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Minzhi Xing, Emory University
E I Parker, Emory University
A Moreno-De-Luca, Geisinger Health System
Elie Harmouche, Emory University
Michael Terk, Emory University

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REVIEW ARTICLE

Radiological and clinical characterization of the lysosomal storage disorders: non-lipid disorders

1M XING, MD, 1E I PARKER, MD, 2A MORENO-DE-LUCA, MD, 1E HARMOUCHE, MD and 1M R TERK, MD

1Division of Musculoskeletal Imaging, Department of Radiology and Imaging Sciences, Emory University Hospital, Atlanta, GA, USA
2Department of Radiology, Geisinger Autism & Developmental Medicine Institute, the Genomic Medicine Institute, Geisinger Health System, Danville, PA, USA

Address correspondence to: Dr Minzhi Xing
E-mail: minzhi.xing@emory.edu

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ABSTRACT

Lysosomal storage diseases (LSDs) are a large group of genetic metabolic disorders that result in the accumulation of abnormal material, such as mucopolysaccharides, glycoproteins, amino acids and lipids, within cells. Since many LSDs manifest during infancy or early childhood, with potentially devastating consequences if left untreated, timely identification is imperative to prevent irreversible damage and early death. In this review, the key imaging features of the non-lipid or extralipid LSDs are examined and correlated with salient clinical manifestations and genetic information. Disorders are stratified based on the type of excess material causing tissue or organ dysfunction, with descriptions of the mucopolysaccharidoses, mucolipidoses, alpha-mannosidosis, glycogen storage disorder II and cystinosis. In addition, similarities and differences in radiological findings between each of these LSDs are highlighted to facilitate further recognition. Given the rare and extensive nature of the LSDs, mastery of their multiple clinical and radiological traits may seem challenging. However, an understanding of the distinguishing imaging characteristics of LSDs and their clinical correlates may allow radiologists to play a key role in the early diagnosis of these progressive and potentially fatal disorders.

Lysosomal storage diseases (LSDs) are genetic disorders that cause metabolic pathway deficiencies and abnormal accumulation of material within the lysosome, leading to excess storage of substances, such as mucopolysaccharides, glycoproteins, amino acids and lipids.1 Although the LSDs encompass a large group of approximately 50 rare inherited metabolic disorders, certain similarities and differences may be appreciated between the LSDs based on the type of enzyme deficiency, the type of abnormal substrate that accumulates and the specific tissue or organs most affected.1 Many LSDs manifest during infancy or early childhood and may have devastating consequences if untreated, including early death.1 Therefore, early recognition is imperative given the availability of new treatment options to prevent irreversible damage.1 Radiologists may benefit from understanding the characteristic clinical and imaging features of the LSDs, including the similarities and differences, and can assist the clinician with both diagnosis and prognosis. This article discusses the clinical and imaging features of those LSDs that involve abnormal accumulation of non-lipid or extralipid substances, including mucopolysaccharides, glycoproteins, glycogen and amino acids.

Mucopolysaccharidoses

The mucopolysaccharidoses (MPSs) are a group of LSDs resulting from a deficiency in enzymes that degrade glycosaminoglycans (GAGs) (mucopolysaccharides). There are seven distinct MPSs—MPS I: Hurler syndrome, MPS II: Hunter syndrome, MPS III: Sanfilippo syndrome, MPS IV: Morquio syndrome, MPS VI: Maroteaux–Lamy syndrome, MPS VII: Sly syndrome and MPS IX: Natowicz syndrome. MPS V and VIII are no longer used as disease designations.2 Genetic mutations and clinical and radiological manifestations of the MPSs are summarized in Table 1.

Mucopolysaccharidosis I: Hurler syndrome

MPS I or Hurler syndrome is due to α-L-iduronidase deficiency, resulting in the abnormal accumulation of GAGs dermatan sulfate and heparan sulfate in the cell.7 MPS I has an autosomal recessive inheritance pattern.8 The incidence
Table 1. Summary of clinical and radiological manifestations of the mucopolysaccharidoses (glycosaminoglycan storage disorders)

<table>
<thead>
<tr>
<th>Mucopolysaccharidoses</th>
<th>Incidence per 100 000 live births</th>
<th>Gene mutation and locus (inheritance)</th>
<th>Deficient enzyme</th>
<th>Accumulated glycosaminoglycans</th>
<th>Clinical and radiological characteristics</th>
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<td>Cardiac</td>
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<td>Respiratory</td>
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<td>Musculoskeletal</td>
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<td>Neurological</td>
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<td>Developmental</td>
</tr>
<tr>
<td>MPS I: Hurler syndrome</td>
<td>0.11–1.67</td>
<td>IDUA ap16.3 (AR)</td>
<td>α-L-iduronidase</td>
<td>Dermatan sulfate, heparan sulfate</td>
<td>Dysostosis multiplex, including thoracolumbar gibbus, cleft palate, thickened clavicles, corneal opacities, J-shaped sella turcica, genu valgum, abnormal dentition, thickened ligaments and atlantoaxial subluxation leading to cord compression</td>
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<td>Brain atrophy</td>
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<td>Speech delay</td>
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<td>Normal development until 2–6 years old.</td>
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<td>Subsequent rapid neurological deterioration</td>
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<td>MPS II: Hunter syndrome</td>
<td>0.10–1.07</td>
<td>IDS Xq28 (XR)</td>
<td>Iduronate-2-sulfatase</td>
<td>Dermatan sulfate, heparan sulfate</td>
<td>Severe form—similar to MPS I</td>
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<td>Similar to MPS I, severe form.</td>
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<td>Severe form due to cognitive function.</td>
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<td>Death in first or second decade</td>
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<td>MPS III: Sanfilippo syndrome</td>
<td>0.29–1.89</td>
<td>II A: SGSH, 17q25.3; II B: NAGLU, 17q21; II C: HGSNAT, 8p11.1; II D: GNS, 12q14 (AR)</td>
<td>Heparan sulfate</td>
<td>Similar to MPS I</td>
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<td>Similar to MPS I, but may be more extensive</td>
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<td>Normal development until 3–6 years old.</td>
</tr>
<tr>
<td>MPS IV: Morquio syndrome</td>
<td>0.15–1.31</td>
<td>IVA: GALNS, 16q24.3; IV B: GLBI, 3p21.33 (AR)</td>
<td>Keratan sulfate, chondroitin sulfate</td>
<td>Similar to MPS I, severe valvular disease</td>
<td>Dyostosis multiplex with similar features to MPS I</td>
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<td>Similar to MPS I</td>
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<td>Typically normal intelligence</td>
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<td>MPS VI: Maroteaux–Lamy syndrome</td>
<td>0.14–0.38</td>
<td>ARSB 5q11–q13 (AR)</td>
<td>Arylsulfatase-β</td>
<td>Dermatan sulfate, chondroitin sulfate</td>
<td>Dyostosis multiplex with similar features to MPS I</td>
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<td>Similar to MPS I</td>
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<tr>
<td>MPS VII: Sly syndrome</td>
<td>0.02–0.29</td>
<td>GUSB 7q21.11 (AR)</td>
<td>β-glucuronidase</td>
<td>Dermatan sulfate, chondroitin sulfate</td>
<td>Dyostosis multiplex with similar features to MPS I</td>
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<td>Similar to MPS I</td>
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</table>

AR, autosomal recessive; ARSB, Arylsulfatase-β; CHF, congestive heart failure; CoA, coenzyme A; GALNS, Galactosamine (N-acetyl)-6-sulfate sulfatase; GLBI, β1-galactosidase; GNS, N-acetylgalactosamine-6-sulfatase; GUSB, β-glucuronidase; HGSNAT, Heparan-α-glucosaminidase N-acetyltransferase; IDS, Iduronate 2-sulfatase; IDUA, α-L-iduronidase; MPS, mucopolysaccharidosis; NAGLU, a-N-acetylgalactosaminidase; OSA, obstructive sleep apnoea; SGSH, N-sulfoglucosamine sulfatohydrolase; XR, X-linked recessive.

Spectrum of radiographic manifestations of dysostosis multiplex includes upper limb deformities, flaring of the iliac wings and hip dysplasia. The terms MPS V and MPS VIII are no longer used as disease designations.6 MPS IX (Natowicz syndrome) is due to a deficiency in hyaluronidase, with four cases having been described in the literature.5,6
of MPS I ranges from 0.11/100 000 to 1.67/100 000 live births, with incidence variation depending on the country reviewed.3 MPS I has traditionally been categorized into Hurler syndrome, Hurler–Scheie syndrome and Scheie syndrome.7 However, biochemical differences have not been identified between these categories.7 Therefore, MPS I is best classified into severe or attenuated forms, a difference which influences therapeutic options.7 In the severe form, early onset of clinical symptoms and earlier death owing to complications (usually in the first decade) are common distinctions from the attenuated form.7

Clinical and radiographic features of MPS I are frequently observed in the other MPSs, as well as in other LSDs. Dysostosis multiplex is the term used to describe progressive skeletal dysplasia seen in MPS I and other MPSs.6,9 The skeletal dysplasia results from a lack of skeletal remodelling and ossification abnormalities owing to abnormal deposition of GAGs in bone and cartilage.8 GAGs also accumulate in tendons, ligaments and joint capsules, and patients may develop joint contractures.8 Radiographic manifestations of dysostosis multiplex include thoraco-lumbar gibbus deformity because of vertebral body wedge deformity or hypoplasia (Figure 1), oar-shaped ribs and thickened clavicles (Figure 2a), flaring of the iliac wings, hip dysplasia and coxa valga (Figure 2b), along with numerous other osseous dysplasias detailed later in this article.4,8,9

Cardiovascular abnormalities observed in MPS I because of GAG infiltration of cardiac tissue include valvular disease, endocardial fibroelastosis, arrhythmias, congestive heart failure, aortic stenosis and myocardial ischaemia.10–14 In addition, patients with MPS I may suffer from respiratory infections and obstructive sleep apnoea, with GAGs infiltrating into airway soft tissues, cartilage and the thoracic cage.13,15

GAGs may also accumulate in the central nervous system (CNS), including within the meninges and even adjacent bone.11 Individuals with the severe form of MPS I may have developmental delay, particularly speech delay, which is then followed by a decline in cognitive, visual and auditory function.13 Other CNS manifestations as a result of abnormal GAG accumulation include brain atrophy, thickened meninges, prominent subarachnoid spaces, patchy white matter signal abnormality, multiple perivascular spaces and hydrocephalus (Figure 2c).13,16–18 Additionally, cervical cord compression from a dysplastic or hypoplastic dens, thickened or abnormal ligaments (Figures 2d and 3) and atlantoaxial subluxation may also occur.13,15

Other clinical features of MPS I include coarse facial features, microcephaly, hearing loss, corneal clouding, hepatosplenomegaly, thickened skin and inguinal hernias.4,13

Mucopolysaccharidosis II: Hunter syndrome
MPS II or Hunter syndrome is due to iduronate sulfatase deficiency resulting in the accumulation of dermatan sulfate and heparan sulfate within the cell. MPS II has an X-linked recessive inheritance pattern.19 The incidence of MPS II ranges from 0.10/100 000 to 1.07/100 000 live births depending on the country reviewed.3 MPS II may be further differentiated into severe and attenuated forms.19 In the attenuated form, patients typically live into early adult years and have little to no CNS involvement. By contrast, there is progressive loss of cognitive function and early death typically in the first or the second decade of life in the severe form.19 Patients with the severe form may exhibit upper respiratory airway narrowing and cardiac valve abnormalities.19

There are many clinical similarities between MPS II and previously discussed MPS I (Hurler syndrome), including dysostosis multiplex.6,8,11,20 Additional examples of skeletal manifestations seen in dysostosis multiplex other than those previously discussed under MPS I include genu valgum, widening of the diaphysis of long bones, hypoplastic distal ulna and tilted radius, varus deformity
of the proximal humerus (Figure 4a), pointed thick and short metacarpals, small and irregular carpal bones, thickened calvarium and a J-shaped sella turcica (Figure 4b). In contrast to MPS I, seizures and severe psychomotor retardation are more common in the severe form of MPS II. Overall, the CNS imaging features may be similar between MPS I and II, including extensive dilated perivascular spaces or cribriform changes (Figure 4c).

Mucopolysaccharidosis III: Sanfilippo syndrome

MPS III or Sanfilippo syndrome is due to an abnormal accumulation of heparan sulfate within the cell. MPS III is divided into the following four subtypes based on the different enzyme deficiencies: (1) MPS IIIA (heparan-N-sulfatase), (2) MPS IIIB (α-N-acetylgalcosaminidase), (3) MPS IIIC (acetyl-coenzyme A: α-glucosaminide acetyltransferase) and (4) MPS IIID (N-acetylgalactosamine-6-sulfatase). The incidence of MPS III or Sanfilippo syndrome ranges from 0.29/100 000 to 1.89/100 000 live births, with variation of incidence reported depending on the country reviewed. The clinical features seen in MPS III are also similar to the features described in MPS I, with a few exceptions. MPS III may have milder dysostosis multiplex than MPS I. However, MPS III may exhibit more extensive CNS abnormalities than the other MPSs. There is often normal neurological development until 2–6 years old, which is followed by rapid neurological deterioration. Findings from CNS imaging are similar to those for MPS I and II, including diffuse or patchy white matter changes and brain atrophy (Figure 5).

Mucopolysaccharidosis IV: Morquio syndrome

MPS IV or Morquio syndrome has two subtypes from different enzymatic deficiencies, with MPS IVA being deficient in galactose-6-sulfatase and MPS IVB having a β-galactosidase deficiency and less severe clinical features. MPS IV is caused by abnormal keratan sulfate and chondroitin sulfate accumulation in cells. This disorder exhibits autosomal recessive inheritance, with an incidence ranging from 0.15/100 000 to 1.31/100 000 live births depending on the country reviewed. Clinical features are similar...
to MPS I or Hurler syndrome, including dysostosis multiplex, which is often severe (Figure 6a). Dens and ligamentous abnormalities may also occur, with complications including cord compression and atlantoaxial subluxation (Figure 6b). Other similar clinical features to MPS I include cardiac valve abnormalities and obstructive respiratory disease. However, MPS IV patients typically exhibit normal intelligence and a longer life span than those with MPS I.

**Mucopolysaccharidosis VI: Maroteaux–Lamy syndrome**

MPS VI or Maroteaux–Lamy syndrome is caused by arylsulfatase-B deficiency, with abnormal accumulation of dermatan sulfate and chondroitin sulfate in cells. This disorder has an autosomal recessive inheritance pattern, with an incidence ranging from 0.14/100,000 to 0.38/100,000 live births depending on the country reviewed. Patients exhibit a spectrum of phenotypic severity, with many clinical features similar to MPS I and the other MPSs, including dysostosis multiplex (Figure 7). However, individuals with MPS VI are typically intellectually normal.

**Mucopolysaccharidosis VII: Sly syndrome**

MPS VII or Sly syndrome results from a β-glucuronidase deficiency with dermatan sulfate, heparan sulfate, chondroitin-4-sulfate and chondroitin-6-sulfate accumulating abnormally in cells. MPS VII has an autosomal recessive inheritance pattern with an incidence ranging from 0.02/100,000 to 0.29/100,000 live births in the countries reviewed. The phenotype varies from a severe form presenting as fatal non-immune hydrops fetalis to a milder form with features similar to MPS I (including hepatosplenomegaly and recurrent respiratory infections). Patients with MPS VII may have similar cardiac manifestations to other MPSs, with the abnormal accumulation of GAGs in cardiac tissue leading to complications of aortic valve stenosis, as seen in Figure 8. As with the other MPSs, the musculoskeletal manifestations in MPS VII include dysostosis multiplex.

**Glycoprotein storage disorders**

There are several LSDs that occur because of a deficiency in enzymes that either degrade glycoproteins or phosphorylate glycoproteins. Mucolipidosis I, mucolipidosis II, mucolipidosis III and alpha-mannosidosis are disorders included within this group of LSDs. Genetic, clinical and radiological features of the glycoprotein storage disorders are summarized in Table 2.
Mucolipidosis I: sialidosis syndrome

Mucolipidosis I or sialidosis is due to lysosomal α-N-acetylneuraminidase deficiency resulting in abnormal accumulation of sialic acid-containing oligosaccharides.32 Mucolipidosis I has an autosomal recessive inheritance pattern and an incidence of 0.02/100,000 live births.29 There are two subtypes, with Type 1 manifesting during childhood or juvenile ages.33 Individuals with Type 1, also known as cherry red spot myoclonus syndrome, have macular cherry red spots, myoclonic epilepsy, progressive loss of vision and ataxia.32,33 Patients with Type 1 lack the somatic changes commonly seen in Type 2.32

Type 2 mucolipidosis I includes congenital, infantile and juvenile forms.34 The congenital form is associated with non-immune hydrops fetalis and ascites.33,34 The infantile form may have similar features to MPS I, including dysostosis multiplex (Figure 9), coarse facies, visceromegaly and developmental delay, but may develop macular cherry red spots in contrast to MPS I.32–34

Mucolipidosis II: I-cell disease

Mucolipidosis II or I-cell disease is caused by a mutation in the N-acetylg glucosamine-1-phosphate transferase, α/β subunits (GNPTAB) gene. This causes a deficiency in N-acetylg glucosamine-1-phosphotransferase, which results in lysosomal acid hydrolase enzymes lacking a normal recognition phosphate group and abnormally accumulating in the extracellular space rather than the lysosome.35 Mucolipidosis II has autosomal recessive inheritance, with a worldwide prevalence of 0.15/100,000 live births.29 Patients with mucolipidosis II usually have a short lifespan, commonly resulting in death in early childhood because of cardiopulmonary problems.35–37 Cardiorespiratory abnormalities are similar to those seen in MPS I (Hurler syndrome), including cardiac valve problems, thickening of the airways and thoracic cage stiffening.35

Other clinical similarities between mucolipidosis II and MPS I may include dysostosis multiplex (Figure 10), short stature and coarse facies.35,37 Compared with MPS I, dysostosis multiplex has been described to occur in a later phase of osseous changes in patients with mucolipidosis II, with the early phase of bone changes in these patients resembling rickets or hyperparathyroidism seen in the neonatal period.35,37 Craniosynostosis, premature closure of sutures that is often sporadic, has been reported in patients with mucolipidosis II (Figure 11).36,37
Individuals with mucolipidosis II may have more extensive delay in motor development than intellectual impairment.\textsuperscript{36,37}

**Mucolipidosis III: pseudo-Hurler polydystrophy**

Mucolipidosis III alpha/beta or pseudo-Hurler polydystrophy syndrome is also caused by $N$-acetylglucosamine-1-phosphotransferase deficiency, with precursor lysosomal acid hydrolase enzymes accumulating in the extracellular space because of lack of a phosphate group as in I-cell disease.\textsuperscript{38} However, mucolipidosis III is a milder and more attenuated form with the mutation of the $\text{GNPTAB}$ gene resulting in more normal enzyme activity than mucolipidosis II.\textsuperscript{38} Mucolipidosis III has an autosomal recessive inheritance pattern, with a prevalence that is probably similar to that in mucolipidosis II.\textsuperscript{38} In contrast to mucolipidosis II, clinical manifestations in mucolipidosis III alpha/beta typically occur around the age of 3 years, with death often occurring early in middle adulthood commonly caused by cardiorespiratory problems.\textsuperscript{38} Dysostosis multiplex (Figure 12), coarse facial features and short stature are also features of mucolipidosis III alpha/beta but are often milder than in mucolipidosis II.\textsuperscript{38}

**Alpha-mannosidosis**

Alpha-mannosidosis results from a deficiency in lysosomal alpha-mannosidase enzyme, with mannose-rich oligosaccharides accumulating abnormally.\textsuperscript{39} This disorder has an autosomal recessive inheritance pattern and is extremely rare with incidences reported from 0.20/100 000 to 0.33/100 000 live births depending on location.\textsuperscript{30} Clinical manifestations of alpha-mannosidosis include intellectual disability, coarse facial features and skeletal abnormalities of dysostosis multiplex (Figure 13), which are similar to the characteristics manifested in MPS I.\textsuperscript{30} In addition, immune deficiencies and ataxia may be observed in patients with alpha-mannosidosis.\textsuperscript{30}

Three clinical subtypes of alpha-mannosidosis have been suggested: severe, moderate and mild forms.\textsuperscript{39} The severe form manifests early and produces skeletal abnormalities, including dysostosis multiplex.\textsuperscript{30} Patients with the severe form typically die from infection, primary CNS involvement or metabolic myopathy early in life.\textsuperscript{30} The moderate form manifests before 10 years old with milder or slower progression of clinical features, including metabolic myopathy and ataxia.\textsuperscript{30} Patients with the moderate form also have dysostosis multiplex, in contrast to the mild form that typically lacks skeletal abnormalities.\textsuperscript{30} Additionally, the mild form has an onset later in life with slower progression.\textsuperscript{30} Neuroimaging features reported in a few
Table 2. Summary of clinical and radiological manifestations of the mucolipidoses (glycoprotein storage disorders)

<table>
<thead>
<tr>
<th>Glycoprotein storage disorders: eponym</th>
<th>Incidence per 100 000 live births29,30</th>
<th>Gene mutation and locus (inheritance)31</th>
<th>Deficient enzyme</th>
<th>Accumulated substance</th>
<th>Clinical and radiological characteristics</th>
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<td>Cardio-respiratory</td>
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<td>Gastrointestinal</td>
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<td>Neurological</td>
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<td>Developmental</td>
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<tr>
<td>Mucolipidosis I: sialidosis syndrome</td>
<td>0.02</td>
<td>NEU1 6p21.3 (AR)</td>
<td>α-N-acetylneuraminidase</td>
<td>Sialic acid-containing oligosaccharides</td>
<td>None</td>
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<td>Type 2: ascites, visceromegaly</td>
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<td></td>
<td>Type 2: dysostosis multiplex with similar features to MPS I</td>
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<td></td>
<td>Type 1: myoclonic epilepsy, progressive ataxia, macular cherry red spots (may also occur in Type 2)</td>
</tr>
<tr>
<td>Mucolipidosis II: I-cell disease</td>
<td>0.15</td>
<td>GNPTAB 12q23.2 (AR)</td>
<td>N-acetylglucosamine-1-phosphotransferase</td>
<td>Lyosomal acid hydrolase enzymes in extracellular space</td>
<td>Similar to MPS I, especially valvular disease</td>
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<td>Umbilical and inguinal hernias</td>
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<td>Early phase (neonatal): rickets or hyperparathyroidism, late phases: dysostosis multiplex with similar features to MPS I, craniosynostosis</td>
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<td>Motor deficits secondary to bony abnormalities</td>
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<tr>
<td>Mucolipidosis III alpha/beta pseudo-Hurler polydystrophy</td>
<td>0.25-1.00</td>
<td>GNPTAB 12q23.2 (AR)</td>
<td>N-acetylglucosamine-1-phosphotransferase (more normal enzyme than in mucolipidosis II)</td>
<td>Lyosomal acid hydrolase enzymes in extracellular space</td>
<td>Similar to mucolipidosis II and MPS I, but may be milder/faster onset</td>
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<td>Dysostosis multiplex with similar features to MPS I, but often milder</td>
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<td>Similar to mucolipidosis II, but often milder</td>
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<td>Alpha-mannosidosis</td>
<td>0.20-0.33</td>
<td>MAN2B1 19cen-q13.1 (AR)</td>
<td>Alpha-mannosidase</td>
<td>Mannose-rich oligosaccharides</td>
<td>Respiratory infections, and other types of infections due to immunodeficiencies</td>
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<td>Visceromegaly</td>
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<td>Dysostosis multiplex with similar features to MPS I in the severe and moderate forms of alpha-mannosidosis, metabolic myopathy</td>
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<td>Cerebellar atrophy, white matter signal abnormality, progressive cortico-subcortical atrophy, enlarged or empty sella, ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intellectual disability, motor developmental delay</td>
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</tbody>
</table>

AR, autosomal recessive; GNPTAB, N-acetylglucosamine-1-phosphate transferase, α/b subunits; MAN2B1, Mannosidase, alpha, class 2B, member 1; MPS, mucopolysaccharidosis; NEU1, Neuraminidase-1.

Spectrum of radiographic manifestations of dysostosis multiplex is similar to that seen in the mucopolysaccharidoses.
patients with alpha-mannosidosis include cerebellar atrophy, white matter signal abnormalities, progressive cortico-subcortical atrophy, particularly within the cerebellar vermis, enlarged or partially empty sella turcica and prominent Virchow–Robin spaces.30,40,41

Glycogen storage diseases

The glycogen storage disorders (GSDs) result from a genetic defect in enzymes regulating synthesis or degradation of glycogen. In contrast to the other GSDs, the underlying pathogenesis...
in glycogen storage disease Type II (GSD II) is due to a defect in lysosomal metabolism. Genetic, clinical and radiological features of GSD II are summarized in Table 3.

**Glycogen storage disease II: Pompe disease**

GSD II or Pompe disease is caused by a deficiency in the lysosomal α-glucosidase enzyme, with glycogen abnormally accumulating within the lysosomes of several cell types, particularly muscle cells. This disease is inherited in an autosomal recessive pattern. The combined incidence of all forms of GSD II varies from 1.00/100,000 in people of European descent to 7.14/100,000 in African-Americans.

GSD II is subdivided into infantile-onset and late-onset disease, with infantile-onset disease further categorized into classic and non-classic types. Clinical features of the infantile-onset type include myopathy with hypotonia, respiratory distress, cardiomegaly and hypertrophic cardiomyopathy, hepatomegaly, feeding difficulties, macroglossia and failure to thrive. Intelligence is usually normal.

The classic infantile-onset type often presents by the first month of life and is usually fatal by the first year if untreated.

![Figure 13. Dysostosis multiplex in an older child with alpha-mannosidosis. Single frontal radiograph of the chest and abdomen demonstrates mild broadening of the ribs bilaterally (arrows).](image)

### Table 3: Summary of clinical and radiological manifestations of Pompe disease and cystinosis (glycogen storage disorders and amino acid storage disorders)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Accumulated substance</th>
<th>Deficiency</th>
<th>Deficiency mutation</th>
<th>Accumulated substance</th>
<th>Deficiency mutation</th>
<th>Accumulated substance</th>
<th>Deficiency mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD II</td>
<td>Glycogen</td>
<td>α-glucosidase</td>
<td>GAA</td>
<td>17q25.2–q25.3</td>
<td>AR</td>
<td>Respiratory distress, cardiomegaly/cardiomyopathy (earlier age onset), hepatomegaly, feeding difficulties, macroglossia and failure to thrive</td>
<td>Normal intelligence</td>
</tr>
<tr>
<td>MPS I</td>
<td>Cystine</td>
<td>Cystinosin (cystine transporter)</td>
<td>CTNS</td>
<td>17p13</td>
<td>AR</td>
<td>Fanconi syndrome, medullary nephrocalcinosis, rickets: metaphyseal cupping, osteopenia, fractures</td>
<td>Photograph due to corneal cystine crystals</td>
</tr>
<tr>
<td>Amino acid disorder</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

AR, autosomal recessive; CTNS, Cystinosin; GAA, Acid α-glucosidase; GSD, glycogen storage disorder; MPS, mucopolysaccharidosis.
Hypotonia and cardiomegaly are seen earlier in the first year of life in the classic type of GSD II than in the non-classic infantile type. Death usually occurs during the first year caused by cardiopulmonary failure in the classic type, with patients often having more severe cardiomegaly than the non-classic type, including left ventricular outflow obstruction from hypertrophy. In the non-classic type, death usually occurs after the first year from respiratory insufficiency. Hypotonia contributes to respiratory insufficiency in both infantile types, and recurrent respiratory infections or pneumonia are commonly seen. Patients with infantile-type GSD II have been reported to have abnormal accumulation of glycogen within the CNS. Neuroimaging findings in patients with infantile GSD II include widening of the lateral ventricles, delayed myelination and abnormal periventricular white matter signal on MRI (Figure 14). 

Late-onset GSD II can present at various ages and may be further subdivided into juvenile late-onset and adult late-onset forms. The juvenile late-onset type occurs between 2 and 18 years old, and the adult late-onset type occurs after 18 years old.

Figure 14. Central nervous system changes in a child with glycogen storage disorder II (Pompe disease). Axial MRI fluid-attenuated inversion-recovery image of the brain demonstrates abnormal hyperintense signal in the periventricular white matter (arrows). Signal is non-specific, but may indicate incomplete myelination, dysmyelination or demyelination.

Figure 15. Diffuse fatty atrophy of the proximal lower limb muscles in an adult with late-onset-type glycogen storage disorder II (Pompe disease) seen on this axial T1 weighted MR image of the thighs.

Figure 16. Hypophosphataemic rickets in a child diagnosed with cystinosis. Anteroposterior radiograph of the knees demonstrates metaphyseal cupping and fraying (arrows) consistent with rickets.

Figure 17. Fractures in a child diagnosed with cystinosis. Coronal short tau inversion-recovery MR image of the pelvis demonstrates insufficiency fractures bilaterally along the proximal femur (arrows).
Cardiomegaly, macroglossia and hepatomegaly are rarer in patients with late-onset type of GSD II, particularly the older the age of onset. Skeletal myopathy and respiratory insufficiency are characteristic features of late-onset type GSD II, and there is usually greater progression of these features with earlier age of onset. Proximal muscle weakness may be the presenting feature in late-onset-type GSD II patients, and musculoskeletal imaging may demonstrate fatty atrophy of the pelvic girdle, paraspinal, psoas and thigh muscles (Figure 15). Respiratory failure is a common cause of death in these patients.

Amino acid disorders

Cystinosis

LSDs may also result from abnormal accumulation of amino acids in the lysosome. Cystinosis is an LSD because of a deficiency in cystinosin, a cystine transporter within the lysosomal wall, resulting in abnormal accumulation of cystine crystals within the lysosome. Cystinosis has an autosomal recessive inheritance pattern, and an incidence of 0.5/100,000–1.0/100,000 live births. Genetic, clinical and radiological features of cystinosis are summarized in Table 3. There are three variants of cystinosis, which include nephropathic, intermediate nephropathic and ocular or non-nephropathic types.

Nephropathic type (infantile) is the most common and severe form, with onset in infancy. Patients with the infantile nephropathic type may have renal tubular Fanconi syndrome, hypophosphataemic rickets, impaired growth, hypothyroidism and renal tubular acidosis with onset in infancy. Renal manifestations may seem overwhelming. However, each disease has an inherent fundamental problem of a metabolic pathway disturbance with abnormal storage of material resulting in cell, tissue or organ dysfunction. Knowing which organ systems are predominately affected and how they are affected within each disease is invaluable in understanding the disease manifestations. Key features of many of the non-lipid or extralipid LSDs are discussed in the article, with several of the diseases having similarities to MPS I or Hurler syndrome. Clinicians and radiologists having knowledge of the basic clinical and radiological features of MPS I can be helpful in recognizing and diagnosing patients with LSDs. However, the key clinical similarities and differences between each disease discussed in this article, and MPS I may help to further identify the storage disorder and diagnose the patient with the correct LSD. Early recognition with the correct diagnosis is a priority considering the availability of new treatment options for several diseases in the setting of potentially devastating consequences if left untreated.

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REFERENCES


46. Slonim AE, Bulone L, Ritz S, Goldberg T, Chen A, Martinui F. Identification of two


