

18.1 Introduction

This chapter deals with the inborn errors of catabolism (degradation) of mucopolysaccharides (or the new term glycosaminoglycans). The mucopolysaccharidoses are a group of heritable disorders of man that are characterized by accumulation of glycosaminoglycans in the lysosomes of all cells of the body (except red blood cells) and increased excretion in the urine.

Patients with the *Hurler syndrome* appear normal at birth. Onset of the disorder occurs between 6 and 24 months of age. Among the earliest features present are enlarged scaphoid head, hernias, thoracic kyphosis, large tongue, and recurrent infections. Infants younger than six months of age with coarse features and symptoms of a lysosomal storage disorder should be differentiated from GM₁-gangliosidosis, mucopolipidosis II, sialidosis, or α -mannosidosis.

Scheie syndrome is a clinically milder form of Hurler syndrome. Onset of the disease occurs at about age 5 years. Growth and intelligence are normal. The development of joint stiffness is pronounced. Clouding of the corneas is severe. With increasing age the development of aortic valve disease becomes apparent. Median nerve compression and cervical cord compression occur and require immediate intervention.

What is referred to as the *Hurler-Scheie compound disorder* is a clinical phenotype intermediate between Hurler syndrome and Scheie syndrome. Onset of the disorder occurs about 3 years of age. Growth is delayed. Intelligence is normal. Corneal clouding and deafness become debilitating.

The incidence of these disorders in British Columbia has been estimated to be about one in 100,000 live births for the Hurler syndrome and one in 500,000 for Scheie [1]. In a study conducted in Australia the prevalence for all type I mucopolysaccharidoses has been estimated to be about 1 in 88,000 [2].

Hunter syndrome is associated with a milder phenotype than that of Hurler syndrome. While there is no corneal clouding as seen in Hurler syndrome, there can be mild retinal degeneration. A gibbus may be present. Developmental delay occurs in the severe type. The hallmark of Hunter syndrome is skin changes. The scapulae contain pebbly, white in color, patches

that may extend to the nape of the neck and to the pits of the arms. The pebbly patches occur after about 2 years of age. Other clinical features are similar to the mucopolysaccharidoses type I. A mild form of Hunter syndrome occurs and survival can be into the fifth decade. The clinical findings in the Hunter syndrome are similar to the Hurler syndrome but, in general, are less severe. The prevalence of Hunter syndrome in the population of Australia is estimated to be 1 in 136,000 [2].

The *Sanfilippo syndrome, type A* presents with severe and progressive mental retardation with sleep disturbances and behavioral problems as the most prominent features. The organ enlargement and joint stiffness seen in the other mucopolysaccharidoses is not present or occurs later in life. Diarrhea can be more severe and recurrent than in the other mucopolysaccharidoses. Onset of the disorder is usually between 1 and 6 years of age. Studies of the basic defect in Sanfilippo syndrome revealed that there are four separate disorders. The type of Sanfilippo syndrome is based on enzyme deficiency. The clinical symptoms in the four types overlap. The prevalence of Sanfilippo syndrome in the Netherlands is estimated at 1 in 24,000 for three of the four types [3]. However, using all four types of Sanfilippo syndrome, the study from Australia estimates the prevalence at 1 in 60,600, which is about 2.5 times lower than that in the Netherlands [2]. The Sanfilippo syndrome, type A, is estimated at 1 in 114,000 [2].

In the *Sanfilippo syndrome, type B*, severe and mild forms exist. The clinical features overlap for each with the type A disorder. Prevalence is estimated at 1 in 211,000 [2].

In the *Sanfilippo syndrome, type C*, clinical features are, in general, milder than those found in Sanfilippo syndrome, type A. Prevalence is estimated at 1 in 1,407,000. This is about 6.5 times lower than that of the Sanfilippo syndrome, type B and over 10 times less frequent than type A [2].

In the *Sanfilippo syndrome, type D*, the clinical features are more variable than any of the other types. The clinical features overlap for each of the Sanfilippo disorders. The urine of patients with Sanfilippo syndrome, type D, shows a variable increased excretion (or normal level) of the glycosaminoglycan, heparan sulfate. The presence of heparan sulfate does not distinguish the type of Sanfilippo syndrome. Measurement of specific enzymes involved in the catabolism of heparan sulfate determines the type.

There are two forms of *Morquio syndrome*. The *Morquio syndrome, type A* is characterized by significant physical and skeletal abnormalities after birth with no neurological problems in childhood. Corneal clouding, enlarged liver, development of abnormal teeth, and hearing loss occur later in the course of the disease. Urinary excretion of increased quantities of keratan sulfate and/or chondroitin-6-sulfate is strongly suggestive of the Morquio syndrome. The prevalence of Morquio syndrome, type A is estimated at 1 in 169,000 [2].

The *Morquio syndrome, type B* is somewhat milder than that of the type A. Onset is about the same as in the type A. The milder clinical manifesta-

tions include short trunk, dwarfism, kyphoscoliosis, and thoracic deformity. Survival is generally longer than in type A. No estimate of the prevalence exists for type B [5].

The *Maroteaux-Lamy syndrome* is characterized by its Hurler-like features with normal intelligence. Skeletal abnormalities, corneal clouding, and joint stiffness are apparent at an early age. The disease is usually recognized in the third or fourth year of life. Clinically, there is a severe form and a mild form of the disease. Dermatan sulfate is the predominant species of glycosaminoglycan found in increased quantities in the urine of patients. The prevalence of Maroteaux-Lamy syndrome is estimated at 1 in 235,000 [5].

The *Sly syndrome* is similar in clinical features to that of the mucopolysaccharidosis type I disorders. Patients have unusual facies, depressed nasal bridge, prominent maxillae, and anteverted nostrils. By 2.5 years of age, developmental retardation is observed. Several cases of β -glucuronidase deficiency have been reported in newborns with non-immune hydrops fetalis. Urinary excretion of glycosaminoglycans are elevated and variable [1]. The prevalence of Sly syndrome is estimated at 1 in 2,111,000, the rarest of all mucopolysaccharidoses [2].

The *Natowicz syndrome* was described in a 14 year-old female with short stature, mildly dysmorphic features, flattened nasal bridge, bifid uvula, soft tissue cleft palate, and multiple periarticular soft-tissue masses in ankle, finger and patella. These masses were associated with pain and swelling. The basic enzyme defect in the Natowicz syndrome is a deficiency of hyaluronidase. Only one case of this disorder has been reported [6].

18.2 Nomenclature

■ Mucopolysaccharidoses: Disorders of Glycosaminoglycan Catabolism

	Type MPS	Syndrome	MIM number	Urinary GAGs	Enzyme deficiency	Chromo- some locus
18.1	IH IH/S IS	Hurler Hurler-Scheie Scheie	252800	Dermatan sulfate Heparan sulfate	α -L-Iduronidase	4p16.3
18.2	II	Hunter (mild or severe)	309900	Dermatan sulfate Heparan sulfate	Iduronate-2-sulfatase	Xq28
18.3	IIIA	Sanfilippo A	252900	Heparan sulfate	Heparin sulfamidase	17q25.3
18.4	IIIB	Sanfilippo B	252920	Heparan sulfate	N-Acetyl- α -D-glucosami- nidase	17q21
18.5	IIIC	Sanfilippo C	252930	Heparan sulfate	Acetyl CoA: α -glucosa- minidase	
18.6	IIID	Sanfilippo D	252940	Heparan sulfate	N-acetyltransferase N-acetylglucosamine-6- sulfatase	14q 12q14
18.7	IVA	Morquio A	253000	Keratan sulfate	N-acetylgalactosamine- 6-sulfatase	16q24
18.8	IVB	Morquio B	253010	Chondroitin-6-sulfate Keratan sulfate	(Galactose 6-sulfatase) β -Galactosidase	3p21
18.9	VI	Maroteaux-Lamy (mild or severe)	253200	Dermatan sulfate	N-acetylgalactosamine- 4-sulfatase	5q12
18.10	VII	Sly	253220	Dermatan sulfate Heparan sulfate Chondroitin sulfate	β -Glucuronidase	7q22

GAG's is the abbreviation for glycosaminoglycans.

18.3 Metabolic Pathways

Catabolism of dermatan sulfate

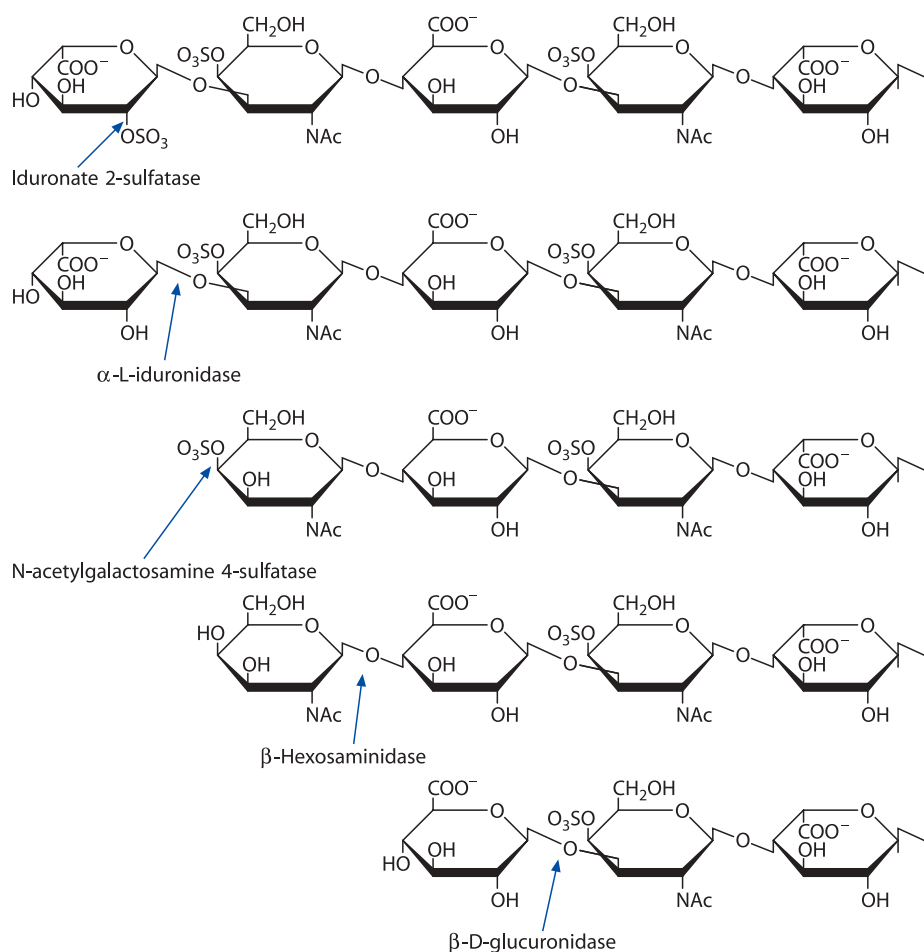


Fig. 18.1. The catabolism of dermatan sulfate. The arrows point to the group removed by the action of a glycosidase (removal of a monosaccharide) or sulfatase (removal of a sulfate group). The degradation starts at the non-reducing terminus of the molecule and removes modifications such as sulfate followed by the removal of the monosaccharide group until the polysaccharide is degraded to its individual components

Catabolism of heparan sulfate

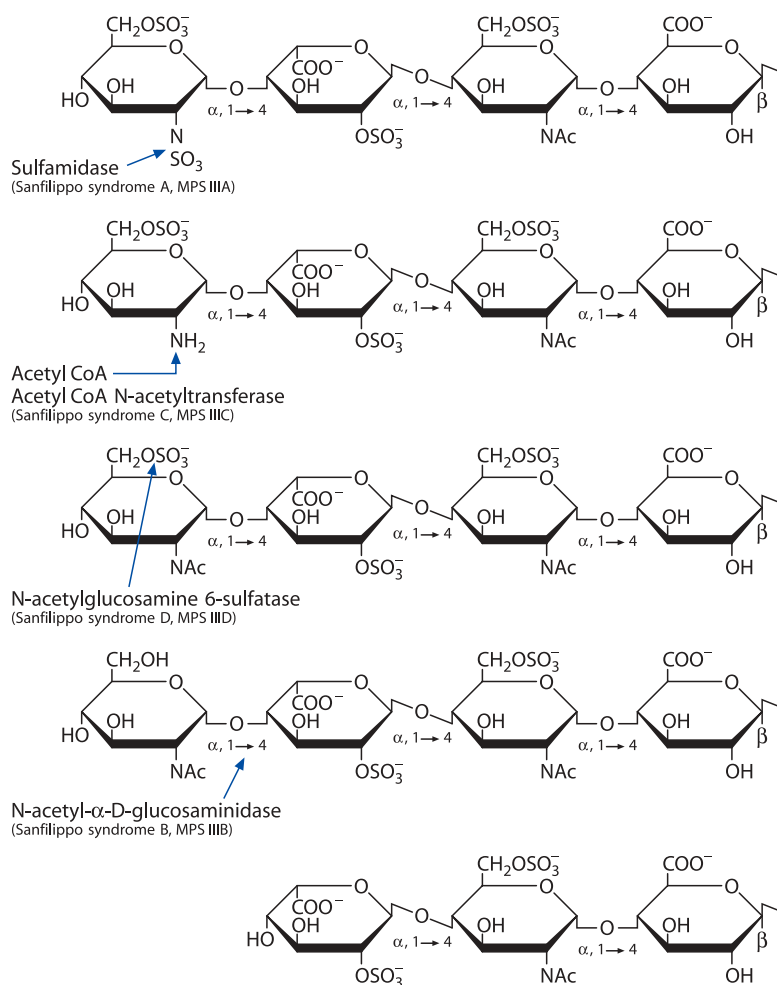


Fig. 18.2. The catabolism of heparan sulfate. The arrows point to the group removed by the action of a glycosidase (removal of a monosaccharide) or sulfatase (removal of both N- and O-sulfate groups)

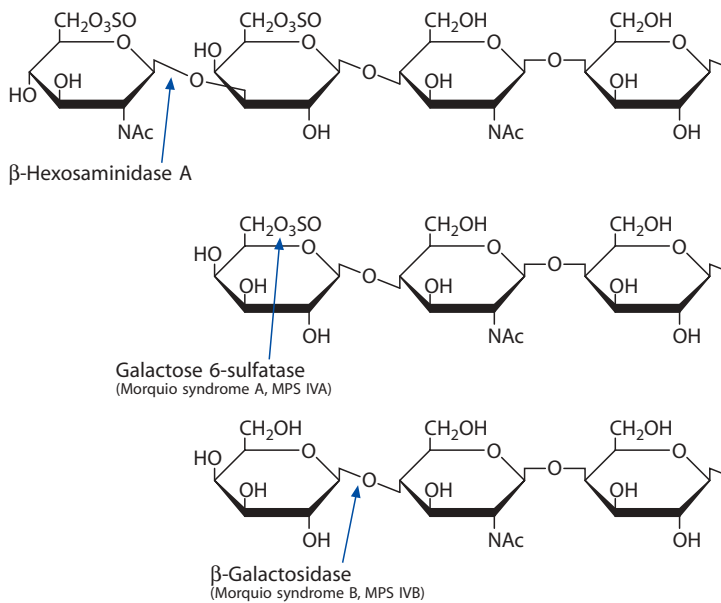
Catabolism of keratan sulfate

Fig. 18.3. The catabolism of keratan sulfate. The arrows point to the group removed by the action of a glycosidase (removal of a monosaccharide) or sulfatase (removal of a sulfate group)

18.4 Signs and Symptoms

Table 18.1 a. α -L-Iduronidase (Hurler syndrome, MPS IH, Severe)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features	±	++	+++		
	Macrocephaly	+	+++	+++		
	Scaphocephaly	+	+	+		
Skeleton	Dysostosis multiplex		++	+++		
	Kyphosis	±	+	++		
	Short stature	+	+	+		
Ear	Hearing loss		+	+		
Eye	Corneal opacities		+	++		
Cardiac	Valvular thickening		+	++		
GI	Hernias	+	++	+++		
	Hepatomegaly	±	++	+++		
Special laboratory	Total urinary GAGs	↑↑	↑↑	↑↑		
	Dermatan sulfate	↑↑	↑↑	↑↑		
	Heparan sulfate	↑↑	↑↑	↑↑		
Enzyme	α -L-iduronidase activity	↓↓↓	↓↓↓	↓↓↓		
CNS	Psychomotor retardation	++	+++	+++		
	Seizures	±	±	+		
Other	Respiratory infection	+	++	+++		
	Splenomegaly		++	+++		
	Joint contractures		++	+++		
	Hypertrichosis		+	++		
	Short neck	+	+	+		
	Enlarged tongue	±	+	+		
	Claw hand		±	++		

Table 18.1 b. α -L-Iduronidase (Scheie syndrome, MPS IS, Mild)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features			±	++	++
	Macrocephaly			+		
Skeleton	Dysostosis multiplex			+	++	+++
	Kyphosis					
	Short stature					
Ear	Hearing loss					+
Eye	Corneal opacities			+	++	+++
	Glaucoma				+	+
Cardiac	Valvular thickening			+	++	+++
GI	Hernias			+	+	+
	Hepatomegaly			+		
Special laboratory	Total urinary GAGs			↑	↑	↑
	Dermatan sulfate			↑	↑	↑
	Heparan sulfate			↑	↑	↑

Table 18.1 b (continued)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Enzyme activity	α -L-iduronidase			↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation					
	Seizures					
Other	Respiratory infection			±	±	±
	Splenomegaly			+	+	+
	Joint contractures			+	++	++
	Hypertrichosis			+		
	Short neck			+	+	+
	Enlarged tongue					
	Claw hand			+	++	+++

Table 18.1 c. α -L-Iduronidase (Hurler-Scheie syndrome, MPS IH/S, Intermediate)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features			+	++	++
	Macrocephaly					
Skeleton	Dysostosis multiplex			+	++	+++
	Kyphosis					
	Short stature					
Ear	Hearing loss				+	++
Eye	Corneal opacities			++	++	+++
	Glaucoma				+	+
Cardiac	Valvular thickening			+	++	+++
GI	Hernias			+	+	+
	Hepatomegaly			+		
Special laboratory	Total urinary GAGs			↑	↑	↑
	Dermatan sulfate			↑	↑	↑
	Heparan sulfate			↑	↑	↑
Enzyme activity	α -L-iduronidase			↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation					
	Spinal cord compression				+	++
Other	Respiratory infection			±	±	±
	Splenomegaly			+	+	+
	Joint contractures			+	++	++
	Hypertrichosis			+	+	+
	Short neck			+	+	+
	Enlarged tongue					
	Claw hand			+	++	+++
	Sleep apnea				+	+

Table 18.2. Iduronate 2-sulfatase (Hunter syndrome, MPS II)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features		+	++	++	++
	Macrocephaly		++	++	++	++
	Skeleton		+	+	++	++
	Kyphosis					
	Short stature		+	+	+	+
Ear	Hearing loss		+	+	+	+
Eye	Corneal opacities					
	Retinal degeneration				+	+
Cardiac	Valvular thickening				+	+
	GI					
	Hernias		+	++	++	++
	Hepatomegaly		+	++	+++	+++
Special laboratory	Total urinary GAGs	↑↑	↑↑	↑↑	↑↑	↑↑
	Dermatan sulfate	↑↑	↑↑	↑↑	↑↑	↑↑
	Heparan sulfate	↑↑	↑↑	↑↑	↑↑	↑↑
Enzyme activity	Iduronate 2-sulfatase	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
	CNS					
	Psychomotor retardation			±	±	±
	Seizures					
Other	Respiratory infection		+	++	++	++
	Splenomegaly		+	++	++	++
	Joint contractures		+	++	++	++
	Hypertrichosis		+	++	++	++
	Short neck		+	+	+	+
	Enlarged tongue		+	+	+	+
	Claw hand		±	+	+	+

Table 18.3. Heparin sulfaminidase (Sanfilippo syndrome, type A, MPS IIIA)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features		±	+	++	++
	Hyperactivity		±	++	++	+
	Aggressiveness		±	++	++	+
Skeleton	Dysostosis multiplex			+	++	++
Ear	Hearing loss			+	+	+
Eye	Corneal opacities					
	Retinal degeneration					+
Cardiac	Valvular thickening					+
GI	Hernias					
	Hepatomegaly			+	+++	+++
Special laboratory	Total urinary GAGs	↑↑		↑↑	↑↑	↑↑
	Heparan sulfate	↑↑		↑↑	↑↑	↑↑
Enzyme activity	Heparin sulfaminidase	↓↓↓		↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation	±		++	+++	+++
	Seizures				+	+
	Cortical atrophy				+	+
Other	Respiratory infection			±	++	++
	Coarse hair			+	+	+
	Hypertrichosis		+	++	++	++
	Diarrhea			+	+	+
	Insomnia			+	+	+

Table 18.4. N-Acetyl- α -D-glucosaminidase (Sanfilippo syndrome, type B, MPS IIIB)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features		±	+	++	++
	Hyperactivity		±	+	++	+
	Aggressiveness		±	+	++	+
Skeleton	Dysostosis multiplex			+	+	+
Ear	Hearing loss			+	+	+
Eye	Corneal opacities					
	Retinal degeneration					+
Cardiac	Valvular thickening					+
GI	Hernias					
	Hepatomegaly			±	++	++
Special laboratory	Total urinary GAGs	↑↑		↑↑	↑↑	↑↑
	Heparan sulfate	↑↑		↑↑	↑↑	↑↑
Enzyme activity	N-acetyl- α -D-glucosaminidase	↓↓↓		↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation	±		+	++	+++
	Seizures				+	+
	Cortical atrophy				+	+
Other	Respiratory infection			±	++	++
	Coarse hair			+	+	+
	Hypertrichosis		+	++	++	++
	Diarrhea			+	+	+
	Insomnia			+	+	+

Table 18.5. Acetyl CoA: α -glucosaminidase N-acetyltransferase (Sanfilippo syndrome, type C, MPS IIIC)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features		±	+	++	++
	Hyperactivity		±	+	++	+
	Aggressiveness		±	+	++	+
Skeleton	Dysostosis multiplex			+	+	+
Ear	Hearing loss			+	+	+
Eye	Corneal opacities					
	Retinal degeneration					+
Cardiac	Valvular thickening					+
GI	Hernias					
	Hepatomegaly			±	++	++
Special laboratory	Total urinary GAGs		↑↑	↑↑	↑↑	↑↑
	Heparan sulfate		↑↑	↑↑	↑↑	↑↑
Enzyme activity	Acetyl CoA α -D-glucosaminidase		↓↓↓	↓↓↓	↓↓↓	↓↓↓
	N-acetyltransferase					
CNS	Psychomotor retardation		±	+	++	+++
	Seizures				+	+
	Cortical atrophy				+	+
Other	Respiratory infection			±	++	++
	Coarse hair			+	+	+
	Hypertrichosis		+	++	++	++
	Diarrhea			+	+	+
	Insomnia			+	+	+

Table 18.6. N-Acetylglucosamine 6-sulfatase (Sanfilippo syndrome, type D, MPS IIID)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features			+	++	++
	Hyperactivity			+	++	+
	Aggressiveness			+	++	+
Skeleton	Dysostosis multiplex			+	+	+
Ear	Hearing loss			+	+	+
Eye	Corneal opacities					
	Retinal degeneration					
Cardiac	Valvular thickening					
	GI					
Special laboratory	Hernias					
	Hepatomegaly			±	++	++
	Total urinary GAGs			n-↑	n-↑	n-↑
	Heparan sulfate			n-↑	n-↑	n-↑
Enzyme activity	Monosulfated monosaccharide			↑	↑	↑
	N-acetylglucosamine 6-sulfatase			↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation			+	++	++
	Seizures				+	+
	Cortical atrophy				+	+
Other	Respiratory infection			±	++	++
	Coarse hair			+	+	+
	Hypertrichosis			++	++	++
	Diarrhea			+	+	+
	Insomnia			+	+	+
	Synophrys			+	++	++

Table 18.7. N-Acetylgalactosamine 6-Sulfatase (Morquio syndrome, type A, MPS IVa)**Table 18.8.** β -D-Galactosidase (Morquio syndrome, type B, MPS IVB)^a

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features			+	+	+
	Growth retardation			++	+++	+++
	Skeleton			+	++	++
	Lumbar gibbus			+	+	+
	Flaring ribs			+	+	+
	Hypoplasia of odontoid			+	+	+
	Sternal bulging			+	++	+++
Ear	Hearing loss			+	+	+
Eye	Corneal opacities			+	++	+++
	Glaucoma				±	±
Cardiac	Valvular thickening				+	+
GI	Hernias					
Special laboratory	Hepatomegaly			+	+++	+++
	Total urinary GAGs		n-↑	n-↑	n	n
	Keratan sulfate		n-↑	n-↑	n	n
	Chondroitin sulfate		↑	↑	n-↑	n-↑
Enzyme activity	MPS IVA N-acetylgalactosamine 6-sulfatase		↓↓↓	↓↓↓	↓↓↓	↓↓↓
	MPS IVB β -galactosidase		↓↓↓	↓↓↓	↓↓↓	↓↓↓
CNS	Psychomotor retardation				±	±
	Spinal cord compression			+	++	++
Other	Respiratory infection			±	++	++
	Knock-knees			+	+	+
	Flat feet			+	+	+

^a The Morquio syndrome, type B phenotype encompasses similar symptoms, is more variable and is rarer than type A.

Table 18.9. N-Acetylgalactosamine 4-sulfatase (Maroteaux-Lamy syndrome, MPS VI)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features			+	++	++
	Growth retardation			+	+	+
Skeleton	Dysostosis multiplex			++	+++	+++
	Lumbar kyphosis			+	+	+
	Sternal protrusion			+	+	+
Ear	Hearing loss				±	±
Eye	Corneal opacities			++	++	+++
	Glaucoma			+	++	++
Cardiac	Valvular thickening			+	++	+++
GI	Hernias			+	+	+
	Hepatomegaly			+	+	+
Special laboratory	Total urinary GAGs			n-↑	n-↑	n-↑
Dermatan sulfate			↑↑	↑↑	↑↑	Enzyme activity
N-acetylgalactosamine 4-sulfatase			↓	↓	↓	CNS
Psychomotor retardation						
Spinal cord compression				+	++	Other
Respiratory infection			±	±	±	
Splenomegaly			+	+	+	
Joint contractures			+	++	++	
Hypertrichosis			+	+	+	
Claw hand			+	++	+++	

Table 18.10. β -D-Glucuronidase (Sly syndrome, MPS VII)^a

System	Symptoms/markers	Neonatal ^b	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Coarse facial features		++	++	++	++
	Macrocephaly	+	+			
	Short stature	+	+	+	+	+
Skeleton	Dysostosis multiplex		+	+	+	++
	Kyphosis			+	++	++
Ear	Hearing loss		+	+		
Eye	Corneal opacities	+	±	++		
Cardiac	Valvular thickening		+	++		
GI	Hernias		++	+++		
	Hepatomegaly		+	++	++	++
Special laboratory	Total urinary GAGs	↑	↑	↑	↑	↑
	Dermatan sulfate	↑	↑	↑	↑	↑
	Heparan sulfate	↑↑	↑↑	↑↑	↑↑	↑↑
	Chondroitin sulfate	↑↑	↑↑	↑↑	↑↑	↑↑
Enzyme activity	β -Glucuronidase	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
	Psychomotor retardation		+	++	++	++
	Seizures	±	±	+		
Other	Hydrocephalus					
	Respiratory infection	+	++	±		
	Splenomegaly		++	+	+	+
	Joint contractures		++	+++		
	Hypertrichosis		+	++		

^a The Sly syndrome spans a wide variety of clinical phenotypes.

^b The neonatal form expresses as nonimmune hydrops fetalis with ascites and survival is not more than a few months [5].

18.5 Reference Values

Age	Uronic acid			N-sulfated hexosamine (years/months) MBTH method ^b
	Number of controls	Carbazole method ^a	Orcinol method ^a	
1–11 mo.	10	25.5±18.3 ^c	15.2±14.9	19.8±22
1–1 y 11 m	10	38.9±30.1	20.9±16.1	31.3±22.2
2–3 y 11 m	10	16.9±9.9	10.7±8.1	15.8±12.3
4–6 y 11 m	10	16.8±14.9	13.7±11.4	20.9±16.1
7–8 y 11 m	10	7.4±5.2	4.6±3.2	12.6±9.8
9 y–11 y 11 m	10	8.3±4.4	5.0±3.2	8.8±5.1
12 y–18 y	5	10.0±2.7	5.0±1.9	4.0±3.0

^a mg/g creatinine.

^b MBTH-3-methyl-2-benzothiazolone hydrazone HCl.

^c Mean ± standard deviation.

18.6 Pathological Findings

Disorder	Urinary glycosaminoglycans Range of values			Qualitative
	Carbazole method	Orcinol method	MBTH method	
18.1a,b,c Hurler, Scheie, Hurler-Scheie	157–537(5)	153–783(5)	20–75(5)	Dermatan sulfate and Heparan sulfate (as 18.1)
18.2 Hunter	311–461(2)	200–302(2)	44–99(2)	Heparan sulfate (as 18.3)
18.3 Sanfilippo A	116–297(7)	29–89(7)	30–88(7)	Heparan sulfate (as 18.3)
18.4 Sanfilippo B	63–272(4)	25–108(4)	37–59(4)	Heparan sulfate (as 18.3)
18.5 Sanfilippo C	180–242(2)	48–135(2)	43–57(2)	Heparan sulfate (as 18.3)
18.6 Sanfilippo D	14–27(2)	7–14(2)	2–6(2)	Keratan sulfate* and chondroitin sulfate (as 18.7)
18.7 Morquio A				
18.8 Morquio B				
18.9 Maroteaux-Lamy	23–108(2)	40–161(2)	2–7(2)	Dermatan sulfate and chondroitin sulfate (as 18.1)
18.10 Sly	148 (1)	103 (1)	14 (1)	

() Numbers in parentheses are the number of individuals studied.

Values for each of the three reactions are expressed in mg/g creatinine.

* Keratan sulfate does not form a reaction product with any of the methods described; subsequently quantitative glycosaminoglycans in Morquio syndrome are not reliable.

18.7 Diagnostic Flow Chart

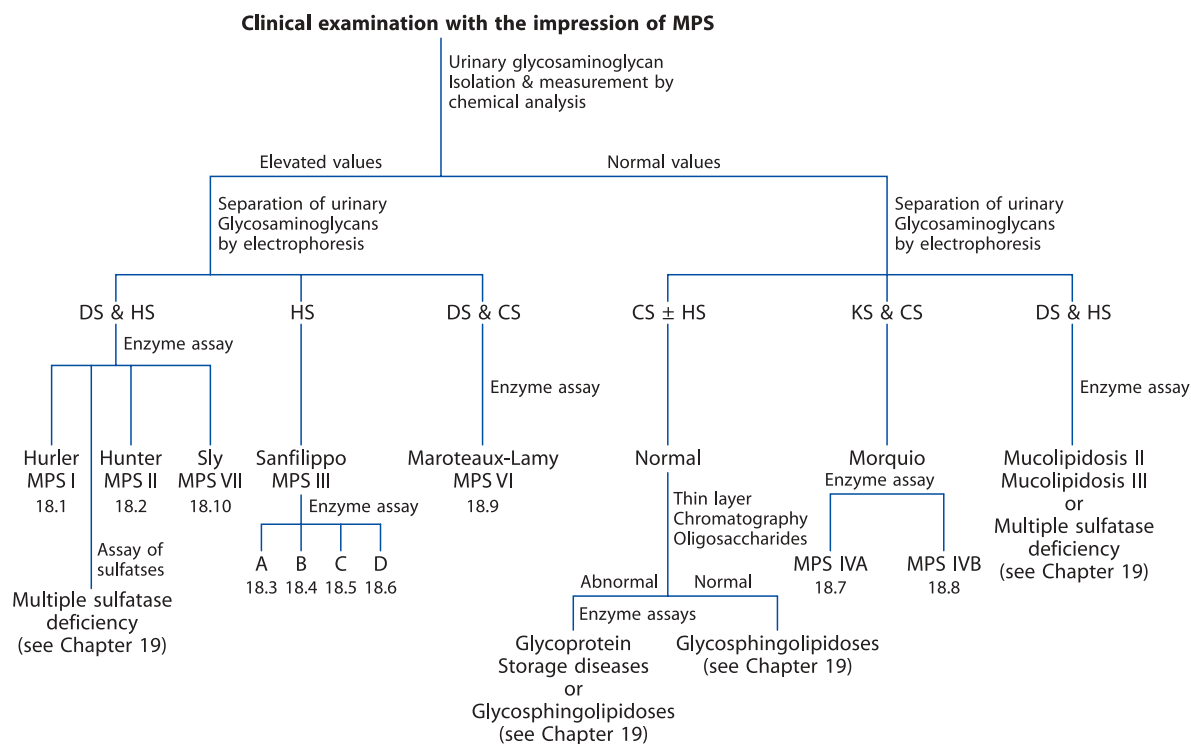


Fig. 18.4. The diagnosis of the mucopolysaccharidoses can be performed by a screening of the urine followed by assay of indicated specific enzymes

18.8 Specimen Collection

Disorder	Procedure	Specimen	Volume	Handling	Interference
18.1	Quantitative and qualitative glycosaminoglycans	Urine	20 ml	Keep frozen (−20 °)	Specimen has low creatinine; concentration; medications; protein in urine; increase in heparan sulfate in certain other diseases (4, 7)
18.2					
18.3					
18.4					
18.5					
18.6					
18.7					
18.8					
18.9					
18.10					
18.7	Carbohydrate analysis	Urine	20 ml	Keep frozen (−20 °)	High carbohydrate diet; medications
18.8	Oligosaccharides				
18.1	Enzyme assay	Leukocytes	5 ml heparinized blood	Room temperature	
18.8		Cultured skin fibroblasts	Skin biopsy	Room temperature	
18.9		(as 18.8)			
18.10		(as 18.8)			
18.2	Enzyme assay	Serum	1 ml	Frozen	
18.4		Plasma	1 ml	Frozen	
18.11		Leukocytes	5 ml	Room temperature	
		Cultured skin fibroblasts	Skin biopsy	Room temperature	
18.3		Cultured skin fibroblasts	Skin biopsy	Room temperature	
18.5		(as 18.3)			
18.6		(as 18.3)			
18.7		(as 18.3)			

18.9 Prenatal Diagnosis

Disorder	Source	Enzyme assay
18.1	Cultured amniocytes	α -L-Iduronidase
18.2	Cell-free amniotic fluid and cultured amniocytes	Iduronate 2-sulfatase
18.3	Cultured amniocytes	Heparin sulfaminidase
18.4	Cultured amniocytes	N-Acetyl- α -D-glucosamidase
18.5	Cultured amniocytes	Acetyl CoA: α -glucosaminide N-Acetyltransferase
18.6	Cultured amniocytes	N-Acetylglucosamine 6-sulfatase
18.7	Cultured amniocytes	N-Acetylgalactosamine 6-sulfatase (galactose 6-sulfatase)
18.8	Cultured amniocytes	β -Galactosidase
18.9	Cultured amniocytes	N-Acetylgalactosamine 4-sulfatase
18.10	Cultured amniocytes	β -Glucuronidase

18.10 DNA Analysis

Disorder		Gene symbol	Tissue	Methods
18.1	Hurler	IDUA	WBC, FB	RT-PCR
	Scheie			Sequencing
	Hurler-Scheie			SSCP
18.2	Hunter	IDS	WBC, P, S, FB	RT-PCR
				Sequencing
				SSCP
18.3	Sanfilippo A	SGSH	WBC, FB	RT-PCR
				Sequencing
18.4	Sanfilippo B	NAGLU	WBC, P, S, FB	RT-PCR
				Sequencing
18.6	Sanfilippo D	GMS	FB	RT-PCR
				Sequencing
18.7	Morquio A	GALN	FB	RT-PCR
				Sequencing
18.8	Morquio B	GLBI	WBC, FB	RT-PCR
18.9	Maroteaux-Lamy	ARSB	WBC, FB	RT-PCR
				Sequencing
18.10	Sly	GUSB	WBC, P, S, FB	RT-PCR
				Sequencing
				SSCP
18.11	Natowicz	HYAL-1	P, S, FB	Sequencing

18.11 Therapy

■ 18.1: Hurler, Scheie, Hurler-Scheie

Bone marrow transplantation has been shown to be an effective therapy for patients with mucopolysaccharidosis, type I. Patients who were less than two years of age responded the best (9.12).

Recently, specific treatment for mucopolysaccharidosis, type I, using replacement therapy of the missing enzyme activity, α -L-iduronidase, with recombinant human enzyme has been successful in a one-year clinical trial involving ten patients [8]. The results are promising in that there was a reduction in size of some of the somatic tissue, i.e., liver and spleen. A reduction in the stiffness of joints was observed. Also, there was a decrease in excretion of urinary glycosaminoglycans by 63% [8].

■ 18.2: Hunter

In contrast to enzyme replacement therapy, one study of gene replacement therapy of a patient with mucopolysaccharidosis, type II, Hunter syndrome, did not show any benefit [10]. While this is discouraging at present this may be modified for future trials and may prove to be successful.

■ 18.9: Maroteaux-Lamy

In general, patients with milder or no neurological involvement will have a better outcome with bone marrow transplantation. Patients with Maroteaux-Lamy syndrome, mucopolysaccharidosis, type VI, have a mild to no neurological involvement. Therefore, bone marrow transplantation has been shown to be an effective therapy for these patients [12].

References

1. Neufeld, E.F. and Muenzer, J. (1995) The mucopolysaccharidoses, in *The Metabolic and Molecular Bases of Inherited Disease* (eds C.R. Scriver, A.L. Beaudet, W.S. Sly and D. Valle). McGraw-Hill, New York, pp. 2465–2494.
2. Meikle, P.J., Hopwood, J.J., Clague, A.E., Carey, W.F. (1999) Prevalence of lysosomal storage disorders. *JAMA* 281, 249–254.
3. van de Kamp, J.J., Niermeijer, M.F., von Figura, K., Giesberts, M.A., (1981) Genetic heterogeneity and clinical variable in the Sanfilippo syndrome (types A, B, and C). *Clin. Genet.* 20, pp. 152–160.
4. Ullrich, K. and Kresse, H. (1996) Mucopolysaccharidoses, in *Physician's Guide to the laboratory diagnosis of metabolic diseases* (eds N. Blau, M. Duran, M.E. Blaskovics). Chapman and Hall Medical, New York, pp. 303–317.
5. Whitley, C.B. (1993) The mucopolysaccharidoses, in *McKusick's Heritable Disorders of Connective Tissue* (P. Beighton), 5th edition, St. Louis, C.V. Mosby, pp. 367–499.

6. Natowicz, M. R.; Short, M. P.; Wang, Y.; Dickersin, G. R.; Gebhardt, M. C.; Rosenthal, D. I.; Sims, K. B.; Rosenberg, A. E. (1996) Clinical and biochemical manifestations of hyaluronidase deficiency. *New Eng. J. Med.* 335, 1029–1033.
7. Steiner, RD, Whyte, MP, Chang, E, Hanks, J, Mattes, C, Senephansiri, H, and Gibson, KM: Increased urine heparan and chondroitin sulphate excretion in patients with osteopetrosis. *J. Inher. Metab. Dis.* 23, 88–90, 2000.
8. Kakkis, E. D., Muenzer, J, Tiller, G.E., Lewis, W., Belmont, J., Passage, M., Izykowski, B, Phillips, J., Doroshow, R., Walot, I., Hoft, R., Yu, K.T., Okazaki, S., Lewis, D., Lachman, R., Thompson, J.N., Neufeld, E.F.: Enzyme-Replacement Therapy in Mucopolysaccharidosis I. *New Eng. J. Med.* 344, 182–188, 2001.
9. Peters, C, Shapiro, E.G., Anderson, J., Henslee-Downey, P.J., Klemperer, M.R., Cowan, M.J., Saunders, E.F., delAlarcon, P.A., Twist, C., Nachman, J.B., Hale, G.A., Harris, R.E., Rozans, M.K., Kurtzberg, J., Grayson, G.H., Williams, T.E., Lenarsky, C., Wagner, J.E., Krivit, W. (1998) Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. *Blood* 91, pp. 2601–2608.
10. Pan, D., Shankar, R., Stroncek, D.F., Whitley, C.B. (1999) Combined ultrafiltration-transduction in a hollow-fiber bioreactor facilitates retrovirus-mediated gene transfer into peripheral blood lymphocytes from patients with mucopolysaccharidosis type II. *Human Gene Therapy* 10, 2799–2810.
11. Krivit, W., Pierpont, M.E., Ayaz, K., Tsai, M., Ramsay, N. K., Kersey, J. H., Weisdorf, S., Sibley, R., Snover, D., McGovern, M. M. (1984) Bone-marrow transplantation in the Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI): biochemical and clinical status 24 months after transplantation. *N. Eng. J. Med.* 311, 1606–1611.
12. Koc, O.N., Peters, C., Aubourg, P., Raghavan, S., Dyhouse, S., DeGasperi, R., Kolodny, E. H., Yoseph, B. Y., Gerson, S. L., Lazarus, H. M., Caplan, A. I., Watkins, P. A., Krivit, W. (1999) Bone marrow-derived mesenchymal stem cells remain host-derived despite successful hematopoietic engraftment after allogeneic transplantation in patients with lysosomal and peroxisomal storage diseases. *Exper. Hemat.* 27, 1675–1681.