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Review

Mucopolysaccharidosis and Therapeutic Agents

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ABSTRACT

Mucopolysaccharidosis (MPS) is a lysosomal storage disease that causes the accumulation of glycosaminoglycans (GAGs) in cells and occurs with the failure of hydrolysis enzymes to function, which divides big molecules into small molecules. Accumulation of GAGs in cells, tissues, and organs causes vital problems. Although various treatments, such as enzyme replacement or hematopoietic stem cell therapy, have been applied, a definitive treatment has yet to be found. This review discusses MPS and its treatment options.

Keywords: Enzyme replacement therapy, hematopoietic stem cell transplantation, mucopolysaccharidosis, therapeutic agent

Mucopolysaccharidosis (MPS) is a type of lysosomal storage disease with seven subtypes: MPS type I, MPS type II, MPS type III, MPS type IV, MPS type VI, MPS type VII and MPS type IX.[1] Lysosomal storage diseases are inherited diseases that occur as a result of the inability to produce sufficient amounts of enzymes as a result of mutation or damage to the genes encoding the hydrolysis enzymes of the lysosome organelle, which is responsible for digesting foreign substances coming into the cell from outside, damaged molecules and organelles within the cell that have lost their ability to function.[2,3]

Mucopolysaccharidosis type I, MPS type II, MPS type III, MPS type IV, MPS type VI, MPS type VII, and MPS type IX are caused by the accumulation of mucopolysaccharides under the main three groups due to the inability to digest them sufficiently in lysosomes.[2] Mucopolysaccharides, also known as glycosaminoglycans (GAGs), are a type of polysaccharide formed by connecting with glycosidic bonds and forming long chains. Mucopolysaccharides can be divided into three main groups: polycarboxylates (hyaluronic acid, chondroitin), polysulfates (keratan sulfates;KS), and polycarboxy-sulfates (chondroitin 4- and 6-sulfates, previously designated chondroitin sulfate A and C, respectively; dermatan sulfates (DS); and heparitin sulfates).[2,4]

MPS TYPE I

Due to the out of the function of α-L-iduronidase (IDUA) enzymes caused by the damage of the genes encoding IDUA enzyme, accumulation of GAG in tissues occurs in MPS type I (Hurler syndrome). Mucopolysaccharidosis type I divides into three groups according to the degree of decreasing severity: Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome.[5,6] Patients' physical appearance varies according to the MPS I types.[2]

The most severe type of MPS type I is also known as Gargoylism in public. As a result of inadequate activation of the IDUA enzyme, GAGs like heparin sulfate and dermatan sulfate accumulate highly in the tissues of several vital organs in the body, so Hurler syndrome occurs.[5] Glycosaminoglycans that accumulate in organs like the spleen, the liver, the heart, and the skin cause enlargement of these organs, deformity, and dysfunction over time. The decisive symptoms usually appear after the age of one year.[6]

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Skeletal system symptoms

Hurler syndrome also affects the skeletal system, causing skeletal dysplasia, a disease that progresses throughout patients' lives. Even if the height of the patients during infancy is at a level that can be considered normal compared to a healthy baby, height growth almost stops when they are 24 weeks old. Therefore they can reach a maximum height of 120 centimeters.[6]

Due to the thickening caused by swelling in the joints due to synovial inflammation and the formation of phalangeal dysplasia, which prevents the proper placement and elongation of the hand bones, the fingers of patients with Hurler syndrome cannot be opened linearly. Hence, their hands resemble a bird's claw.[5,7] Carpal tunnel syndrome and joint stiffness are seen with entrapment of the median nerve in the carpal tunnel in the wrist.[5,8,9]

The collarbones (clavicles) are thicker, shorter, and more irregular than they should be.[5] The deformity seen in the vertebrae due to defective ossification centers of the vertebral bodies causes kyphosis or scoliosis, known as the curvature of the lower spine, and appears as a hump from the outside.[5,6,10]

Humerus, radius, ulna, metacarpals, phalanges in fingers and toes, femur, tibia, and metatarsals are short in length and wide in width.[5] Due to incomplete ossification of the bones in the proximal tibial metaphyseal region, valgus deformity, which gives the appearance of parenthesis to the legs, is observed.[10]

Ocular symptoms

The most common ocular symptom is corneal clouding due to inflammation. Night blindness and peripheral vision loss due to strabismus, optic nerve entrapment, and retinal degeneration are among the most common effects. Cortical damage, retinal damage, and corneal clouding caused by fluid accumulation in the brain can lead to blindness if left untreated.[5,11]

Cardiovascular symptoms

Although not noted in newborn babies, cardiovascular diseases such as thickening of the heart wall, mitral valve regurgitation, thickening of the heart valves, rhythm disorder and heart failure occur over time are the major cardiovascular diseases.[5,6]

Ear-nose-throat, speech, and hearing symptoms

Ear, upper respiratory tract, and lower respiratory tract infections are frequently observed in patients.[5] Since GAGs accumulated in the tongue and tonsils cause thickening of the tongue and tonsils, patients cannot breathe properly. As a result, sleep apnea, wheezing, speaking and pronouncing difficulty, drooling, and snoring are detected.[5,12] Repetitive otitis media and thickening of the pharynx and tonsils due to accumulated GAGs put pressure on the Eustachian tube. This situation causes hearing loss by disrupting the functionality of the Eustachian tube, which provides the balance between middle ear pressure and external pressure.[5,12,13]

Neurological symptoms

Although the physical and neurological development stages, usually up to 18 or 24 months, progress as they should, after 24 months at the latest, psychomotor skills begin to pause and regress. It is known that patients with a general life span of eight to 10 years lose almost all their psychomotor abilities in the last stage of the disease.[5]

Physical appearance symptoms

Individuals with Hurler syndrome share common physical appearances regardless of race. For instance, these physical features are a large head, a protruding and wide forehead, large and bulging eyes, a flat face, chubby cheeks, a dented nasal bridge and a wide nose tip, large lips, and a thick and short neck.[5,6]

Hurler-Scheie Syndrome/Scheie Syndrome

Although symptoms usually begin between the ages of three and ten, diagnosis usually takes longer, for the symptoms are milder than in Hurler syndrome.[14]

Skeletal system symptoms

Since people suffering from Hurler-Scheie and Scheie syndrome do not experience any mental retardation, as in Hurler syndrome, one of the most important symptoms in diagnosing the disease is disorders in the skeletal system.[15] Claw hand appearance, carpal tunnel syndrome, severe back and neck pain, scoliosis, kyphosis, and joint stiffness that limits mobility are observed extensively, like in Hurler syndrome.[5]

Ocular symptoms

Corneal clouding, retinal damage, and peripheral vision loss are commonly observed disorders.[5]

Cardiovascular symptoms

As in Hurler syndrome, thickening of the heart wall and mitral valve regurgitation are observed.

Ear-nose-throat, speech, and hearing symptoms

Sinusitis and consequently a runny nose are common. Obstructive sleep apnea, snoring, and drooling are observed as the upper respiratory tract muscles expand and weaken due to the accumulated GAG.[5,16] Moderate hearing loss is observed as GAG accumulation affects the functionality of the Eustachian tube.[5]

Neurological symptoms

Intelligence and psychomotor skills, which progress smoothly in childhood, weaken with the onset of learning difficulties in adolescence.[5,6]

MPS TYPE II

Mucopolysaccharidosis type II is the accumulation of DS and heparan sulfate in the tissues due to the loss of functionality of the iduronate-2-sulfatase (IDS) enzyme as a result of mutations and damages occurring in the gene encoding a lysosomal enzyme iduronate-2-sulfatase and in the Xq28 gene region.[17] It is examined in two types: rapidly progressing/severe (Hunter syndrome) and slowly progressive/mild. Although clinical symptoms are similar in both types, they differ from each other thanks to intelligence, behavior, and some features. As a result of GAG accumulated on the face, they have physical features such as a large head, large forehead, large round nose, dented nasal bridge, large lips and ears, bad teeth, and bulging eyes.[17,18]

Dental symptoms

Incorrect closure of the mouth occurs as a result of dental caries, gingival enlargement, tooth enamel diseases, and incorrect ossification of the jawbone.[18]

Ear-nose-throat, speech, and hearing symptoms

Like MPS type I, patients with MPS type II, which progresses rapidly as a result of chronic otitis media and loss of functionality of the Eustachian tube due to the pressure of GAG accumulation on the Eustachian tube, experience hearing loss early in life.[17] Upper respiratory tract infections are common. It is difficult for patients to breathe and speak because of the accumulation of GAGs in the throat, tongue, and tissues, intense mucosal discharge from the nose, and improper placement of the ribs. Due to unhealthy breathing, sleep apnea, snoring, and wheezing are often observed.[18]

Cardiovascular symptoms

Factors such as thickening of the heart walls and vessels due to GAG accumulation manifest themselves as heart failure, murmur, and mitral valve regurgitation.[17,18]

Skeletal system symptoms

Glycosaminoglycan accumulation causes an inability to elongation of the bones in the ossification centers and growth plates of the skeletal system. This situation not only makes patients shorter than normal but also leads to kyphosis, hunchback, and scoliosis.[17,18] As the disease progresses, this pressure on the spinal cord can lead to functional impairment of the bowel and bladder and incontinence.[18] The accumulation of GAGs in the joints causes joint stiffness and pain, severely limiting mobility. Another symptom is that the hands resemble claws in appearance.[5,7,18]

Ocular symptoms

Mucopolysaccharidosis type II does not significantly affect the eyes and eyesight. Vision loss due to corneal clouding and optic nerve entrapment is rare.[17]

Neurological symptoms

The effect of Hunter syndrome on the central nervous system (CNS) reveals itself with stagnation and regression in development between the ages of six and eight years. This leads to mental retardation, impaired motor skills, and aggressive and hyperactive behavior. In the slowly developing MPS Type II syndrome, mental retardation, hyperactivity and aggressive behavior are not present.[17]

MPS TYPE III

Mucopolysaccharidosis type III (Sanfilippo syndrome) is the most common MPS disease. There are four types, MPS type IIIA, MPS type IIIB, MPS type IIIC, and MPS type IIID. This distinction is not based on differences in clinical symptoms but on the type of enzyme with insufficient activity.[19]

Mucopolysaccharidosis type III variants are caused by the accumulation of heparan sulfate in tissues and organs due to the deficiency of hydrolysis enzymes like heparan-N-sulfatase in MPS type IIIA, α-N-acetylglucosaminidase in MPS type IIIB, α-glucosaminidase-N-acetyltransferase in MPS type IIIC and N-acetyl-glucosamine 6-sulfatase in MPS type IIID.[1,19]

Skeletal system symptoms

As in other types of MPS, inability to fully open the fingers, joint stiffness, ligament laxity, carpal tunnel syndrome, spine damage, spine straightening, scoliosis, and hip tenderness are observed. The height of patients with Sanfilippo syndrome is almost the same as that of healthy individuals.[20,21]

Ocular symptoms

Although corneal clouding is not common, optic nerve compression and retinal damage are common.[20,21]

Ear-nose-throat, speech, and hearing symptoms

Deafness can occur as a result of chronic otitis media, problems with the ossicles in the middle ear, and loss of functionality of the Eustachian tube. With the increase in body fluids, the mucosal fluid in the respiratory tract also increases, making breathing difficult. Respiratory tract infections are also common.[20,21]

Neurological symptoms

Aggressive attitudes and behaviors, sleep apnea, insomnia, and hyperactivity are observed due to damage to the CNS. After the age of two, symptoms begin to appear. After the age of ten, patients slowly lose motor skills such as walking and speaking.[20,21]

MPS TYPE IV

Mucopolysaccharidosis type IV (Morquio A syndrome) occurs as a result of the accumulation of keratan sulfate and chondroitin-6-sulfate in cells and tissues, especially in the extracellular matrix of bone and cartilage cells as a result of the loss of activity of the enzyme N-acetylgalactosamine-6-sulfate sulfatase.[22] There is no mental retardation. Most deaths are due to spinal cord injuries, cardiovascular disease, or respiratory failure.[22,23]

Skeletal system symptoms

Patients appear healthy at birth, except for the deformity of their spine, but clinical symptoms begin to appear at 24-36 months of age.[22] Since most of the KS is produced in cartilage, it has a major impact on cartilage health and ossification. Short stature and neck, spinal problems such as scoliosis and kyphosis, odontoid fractures, genu valgum, which gives the appearance of crooked knees, protrusion of the rib cage, popularly called pigeon chest, hardening of the joints and shortening of the muscles are frequently observed.[22,23] Ligaments that can move abnormally due to the looseness of the connective tissue connecting the bones are also noticed.[24]

Ocular symptoms

It is possible to experience corneal clouding and loss of vision in the later stages of the disease.[23]

Cardiovascular symptoms

After cartilage, the heart is the most common place where KS accumulates. This leads to the thickening of the heart, mitral valve insufficiency, and thickening of the arteries due to KS accumulation.[23]

Respiratory distress

Respiratory tract infections are common. Respiratory failure due to upper and lower respiratory tract obstruction caused by spinal injuries is among the symptoms. Most deaths are caused by respiratory failure.[22,23]

Ear and hearing symptoms

Like other types of MPS, chronic otitis media and loss of function of the Eustachian tube cause hearing and balance loss in the later stages of the disease.[23]

MPS TYPE VI

It occurs due to the activity loss of the enzyme arylsulfatase B, which breaks down chondroitin-4-sulfate and DS, resulting in the accumulation of chondroitin-4-sulfate and DS in the cells.[1,19] Mucopolysaccharidosis Type VI (Maroteaux–Lamy syndrome) is analyzed under two sub-headings: slow progressive and rapidly progressive. Physical features can be listed as a big head, bulging eyes, short neck, and protruding rib cage, just like in Hurler syndrome.[25] Mental retardation is not observed in MPS Type VI patients. Rapidly progressing MPS Type VI begins to show significant symptoms before 24 months of age.[25] Patients usually die between the ages of 20-30. Slowly progressing MPS Type VI may take a long time to be diagnosed. Patients can live an average of 20 years longer than rapidly progressing MPS Type VI.[25]

Skeletal system symptoms

Patients are shorter in height compared to healthy individuals of the same age.[25] Pressure on the spinal cord, scoliosis, and kyphosis are common disorders. As a result of the shortening of the muscles, the joints harden, thicken and change shape.[1,25] Breathing difficulty due to pressure on the lungs caused by kyphosis and scoliosis is common.[1]

Cardiovascular symptoms

There is a thickening of the heart valves, walls, and blood vessels. Mitral valve regurgitation is common.[1,25]

Visual and hearing impairments

Corneal clouding is common. Rapidly progressing MPS Type VI patients may lose their sight and hearing.[1,25]

MPS TYPE VII

Deficiency of the enzyme ß-glucuronidase leads to the accumulation of chondroitin sulfate, DS, and heparin sulfate in cells and tissues.[1] There are two types: fast progress and slow progress.[25]

Ocular symptoms

The biggest preliminary symptoms for diagnosing MPS Type VII (Sly syndrome) are corneal clouding, light sensitivity, and ocular nerve compression in the eyes. Vision loss may occur in the later stages of the disease.[26]

Skeletal system symptoms

Kyphosis, scoliosis, joint stiffness, and genu valgum are common.[25,26]

Cardiovascular symptoms

Thickening of the aorta and thickening of the heart walls and heart valves are observed at high rates.[25,26]

ENZYME REPLACEMENT THERAPY

Developed through recombinant DNA technology, enzyme replacement therapy (ERT), as the name suggests, is to replace enzymes that cannot fulfill their function in the body. Patients receive a solution containing the target enzyme intravenously every week.[27,28]

Enzyme replacement therapy has been observed to be effective in reducing the size of the liver and spleen, which are enlarged due to GAG deposition, and in increasing the activity of daily living (ADL). However, it mostly does not affect the CNS, cardiovascular and skeletal systems.[28,29]

The ERT approved for MPS type I is a recombinant protein, an IDUA enzyme called laronidase. It has shown efficacy in ADL elevation. There was no effect on the CNS and ocular systems, although the cardiovascular and skeletal systems showed a slight improvement.[29]

There are two ERT drugs approved for MPS type II that have passed phase studies. Idursulfase is a recombinant human protein.[29] Idursulfase has shown good efficacy in increasing endurance and ADL, which patients need in their daily lives, as well as minimal efficacy in promoting height growth.[29,30] The second ERT is a treatment using idursulfase beta, but the source of the recombinant protein is different. Idursulfase beta is derived from Chinese hamster ovary cells. Although it contains the same amino acids, the enzyme spends less time in the vasculature as idursulfase beta, which is more readily and rapidly taken up by fibroblasts, which suppresses the patient's immune response.[29,31]

Phase I/II clinical trials for MPS type III were examined by administering α-N-acetylglucosaminidase, a recombinant protein obtained from human fibroblast cells, to the patient at various concentrations and time intervals. However, its therapeutic effect could not be determined.[29]

The recombinant enzyme N-acetylgalactosamine 6-sulfatase is used as ERT for MPS type IV. Although it increased endurance and ADL in patients, it did not affect the cardiovascular, ocular, or skeletal systems.[29]

Arylsulfatase B, also known as galsulfase, is a recombinant protein derived from human fibroblast cells that have been clinically studied for MPS type VI.[29] It has been observed to improve respiration and increase endurance and ADL. It has not been found to have any therapeutic effect on the cardiovascular system but has been observed to help stabilize it.[29,32]

The recombinant human β-glucuronidase (rhGUS) enzyme, also known as vestronidase alfa, produced from human fibroblast cells, is used for ERT in MPS type VII.[29] According to an experiment on puppies, ERT with the rhGUS enzyme showed a positive effect on mitral valve regurgitation.[29,33] Intravenous fluid administration of rhGUS to a newborn infant resulted in ease of breathing, increased endurance, and an improvement in mitral valve regurgitation, with no sensitization or complications from the treatment.[29,34]

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation is a frequently preferred type of therapy after ERT.[35] Hematopoietic stem cell transplantation, which is especially used for individuals diagnosed with MPS type I, can also be used for individuals

with other MPS syndromes.[36] Healthy stem cells derived from bone marrow, peripheral blood stem cells, and cord blood are given to MPS patients by blood transfusion.[35,37,38] The enzymes secreted by healthy stem cells mixed into the patient's blood are transferred to the cells of the patient.[35,39,40] The difference between hematopoietic stem cell transplantation (HSCT) and ERT is that in ERT, the dysfunctional enzyme that causes accumulation in the body is given to the patient through intravenous fluid and directly reaches the lysosome, cannot cross the blood-brain barrier and does not affect the CNS.[35] However, in HSCT, since the enzymes are produced in the individual's body by donor stem cells given into the patient's bloodstream and stem cells have the opportunity to reach everywhere in the body, they can cross the blood-brain barrier and affect the CNS. For HSCT to be optimally effective, the age at which treatment is started is crucial.[35] The sooner symptoms are recognized and the diagnosis made, the stronger the effect of the therapy on vision, hearing, breathing difficulties, stiff joints, and rough facial features. However, no matter how early it is started, it is not a sufficient therapy to cure cardiovascular disease, skeletal disorders, and mental retardation.[35,41,42]

In conclusion, MPS diseases are characterized by symptoms such as mental retardation, cardiovascular disorders, stiff joints, and rough facial features that affect every aspect of the individual's life. Although there are various ideas and studies for its treatment, none of them has achieved a definitive result. Even though ERT and HSCT are the most effective and frequently used treatments among the proposed treatments, no other solution has been found to extend the life span of the patients and make them healthy individuals, apart from relieving them a little during their short lives.

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