SCHOOL OF STUDIES IN ZOOLOGY
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MUCOPOLYSACCHARIDES AND RELATED DISORDERS

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INTRODUCTION-

- Mucopolysaccharides are glycosamino-glycans, i.e., hetero-polysaccharides composed of hexosamines and non-nitrogenous sugars linked by glycosidic bonds; some also contain various substituent groups.

- The mucopolysaccharides of mammalian tissues may be classified as-

(1) Polycarboxylates (hyaluronic acid, chondroitin),
(2) Polysulfates (keratan sulfates)
(3) Polycarboxy-sulfates (chondroitin 4- and 6-sulfates, previously designated chondroitin sulfate A and C, respectively; dermatan sulfates; and heparitin sulfates).

Disorders-

- Mucopolysaccharidosis are a group of lysosomal storage disorders caused by deficiency of enzymes catalyzing the stepwise degradation of glycosaminoglycans (GAGs) or mucopolysaccharides.
- Since lysosomes are involved in their degradation, the deficiency in lysosomal enzymes leaves undegraded GAGs to be stored in the lysosomes or excreted in the urine.
- These diseases are rare with an incidence of around 1 in 1, 32,000 live births.
- Mucopolysaccharides are widely distributed in the human tissues; the clinical features may involve virtually all organ systems.
- Excess of one or more of the GAGs results in numerous physical and mental features, visual and hearing defects, cardiovascular functional impairments, hepatosplenomegaly, and dysostosis multiplex.

- Excess of one or more of the GAGs results in numerous physical and mental features, visual and hearing defects, cardiovascular functional impairments, hepatosplenomegaly, and dysostosis multiplex.
- Morquio syndrome is a member of a group of inherited metabolic disorders collectively termed mucopolysaccharidosis (MPSs). It is estimated to occur in 1 in 2, 00,000 live births.
- Morquio syndrome is divided into two subtypes; Type A & Type B.
- Theses subtypes result from the missing or deficient enzymes *N*-acetylgalactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B) needed to break down the keratan sulfate sugar chain.
- Clinical features are similar in both types but appear milder in Morquio Type B.

Classification

TYPE	Gene/locus	Enzyme deficient	GAG accumulation
MPS 1 (Hurler, Hurler-Scheie, Scheie syndromes)	IDUA(4p16)	α-L-iduronidase	Dermatan sulphate Heparan sulphate
MPS II (Hunter syndrome)	IDS (Xq28)	Iduronate 2-sulphatase	Dermatan sulphate Heparan sulphate
MPS III (Sanfilippo) Type A Type B Type C Type D	 SGSH (17q25) NAGLU (17q21) HGSNAT (8p11) GNS (12q14)	 Heparan sulphatase N acetylglucosaminidase Acetyl coA:Glucosaminide acetyltransferase Acetylglucosamine-6-sulphatase	Heparan sulphate
MPS IV (Morquio) Type A Type B		 Galactose-6-sulphatase β Galactosidase	 Keratan sulphate Chondriotin sulphate
MPS VI (Maroteaux-Lamy)	ARSB (5q14)	Arylsulphatase B	Dermatan & Chondriotin sulphate
MPS VII (Sly)	GUSB (7q11)	β Glucoronidase	Dermatan/Heparan/ Chondriotin sulphate
MPS IX	HYAL1 (3p21)	Hyaluronidase	Hyaluronan

http://www.genetics4medics.com/mucopolysaccharidoses.html

Classification contd…

- According to their dominant clinical features MPSs can be grouped into four broad categories:
- Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII)
- Soft tissue and skelatal disease (MPS VI)
- Primarily skeletal disorders (MPS IVA, IVB)
- Primarily central nervous system disorders (MPS III A-D)

Types-

MPS I

- MPS I is one of the mucopolysaccharide storage diseases. MPS I includes Hurler, Hurler-Scheie and Scheie diseases.
- Based on the presence of symptoms Hurler disease was first described by Dr Hurler in 1919, later in 1962 Dr Scheie identified a less severe form and referred to is as Scheie disease.
- People with MPS I who appear not to fit clearly at either end of the spectrum of Hurler or Scheie are classified with Hurler-Scheie disease.
- Mucopolysaccharides are long chains of sugar molecules used in the building of bones, cartilage, skin, tendons and many other tissues in the body.
- “Muco” refers to the thick jelly-like consistency of the sugar molecules, “poly” means many, and “saccharide” is a general term for the sugar part of the molecule.
- In the course of normal life there is a continuous recycling process of building new mucopolysaccharides and breaking down old ones. The breakdown and recycling process requires a series of special biochemical tools called enzymes.

MPS II

- MPS II, known as Hunter disease, is one of the mucopolysaccharide storage diseases.
- MPS II was first identified by Dr Hunter in 1971 and includes a spectrum of symptoms from mild to severe.
- Mucopolysaccharides are long chains of sugar molecules used in the building of bones, cartilage, skin, tendons and many other tissues in the body.
- “Muco” refers to the thick jelly-like consistency of the sugar molecules, “poly” means many, and “saccharide” is a general term for the sugar part of the molecule.
- In the course of normal life there is a continuous recycling process of building new mucopolysaccharides and breaking down old ones.
- The breakdown and recycling process requires a series of special biochemical tools called enzymes.

MPS III

- It is also known as Sanfilippo disease, is one of the mucopolysaccharide storage diseases.
- MPS III was first identified by Dr Sanfilippo in 1963 and includes 4 different types A, B, C and D.
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- In the course of normal life there is a continuous recycling process of building new mucopolysaccharides and breaking down old ones.
- The breakdown and recycling process requires a series of special biochemical tools called enzymes.

- People with MPS III are either type A, B, C or D. Each type is missing or low in a specific enzyme
- MPS III A is caused by missing or altered heparan N sulphatase
- MPS III B is caused by missing or low in alpha-Nacetylglucosaminidase
- MPS III C is caused by missing or altered acetyl-CoAlpha-glucosaminide acetyltransferase
- MPS III D is caused by missing or low in N-acetylglucosamine-6-sulphatase
- These enzymes are essential in breaking down mucopolysaccharides heparan sulphate.
- When heparan sulphate is not completely broken down it remains stored in the body. The symptoms of MPS III are a result of the build-up of heparan sulphate in the body.
- Babies may show little sign of the disease but as more and more cells build-up of partially broken down heparan sulphate symptoms start to appear.

MPS IV

- It is also known as Morquio disease, is one of the mucopolysaccharide storage diseases.
- MPS IV disease was first identified by Dr Morquio in 1929 and includes 2 different types A and B.
- People with MPS IV are either type A or B. Each type is missing or low in in a specific enzyme
- MPS IVA is missing or low in N-acetyl-galactosamine 6-sulfatase
- MPS IVB is missing or low in beta-galactosidase
- These enzymes are essential in breaking down mucopolysaccharides keratan sulphate and chondroitin sulphate in type A and keratan sulphate in type B.
- When these mucopolysaccharides are not completely broken down they remain stored in the body. The symptoms of MPS IV are a result of the build-up of keratan sulphate and chondroitin sulphate in the body.
- Babies may show little sign of the disease but as more and more cells build-up of partially broken down keratan sulphate and chondroitin sulphate symptoms start to appear.

MPS VI

- It is also known as Maroteaux-Lamy disease, is one of the mucopolysaccharide storage diseases.
- MPS VI was first identified by Dr Maroteaux and Dr Lamy in 1963.
- People with MPS VI are missing or are low in an enzyme called N-acetylgalactosamine-4-sulfatase, which is essential in breaking down mucopolysaccharides dermatan sulphate.
- When dermatan sulphate is not completely broken down it remains stored in the body. The symptoms of MPS VI occur when there is a build-up of dermatan sulphate in the tissues in the body.
- Babies may show little sign of the disease but as more and more cells build-up of partially broken down dermatan sulphate, symptoms start to appear.

MPS VII

- MPS VII, known as Sly disease, is one of the mucopolysaccharide storage diseases.
- MPS VII was first identified by Dr Sly in 1972 and includes a spectrum of symptoms from mild to severe.
- People with MPS VII are missing or are low in an enzyme called beta-glucuronidase which is essential in breaking down 3 mucopolysaccharides dermatan sulphate, heparan sulphate and chondroitin sulphate.
- When mucopolysaccharides are not completely broken down they remain stored in the body.
- The symptoms of MPS VII are a result of the build-up of dermatan sulphate, heparan sulphate and chondroitin sulphate in the tissues in the body.
- Babies may show little sign of the disease but as more and more cells build-up of partially broken down dermatan sulphate, heparan sulphate and chondroitin sulphate, symptoms start to appear.

MPS IX

- MPS IX, known as Natowicz disease, is one of the mucopolysaccharide storage diseases.
- MPS IX was first noted in 1996.
- People with MPS IX are low in an enzyme called hyaluronidase which is essential in breaking down mucopolysaccharide hyaluronan. When hyaluronan is not completely broken down it remains stored in the body.
- The symptoms of MPS IX are a result of the build-up of hyaluronan in the tissues in the body.
- Babies may show little sign of the disease but as more and more cells build-up of partially broken down mucopolysaccharides, symptoms start to appear.

Preventions

- **Primary prevention**

  Through genetic counseling

- **Tertiary prevention**

  To avoid or treat complications remains the mainstay of supportive pediatric care

Prevention (Cont.)

- Multidisciplinary attention to :
- Respiratory and cardiovascular complications
- Hearing loss
- Carpal tunnel syndrome
- Spinal cord compression
- Hydrocephalus, and other problems

Can greatly improve the quality of life for patients and their families

The progressive nature of clinical involvement in MPS patients dictates the need for specialized and coordinated evaluation

Summary

- Biochemical evaluation includes measurement of urinary GAG concentration
- Definitive diagnosis requires assay of enzyme activity, usually in peripheral blood leukocytes
- Supportive management can improve the quality of life for affected individuals and their families
- ERT, HSCT reduce the progression of somatic involvement but not neurological nivolvement.
- Mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for breakdown of glycosaminoglycans (GAGs).
- GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities.
- An MPS disorder should be suspected in a child with coarse facial features, short stature, corneal clouding , developmental delay, bone disease (dysostosis multiplex)