and/or the gene one.¹⁶ The analysis of the deoxyribonucleic acid (DNA) is performed from the DNA extracted from leucocytes. Around two thirds of gene mutations for dystrophin are large deletions, while the remaining third of mutations relates to small and spotty mutations. If the mutation cannot be determined in a boy with DMD, it is necessary to run a DNA test in several family members and do the sequencing of the entire gene of DMD.^{1-3,7} The DNA analysis of female members of the family of a DMD patient is extremely important in order to identify the agent of the disease.

As a part of the diagnostic protocol and monitoring of the patient, it is necessary to make a detailed cardio and pulmonary analysis.

Therapy. The steroid therapy is one of many attempts of therapy which demonstrated certain efficiency in slowing down the development of immobility and contractures in boys with DMD. Prednisone induces myogenesis, inhibits proteolysis and entry of calcium iodine thus inhibiting apoptosis. Furthermore, it increases the expression of urotrophine, compensatory protein for dystrophin, which to a certain extent can make up for shortage of dystrophin. Various dosage regimes are recommended, from 0.35 to 1 mg/kg per day, every other day, several days a week or several days in a month (e.g. 10 days of therapy then 20 days break). The optimal therapy dose of prednisone based on the overwhelming experience is 0.75mg/kg per day. In addition to prednisone, positive results were also achieved with application of other steroids - fluocortolon, deflazacort.^{7, 17-18} The question, however, remains when to initiate therapy. It should be verified whether the child had measles i.e. whether it was vaccinated against it. If the answer is no, the child

should first be vaccinated and therapy introduced three months following the vaccination. One should also bear in mind the side effects of corticosteroids. The most common side effect is weight-gaining, which is not a good "ally". Ceasing to walk is usually the time to start abandoning the steroid therapy.

A continued physical therapy with moderate kinesiotherapy programs is absolutely indicated. The application of an orthosis which is used to arrest the joints enables those functions which the patients cannot perform on their own, such as standing or walking. The contractures are surgically treated only if fixed. In immobile patients, surgical treatment of contractures is justified if they are additionally disabling (difficult to sit alone, care of patient). It is important to put the patient in pronation from time to time, and to ensure passive stretching of joints and wearing of orthoses during the night in order to prevent or slow down the development of contractures. Early postoperative mobilization is also very important.^{7,19}

BECKER MUSCULAR DYSTROPHY

In 1955, Becker and Kiener described progressive muscular dystrophy, (later on named Becker muscular dystrophy, BMD), which is clinically different from DMD in that it has a moderate clinical course. This is why this disease is also classified as benign pseudohypertrophic muscular dystrophy.



Figure 5. *Becker muscular dystrophy – hyperlordosis, scapulae alatae, pseudo-hypertrophy of calves*

It has been thought for a long time that both DMD and BMD are X-linked muscular dystrophies with different genetic "backgrounds".^{3,20} Only in 1983, Kingston and his associates demonstrated using the findings of molecular genetics that both diseases are linked to the same Xp21 chromosome region and that they are most likely allelic disorders caused by the mutations of the same gene.^{3,21}

The reports on incidence of BMD vary; however, significantly lower incidence than that of DMD was emphasized in the past. It was estimated that the incidence for BMD was around 1 to 30 000 of newborn boys.^{1,3} However, with the advancement of molecular genetics in the diagnostics of neuromuscular diseases, it has been shown that many boys, who in the past were diagnosed with DMD or limb girdle muscular dystrophy, have in fact BMD, so that some reports even indicate almost the same incidence of BMD and DMD,³ which means significantly higher than thought before (around 1 to 14 000 of male infants born alive).¹

The symptoms and signs of BMD significantly vary, with a long time span for manifestation (from one to 70 years of age), most commonly between the age of six and 18, averaging around the age of 11. The nature of the first symptoms is similar to that described above for DMD, including somewhat slower motor development (Figures 5 and 6). Other symptoms include exercise-induced myalgia or spasms in leg muscles, and occasional rhabdomyolysis.



Figure 6. *Becker muscular dystrophy – having difficulty getting up from the floor*

The muscle weakness originates in proximal muscles of the pelvic girdle (Figure 6), gradually spreading to the proximal muscles of legs, dorsal muscles of the trunk, muscles of the shoulder girdle and the proximal muscles of arms (Figure 5). Muscular (pseudo)hypertrophy of calves is usually (but not always) present and may precede the muscle weakness.¹ The heart is affected similarly to the case of DMD (cardiomyopathy and conduction disorders) and is very common

for BMD. The loss of mobility commonly occurs in the forties, but can occur even considerably earlier or considerably later (averaging at around 35 years of age).²

DYSTROPHINOPATHIES IN GIRLS

Due to the fact that dystrophinopathies are inherited through the X chromosome, almost all patients are male, while females are agents. Still, the disease can manifest moderately even in women ranging from hypertrophy of calves, elevated values of creatine kinase to somewhat more pronounced weakness of girdle muscles in the following situations: weakness of inactivation of the mother's X chromosome (manifesting agent), Turner syndrome (X0), Turner mosaic (X/XX or X/XX/XXX), structurally abnormal X chromosome and X-autosomal translocation.^{1,2}

LIMB GIRDLE MUSCULAR DYSTROPHIES

Limb girdle muscular dystrophies (LGMD) is an extremely heterogeneous group of muscular dystrophies, whose common characteristic is muscle weakness located in a girdle (shoulder and pelvic girdle and proximal muscles of extremities), occurring in all forms. The term LGMD was first introduced in the early fifties of the nineteenth century, while the definition of the syndrome has been attributed to Walton and Nattrass, who provided its first extensive description in 1954.²²⁻²³ The classification of these diseases is based on the way it is inherited and genetic abnormality.

They are classified into two groups: LGMD1 with the autosomal dominant inheritance (seven forms) and LGMD2 (13 forms) with the autosomal recessive inheritance (Table 1).^{1,2,7} The most common are those inherited autosomally recessively (prevalence 0.9-1.3/100 000). Those inherited autosomally dominantly occur in 5-10% of all cases, while the sporadic forms are very common (around 41%). The most prevalent form is LGMD 2A, then LGMD2B, 2I, and LGMD2C- 2F. They occur in both sexes. The onset of the disease varies from early to late childhood.¹ It first manifests in the region of pelvic girdle (Figure 7a); however, the weakness can first occur in the region of shoulder girdle and then affect the pelvic muscles. Some forms of LGMD develop very slowly but some develop substantially faster, as in case of the Duchenne muscular dystrophy. In case of spreading to the shoulder girdle, selective spreading is manifested in the so called slouched shoulders, wing-like shoulder blades (scapulae alatae) (Figure 7b) or "Popeye-like" shoulders (as in facioscapulohumeral muscular dystrophy).⁷

Some patients have only minimal muscle weak-

ness but frequent muscle spasms which remind of some metabolic myopathies. In the pelvic region, hip muscles and m.quadriceps femoris are particularly affected, which leads to the pronounced lumbar lordosis and a waddle.

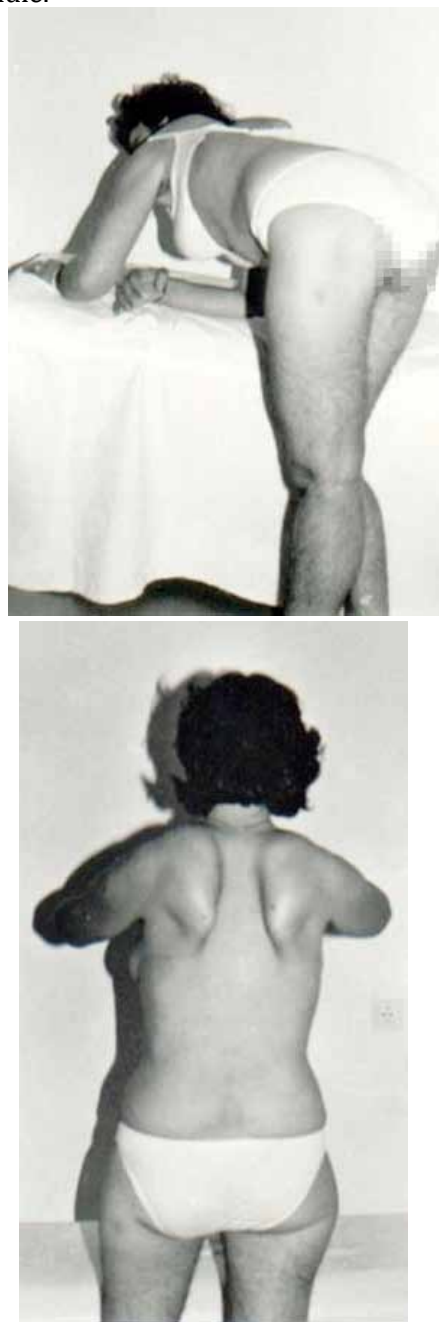


Figure 7. Limb girdle muscular dystrophy – weakness of muscles of the pelvic region, scapulae alatae

The muscle-tendon reflexes are reduced or absent, while the Achilles reflex, as is the case with DMD, can be preserved for a long time.⁷⁻⁸

It is usually not possible to clinically distinguish different forms of LGMD; however, there are some typical signs for some of the above forms, such as suddenly having early difficulties, in the teenage years, to stand on toes in case of LGMD2B. Furthermore, pseudo-hypertrophy of calves is typical of LGMD1C, 2C-F and 2I, with early contractures in case of LGMD1B.^{1,2}

Table 1. Classification of limb girdle muscular dystrophies

Type of inheritance	Gene locus	Gene product
Autosomally dominant		
LGMD 1A	TTID	Miotilin
LGMD 1B	LNMA	Lamin A/C
LGMD 1C	CAV3	Caveolin-3
LGMD 1D	6q23	Unknown
LGMD 1E	7q	Unknown
LGMD 1F	7q32	Unknown
LGMD 1G	4p21	Unknown
Autosomally recessive		
LGMD 2A	CAPN3	Calpain-3
LGMD 2B	DYSF	Dysferlin
LGMD 2C	SGCG	γ -sarcoglycan
LGMD 2D	SGCA	α -sarcoglycan
LGMD 2E	SGCB	β -sarcoglycan
LGMD 2F	SGCC	δ -sarcoglycan
LGMD 2G	TCAP	Telethonin
LGMD 2H	TRIM32	E3-ubiquitin ligase
LGMD 2I	FKRP	Fucutin-like protein
LGMD 2J	TTN	Titin
LGMD 2K	POMT1	Protein-mannosyltransferase-1
LGMD 2L	FCMD	Fucutin
LGMD 2M	11p13-p12	Unknown

CK is elevated in most forms of LGMD. Very high values (20-150 times higher than the upper normal values) are detected in case of LGMD2B and 2C-F. In most cases, a typical myopathic pattern can be registered electromyographically.

The diagnosis requires a muscle biopsy to exclude other myopathies which have similar clinical presentation as LGMD, and to detect the abnormal protein by the immunohistochemical method or Western-blot technique. DNA analysis is often necessary to further define the form of the disease and, if possible, performed at the same time as the biopsy or after the biopsy analysis.

The primary methods of treatment are those of physical rehabilitation in order to preserve mobility and prevent contractures. Corticosteroids may have some effect in sarcoglycanopathies as in dystrophinopathies.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHD) is a disease which is inherited autosomally dominantly with a high gene penetration and variable expression. The first description was given by Landouzy and Dejerine back in 1884. In 95% of the cases, the gene is

located on the 4q35 chromosome in the subtelomeric region.^{1-2, 7} The prevalence of FSHD ranges from 1 to 20 000 to 1 to 45 000, depending on the geographical area.

The disease affects both sexes, but more commonly women. In around 5% of cases, it occurs by the age of four and in 95% of cases, at the age of 15-19. The clinical presentation varies significantly, from the minimal weakness of the facial muscles to the substantial generalized weakness. It can present with very early weakness of the facial muscles. The facial expression is myopathic, the patient has difficulty to close eyes, cannot pout lips, has difficulty or cannot whistle at all. The spreading to the muscles of the scapulae causes development of scapula alata. The patient has difficulty to raise arms above the horizontal line. The deltoid muscle is usually not affected, while the biceps is less affected than the triceps (Popeye look). The muscles of the pelvic girdle become affected later than those of the shoulder girdle. The muscle weakness may also be present in the distal muscles of the lower extremities with the occurrence of foot drop. A substantial number of patients (around 75%) has muscle pain. Out of the total number, around 20% of the patients become wheelchair-dependent over time.²⁴

Attempts of therapy with corticosteroids give modest results. Physical therapy is necessary.

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