Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Clinical Biochemistry and Research

Journal homepage: https://www.ijcbr.in/

Review Article

Mucopolysaccharidoses: An overview and new treatment modalities

Keerthiga M[1], Arpita Chakraborty[2], Wilma Delphine Silvia CR[2,*], Akshay Atre[3], Preksha Shivakumar[1]

[1]*Dept. of Biochemistry, Shri Atal Bihari Vajpayee Medical College and Research Institute, Bengaluru, Karnataka, India*
[2]*Dept. of Biochemistry, Akash Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India*
[3]*Dept. of Phamacology, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka, India*

ARTICLE INFO

Article history:
Received 19-06-2023
Accepted 03-07-2023
Available online 14-07-2023

Keywords:
Enzyme replacement therapy
Hematopoietic stem cell therapy
Lysosomal storage disorder
Mucopolysaccharidosis
Substrate reduction therapy

ABSTRACT

Mucopolysaccharidoses are a group of inherited lysosomal storage disorders, caused due to deficiency of enzymes required for the breakdown of Mucopolysaccharides. These undegraded Mucopolysaccharides accumulate in various tissues and cause characteristic features like neurological deficit, impaired motor function, developmental delay, hearing loss, behavioral problems, corneal clouding, glaucoma, respiratory distress, coarse facial features, skeletal deformities, and organomegaly. Based on deficient enzymes they have divided into subtypes Mucopolysaccharidosis I (MPS I) Hunter syndrome (I H / I HS / I S), Mucopolysaccharidosis II(MPS II) Hunter syndrome (severe and mild form), Mucopolysaccharidosis III (MPS III) Sanfilippo syndrome, Mucopolysaccharidosis IV(MPS IV) Morquio syndrome, Mucopolysaccharidosis VI(MPS VI) Maroteaux Lamy syndrome, Mucopolysaccharidosis VI (MPS VII) Sly syndrome. Diagnosis is classically based on clinical examination and urine analysis. Enzyme assay can also aid in diagnosis. Chorionic villi sampling and amniocentesis are also becoming popular. The main objective of treatment is to improve the quality of life. Symptomatic management includes daily exercise, physiotherapy, tonsillectomy, shunting surgery, and corneal transplantation. There are various recent concepts utilized for the treatment of Mucopolysaccharidosis. This review article emphasizes such treatment aspects as Hematopoietic stem cell therapy, Enzyme replacement therapy, Gene therapy, Nano-enabled therapy, and Substrate reduction therapy.

1. Introduction

1.1. Mucopolysaccharides also known as Glycosaminoglycans (GAGs), are negatively-charged polysaccharide compounds

Mucopolysaccharides or Glycosaminoglycans, are composed of uronic acid and amino sugar to form heteropolysaccharides which are unbranched. They were first secluded from mucin hence called mucopolysaccharides. They are predominantly present in extracellular compartment.[1] Their functions within the body are widespread and determined by their molecular structure. GAGs play a key role in cell signaling, which regulates many biochemical processes. Some of these processes include regulation of cell growth and proliferation, promotion of cell adhesion, anticoagulation, and wound repair. The four primary groups of GAGs are classified based on their core disaccharide units and include heparin/heparan sulfate, chondroitin sulfate/dermatan sulfate, keratan sulfate, and hyaluronic acid.

* *Corresponding author*.
E-mail address: biochemaimsrcwds@gmail.com (W. D. Silvia CR).

https://doi.org/10.18231/j.ijcbr.2023.016

1.2. Properties of glycosaminoglycans

The slippery nature of the mucous and synovial fluid is due to the presence of numerous negative charges on heteropolysaccharide chains making them repulse each other. This is responsible for them to revert to a hydrated state when the compression force is released, hence the pliant nature of synovial fluid and vitreous humor.[1]

1.3. Enzymes involved in glycosaminoglycans degradation

The enzymes are 3 exo – glycosidase (Alpha L-Iduronidase, beta – glucuronidase and beta hexosaminidase) and 2 sulfatase (iduronate -2- sulfatase and N – acetyl galactosamine -4- sulfatase).

2. Dermatan Sulfate Catabolism

Dermatan sulfate is made up of sulfated N- acetyl galactosamine alternating with uronic acid. Degradation of dermatan sulfate starts from a non-reducing end by the successive action of 3 exo – glycosidase (Alpha L-Iduronidase, beta–glucuronidase and beta-hexosaminidase) and 2 sulfatase (iduronate -2- sulfatase and N – acetyl galactosamine -4- sulfatase). Alpha – L- iduronidase also known as Hurler's corrective factor degrades Alpha – L – iduronic acid residues of dermatan and Heparan sulfate, a deficiency of which is seen in Hurler's syndrome.[2] Alpha – L – Iduronidase is present in precursor form, which undergoes intracellular modification to a shorter form by losing 10 amino acids and contains Mannose – 6- phosphate marker for targeting lysosomes.[3] Beta – glucuronidase detaches glucuronic acid in dermatan, chondroitin, and heparan sulfate. A deficiency of this enzyme is seen in Mucopolysaccharidosis VII (MPS VII). Beta – hexosaminidase present as 3 isoenzymes A, B, and S removes N- acetyl galactosamine from dermatan sulfate. The absence of isoenzymes A and B results only in a milder form of Sanfilippo syndrome, whereas frank Mucopolysaccharidosis is seen only when all 3 isoenzymes are absent. This suggests that isoenzyme S is involved in the degradation of dermatan sulfate in the absence of isoenzymes A and B.[4] The enzyme deficient in MPS II, Iduronate sulfatase also known as Hunter corrective factor cleaves the sulfate group from L – iduronic acid present in dermatan sulfate. Removal of sulfur from N – acetylgalactosamine -4- sulfate is carried out by arylsulfatase B, the enzyme that is absent or deficient in Maroteaux – Lamy syndrome.

3. Heparan Sulfate Catabolism

Heparan sulfate is made up of glucuronic acid and L – iduronic acid, some of which are sulfated. Alpha – Iduronidase and beta–glucuronidase cleaves terminal L – iduronic acid and glucuronic acid respectively.[5] Alpha – N – acetylglucosaminidase, the enzyme that is scarce in MPS III B, is required for the removal of N- acetyl glucosamine that is present in heparan sulfate.[6] Iduronate sulfatase causes desulfation of 2- sulfated iduronic acid in heparan sulfate. Therefore, patients with alpha – L – Iduronidase deficiency (MPS I), beta – glucuronidase deficiency (MPS VII), or iduronate sulfatase deficiency (MPS II) will have defects in the degradation of both heparan sulfate and dermatan sulfate.

4. Keratan Sulfate Catabolism

Glycosaminoglycans that do not contain uronic acid are keratan sulfate. Instead of uronic acid, sulfated galactose alternates with sulfated N- acetyl glucosamine. Any alternations in the pathway of degradation of keratan sulfate lead to MPS IV. The restricted distribution of keratan sulfate in cartilage and cornea is responsible for its distinctive clinical features, compared to dermatan and heparan sulfate which have wide distribution. Beta–galactosidase removes galactose from non-reducing end of keratan sulfate. Complete absence of beta–galactosidase leads to GM 1 gangliosidosis whereas Morquio syndrome is due to mutations that mainly affect the catabolism of heparan sulfate. Beta – hexosaminidase cleaves terminal N- acetylglucosamine and its deficiency leads to Tay – Sach's and Sandhoff syndrome.[7] Sulfatase removes 6-sulfate from galactose, its deficiency is seen in MPS IV. Apart from glycosaminoglycans, gangliosides GM2 and GM3 also concentrate in the brain parenchyma of MPS patients. Glycosaminoglycans accumulation leads to secondary inhibition of enzymes of gangliosides metabolism. Gangliosides accumulation is seen in the brains of patients with MPS I, MPS II (severe) and MPS III A, MPS III B, MPS III D and all of them show mental retardation, but gangliosides are not accumulated in the brain of patients with MPS I whose intelligence quotient is normal.

4.1. Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) is a group of metabolic disorders caused due to deficiency or malfunctioning of lysosomal enzymes required for the degradation of glycosaminoglycans.[1] Lysosome is a cell organelle containing various enzymes, which will process and degrade excess heteropolysaccharide chains to their simpler forms, therefore popularly known as a suicide bag. Inadequate or impaired production of these enzymes from lysosomes results in the accumulation of long heteropolysaccharide chains in various tissues. Such large accumulation will eventually cause cellular injury which hampers cell or organ function and its appearance and physical abilities. This condition which is caused due to decreased production

or malfunctioning or absence of release of enzymes from lysosome is called lysosomal storage disorder. Based on the deficient enzyme, the catabolism of dermatan sulfate, keratan sulfate, chondroitin sulfate, or hyaluronate may be blocked. There is activation of an alternative pathway and products formed in this alternative pathway are excreted through urine. Each enzyme has unique genes and cDNA encoded which can be used for the production of recombinant enzymes and to identify mutation-causing diseases. Mutations of Mucopolysaccharidosis are heterogeneous, but specific populations have one / a few mutant alleles which are predominant. Except for MPS II which is X-linked, all other Mucopolysaccharidosis are Autosomal Recessive. Most Mucopolysaccharidosis have either point mutations or small changes in genes, whereas large deletion and major rearrangement occur in MPS II.[8]

4.2. MPS I (Hurler, Hurler – Scheie syndrome, Scheie)

MPS I is caused due to deficiency of alpha – L – Iduronidase and is characterized by a wide spectrum of manifestations with Hurler and Scheie syndrome representing extreme ends, whereas Hurler – Scheie syndrome represents intermediate severity. Classification of MPS I into 3 subtypes is based on clinical features, as these subtypes cannot be distinguished based on the diagnostic procedure (Table 1).

4.3. MPS I H (Hurler syndrome)

Hurler syndrome occupies the severe end of the clinical spectrum with multisystem involvement in a progressive manner. Diagnosis of a case of Hurler syndrome is usually made between 4-8 months, only umbilical hernia or inguinal hernia may be present at birth and as an infant, they are usually normal as it takes time for accumulation of glycosaminoglycans and cause cell injury. Deceleration of growth is seen between 6-8 months. Developmental delay begins in 12-24 months and is obvious by 2-4 years. Macroglossia first clues about medical recognition. Most children with this syndrome have limited language skills due to hearing loss, developmental delay, and macroglossia. Other features include recurrent ear, nose, and throat infections, coarse facial features, hepatosplenomegaly, and skeletal abnormalities. Most children with Hurler have recurrent upper respiratory tract infections, noisy breathing, and profuse nasal discharge. By the first year of age, corneal clouding becomes apparent. Cardiac complications and respiratory infections are common causes of death. Radiological features include a large skull, with untimely closure of sagittal and lambdoid sutures, thickening of the calvarium, shallow orbit, large – J – shaped sella, and atypical spacing of teeth with a dentigerous cyst, kyphosis with anterior hypoplasia of lumbar vertebrae, diaphyseal enlargement of long bones with irregular metaphyses. Coxa Volga, poorly formed pelvis with the short head of the femur. The ribs have characteristic oar – shape, flat at the sternal end and narrow at the vertebral end. Short phalanges are also seen.

4.4. MPS I H/S (Hurler/Scheie syndrome)

The features are intermediate between Hurler and Scheie syndrome. Symptoms start between 3-8 years. Deafness, corneal clouding, and skeletal abnormalities begin early to mid–teens. Micrognathia is a characteristic facial feature in patients with H-S syndrome. Accumulation of glycosaminoglycans in the spinal sheath leads to compression of the cervical cord, but intelligence is normal.

4.5. MPS I S (Scheie syndrome)

Scheie syndrome is the mildest form with onset of symptoms after 5 years of age and diagnosis is usually made between 10- 20 years of age. Corneal clouding, skeletal abnormalities, and coarse facial features are seen but stature and intelligence are normal. Skeletal abnormalities are more confined to hands causing claw–hand and carpal tunnel syndrome limiting daily functions. Apart from corneal clouding, glaucoma, and retinal degeneration are also seen causing visual impairment. Accumulation of glycosaminoglycans on valves and chordae tendinae leads to aortic valve stenosis and/or regurgitation.

4.6. MPS II (Hunter's syndrome)

Based on clinical features they are recognized in milder and more severe form. MPS II is transmitted in an X – linked Recessive manner, therefore affected females are rare to find, however, there are few female patients with milder forms and these females could have some additional mutations, preventing the expression of normal alleles (Table 1).

4.7. MPS II (Severe form)

The onset of disease is between 2-4 years with progressive neurological deficit. Communicating hydrocephalus exacerbates neurological deficit with increased intracranial pressure after 7 years of age and is apparent by 10- 15 years. Corneas are characteristically clear but retinal detachment can be seen. Involvement of autonomic nervous system causing persistent diarrhea is troublesome to younger patients. Neurological complications are very severe in these patients with deterioration of central nervous system after 7-10 years of age. Cardiac failure due to myocardial thickening, valvular dysfunction, pulmonary hypertension, coronary narrowing is the common cause of death. Other atypical features include ptosis and early onset of seizures.

4.8. MPS II (Mild form)

Patients with a milder form of Hunter syndrome have normal intelligence and will survive into adulthood. Clinical features are similar to severe forms of MPS II but at a reduced rate of progression. Corneal papilledema is evident due to the deposition of glycosaminoglycans in the sclera, causing optic nerve compression.

4.9. MPS III (Sanfilippo syndrome)

MPS III is divided into four types based on enzyme deficiency which are required for the degradation of heparan sulfate. The enzyme deficiency in type A is N – sulfatase, alpha – N- acetylglucosaminidase in type B, alpha – glucosaminide acetyltransferase in type C and N – acetylglucosamine – 6 – sulfatase in type D. Clinical features manifest by 2-6 years of age. Hyperactivity with wild behavior, developmental delay, hirsutism, coarse hair, and insomnia is presenting features. Coarse facial features are not prominent and some patients have normal features as adults. Stature is normal and skeletal deformities are mild. Due to poor articulation development of language skills is poor. Severe hearing loss is common. By 16 years of age, there is cortical atrophy leading to severe neurological deficit. Dementia, insomnia, poor attention span, hyperactivity, aggressive behavior, temper tantrums, and profound mental retardation is seen (Table 1).

4.10. MPS IV (Morquio syndrome)

The two types of MPS IV TYPE A and TYPE B are caused due to deficiency of enzymes of keratan sulfate metabolism, N- acetylgalactosamine-6–sulfatase and beta–galactosidase respectively. Both types are characterized by skeletal deformities resulting in dwarfism (short stature), with normal intelligence making them unique from other forms of MPS. Patients appear normal at birth. Short stature, genu valgum, kyphosis, and waddling gait with a tendency to fall frequently are early symptoms. Other skeletal abnormalities include platyspondylia, odontoid hypoplasia, hyperlordosis, kyphoscoliosis, ovoid deformities of vertebrae, ulnar deviation at the wrist joint, cubitus valgus, short Phalanges, and osteoporosis. Atlantoaxial subluxation is a unique feature of Morquio syndrome. Extra-skeletal manifestations include recurrent upper respiratory tract infection, small teeth, valvular disease, hearing impairment, and facial features like prognathism, and broad mouth (Table 1).

4.11. MPS VI (Maroteaux – Lamy syndrome)

N – acetylgalactosamine deficiency is responsible for MPS VI. Neurological development is normal whereas physical development is impaired. Presentation at birth would be macrocephaly, inguinal hernia, or Umbilical hernia. An obvious clouding of the cornea is seen. Growth is normal for the first few years of life but slowly deteriorate after 6 or 8 years. Restriction of movement at large joints results in a crouched stance. Hepatosplenomegaly is always present. The typical presentation of MPS VI includes patients with short stature, protuberant abdomen, and lumbar lordosis. Radiological changes are macrocephaly, ovoid shape vertebrae, acetabulum hypoplasia, and small flared iliac wings (Table 1).

4.12. MPS VII (Sly syndrome)

Patients with the sly syndrome have coarse facial features, protruding sternum, hepatosplenomegaly, umbilical/ inguinal hernia, thoracolumbar gibbus, and mild–moderate mental retardation. Granulocytes showing coarse metachromatic granules are striking. The severe forms of the Sly syndrome are characterized by hydrops foetalis, dysostosis multiplex and features of lysosomal storage disorder. The neonatal form itself is heterogeneous, ranging from death in utero to mild or no hydrops at birth. A review of other pregnancies among mothers of MPS VII patients suggests an increase number of spontaneous abortions. Most patients presenting beyond the neonatal period have increased urinary excretion of glycosaminoglycans. MPS VII patients who present as infants or young children have hepatosplenomegaly, Umbilical/inguinal hernia, short stature, repeated upper respiratory tract infection, pneumonia, and developmental delay.

5. Diagnosis

Diagnosis is based on clinical examination, Mucopolysaccharides excreted in urine can also be detected in urine analysis. Deficient enzymes can be detected by enzyme assay which aids in definitive diagnosis. Nowadays prenatal tests like chorionic villus sampling and amniocentesis are becoming popular which identify the defective or mutated gene in the fetus. Genetic counseling plays a pivotal role in backstopping parents with a family history of Mucopolysaccharidosis.

6. Treatment

6.1. Symptomatic management

Early initiation of daily exercise, physiotherapy, and counseling helps in improving the quality of life. Dietary modification like restricting sugar, milk, and dairy products will not prevent the progression of disease but has helped people with excessive mucus. Polysomnography can be done to assess the requirements of nighttime oxygen. Tonsillectomy and adenoidectomy can also help to relieve obstructive airway pressure in individuals with obstructive sleep apnea. Shunting surgery helps to drain excess cerebrospinal fluid. Corneal transplantation can be used to

Table 1: Recognition pattern of Mucopolysaccharidoses [1]

Clinical features	**MPS lH**	**MPS lS**	**MPS ll**	**MPS lll**	**MPS IV**	**MPS Vl**	**MPS Vll**
Common name	Hurler's syndrome	Scheie syndrome	Hunter syndrome	Sanfilippo syndrome	Morquio syndrome	Maroteaux-Lamy syndrome	Sly syndrome
Mental deficiency	+	-	+	+	-	-	?
Coarse facial features	+	+	+	-	-	+	?
Corneal clouding	+	+	-	-	+	+	?
Visceromegaly	+	+	+	-	-	+	+
Short stature	+	+	+	+	+	+	+
Joint contractures	+	+	+	-	-	+	+
Dysostosis multiplex	+	+	+	+	+	+	+
Leucocyte inclusions	+	+	+	+	-	+	+
Mucopolysaccharidurıa	+	+	+	+	+	+	+

(+): Clinical feature is present
(-): Clinical feature is absent
(?): Status not known

Table 2: Enzyme therapy with indication with their dilution and dosage

Enzyme	**Indication for Administration**	**Dilution**	**D osage**	
			Children	**Adult**
Aldurazym	Mucopolysaccharidosis type I	0.9% sodium chloride containing 0.1% albumin	> 5 years - 0.58mg/ kg once weekly	Adults - 0.58 mg / kg once weekly
Elaprase	Mucopolysaccharidosis type II	0.9% sodium chloride.	>16 months – 0.5 mg/kg once a week	0.5mg/ kg once a week.
Naglazyme	Maroteaux-Lamy syndrome (MPSlV),	0.9% normal saline.	Infants: 1 or 2 mg / kg once weekly. Children and adolescents – 1 mg/ kg once weekly.	

tackle corneal clouding to improve vision. [9]

6.2. Bone marrow therapy / Hematopoietic stem cell therapy/ Umbilical cord blood transfusion

Although these procedures are risky with increased mortality and morbidity, if they are done at the right time before significant accumulation in neurons, then the benefits outweigh the risk of causing drastic changes in the natural history of disease and increasing life expectancy. [10] Hematopoietic stem cell therapy consists of transferring stem cells from a healthy donor to a patient affected, if the procedure is successful, the donated stem cells begin to multiply and produce all the enzyme which was deficient or malfunctioning in the recipient. Except for skeletal and eye abnormalities, rest all physical abnormalities can be rectified. But coming to neurological outcomes it always shows varied results. Since these procedures are risky extensive counseling of family members is essential before initiation of the procedure.

6.3. Enzyme therapy

Nowadays enzyme replacement therapy is gaining more popularity amongst the treatment options available for Mucopolysaccharidosis, due to its ability to alleviate somatic symptoms. Enzyme replacement therapy is based on the principle of the production of recombinant enzymes in continuous human or animal cell lines. These specific enzymes produced by recombinant DNA technology will have mannose – 6- phosphate residue, which will bind to their respective mannose – 6- phosphate receptor present on the cell surface and gain entry into the cell, subsequently executing their action of catabolism on accumulated Glycosaminoglycans. This novel therapy is approved in various countries for patients with moderate to severe grades or for those with complications (Table 7). However, hematopoietic stem cell therapy remained the best

choice for patients less than 2 years of age if a suitable donor is available. In such cases, enzyme replacement therapy is usually initiated in the period between diagnosis and transplantation to reduce the mortality and morbidity associated with transplantation.[11–14]

6.3.1. Aldurazym

Table 3: Aldurazym infusion volume 100 ml for weight < 20 kg

ml/hour	Rate (mcg / kg/hour)	Duration in minutes
2	10	15
4	20	15
8	50	15
16	100	15
32	200	15

Table 4: Aldurazym nfusion volume 250 ml for weight > 20 kg

ml/hour	Rate (mcg/ kg/hour)	Duration in minutes
w 5	10	15
10	20	15
20	50	15
40	100	15
80	200	15

Infusion-related reactions are very common therefore pretreatment with antihistamines and antipyretics is very essential. If in case patients develop any Infusion-related reactions like rashes, fever, pruritis, angioedema, respiratory distress, or urticaria then immediately the rate of infusion should be decreased and antihistamines should be administered.[15–17]

6.3.2. Elaprase

Table 5: Total volume 100 ml

ml/ hour	Duration
8	15
16	15
32	15
64	15

Total volume should be infused over 3 hours starting at a rate of 8 ml/hour and incrementing every 15 minutes, but the rate should not exceed 100 ml/hour. Infusion-related reactions are common therefore pretreatment with antihistamines and antipyretics should be given.[18]

6.3.3. Naglazyme

A total volume of 250 ml should be infused over at least 4 hours, starting at a rate of 6 ml/hour for the first hour and if there are no infusion-related reactions, then infuse at 80 ml/hour for the next 3 hours. The total volume can be reduced to 100 ml if patients require fluid restrictions.[19]

Table 6: Total volume 250 ml

Rate (ml/hour)	Duration (hours)
6	1
80	1
80	1
80	1

6.4. Intervention to ease penetration of enzymes across blood-brain barrier

6.4.1. Trojan horse strategy

An alternate approach to facilitate enzymes to cross blood-brain barrier is to combine the enzyme with a genetically engineered molecule like an antibody, that binds to receptors present on blood-brain barrier and allows enzymes to enter the CNS through receptor-mediated transcytosis. This is known as the Trojan horse strategy.[20] Clinical trials conducted on mice have been successful when Alpha – L-Iduronidase is fused with transferrin or apolipoprotein to cross blood-brain barrier. But for humans, it's still in phase 1 of clinical trials.[21]

6.4.2. Direct delivery of enzymes in cerebrospinal fluid

ERT can be delivered directly through intracerebroventricular injection, where the enzyme is injected into the lateral ventricle, or can also be injected intrathecally into subarachnoid space. Clinical trials in mice are found to be safe and effective, while study on humans is still going on.[22]

6.5. Gene therapy

Gene therapy has derived much attention due to its ability to provide a constant source of deficient enzymes. cDNA of the enzyme prepared by recombinant technique can be given either in vivo or ex vivo.[23]

The in vivo method includes the injection of a vector containing cDNA systemically or locally, resulting in the expression of enzymes by cells in the target tissue.

The viral vectors used in this technique were procured from adeno- associated viruses (AAV), lentiviruses, or retroviruses (Table 7).

The ex vivo technique involves the transfer of modified autologous cells, which will express the new cDNA deficit of early steps of the lysosomal degradation pathway. Genistein and Rhodamin B are the molecules used for substrate reduction therapies. Genistein is a tyrosine kinase inhibitor that inhibits signal transduction mediated by epidermal growth factor, responsible for expressing glycosaminoglycans synthesizing genes. The antioxidant and anti-inflammatory properties of genistein provide an additional advantage in decreasing proinflammatory cytokines.[27] Rhodamin B is a nonspecific inhibitor of glycosaminoglycan synthesis.[28]

Table 7: Routes of administration of vectors for Mucopolysaccharidosis

Vector	Route	Animal model	Outcomes
AAV2	Intrathecal	Adult mouse with MPSIIIB	• Enzyme activity increased • Glycosaminoglycans storage decreased • Improvement in behavioral deficits is seen [24]
AAV2	Intracerebral	Adult mouse with MPS IIIB	• Enzyme activity increased • Glycosaminoglycans storage decreased. • Improvement in behavioral deficits is seen
AAV2/5	Intracerebral	Neonatal mouse with MPSIIIB	• Enzyme activity increased • Glycosaminoglycans storage decreased. • Improvement in behavioral deficits is not determined [25]
AAV2/5	Intra-cerebroventrical	Neonate mouse with MPSIIIA	• Enzyme activity increased • Glycosaminoglycans storage decreased • Decrease in inflammation and neurodegeneration • Improvement in behavioral deficits is seen [25]
AAV2/8	Intra-cerebroventrical	Adult mouse with MPSIIIA	• Enzyme activity increased • Glycosaminoglycans storage decreased • Decrease in inflammation and neurodegeneration • Improvement in behavioral deficits is seen [25]
AAV4	Intra-cerebroventrical	Adult mouse with MPSVII	• Enzyme activity increased • Glycosaminoglycans storage decreased • Improvement in behavioral deficits is not determined[36]
AAV5	Intracerebral and intracerebroventrical	Adult mouse with MPS I H	• Enzyme activity increased • Glycosaminoglycans storage decreased • Improvement in behavioral deficits is not determined [25]
AAV9	Intrathecal	Adolescent feline with MPS I	• Enzyme activity increased • Glycosaminoglycans storage decreased. • Improvement in behavioral deficits is not determined [25]
AAV9	Intracisternal	Adult mouse with MPS IIIA, IIIB, IIID	• Enzyme activity increased • Glycosaminoglycans storage decreased • Decrease inflammation and neurodegeneration seen • Improvement in behavioral deficits is seen [25]
AAV9	Intravenous	Adult mouse with MPS I	• Enzyme activity increased • Glycosaminoglycans storage decreased • Improvement in behavioral deficits is not determined [25]
AAV9/rh10	Intrathecal	Neonatal canine with MPS VII	• Enzyme activity increased • Glycosaminoglycans storage decreased • Decrease inflammation and neurodegeneration seen • Improvement in behavioral deficits is not determined [25]
AAVrh10	Intracerebral	Adult mouse with MPS IIIA	• Enzyme activity increased • Glycosaminoglycans storage decreased • Decrease inflammation and neurodegeneration seen • Improvement in behavioral deficits is not determined [26]
Lentiviral	Intra-cerebroventrical	Adult mouse with MPSIIIA	• Enzyme activity increased • Glycosaminoglycans storage decreased • Improvement in behavioral deficits is seen [27]

All these new modalities of treatment like direct delivery of enzymes into the cerebrovascular system, gene therapy, substrate reduction therapies, Nano-enabled therapy have shown improvement in neural symptoms to various extents, but all these studies have been conducted on animal models, while studies in human are still in progress.

7. Conclusion

Mucopolysaccharidoses is a group of disorders caused due to deficiency of lysosomal enzymes which are required for glycosaminoglycans breakdown. These glycosaminoglycans which are not degraded accumulate in various tissues and cause characteristic features. Bone marrow transplant became the first treatment to be successful. Over the last few decades, various other approaches have developed in addressing this problem. Hematopoietic stem cell therapy has gained popularity among all the new approaches because of its promising effects on deteriorating the natural history of disease and improving the quality of life. Enzyme replacement therapy which involves regular infusion of deficient enzymes is gradually becoming successful. It has shown improvement in pulmonary function, cardiovascular function, and organomegaly. However neurological improvement is poor due to the inability of enzymes to cross the blood brain barrier. This paved way for other new modalities trials like direct delivery of enzymes into the cerebrospinal fluid, gene therapy, substrate reduction therapy, and nanotherapy that succeeded in an animal model.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Casale J, Crane JS. Biochemistry, Glycosaminoglycans [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Wang W, Shi L, Qin Y, Li F. Research and Application of Chondroitin Sulfate/Dermatan Sulfate-Degrading Enzymes. *Front Cell Dev Biol*. 2020;8:560442.
3. Zeng Y, He X, Danyukova T, Pohl S, Kermode AR. Toward Engineering the Mannose 6-Phosphate Elaboration Pathway in Plants for Enzyme Replacement Therapy of Lysosomal Storage Disorders. *J Clin Med*. 2019;8(12):2190.
4. Awolade P, Cele N, Kerru N, Gummidi L, Oluwakemi E, Singh P. Therapeutic significance of β-glucuronidase activity and its inhibitors: A review. *Eur J Med Chem*. 2020;187:111921. doi:10.1016/j.ejmech.2019.111921.
5. Shriver Z, Capila I, Venkataraman G, Sasisekharan R. Heparin and heparan sulfate: analyzing structure and microheterogeneity. *Handb Exp Pharmacol*. 2012;207:159–76.
6. Birrane G, Dassier AL, Romashko A, Lundberg D, Holmes K, Cottle T, et al. Structural characterization of the α-N-acetylglucosaminidase, a key enzyme in the pathogenesis of Sanfilippo syndrome B. *J Struct Biol*. 2019;205(3):65–71.
7. Leal AF, Benincore-Flórez E, Rintz E, Herreño-Pachón AM, Celik B, Ago Y, et al. Cellular Consequences of Glycosaminoglycans Accumulation and Potential Targets. *Int J Mol Sci*. 2022;24(1):477.
8. Huang YF, Mizumoto S, Fujita M. Novel Insight Into Glycosaminoglycan Biosynthesis Based on Gene Expression Profiles. *Front Cell Dev Biol*. 2021;9:709018. doi:10.3389/fcell.2021.709018.
9. Hegerová P, Dědková Z, Sobotka L. Early nutritional support and physiotherapy improved long-term self-sufficiency in acutely ill older patients. *Nutrition*. 2015;31(1):166–70.
10. Taylor M, Khan S, Stapleton M, Wang J, Chen J, Wynn R, et al. Hematopoietic stem cell transplantation for mucopolysaccharidoses: past, present, and future. *Biol Blood Marrow Transplant*. 2019;25(7):226–46.
11. Poe MD, Chagnon SL, Escolar ML. Early treatment is associated with improved cognition in Hurler syndrome. *Ann Neurol*. 2014;76(5):747–53.
12. Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. *Pediatrics*. 2009;123(1):229–40.
13. Jameson E, Jones S, Remmington T. Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I. *Cochrane Database Syst Rev*. 2019;6(6):CD009354. doi:10.1002/14651858.CD009354.pub5.
14. Concolino D, Deodato F, Parini R. Enzyme replacement therapy: efficacy and limitations. *Ital J Pediatr*. 2018;44(Suppl 2):120.
15. Cáceres MC, Guerrero-Martín J, Pérez-Civantos D, Palomo-López P, Delgado-Mingorance JI, Durán-Gómez N. The importance of early identification of infusion-related reactions to monoclonal antibodies. *Ther Clin Risk Manag*. 2019;15:965–77.
16. Muenzer J, Bodamer O, Burton B, Clarke L, Frenking GS, Giugliani R, et al. The role of enzyme replacement therapy in severe Hunter syndrome-an expert panel consensus. *Eur J Pediatr*. 2012;171(1):181–8.
17. daSilva EMK, Strufaldi MWL, Andriolo RB, Silva LA. Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome). *Cochrane Database Syst Rev*. 2016;2016(2):CD008185.
18. Naglazyme FDA Approval History. [Cited 2023 Jul 1]. Available from: https://www.drugs.com/history/naglazyme.html.
19. Harmatz P, Whitley CB, Waber L, Pais R, Steiner R, Plecko B, et al. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *J Pediatr*. 2004;144(5):574–80.
20. Begley DJ, Pontikis CC, Scarpa M. Lysosomal storage diseases and the blood-brain barrier. *Curr Pharm Des*. 2008;14(16):1566–80.
21. Dickson P, Mcentee M, Vogler C, Le S, Levy B, Peinovich M, et al. Intrathecal enzyme replacement therapy: successful treatment of brain disease via the cerebrospinal fluid. *Mol Genet Metab*. 2007;91(1):61–8.
22. Aronovich EL, Hackett PB. Lysosomal storage disease: Gene therapy on both sides of the blood-brain barrier. *Mol Genet Metab*. 2015;114(2):83–93.
23. Heldermon CD, Ohlemiller KK, Herzog ED, Vogler C, Qin E, Wozniak DF, et al. Therapeutic Efficacy of Bone Marrow Transplant, Intracranial AAV-mediated Gene Therapy, or Both in the Mouse Model of MPS IIIB. *Mol Ther*. 2010;18(5):873–80.
24. Liu G, Martins I, Wemmie JA, Chiorini JA, Davidson BL. Functional correction of CNS phenotypes in a lysosomal storage disease model using adeno-associated virus type 4 vectors. *J Neurosci*. 2005;25(41):9321–7.
25. Winner LK, Beard H, Hassiotis S, Lau AA, Luck AJ, Hopwood JJ, et al. A preclinical study evaluating AAVrh10-based gene therapy for Sanfilippo syndrome. *Hum Gene Ther*. 2016;27(5):363–75.
26. Mcintyre C, Derrick-Roberts AL, Byers S, Anson DS. Correction of murine mucopolysaccharidosis type IIIA central nervous system pathology by intracerebroventricular lentiviral-mediated gene delivery. *J Gene Med*. 2014;16(11-12):374–87.
27. Gaillard PJ, Visser CC, deBoer AG. Targeted delivery across the blood-brain barrier. *Expert Opin Drug Deliv*. 2005;2(2):299–309.

28. Salvalaio M, Rigon L, Belletti D, 'avanzo FD, Pederzoli F, Ruozi F, et al. Targeted polymeric nanoparticles for brain delivery of high molecular weight molecules in lysosomal storage disorders. *PloS One*. 2016;11(5):e0156452.

Author biography

Keerthiga M, Junior Resident

Arpita Chakraborty, Assistant Professor

Wilma Delphine Silvia CR, Professor and HOD https://orcid.org/0000-0002-6503-8099

Akshay Atre, PG Student

Preksha Shivakumar, Junior Resident

Cite this article: Keerthiga M, Chakraborty A, Silvia CR WD, Atre A, Shivakumar P. Mucopolysaccharidoses: An overview and new treatment modalities. *Int J Clin Biochem Res* 2023;10(2):101-109.