EDITORIAL

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Molecularly targeted therapy for Duchene Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA): Kuwait Experience

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Abstract

Spinal muscle atrophy (SMA) is an autosomal recessive motor neuron disease caused by progressive degeneration of motor neurons in the spinal cord and in specific motor nuclei of the brainstem (cranial nerve nuclei V, VII, IX, and XII). The disease causes the voluntary muscles to become sluggish and wasted. Symptoms of spinal muscle atrophy differ, and may be mild or disabled, but include a muscle weakness which controls movement. Involuntary muscles are not affected, such as those in the heart, the blood vessels and the digestive tract. SMA weakens the muscles that are nearest to the body's core, including the elbows, knees, thighs and upper back. Within the spine (scoliosis) the affected child can develop a curve due to loss of size and strength of the back muscles. SMA development can also affect respiration and chewing, which can endanger the patient's life.

Spinal muscular atrophy has four types include:

SMA Type 1 (Severe): The term for this condition is also called as Werdnig-Hoffmann Disease. It is the most extreme and prevalent form of SMA. This is usually apparent at birth or during the first few months (0-6 months) afterwards. Symptoms include thin spine and flexible limbs. Generally children with this form have very little capacity to travel around. You may also have trouble eating and drinking, keeping up their head and breathing. Type 1 SMA is progressing rapidly, with muscle weakness leading to recurrent respiratory infections and usually death by age 2. Infants with form 1 SMA are rarely allowed to sit.

SMA Type 2 (Intermediate): Symptoms typically grow from 7 and 18 months of age. Progress rate can vary greatly. The disorder has more effect on the children's legs than on their bodies. Kids with form 2 SMA are rarely allowed to stand. Such form of SMA is also popular in respiratory infections. Depending on the extent of the patient's disease, life expectancy may vary from early childhood to adulthood.

SMA Type 3 (Mild): This form of SMA is also called Kugelberg-Welander or Muscular Atrophy in the Juvenile Spinal. Over a wide range of years, from 18 months to early adulthood, symptoms can first manifest. Type 3 SMA patients may be able to stand and walk but they may have difficulty getting up from sitting. These can also have moderate muscle fatigue and may be at higher risk for respiratory infections. Many Type 3 SMA patients have a lifespan near normal.

SMA Type 4 (Adult): Symptoms for this unusual SMA type typically do not grow until the second or third decade of life. Type 4 SMA patients may walk during adulthood but will typically experience progressive muscle weakness and other common SMA symptoms.

The most common type of SMA occurs due to defects on chromosome 5q in both copies of the survival motor neuron 1 gene (SMN1). This gene produces the motor survival neuron (SMN) protein that preserves motor neuron safety and normal function. Individuals with SMA have inadequate amounts of the SMN protein, resulting in loss of motor neurons in the spinal cord, resulting in weakness and skeletal muscle wastage. Such weakness is much more extreme in the muscles of the spine and upper legs and arm relative to those of the hands and feet. The prevalence of spinal muscle atrophy varies from 4 to 10 per 100,000 live births, and the carrier level of SMN1 mutations causing the disease varies from 1/90 to 1/47. SMA is the single most frequent source of child mortality.

Duchenne muscular dystrophy (DMD) is a severe degenerative muscle disease that affects young males. It is an X-linked recessive disease caused by a mutation in DMD gene on chromosome Xp21. These mutations prevent the production of a connective protein dystrophin. A lack of this connective protein results in severely weakened muscle cells and loss of muscle functions accompanied by muscle tissue replacement by fat and connective tissue. The primary symptom of DMD is muscle fatigue. This can start as early as age 2 or 3, affecting first the proximal muscles (those close to the body's core) and then the distal limb muscles (those close to the extremities). The lower outside muscles are usually affected in front of the upper outer muscles.

The child affected may have trouble jumping, running and walking. Many signs include calf enlargement, a waddling gait, and lumbar lordosis (an inward spine curve). Later it also affects the heart and respiratory muscles. Progressive weakness and scoliosis contribute to compromised pulmonary function and can eventually lead to acute respiratory failure.

Duchenne is caused by a genetic mutation that makes it difficult for the body to produce dystrophin, a protein that muscles need to function properly. Muscle cells without dystrophin are impaired and weakened. Over time, children with Duchenne experience walking and breathing issues, and eventually the muscles that help them breathe and the heart stop functioning. Duchenne is a chronic condition which is permanent. There is no treatment for Duchenne at this time.

Dystrophin plays an essential structural role in the muscle as it binds the internal cytoskeleton to the extracellular matrix. Dystrophin's amino-terminus binds to the sarcolemma-associated protein complex (DAPC) with F-actin, and the carboxyl terminus. The DAPC contains dystroglycans, sarcoglycans, integrins, and caveolin, and mutations that cause autosomally inherited muscle dystrophies in some of those components. When dystrophin is absent, the DAPC is destabilized which results in diminished levels of member proteins. It in turn results in incremental damage to the fiber and leakage to the membrane. The DAPC has a major function, the loss contributing to pathogenesis as well. DMD patients are usually wheelchair-bound by age 12 and die of respiratory failure in their late adolescents or early 20's. Most boys have an irregular electrocardiogram by the age of 18, suggesting that the diaphragm and cardiac muscle must also be addressed by any therapist.