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Duchenne Muscular Dystrophy: Sign and its Symptoms

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ABSTRACT:

Duchenne muscular dystrophy is a severe, progressive, muscle-wasting condition that causes movement problems, the need for assisted breathing, and ultimately, early death. The dystrophin gene (which codes for the condition) is mutated, which stops the muscle's ability to produce dystrophin. Without dystrophin, muscles are more vulnerable to injury, leading to cardiomyopathy as well as a progressive loss of muscular mass and function. Our comprehension of the basic and secondary pathogenesis pathways has substantially increased as a result of recent investigations. The management of the many components of the disease as well as guidelines for interdisciplinary treatment of Duchenne muscular dystrophy has been established. In addition, a number of therapies that aim to restore the missing dystrophin protein or address secondary pathology have received regulatory approval and many others are in clinical development.

KEYWORDS: Dystrophin gene, Cardiomyopathy

INTRODUCTION:

One in 3600-6000 live male newborns are affected by the severe, progressive condition known as Duchenne muscular dystrophy (DMD).Although there are guidelines for certain elements of DMD, there are no recommendations for overall clinical therapy. Mutations in several genes are the cause of the inherited illnesses known as muscular dystrophies. These genetic defects result in the dysfunction or lack of proteins necessary for the integrity of muscle cells, which causes the muscles to gradually deteriorate and become weaker (1).Nearly every system, including the endocrine system, is impacted by myotonic dystrophy, which is not just characterized by muscle weakness and myotonia clinical characteristics (2). An atypical genetic musculoskeletal ailment called Duchenne muscular dystrophy (DMD) manifests clinically as progressive muscular weakening early on and pathologically as fibrosis and fatty replacement later in the disease's course. It is an X-linked recessive condition that affects 1 in every 3500 live male births. In 1860, French neurologist Guillaume Benjamin Amand Duchenne gave it its name (3). Beginning between the ages of three and five, it is the most prevalent and severe kind of muscular dystrophy. Affected males tend to have calf enlargement and proximal muscle weakness (4). The dystrophin gene is still the most prevalent gene connected to a known disease (2.4 million base pairs). It has at least 85 exons and 98% of the gene is made up of introns, requiring more than 24 hours to be transcribed.

Years of extensive research had failed to pinpoint the fundamental molecular flaw causing Duchenne-type dystrophy. However, using chromosomally defined DNA markers, it was the first disease-associated gene to be localised in 1982 (5). Understanding how sarcolemma damage is caused, how it is healed, and how the sarcolemma can be protected (or the damage mitigated) by pharmacological or therapeutic interventions is one of the objectives of MD research. These are the same objectives for those who investigate muscular damage. The membrane and cytoskeleton are destroyed in skeletal muscle injuries, particularly those brought on by lengthening ("eccentric") contractions (6)..

PATHOLOGICAL MECHANISM IN DMD:

Muscle fibre degeneration results from a series of degenerative events that start when dystrophin is lost. Muscle fibres are gradually replaced by collagen, fibroblasts, and fat deposits as the degenerative process eventually outpaces the muscle's ability to repair. As less functioning muscle fibres are present in the muscles, and reduced contractility. Muscle inflammatory response triggered by additionally causing the degradation is the necrotic, deteriorating fibers, deterioration of muscular strength (7) (8) (9).

Dystrophic muscle fibbers' greater susceptibility to membrane rupture brought about the discovery that their sarcolemma was leaky (10). Loss of sarcolemma integrity results in an increase in intracellular calcium concentration because extracellular calcium concentration is four orders of magnitude higher than the intracellular concentration (11) (12). Although nonselective ion channels, such as transient receptor potential channels, or passive calcium

entry through microlesions (9). Calpains, a class of calcium-dependent proteases, are thought to play a role in the pathophysiology that leads to DMD by increasing the breakdown of muscle proteins when they are activated (13). Due to the active import of calcium from the cytosol, excess cytosolic calcium also causes the mitochondrial malfunction seen in muscular dystrophy cell cytosol (14). Another problematic mechanism that has been linked to increased cytosolic calcium levels is the pro-inflammatory nuclear factor-B (NFB) pathway (11) (15).

OXIDATIVE STREES:

It is believed that oxidative damage has a significant impact on the pathogenesis of DMD. In dystrophic muscle, a rise in lipid and protein oxidation has been noted (16) (17). In dystrophic skeletal muscle and the heart, NAD(P)H oxidase levels, a crucial enzyme mediating the generation of reactive oxygen species (ROS), were shown to be increased (18) (19). ROS can also develop in the dystrophic muscle as a result of infiltrating neutrophils and macrophages (20).

FIBROSIS:

There is a decline in muscle mass as a result of the loss of muscle fibers, accumulation of fibroblasts, and increased deposition of ECM proteins such collagen and fibronectin. A measure of muscle contraction. Muscle function is disrupted by fibrosis by both by acting as a physical barrier and by reducing the delivery of nutrients for the regrowth of muscle. TGF- serves as a key modulator of fibrosis, which triggers signaling through the auto phosphorylation of TGF- receptors and ultimately results in the phosphorylation of the proteins smad2/3 (9).

SIGN AND SYMPTOMS:

The muscles in the limbs closest to the trunk are selectively impacted by Duchenne muscular dystrophy (DMD) weakness before those farthest from the trunk; the legs are damaged before the arms. Growth velocity with DMD is typically slower than normal in the first years of life, leading to short stature. Boys with DMD are often late walkers. It is known that changes in the regulatory region of the SPP1 gene and the LTBP4 gene can affect the age at which ambulation and/or muscle strength decline.

In toddlers, parents may notice enlarged calf muscles (see below image)

Because the muscle tissue is aberrant, this expansion is known as pseudo hypertrophy, or "false enlargement." The muscles in the thighs might also experience pseudohypertrophy. The muscles in the thighs might also experience pseudohypertrophy. Preschoolers with DMD may come out as awkward and prone to falling. Parents may also observe that kids struggle to run, get up off the floor, or climb stairs. Affected boys may use hand help to bring themselves to an upright position when getting up from the floor.

By the time they reach school age, kids may frequently trip over themselves and walk on their toes or the balls of their feet with a little waddle. They could pull their shoulders back and stick out their tummies in an effort to maintain their equilibrium. Children find it challenging to raise their arms.

By the age of 12, many children with DMD start using a wheelchair. The process of switching to a wheelchair is typically gradual; initially, the chair may only be necessary to save the child's energy while travelling lengthy distances. When a child fully transitions to a power wheelchair, they frequently enjoy a sense of fresh independence. Activities involving the arms, legs, or trunk may need assistance or mechanical support during the teen years. Few DMD patients live through the third decade; most may away in their late teens or early 20s from cardiomyopathy or respiratory failure.

PAIN AND SENSATION:

DMD's muscular degeneration rarely causes discomfort on its own. Muscle cramps are occasionally reported by some people; they can typically be managed with over-the-counter painkillers. Touch and other sensations, as well as control over the smooth, or involuntary, muscles of the bladder and colon, as well as sexual activities, are unaffected by muscular dystrophy because it does not directly damage nerves.

THE HEART:

Lack of dystrophin can weaken the heart's muscle layer (myocardium), which can lead to cardiomyopathy, a disorder marked by significant scarring of the tissue. Conduction problems in the heart can also be brought on by DMD. According to reports, cardiomyopathy symptoms are present in all individuals above the age of 18. The cardiac damage caused by DMD can eventually prove fatal, possibly as early as the teen years. The heart needs to be closely watched, typically by a pediatric cardiologist.

RESPIRATORY FUNCTION:

At age 5 or 6, breathing capacity serial monitoring should begin. The lungs may become less efficient in exhaling and inhaling air when the diaphragm and other muscles that control the lungs deteriorate. Even though a child may not complain of having trouble breathing, other symptoms of poor respiratory health include headaches, mental drowsiness, trouble staying awake or focused, and nightmares. Wheelchair-bound children tend to have evidence of poor pulmonary function.

Coughing becomes challenging due to weakened respiratory muscles, increasing the risk of a major respiratory infection. Pneumonia can develop fast from a mild cold. It's crucial to get vaccinated against the flu and to seek medical attention right away if you become ill.

LEARNING:

Though few have severe cognitive impairment, about one-third of boys with DMD have some kind of learning difficulties. Dystrophin abnormalities in the brain are thought to have a mild impact on cognition and behavior. Attention focusing, language learning and memory, and emotional interaction are the three main areas where learning difficulties in DMD manifest.

The school system's special education division or an MDA Care Center can refer children who may have learning disabilities for an evaluation by a developmental or pediatrics neuropsychologist.

Interventions in education and psychology might start straight once if a learning disability is identified. Exercises and methods may be recommended by an expert to aid with these issues, and schools may also offer specialized learning assistance (21) (22) (23) (24) (25).

TREATMENT:

Deflazacort and prednisone are corticosteroids.

The most common medications used to treat DMD are glucocorticoids, specifically prednisone and deflazacort. Since they have been in use for more than 20 years, the advantages are now widely recognized. The only medicine that has been proven to boost muscle strength is this one. Early research has shown that its use increased functionality in daily tasks and sustained ambulation. Long-term research has demonstrated that they also lessen the requirement for scoliosis surgery, improve lung function, and support cardiac function. (26) (27).

Both an American Academy of Neurology review from 2005 and a Cochrane review from 2008 evaluated all randomized controlled trials involving the use of corticosteroids and came to the conclusion that prednisone given at doses of 0.75 mg/kg/day increased muscular strength and improved outcomes in short-term standard functional tests (28) (29). The first six months of treatment result in a gain in muscle strength, which is followed by a stabilization phase of two years, and a subsequent decline that is slower than in untreated patients (30).

OTHER IMMUNOSUPRESSENT-

It has been suggested that the immunosuppressive impact of corticosteroid therapy may be responsible for its positive effects. Therefore, additional research using different immunosuppressant's was done. However, a randomized, controlled research with 99 DMD boys found no benefit for azathioprine, whether it was used alone or in conjunction with prednisone (31).

There was no change in the treatment groups' muscle strength and functional capacities among the 146 ambulant DMD patients who got cyclosporine-A or a placebo both alone and in conjunction with prednisone in a placebo-controlled, double-blind research (32).

GENETIC THERAPY:

The possibility of genetic treatment, in which the dystrophin gene is introduced, has lately been studied. There have, however, been a number of difficulties. It is challenging to use the dystrophin gene in gene therapy because of its size. Thus, smaller genes called micro- or mini-dystrophin that can be put into a vector have been created. The virus connected to the adenovirus, a non-pathogenic parvovirus that has been shown to elicit an immune response, has been identified as the most promising vector thus far. There is evidence that when the gene is injected, the dystrophin is partially produced and muscle strength is improved. Mdx mice dys-/dys- have been developed to test the response. However, in preliminary studies on humans, 90 days after treatment initiation this gene expression was not observed. Results suggest that cellular immunity inhibits the success of this therapy (33) (34).

EXON SKIPPING:

The dystrophin protein is smaller and less functional in Becker's muscular dystrophy, leading to a less severe illness. As previously indicated, the defective gene displays deletions, duplications, and point mutations in DMD patients, which disrupt the reading frame of the genetic material. In order to restore the reading frame and allow for the expression of a protein that is smaller but partially functional, as with patients who have Becker muscular dystrophy, researchers are currently working to inject a molecule that can interfere with the RNA splicing signals to omit an additional adjacent exon. An antisense oligonucleotide (AO) is a synthetic, modified RNA molecule that has the ability to attach to certain pre-RNA sites, masking and omitting this exon from the splicing process (35).

AMINOGLYCOSIDE:

In cell cultures, gentamicin interacts with the 40s ribosomal subunit in the transcription of RNA, suppressing the termination codons and inserting in its place another amino acid which replaces it. In studies on *mdx mice* and in humans, gentamicin was capable of producing dystrophin expression in muscle fibers at 20% of normal levels (35). However, studies on DMD patients remain controversial. In fact one of them showed a beneficial effect of the muscle strength and a re-expression of dystrophin in muscles (36).

DEFLAZACORT SIDE EFFECTS:

- fever, chills, sore throat, weakness
- severe or ongoing diarrhea
- Blurred vision, tunnel vision, eye pain, or the perception of haloes around lights
- swelling in your hands, feet, or lower legs
- any skin rash, regardless of how small
- severe muscle weakness

CONCLUSION:

A genetically X-linked skeletal muscle condition called Duchenne muscular dystrophy (DMD) is characterized by progressive muscle atrophy. DMD is caused by various mutations in the DMD gene and result in a loss of the skeletal muscle protein dystrophin, which leads to a degradation of skeletal muscle.

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