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DIAGNOSTICS OF THE ORIGIN OF DUCHENNE MYOPATHY AND MODERN CLINICAL DIAGNOSTIC METHODS

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Abstract: Duchenne muscular dystrophy and Becker muscular dystrophy are X-linked recessive diseases characterized by proximal muscle weakness resulting from degeneration of muscle fibers. Becker dystrophy has a later onset and causes milder symptoms. Diagnosis is clinically suggestive and confirmed by genetic testing or analysis of the protein product of the mutant gene (dystrophin). Treatment is aimed at maintaining function with physiotherapy, orthotic braces, and orthotics. Patients with Duchenne dystrophy should be offered prednisone or deflazacort, and sometimes gene therapy.

Key words: Clinical manifestations, Diagnostics, Treatment, Basic rules, Additional information

Muscular dystrophies are hereditary, progressive diseases of the muscular system caused by defects in one or more genes essential for the normal structure and function of muscles. Biopsy specimens show dystrophic changes (e.g., necrosis and regeneration of muscle fibers).

The most common muscular dystrophies are Duchenne dystrophy and Becker dystrophy. These diseases are caused by mutations in the dystrophin gene, the largest known human gene, located at the Xp21.2 locus. Up to 70% of Duchenne dystrophy cases are caused by deletions of one or more exons, about 10% by duplications, and 20% by point mutations. In Becker dystrophy, about 70% of patients have deletions, 20% by duplications, and up to 10% by point mutations (1).

In Duchenne dystrophy, these mutations result in a severe deficiency (< 5%) of dystrophin, a protein in the membrane of muscle cells. In Becker dystrophy, mutations result in the production of abnormal dystrophin or its deficiency.

Duchenne dystrophy and Becker dystrophy together affect approximately 1/5000–1/6000 live births of boys (1); the majority of these have Duchenne dystrophy. Female carriers may have asymptomatic elevations in creatine kinase levels and, in some cases, posterior tibial hypertrophy.

General references

1. Duan D, Goemans N, Takeda S, et al.: Duchenne muscular dystrophy. Nat Rev Dis Primers 7(1):13, 2021. doi: 10.1038/s41572-021-00248-3

Clinical manifestations

Duchenne dystrophy

This disease affects approximately 20 out of 100,000 live births and usually presents between the ages of 2 and 3 years (1). Weakness affects proximal muscles, usually primarily in the lower extremities. Children often walk on their toes, have a walking gait, and lordosis. Such children have difficulty

running, jumping, climbing stairs, and getting up from the floor. Such children often fall and break their arms or legs (in about 20% of patients) (2). There is a steady progression of weakness, and almost all children develop flexion contractures of the limbs and scoliosis. A bony pseudohypertrophy develops (replacement of individual enlarged muscle groups with fat or fibrous tissue, especially in the ankles). Most children require a wheelchair by age 12, and without mechanical ventilation, most die of respiratory complications by age 20. Children supported by ventilation can live another 10-20 years.

Consequences of cardiac involvement include dilated cardiomyopathy, conduction abnormalities, and arrhythmias. These complications occur in approximately one-third of patients by age 14 and in all patients over age 18; however, because these patients are unable to engage in physical activity, cardiac involvement is usually asymptomatic until late in the disease. Approximately one-third of these patients have mild, nonprogressive dementia, which affects verbal abilities more than productivity.

Becker's dystrophy

Compared with Duchenne muscular dystrophy, Becker muscular dystrophy affects <8/100,000 live births in boys and has a much later onset and milder course (3). The ability to walk is usually maintained until at least 15 years of age, and many children remain ambulatory into adulthood. Most sufferers live into their 30s and 40s.

Reference materials on symptoms

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Diagnostics

DNA analysis for mutations

Sometimes muscle biopsy with dystrophin immunostaining

The diagnosis is suspected based on characteristic clinical features, age of onset, and family history suggesting X-linked recessive inheritance. Electromyography shows myopathic changes (motor unit potentials are rapidly increasing, short-lived, and low-amplitude), and muscle biopsy, when performed, shows necrosis and marked changes in the size of muscle fibers not separated from motor units. Creatine kinase levels are 100 times higher than normal.

Mutational analysis of peripheral blood leukocyte DNA using multiplex ligase-dependent DNA probe amplification (MLPA) is the main confirmatory test; it can detect abnormalities in the dystrophin gene. If multiplex ligase-dependent DNA probe amplification (MLPA) does not reveal pathology, but Duchenne or Becker dystrophy is still suspected, complete sequencing of the dystrophin gene can be performed to detect small genetic changes such as point mutations.

If genetic testing does not confirm the diagnosis, dystrophin testing should be performed by immunostaining muscle biopsies. Dystrophin is not detectable in patients with Duchenne dystrophy. Dystrophin is usually present in abnormal (low molecular weight) or low concentrations in patients with Becker dystrophy.

Patients with Duchenne muscular dystrophy should undergo an initial cardiac evaluation using ECG and echocardiography at the time of diagnosis or by the age of 6 years.

Carrier identification and prenatal diagnosis are possible using routine tests (e.g., pedigree, creatine kinase, fetal sex) as well as recombinant DNA analysis and dystrophin immunostaining in muscle tissue.

Treatment

Supportive measures

Sometimes corrective surgery

Angiotensin-converting enzyme inhibitors and/or beta-blockers are sometimes used for cardiomyopathy.

For Duchenne muscular dystrophy: prednisone or deflazacort, sometimes genetic therapy

Treatment involves a multidisciplinary approach that includes both pharmacological and non-pharmacological interventions, including genetic therapy. Mild (i.e., submaximal) strength training is recommended for as long as possible to prevent complications from dysfunctional atrophy or physical inactivity. Passive exercise can prolong the ambulation period. Orthopedic interventions should be aimed at preserving function and preventing contractures. An ankle brace worn while sleeping can help prevent ankle flexion contracture. Foot orthoses can temporarily help maintain the ability to stand and walk. Sometimes corrective surgery is needed, especially for scoliosis. Obesity should be avoided; caloric needs are usually lower than normal due to decreased physical activity.

Respiratory failure can be treated with noninvasive respiratory support (such as a nasal mask) and sometimes mechanical ventilation. Elective tracheotomy is becoming increasingly common, allowing children with Duchenne muscular dystrophy to live to 30 years or more.

For children with dilated cardiomyopathy, angiotensin-converting enzyme inhibitors and/or beta-blockers can help prevent or slow the progression of the disease (1).

Experimental treatments for Duchenne dystrophy and Becker dystrophy include gene therapy, creatine, myostatin inactivation, myogenic progenitor cells, and the antioxidant idebenone (2).

Genetic counseling is indicated.

Corticosteroids for Duchenne muscular dystrophy

In Duchenne muscular dystrophy, daily corticosteroids (prednisone or deflazacort) are the mainstay of therapy for patients older than 4 years who are no longer developing motor skills or who have decreased motor activity (3). Corticosteroids begin to work within 10 days of starting therapy; peak efficacy occurs at 3 months and lasts for 6 months. Long-term use improves strength, delays the age of loss of ambulation by 1.4 to 2.5 years, improves timed functional tests (measures how quickly a child can perform a functional task such as walking or standing up from the floor), improves pulmonary function, reduces orthopedic complications (eg, the need for scoliosis surgery), stabilizes cardiac function (eg, delays the onset of cardiomyopathy by 18 years), and increases survival from 5 to 15 years (3). Daily administration of prednisone is ineffective. Weight gain and Cushingoid facial features are the most common side effects seen 6 to 18 months after starting treatment. The risk of vertebral compression fractures and long bone fractures is also increased.

Deflazacort may be associated with a greater risk of cataracts than prednisone.

The use of prednisone or deflazacort in Becker's dystrophy has not yet been fully studied.

Genetic therapy for Duchenne dystrophy

Genetic therapy to increase dystrophin levels is available in some countries, but it is expensive and its benefits are questionable (4). The use of such treatments requires careful consideration and shared decision-making.

Exon skipping therapy (IV eteplirsen, holodirsen, viltolarsen, and casimersen) uses antisense oligonucleotides that act as molecular patches to the abnormal dystrophin gene that is missing one or more exons (the missing exons prevent the complete protein from being assembled, thereby causing severe symptoms). The drugs mask the exon so that it is skipped and ignored during protein production, allowing the production of dystrophin protein that, although not normal, is still able to

perform its function and could theoretically reduce symptoms so that the function is similar. In boys with less severe Becker muscular dystrophy.

Eteplirsen skips exon 51. Limited data suggest that eteplirsen increases muscle dystrophin levels and improves walking ability in 13% of patients with Duchenne muscular dystrophy who have a mutation in the dystrophin gene that can skip exon 51. This study relied on a surrogate outcome (dystrophin biopsy for muscle) (5) and has not demonstrated clinical benefit.

Holodirsen and viltolarsen skip exon 53. They can be used in the 8% of patients with Duchenne dystrophy who have a mutation in the dystrophin gene that can be corrected by skipping exon 53. Clinical benefit has not been proven.

Casimersen skips exon 45. It can be used in the 8% of Duchenne patients with a confirmed exon 45 mutation, which increases dystrophin production, but clinical benefit has not been demonstrated.

Stop codon-sensing drugs (such as oral ataluren [PTC124]) bypass premature stop codons, allowing the production of functional proteins. Stop codons are nonsense mutations that stop the production of a working protein too early, resulting in a truncated, non-functional protein.

Ataluren stimulates ribosomal premature, but not normal, stop codons and targets the production of functional dystrophin protein. This option is suitable for patients aged 2 years and older with Duchenne muscular dystrophy caused by nonsense mutations who are receiving outpatient treatment. Ataluren is available in the European Union and the United Kingdom. Clinical benefit has not been demonstrated (6).

In gene transfer via viral vectors (e.g., delandyestrogen moheparvovec), viral vectors are used to deliver corrective genetic material to affected muscles.

Although there is no proven clinical benefit, delandyestrogen moheparvovec is the only drug approved for viral vector gene transfer therapy, in which the transgene microdystrophin can be delivered to skeletal muscle and heart muscle using an adeno-associated viral capsid (AAVrh74). No functional improvement was observed in the study (7), but some functional improvement was observed in a subgroup analysis in the 4–5 year age group (8). Side effects include nausea, vomiting, fever, liver dysfunction, and thrombocytopenia, as well as life-threatening immune inflammatory reactions. Further studies are needed to determine the place of this agent in the therapeutic arsenal for Duchenne muscular dystrophy.

Basic rules

Duchenne dystrophy and Becker dystrophy are X-linked recessive diseases that result in a decrease in the concentration of dystrophin, a protein, in muscle cell membranes.

Patients have significant, progressive weakness, leading to severe physical disability, including difficulty walking, frequent falls, dilated cardiomyopathy, and premature death due to respiratory failure.

Patients benefit from active and passive exercises along with the use of foot orthoses and ankle orthoses.

In patients with Duchenne muscular dystrophy, daily administration of prednisone or deflazacor increases muscle strength and mass, improves respiratory function, and helps delay the progression of cardiomyopathy, but often causes side effects.

Patients with Duchenne dystrophy with certain mutations may also be given eteplirsen, holodirsen, viltolarsen, casimersen, and ataluren, although there is limited data on their clinical benefit.

The use of an angiotensin-converting enzyme inhibitor and/or beta-blockers can help prevent or slow the progression of cardiomyopathy.

Assisted ventilation (non-invasive and later invasive) helps prolong life.

Additional Information

Below are some English language resources that may provide information. Please note that the guide is not responsible for the content of these resources.

Muscular Dystrophy Association: Information about research, treatment, technology, and support for patients living with Duchenne muscular dystrophy and Becker muscular dystrophy

National Organization for Rare Diseases: Detailed information about Duchenne muscular dystrophy and Becker muscular dystrophy, including standard and experimental treatments and links to related topics

Emery-Dreyfuss dystrophy is a muscular dystrophy with multiple hereditary patterns. In addition to weakness and muscle wasting, patients often have cardiac abnormalities that can lead to sudden death. Treatment is symptomatic.

Muscular dystrophies are hereditary, progressive diseases of the muscular system caused by defects in one or more genes essential for the normal structure and function of muscles. Biopsy specimens show dystrophic changes (e.g., necrosis and regeneration of muscle fibers).

Emery-Dreyfus muscular dystrophy can be inherited in an autosomal dominant, autosomal recessive (less common) or X-linked manner. The overall frequency is unknown. Females can be carriers, but in X-linked inheritance, the disease is clinically apparent only in males.

Links for treatment

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