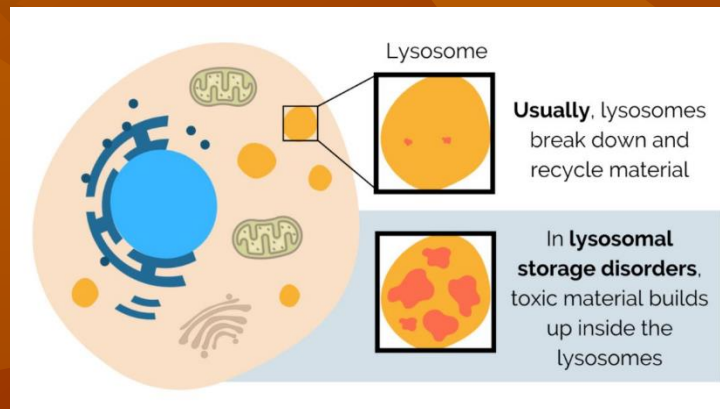


Important Clinical and Paraclinical points in Lysosomal Storage Disorders



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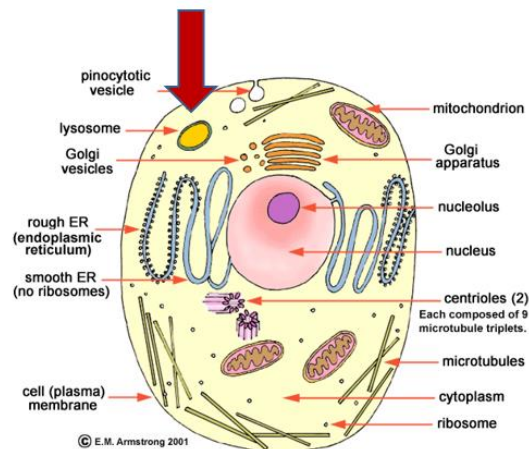
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Lysosome

- The Nobel Prize-winning discovery by de Duve in the 1950s established lysosomes as central degradative and metabolic organelles in cells .
- The Lysosome plays an essential role within the cell acting as the major recycling center to dismantle surplus and functionally redundant material including carbohydrates, lipids, nucleic acids and proteins, originating from both inter- and intracellular environments.

Lysosomes are subcellular organelles containing hydrolytic enzymes (acid Hydrolases) that catalyze the degradation of macromolecules .



Lysosomal Storage Disorders

- Lysosomal storage diseases (LSDs) are a heterogeneous group of heritable (inborn) metabolism defects that affect the function of lysosomes.
- This group comprises over 70 monogenic disorders of lysosomal catabolism and is characterized by a gradual accumulation of non-degraded substrates inside the lysosome, which in turn leads to cellular dysfunction, tissue damage, and death .

Platt, F.M., d'Azzo, A., Davidson, B.L. et al. Lysosomal storage diseases. Nat Rev Dis Primers 4, 27 (2018)

Lysosomal Storage Disorders

- The majority of LSDs are inherited as autosomal recessive traits **(except for Fabry, Hunter, and Danon diseases that are X-linked)** and are caused by mutations in genes encoding lysosomal proteins (i.e., acidic hydrolases, integral membrane proteins, and activator or carrier proteins) whose functional deficiencies trigger the pathogenetic cascade .
- Although each disorder is rare, per se, with estimated incidences ranging from 1 in 50,000 to 1 in 250,000 live births, LSDs as a group are relatively common disorders **(combined prevalence of all LSD is 1 in 6,600 to 1 in 7,700 live births)**.

collectively affect 1 in 5,000 live births

Lysosomal Storage Disorders

Clinically, LSDs may present with a broad range of phenotypes reflecting :

- The age of onset (more severe infantile forms vs. later/adult milder forms).
- The extent and severity of nervous system and/or systemic involvements.
- The related variability of signs and/or symptoms.
- **While clinical features vary amongst the disorders, they all share a progressive course.**

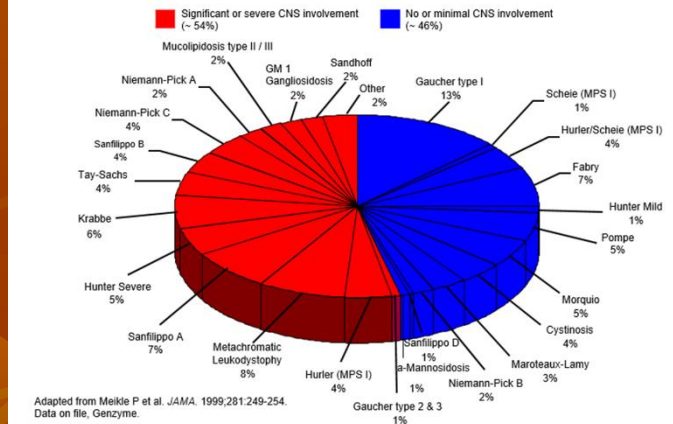
LSD Classification

- Sphingolipidoses
- Mucopolysaccharidoses
- Mucolipidoses
- Glycoprotein degradation disorders
- Glycogenoses (GSD)
- Acid lipase deficiency diseases
- Neuronal ceroid lipofuscinosis (NCL)



- GM1 Gangliosidosis
- GM2 Gangliosidosis
- Gaucher disease
- Niemann-pick disease
- Metachromatic leukodystrophy
- Globoid cell leukodystrophy (Krabbe Disease)
- Multiple Sulfatase Deficiency

The Scope of Lysosomal Storage Disorders



Disorders of lysosomes and lysosome-related organelles (LROs)

Sphingolipidoses

- Fabry disease (*GLA*)
- Farber lipogranulomatosis (*ASAHI*)
- Gaucher disease (*GBA*)
- GM1 gangliosidosis (*GLB1*)
- GM2 gangliosidosis or Tay–Sachs disease (*HEXA*)
- GM2 gangliosidosis or Sandhoff disease (*HEXB*)
- GM2 gangliosidosis or GM2 activator deficiency (*GM2A*)
- Krabbe disease (*GALC*)
- Metachromatic leukodystrophy (*ARSA* and *PSAP*)
- Niemann–Pick (A/B) (*SMPD1*)

Lipid storage diseases

- Acid lipase deficiency: Wolman disease and cholesterol ester storage disease (*LIPA*)

Mucopolysaccharidoses

- MPS I or Hurler Syndrome (*IDUA*)
- MPS II or Hunter syndrome (*IDS*)
- MPS IIIA (*SGSH*)
- MPS IIIB (*NAGLU*)
- MPS IIIC (*HGSNAT*)
- MPS IIID (*GNS*)
- MPS IVA (*GALNS*)
- MPS IVB (*GLB1*)
- MPS VI (*ARSB*)
- MPS VII (*GUSB*)
- MPS IX (*HYAL1*)

Post- translational modification defects

- Multiple sulfatase deficiency (*SUMF1*)
- Mucopolidosis II α/β , I-cell disease (*GNPTAB*)
- Mucopolidosis II α/β , pseudo-Hurler polydystrophy (*GNPTAB*)
- Mucopolidosis III γ , variant pseudo-Hurler polydystrophy (*GNPTG*)

Glycoproteinoses

- α - Mannosidosis (*MAN2B1*)
- β - Mannosidosis (*MANBA*)
- Fucosidosis (*FUCA1*)
- Aspartylglucosaminuria (*AGA*)
- Schindler disease (*NAGA*)
- Sialidosis type I (*NEU1*)
- Sialidosis type II (*NEU1*)
- Galactosialidosis (*CTSA*)

Integral membrane protein disorders

- Cystinosis (*CTNS*)
- Danon disease (*LAMP2*)
- Action myoclonus-renal failure syndrome (*SCARB2*)
- Sialic acid storage disease (*SLC17A5*)
- Niemann–Pick disease types C1 and C2 (*NPC1* and *NPC2*)
- Mucopolidosis IV (*MCOLN1*)

LRO disorders

- Hermansky–Pudlak disease type 1 (*HPS1*)
- *HPS2* (*AP3B1*)
- *HPS3*
- *HPS4*
- *HPS5*
- *HPS6*
- *HPS7*
- *HPS8* (*BLOC1S3*)
- *HPS9*
- Griscelli syndrome 1 (*MYO5A*)
- Griscelli syndrome 2 (*RAB27A*)
- Chédiak–Higashi disease (*LYST*)

Glycogen storage disease

- Pompe disease (*GAA*)

Neuronal ceroid lipofuscinoses

- CLN1 (*PPT1*)
- CLN2 (*TPP1*)
- CLN3 (*CLN3*)
- CLN4 (*DNAJC5*)
- CLN5 (*CLN5*)
- CLN6 (*CLN6*)
- CLN7 (*MFSD8*)
- CLN8 (*CLN8*)
- CLN9 (N/A)
- CLN10 (*CTSD*)
- CLN11 (*GRN*)
- CLN12 (*ATP13A2*)
- CLN13 (*CTSF*)
- CLN14 (*KCTD7*)

**Important
Clinical points in
Lysosomal Storage Disorders**

Clinical Findings that Suggest IEM in Neonate/Hydrops Fetalis

- Hydrops fetalis (fetal hydrops) is a serious fetal condition defined as abnormal accumulation of fluid in two or more fetal compartments, including ascites, pleural effusion, pericardial effusion, and skin edema.
- In some patients, it may also be associated with polyhydramnios and placental edema.



- Cardiovascular (21.7%)
- Hematologic (10.4%)
- Chromosomal (13.4%)
- Syndromic (4.4%)
- Lymphatic dysplasia (5.7%)
- Inborn errors of metabolism (1.1%)
- Infections (6.7%)
- Thoracic (6%)
- Urinary tract malformations (2.3%)
- Extrathoracic tumors (0.7%)
- Placental (5.6%)
- Gastrointestinal (0.5%)
- Miscellaneous (3.7%)
- Idiopathic (17.8%)

Possible occurrence of hydrops fetalis in hereditary metabolic diseases

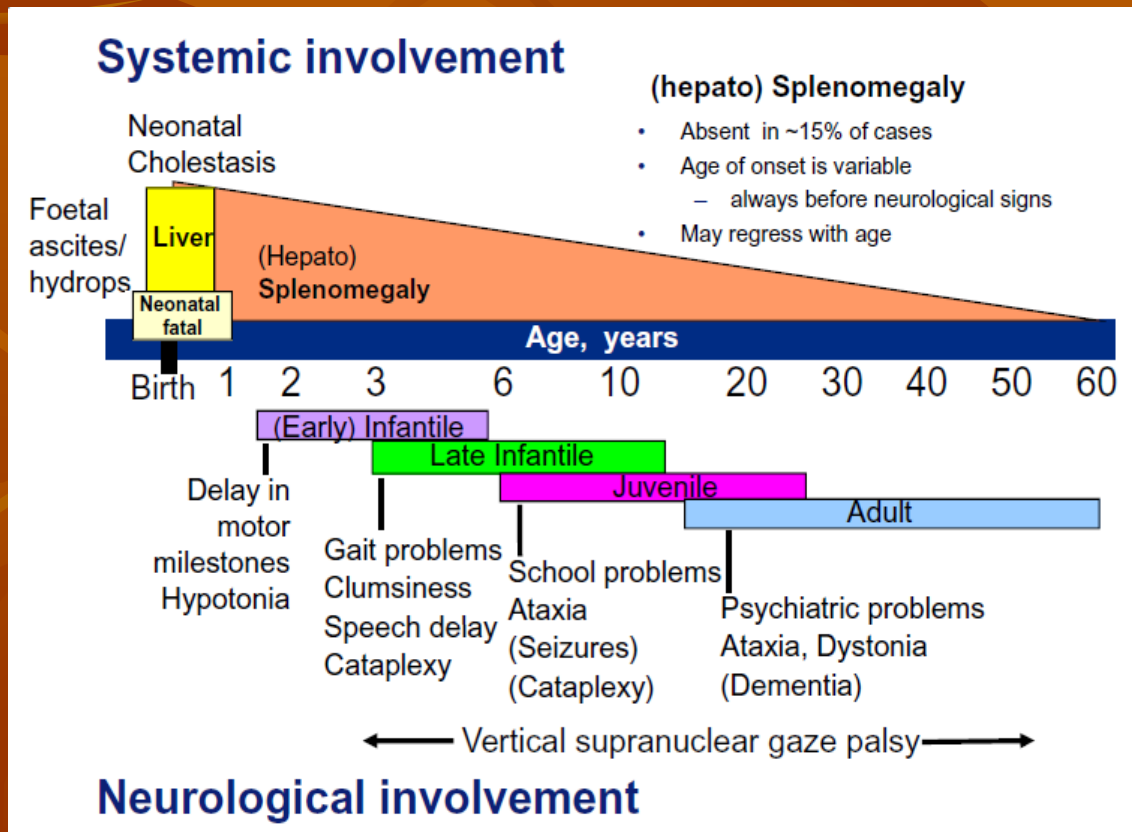
❖ Fetal hydrops may suggest LSD :

- I-cell disease (ML II)
- Sly disease (MPS VII)
- Alpha-Mannosidosis
- Sialidosis II
- Gaucher Disease
- NP-C
- Galactosialidosis
- Sialic acid storage disease
- **GSD IV**
- **Congenital disorder of glycosylation**



Clinical Findings that Suggest IEM in Neonate/ Cholestatic liver disease

- NP-C is a significant cause of neonatal cholestatic liver disease .

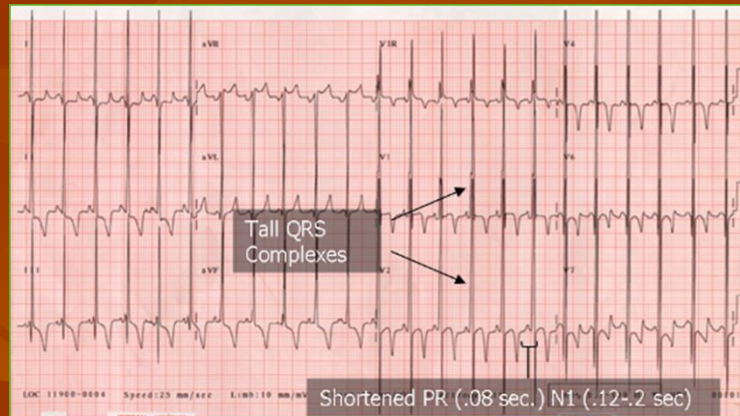


Clinical Findings that Suggest IEM in Neonate/ Cardiomegaly

MAJOR PHENOTYPIC EXPRESSION

Cardiomegaly and congestive cardiac failure, macroglossia, weakness of skeletal muscles, accumulation of glycogen in lysosomes of cardiac and skeletal muscle, and absence of acid α -1,4-glucosidase.

In the classic infantile form of Pompe Disease poor sucking, dyspnea hypotonia and cardiac dysfunction and occasionally seizures are seen.



Clinical Findings that Suggest IEM in Neonate/ Dysmorphic facial feature

- In most storage disease dysmorphism develop insidiously and is not recognized until late infancy or early childhood .



GM1 Gangliosidosis



PDHC Deficiency

Clinical Findings that Suggest IEM / Progressive Coarse Feature

Mucopolysaccharidosis



10 months



12 months



39 months



22 months



34 months

Clinical Findings that Suggest IEM / Progressive Coarse Feature

MAJOR PHENOTYPIC EXPRESSION

Coarse features, shortness of stature, progressive developmental retardation, limitation of joint motion, dysostosis multiplex, cytoplasmic inclusions in fibroblasts, deficient intracellular activity of many hydrolases, and elevated activity of these enzymes in serum because of defective post-translational modification of acid hydrolases, a consequence of the fundamental defect in N-acetylglucosaminyl-(GlcNAc) 1-phosphotransferase.



I-cell Disease (Mucopolipidosis II)

Tay-Sachs & Sandhoff Disease



Patients often have a doll-like facial appearance with clear, translucent skin, long eyelashes, fine hair and delicate pink coloring.



Visceromegaly

- ✓ GM1 Gangliosidosis
- ✓ Sandhoff Disease
- ✓ Niemann-Pick
- ✓ Gaucher Disease
- ✓ MPS
- ✓ Mannosidosis
- ✓ Fucosidosis
- ✓ Austin Disease (M S D)
- ✓ Wolman





Clinical presentation and outcome in infantile Sandhoff disease: a case series of 25 patients from Iranian neurometabolic bioregistry with five novel mutations

Abstract

Background: Infantile Sandhoff disease (ISD) is a GM2 gangliosidosis that is classified as a lysosomal storage disorder. The most common symptoms of affected individuals at presentation are neurologic involvement. Here we report clinical course and demographic features in a case series of infantile Sandhoff disease. Enzymatically and some genetically proven cases of ISD were extracted from the Iranian Neurometabolic Registry (INMR) in Children's Medical Center, Iran, Tehran from December 2010 to December 2016.

Result: Twenty five cases of infantile SD (13 female, 12 male) were included in this study. The age range of patients was 9–24 months with a mean of 15.8 months. The consanguinity rate of parents affected families was about 80%. The mean age of patients at disease onset was 6.4 months and the mean age at diagnosis was 14 months. Patients were diagnosed with a mean delay of 7.8 months. Eleven of patients died due to aspiration pneumonia and intractable seizure. The most common features at presentation (92%) were developmental delay or regression in speech and cognitive domains. Cherry red spots were detected in 17 patients (68%). Organomegaly was detected only in two patients. Enzyme studies showed marked reductions of both Hexosaminidase A and B in all patients. *HEXB* gene mutation studies performed in eight patients identified 6 different mutations, which five of them were novel.

Conclusion: Infantile SD should be considered for each child presented with neurologic symptoms such as developmental delay and regression and cherry red spots in ophthalmic examination. Organomegaly is not a frequent clinical finding in infantile SD. Additionally; there are a genetic heterogeneity among Iranian patients.

Keywords: Infantile Sandhoff disease, Organomegaly, Cherry red spot, *HEXB* gene

**Ali Reza Tavasoli, Nima Parvaneh, Mahmoud Reza Ashrafi, Zahra Rezaei,
Johannes Zschocke and Parastoo Rostami
Orphanet Journal of Rare Diseases (2018) 13:130**

Macrocephaly

- ✓ GM1 Gangliosidosis
- ✓ Tay-Sachs Disease
- ✓ Sandhoff Disease
- ✓ MLD
- ✓ Krabbe Disease
- ✓ Glutaric aciduria type 1
- ✓ Canavan Disease
- ✓ Alexander Disease
- ✓ Vander knapp Disease
- ✓ Vanishing WMD
- ✓ Neonatal ALD
- ✓ Hurlur Disease
- ✓ Mannosidosis
- ✓ Pyruvate carboxylase deficiency



Macrocephaly

- Gangliosidoses (GM1 or GM2)
- Metachromatic Leukodystrophy (early)
- Mucopolysaccharidoses (Hunter & Hurler)

❖ Hyperacusis

- Exaggerated startle response
 - ✓ GM1 Gangliosidosis
 - ✓ Tay-Sachs Disease
 - ✓ Sandhoff Disease



❖ Hypoacusis

- ✓ Niemann-Pick

Dermal Melanocytosis (Extensive Mongolian Spot)

- ✓ Hurler Syndrome
- ✓ Hunter Syndrome
- ✓ GM1 Gangliosidosis type I
- ✓ Niemann-Pick Disease
- ✓ Mannosidosis



Dermal Melanocytosis (Extensive Mongolian Spot)



Extensive Mongolian Spots: A Clinical Sign Merits Special Attention

**Mahmood Reza Ashrafi, MD,
Reza Shabanian, MD,
Mahmood Mohammadi, MD, and
Susan Kavusi, MD**

Pediatr Neurol 2006;34:143-145.



Dermal Melanocytosis (Extensive Mongolian Spot)

- ✓ Hurler Syndrome
- ✓ Hunter Syndrome
- ✓ GM1 Gangliosidosis type I
- ✓ Niemann-Pick Disease
- ✓ Mannosidosis
- ✓ GM2 Gangliosidosis
- ✓ MPS VI



2014, 53, 736–738

International Journal of
Dermatology

Medical genetics

Diffuse dermal melanocytosis in two patients with Sandhoff disease and mucopolysaccharidosis VI

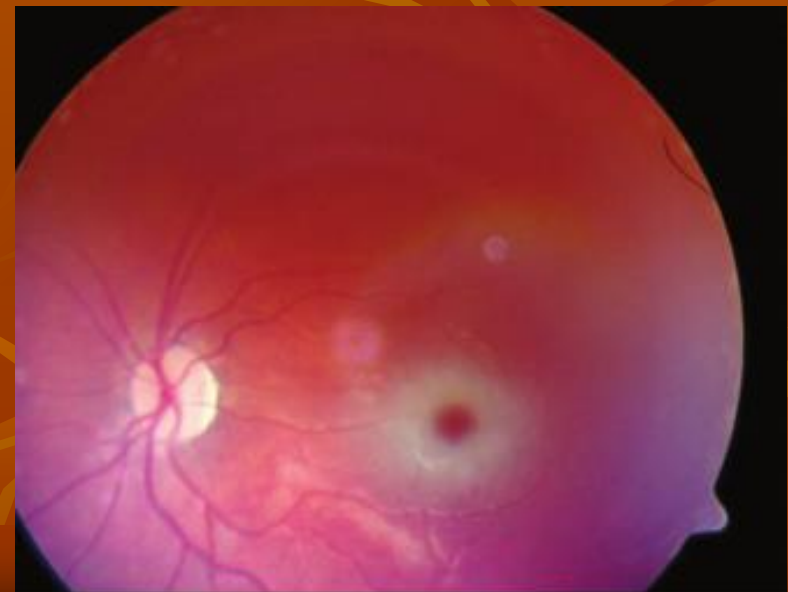
Mahmoud Reza Ashrafi¹, MD, Alireza Tavasoli¹, MD, Shadi Shiva¹, MD, Nima Parvaneh², MD, and Banafshe Tamizifar³, MD

Ocular Manifestations of LSD

Cherry-red spot & Perifoveal white patch

- A cherry-red spot is a finding in the macula of the eye in a variety of **lipid storage disorders and in central retinal artery occlusion**.
- The sign was first described by Warren Tay, in 1881, with reference to a patient with Tay-Sachs disease.

- The lipids (sphingolipid) accumulate in the ganglion cell layer of the retina, giving the retina a white appearance.
- The fovea, being the thinnest part of the retina and devoid of ganglion cells, retains relative transparency, allowing persistent transmission of the underlying highly vascular choroidal hue.
- Perifoveal white patch is a better term than CRS .
- In some ethnic group, Cherry Black Spot or Cherry Brown Spot may be seen .



Cherry-red spot

Perifoveal white patch

- ✓ GM1 Gangliosidosis
- ✓ Tay-Sachs Disease
- ✓ Sandhoff Disease
- ✓ Niemann-Pick
- ✓ Farber Disease
- ✓ Sialidosis
- ✓ MLD
- ✓ Multiple sulfatase deficiency
- ✓ Wolman disease
- ✓ MPS



Ocular Manifestations of LSD

Lens opacities :

- ★ Fabry Disease
- ★ Mannosidosis
- ★ Sialidosis I



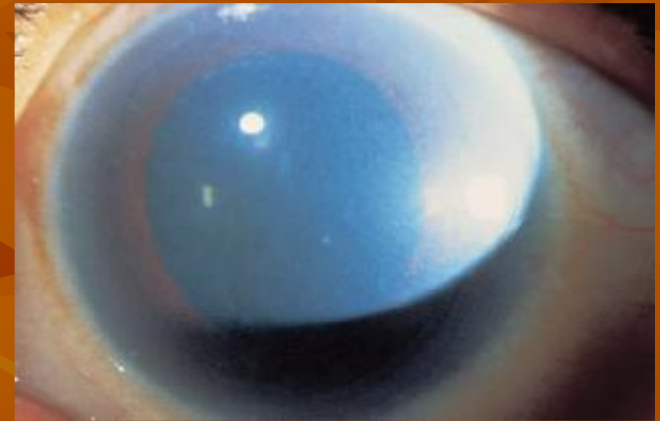
Lens

Cerebrotendinous xanthomatosis
Fabry's disease
Galactosemia
Homocystinuria
Lowe syndrome
Myotonic dystrophy

Ocular Manifestations of LSD

Corneal Clouding :

- * MPS I,IV,VI,VII
- * Mucopolipidosis II,III,IV
- * GM1 Gangliosidosis
- * Fucosidosis I



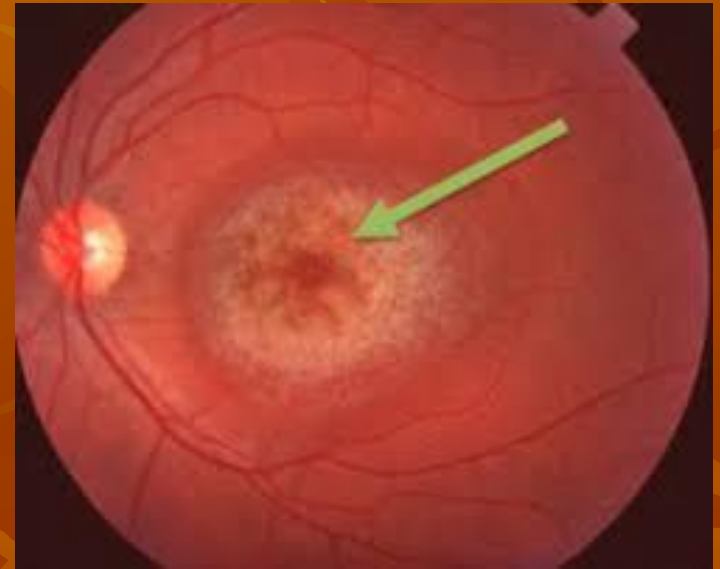
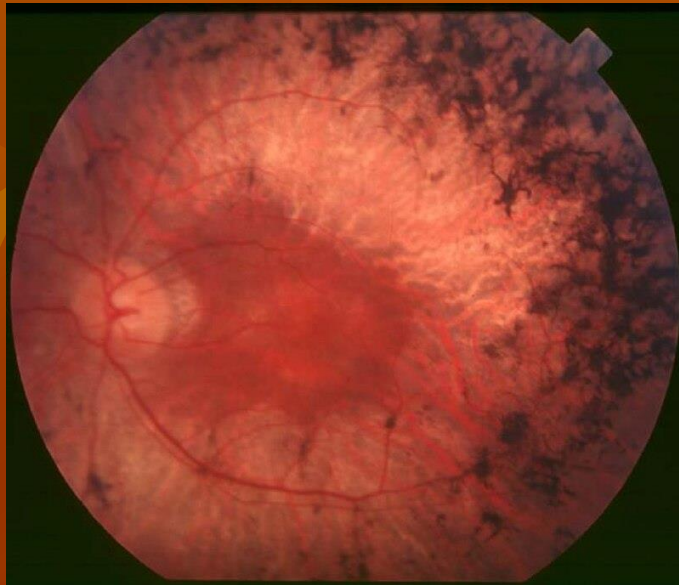
Cornea

Aspartylglucosaminuria
Fucosidosis
Hurler's disease
Mannosidosis
Maroteaux-Lamy's disease
Morquio's disease
Mucopolipidosis type IV
Wilson's disease

Ocular Manifestations of LSD

Pigmentary retinopathy:

- * Juvenile Neuronal Ceroid Lipofuscinoses (Batten disease)



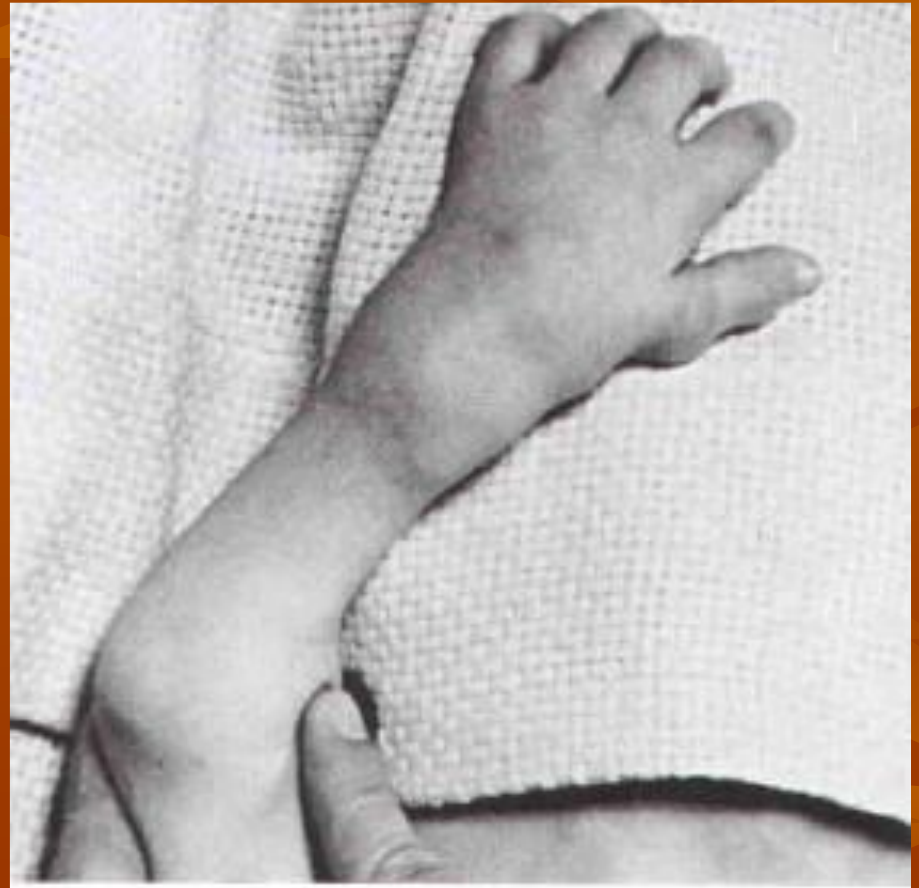
Ocular Manifestations of LSD

Vertical Supranuclear Gaze Palsy



Cutaneous Manifestations of LSD

Swollen, painful joints - Subcutaneous nodules
Farber Disease



Farber Disease



Cutaneous Manifestations of LSD

Angiokeratoma Corporis/Fabry Disease



Sanfilippo Disease (MPS III)

MAJOR PHENOTYPIC EXPRESSION

Severe mental deterioration, mild skeletal dysostosis multiplex and urinary excretion of heparan sulfate. The Sanfilippo disease type A is due to a deficiency of heparan-N-sulfatase, type B to a deficiency of α -N-acetylglucosaminidase, type C to acetylCoA: α -glucosaminide acetyl transferase, and type D to N-acetylglucosamine-6-sulfatase.



Neurometabolic Disorders Diagnosis

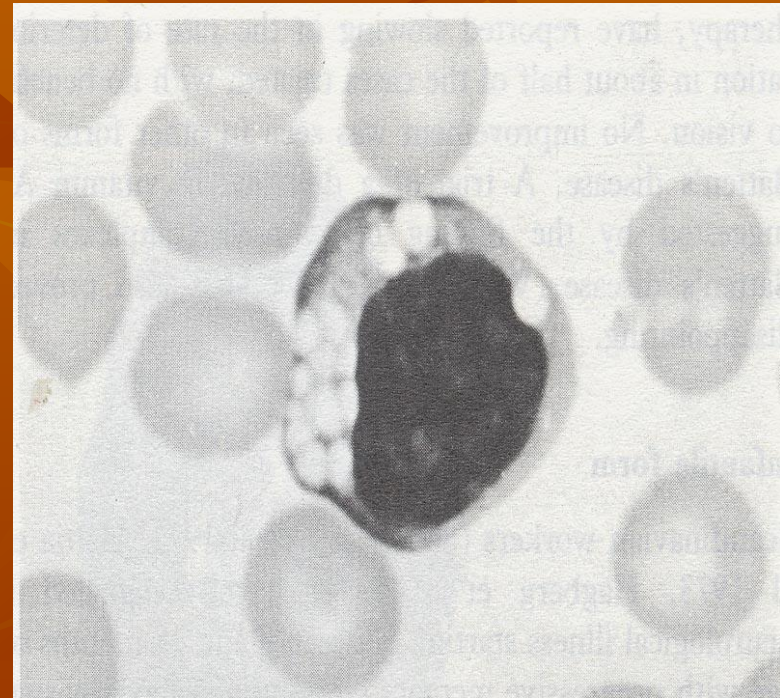
- ✓ A detailed **History** remains the most important basis for suspecting a metabolic disorder .
- ✓ A positive **Family History** is also helpful, especially if the symptoms coincide with those now presenting .
- ✓ Once one is considering a diagnosis of NM disorders the next step is to carry out readily available **Laboratory Studies** to confirm this suspicion .

**Important
Para Clinical points in
Lysosomal Storage Disorders**

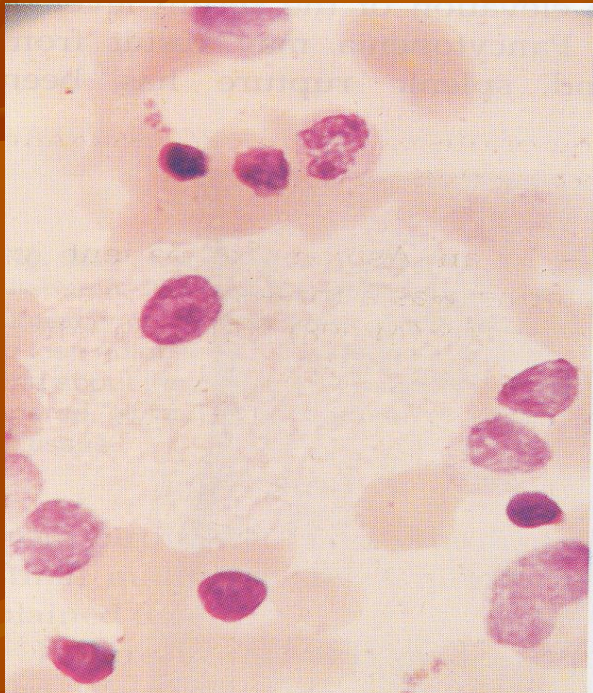
Peripheral Blood Findings of LSD

Vacuolated Lymphocyte

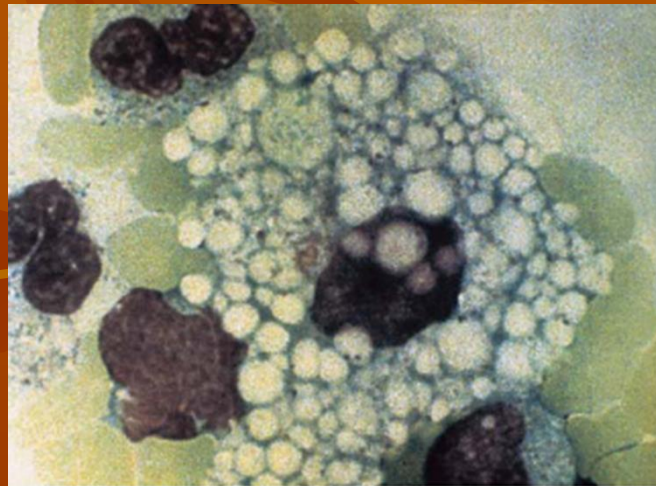
- ✓ Juvenile NCL
- ✓ GM1gangliosidosis
- ✓ Niemann-Pick type A
- ✓ Mannosidosis
- ✓ Fucosidosis
- ✓ Pompe Disease



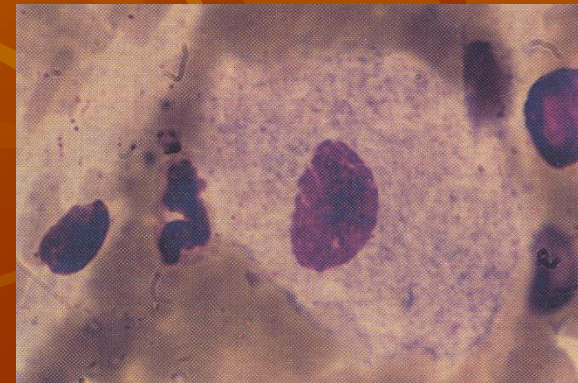
Bone Marrow Puncture Findings of LSD



Vacuolated Lymphocyte/Niemann-Pick



Histiocytic foam cell/GM1 gangliosidosis



foam cell/Gaucher Cell

Blood & Urine Biomarkers of LSD

- MLD (Metachromatic granules in urine sediment)
- Gaucher Disease (Acid phosphatase / ACE)

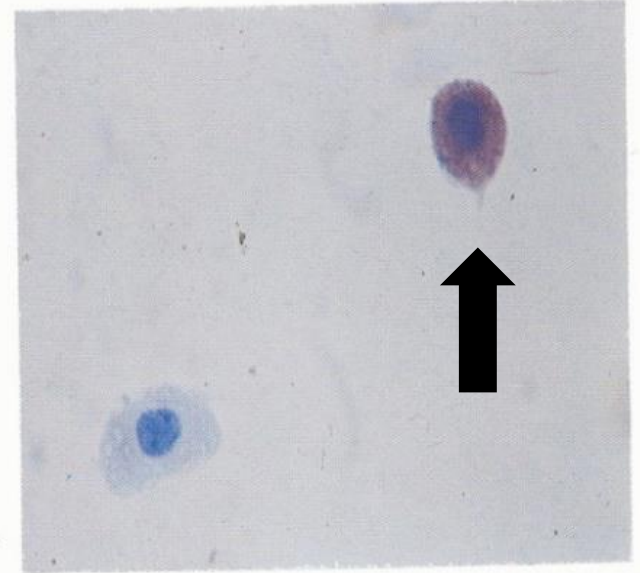


Plate 4 Urinary deposit; metachromatic leucodystrophy. Stained with toluidine blue showing a normal bladder epithelial cell (lower right) and a renal tubular cell containing abundant brown metachromatic sulphatide

Radiologic Findings of LSD

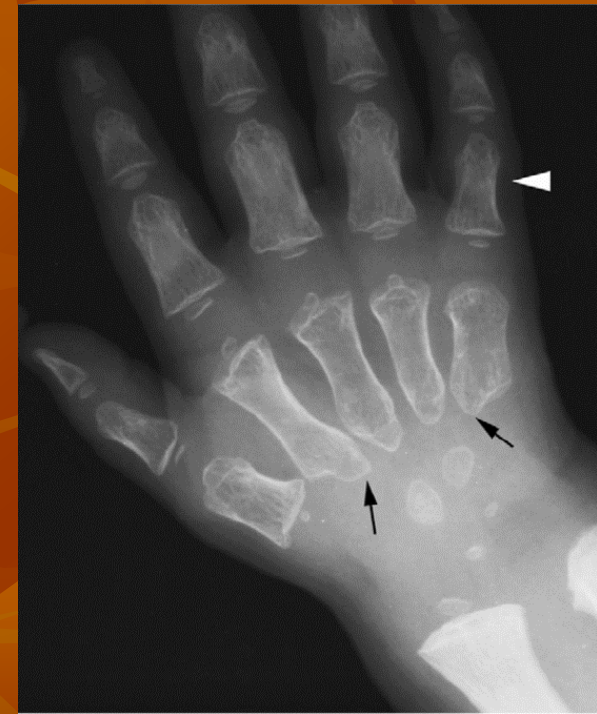
Dysostosis Multiplex

- * 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 .

- * Bullet-shaped phalanges (arrowhead)
Widened metacarpals pointed proximally (arrows)
Mucopolidosis III

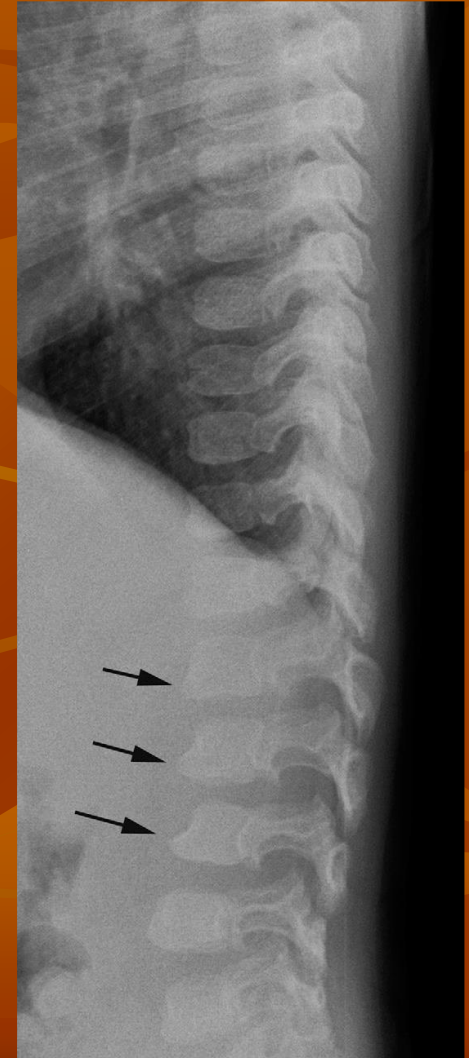


- * J-shaped sella turcica (arrow)
Mucopolysaccharidosis II (Hunter syndrome)



Radiologic Findings of LSD/Dysostosis Multiplex

Paddle shape ribs/Beaking of lumbar vertebra
GM1 gangliosidosis



Radiologic Findings of LSD/Dysostosis Multiplex

Significant cord compression-Gibbus formation Morquio Disease

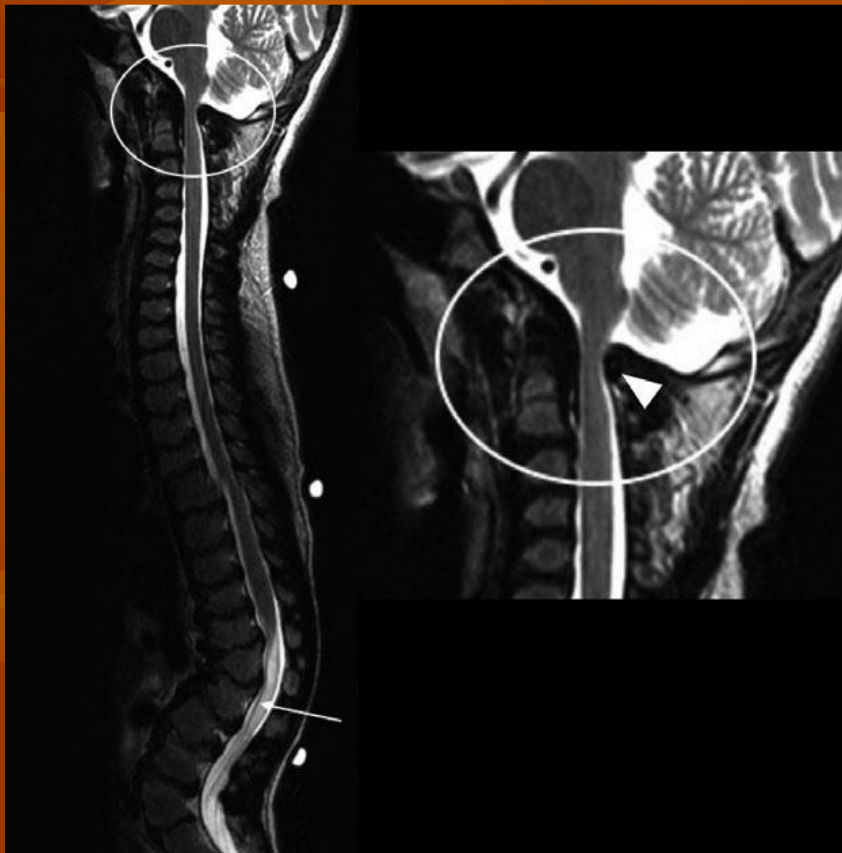


Fig. 14. Sagittal T2-weighted image of the spine in a patient with Morquio disease showing bullet-shaped vertebral bodies and thickened intervertebral discs characteristic of mucopolysaccharidoses. There is gibbus formation (arrow) centered at L1 with no significant mass effect on the cauda equina. At cervical level, the posterior arcus of the atlas is hypoplastic (arrowhead) predisposing to repetitive atlantoaxial subluxation and reactive ligamentous thickening at its posterior aspect resulting in significant cord compression near the foramen magnum (circle).

Multiple Sulfatase Deficiency

MAJOR PHENOTYPIC EXPRESSION

Facial and somatic features and dysostosis multiplex of a mucopolysaccharidosis; ichthyosis; neurologic features of a late infantile metachromatic leukodystrophy; mucopolysacchariduria; defective activity of arylsulfatase A, B and C, steroid sulfatase and the mucopolysaccharide sulfatases, including iduronate sulfatase, heparan-N-sulfatase, N-acetylgalactosamine-6-sulfatase and N-acetylglucosamine-6-sulfatase; and defective post-translational change of sulfatase cysteine-69 to aminopropionic acid.

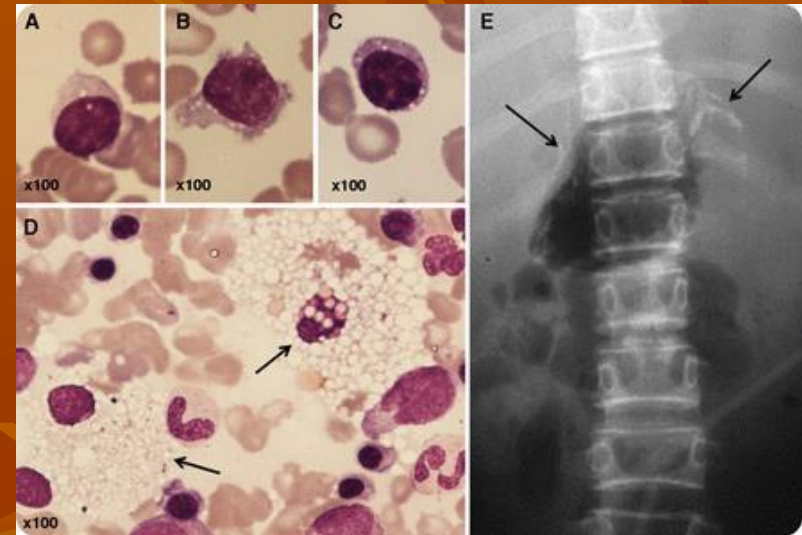


Wolman Disease

Acid Lipase Deficiency

MAJOR PHENOTYPIC EXPRESSION

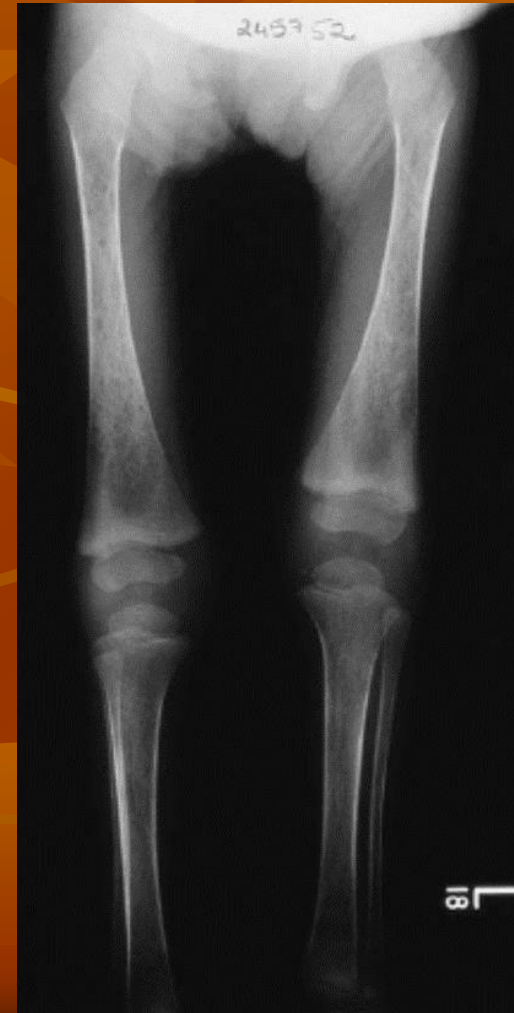
Vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, adrenal calcification, vacuolated peripheral lymphocytes and foam cells in the marrow, storage of cholesterylesters and triglycerides, and deficiency of lysosomal acid lipase.



Radiologic Findings of LSD

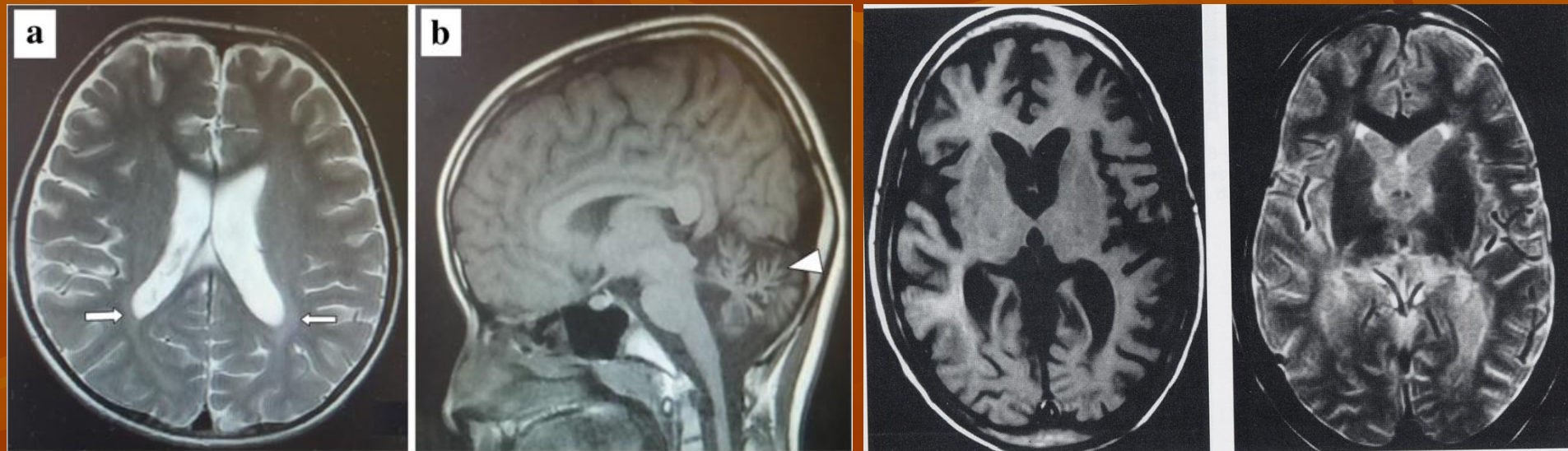
Erlenmeyer appearance and Osteoporosis Gaucher Disease

- * Erlenmeyer flask bone deformity (EFD) is a long-standing term used to describe a specific abnormality of the distal femora.
- * The deformity consists of lack of modeling of the di-metaphysis with abnormal cortical thinning and lack of the concave di-metaphyseal curve resulting in an Erlenmeyer flask-like appearance.



MRI Findings of LSD

Progressive Brain atrophy
Batten Disease (NCL)

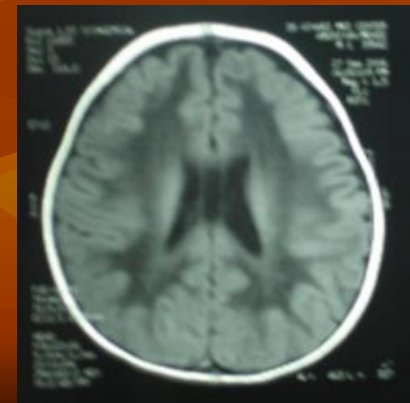
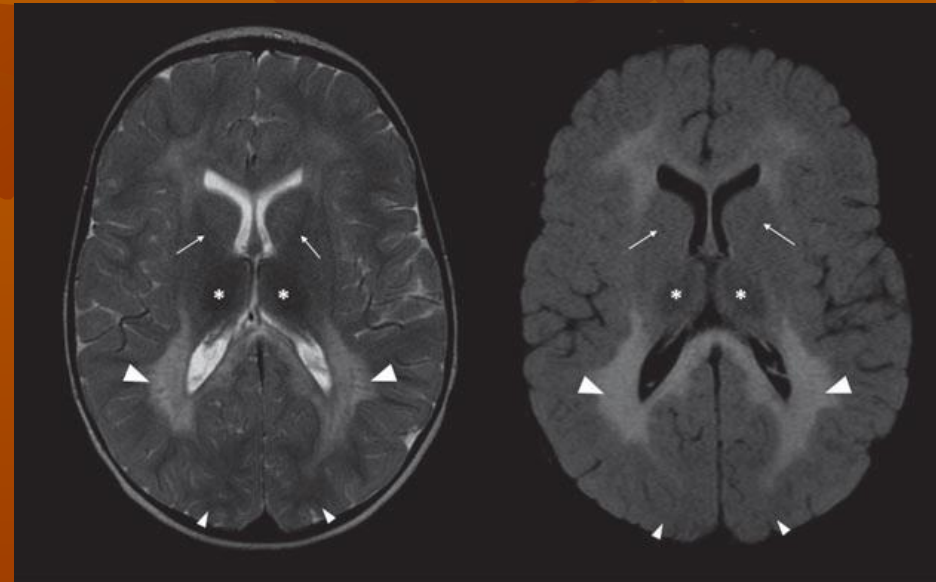


MRI Findings of LSD

Leukodystrophy Pattern

Metachromatic Leukodystrophy

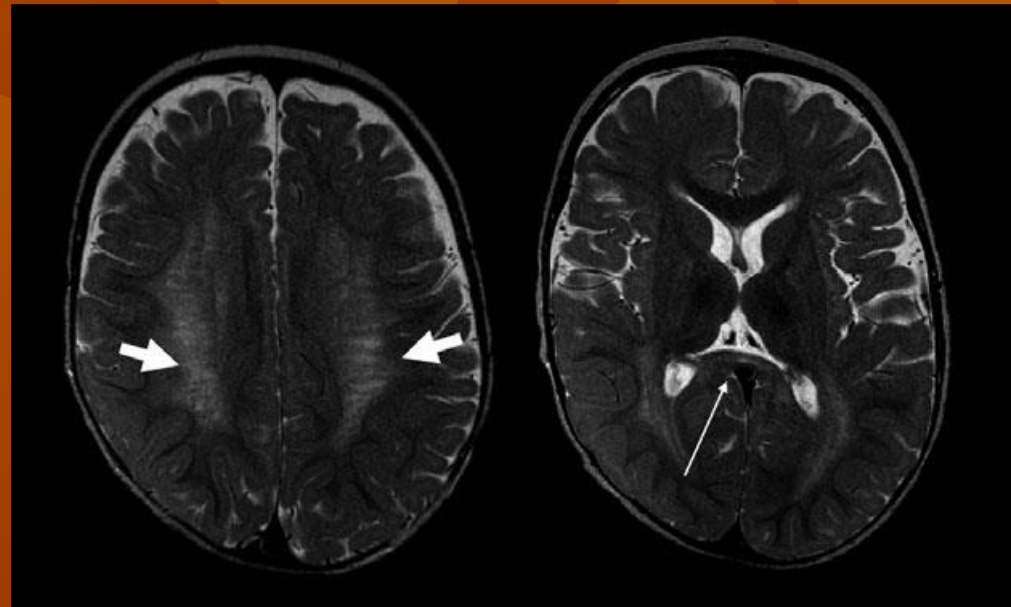
- * Axial T2 (a) and FLAIR (b) images in a patient with MLD.
- * The hallmark of the disorder is rapidly progressive leukodystrophy with the periventricular white matter taking on the typical MRI appearance of symmetric, confluent, 'butterfly' T2/FLAIR hyperintensity, often with a tigroid appearance (large arrowheads).



MRI Findings of LSD

Leukodystrophy Pattern Globoid Cell Leukodystrophy (GLD) Krabbe Disease

- * Axial T2-weighted images in a 6-year-old male with Krabbe's disease.
- * Often, like many other LSDs, the periventricular white matter will take on a tigroid appearance (large arrows).
- * However, unlike the others, the corpus callosum is often involved earlier in the disease process (small arrow).



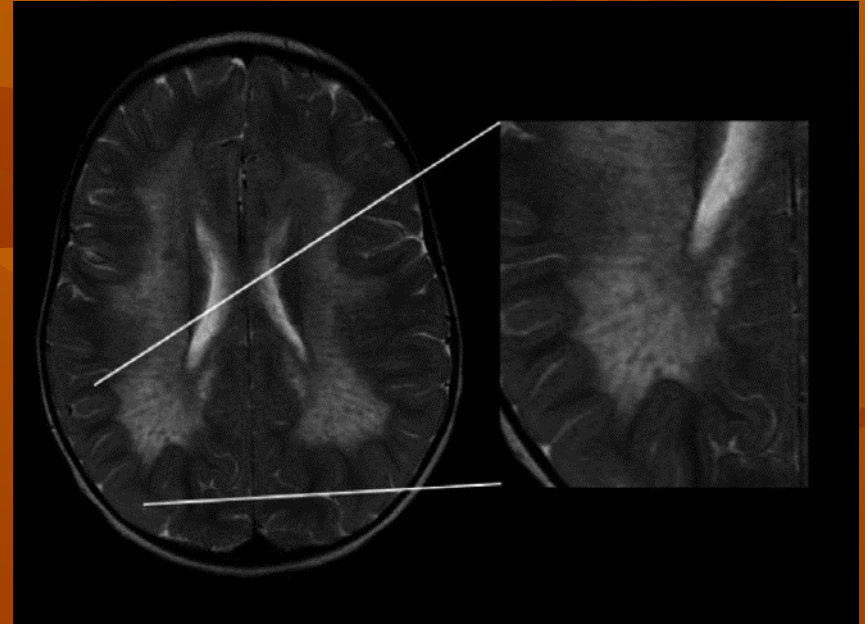
Early corpus callosum
involvement

- Krabbe's Disease

MRI Findings of LSD

Tigroid white matter

- * Axial T2-weighted image through the brain showing the classic finding among the majority of LSD cases, 'tigroid' appearance to the periventricular white matter.
- * Findings are thought to be related to periventricular lipid accumulation (low signal) on a background of absent myelin (high signal).

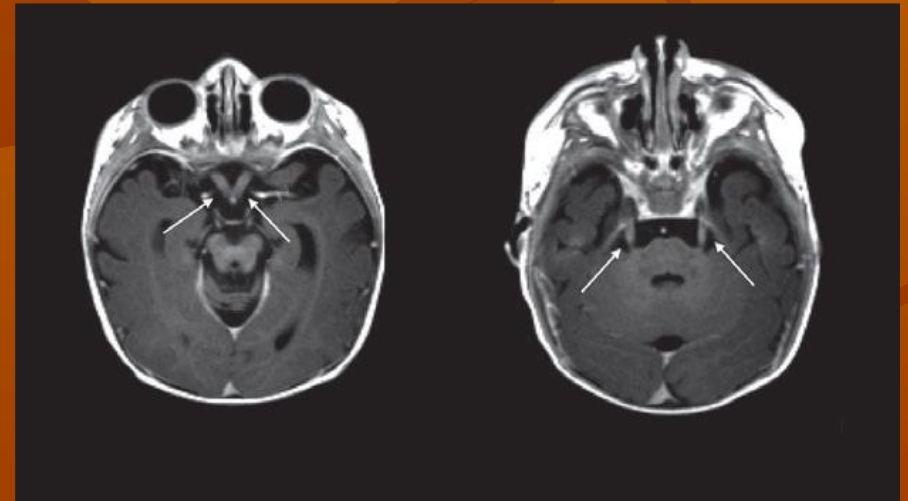


- Metachromatic Leukodystrophy
- Krabbe's Disease
- Gangliosidoses
- Mucopolysaccharidoses

MRI Findings of LSD

Cranial nerve Enhancement

- * While CN enhancement can be seen in many different forms of LSD, enlarged and enhancing optic nerves bilaterally (a, arrows) are typically seen in cases of Krabbe's disease.
- * In this case, bilateral trigeminal nerve enhancement (b, arrows) is also present.



Cranial nerve
enhancement

- Metachromatic Leukodystrophy
- Krabbe's Disease

MRI Findings of LSD

- * Cranial and spinal nerve enhancement are known to occur in MLD and Krabbe disease .



Figure 2. Axial T_1 -weighted ($TR = 900$ ms; $TE = 15$ ms) postgadolinium MR image demonstrates enhancing ventral and dorsal roots (black arrows) of the cauda equina at the level of the conus medullaris.



Figure 1. Sagittal T₁-weighted MR image (TR = 500 ms; TE = 15 ms) of the thoracolumbar spine after gadolinium administration demonstrating abnormal enhancement of the roots of the cauda equina. No abnormal enhancement is observed within the spinal cord.

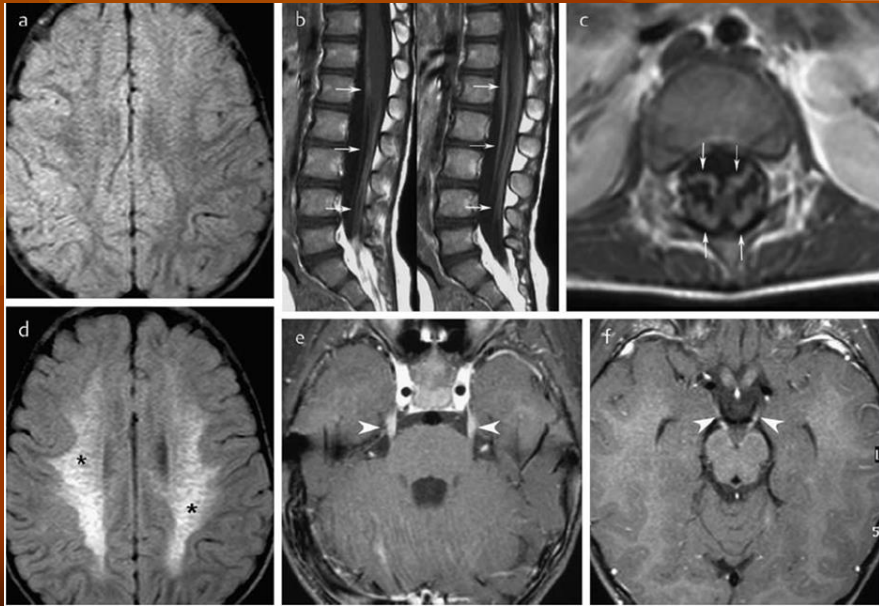


Fig. 1 MR imaging studies in a patient with metachromatic leukodystrophy (case 1). **a** Axial FLAIR image obtained at age 17 months is unrevealing, only showing a very mild, aspecific hyperintensity of the deep white matter in the centrum semiovale bilaterally. **b** Contrast-enhanced sagittal and **c** contrast-enhanced axial T₁-weighted images of the spine obtained at age 22 months show diffusely enhancing cauda equina nerve roots (white arrows). **d** Axial FLAIR image obtained at age 36 months shows leukoencephalopathy with tigroid pattern (asterisks). **e**, **f** Contrast-enhanced, fat-suppressed axial T₁-weighted images also obtained at age 36 months show enhancing V and III cranial nerves bilaterally (arrowheads).

MRI Findings of LSD

Enlarged Virchow–Robin perivascular spaces

Hurler Disease

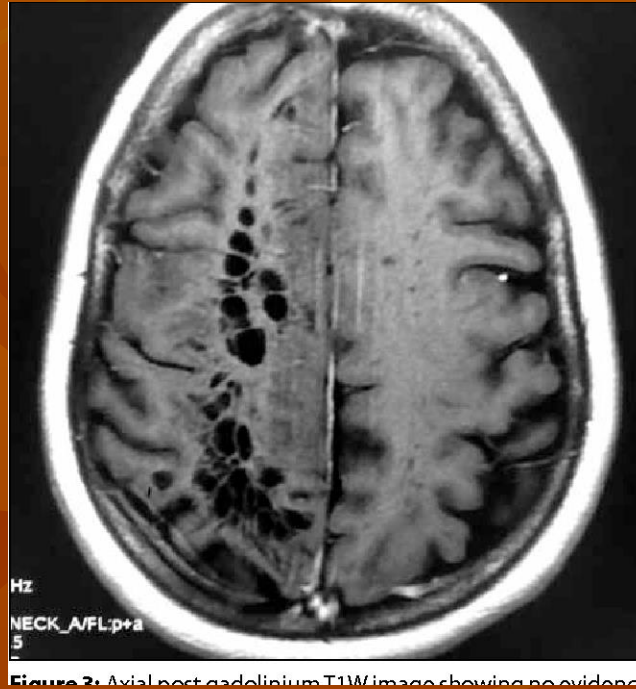
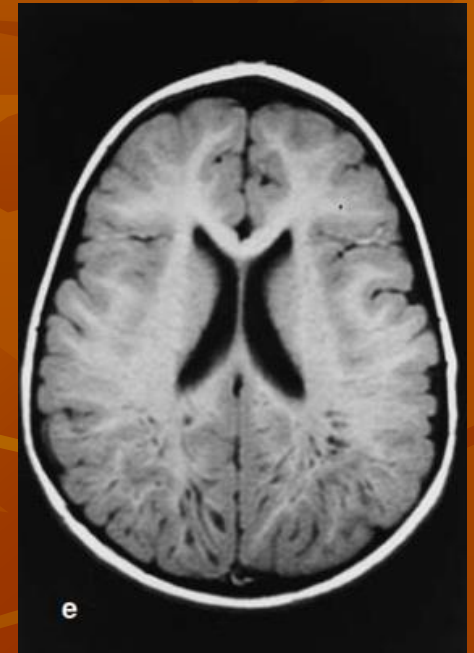


Figure 3: Axial post-contrast T1W image showing no evidence

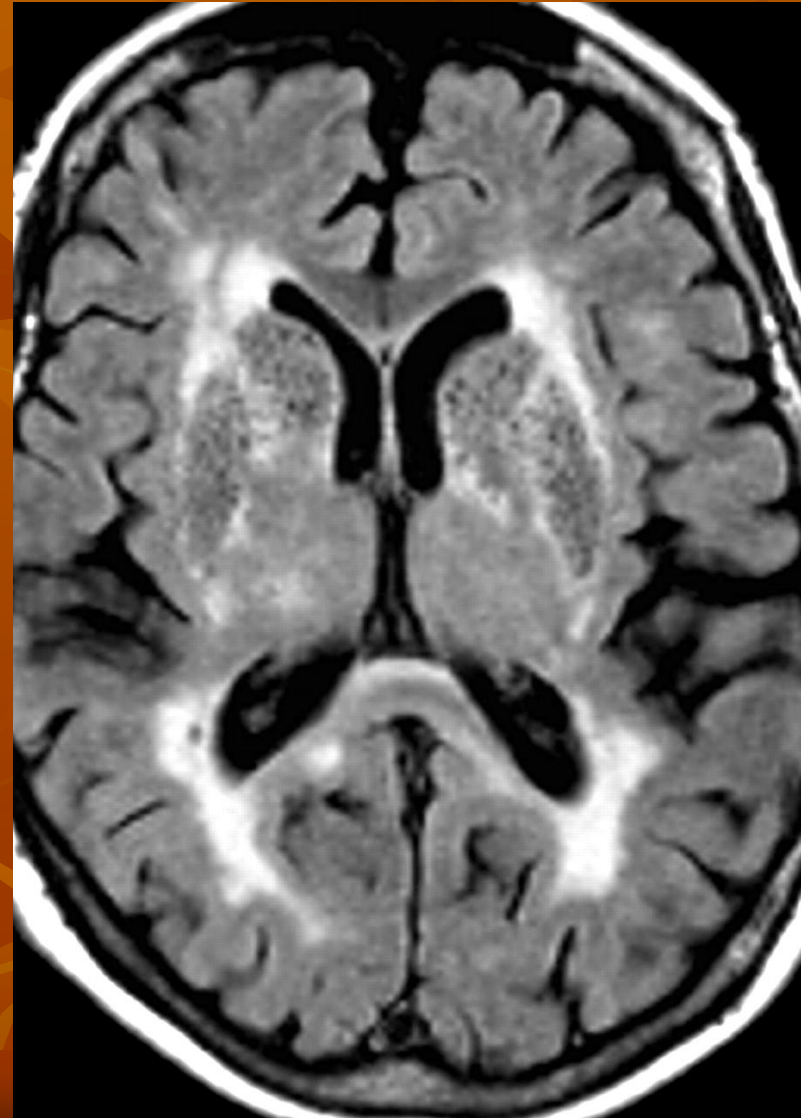
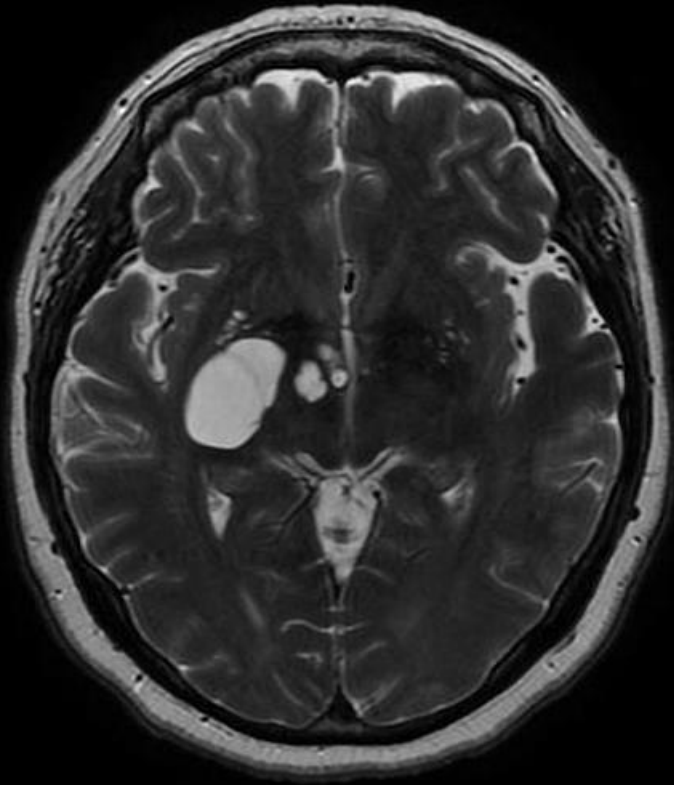


Enlarged perivascular spaces (EPVS), or Virchow-Robin spaces, are cerebrospinal fluid-filled cavities that surround small penetrating cerebral arterioles and correspond with extensions of the subarachnoid space

MRI Findings of LSD

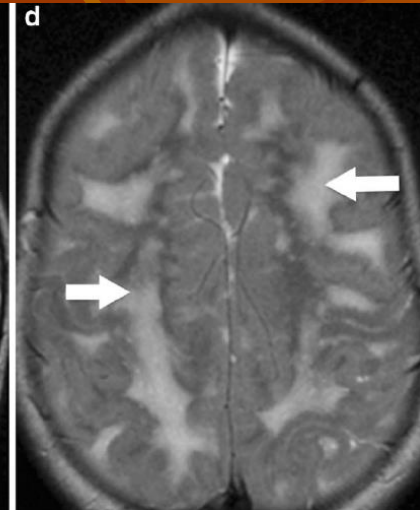
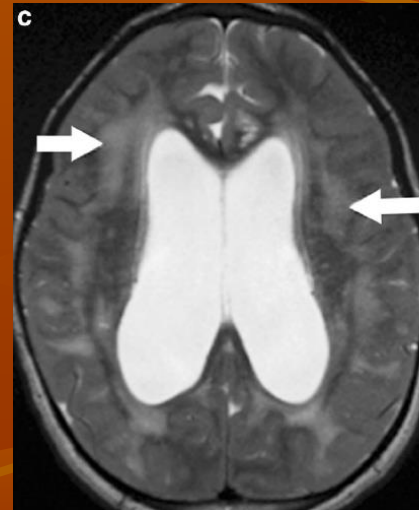
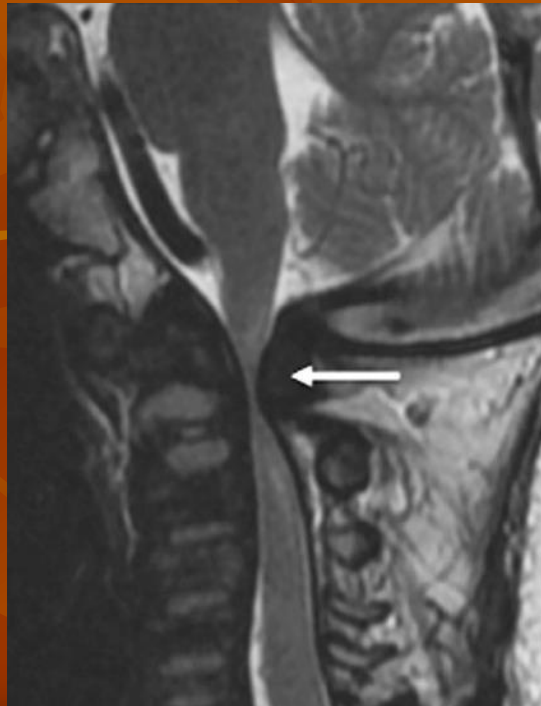
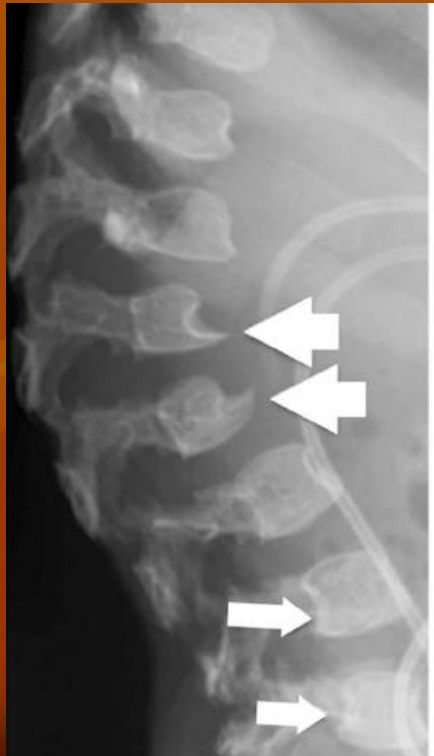
Enlarged Virchow–Robin perivascular spaces

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Summary of neuroimaging manifestations of mucopolysaccharidosis (MPS)

Skull	J-shape, omega-shape or enlarged sella; macrocephaly; scaphocephaly; midline frontal crest; calvarial thickening
Craniocervical junction	Odontoid hypoplasia, atlanto-axial instability/subluxation, periodontoid soft-tissue thickening, invagination of C1, spinal stenosis, cord compression
Spine	Platyspondyly, anterior beaking (central in MPS IV, anterior-inferior in other MPS), posterior vertebral scalloping, thoracolumbar gibbus, scoliosis, compressive myelopathy, syringohydromyelia
Brain	Enlarged perivascular spaces, hydrocephalus, atrophy, white matter signal abnormality, enlarged cerebrospinal fluid spaces, arachnoid cysts, enlarged cisterna magna, closed cephalocele, enlarged optic nerve sheaths



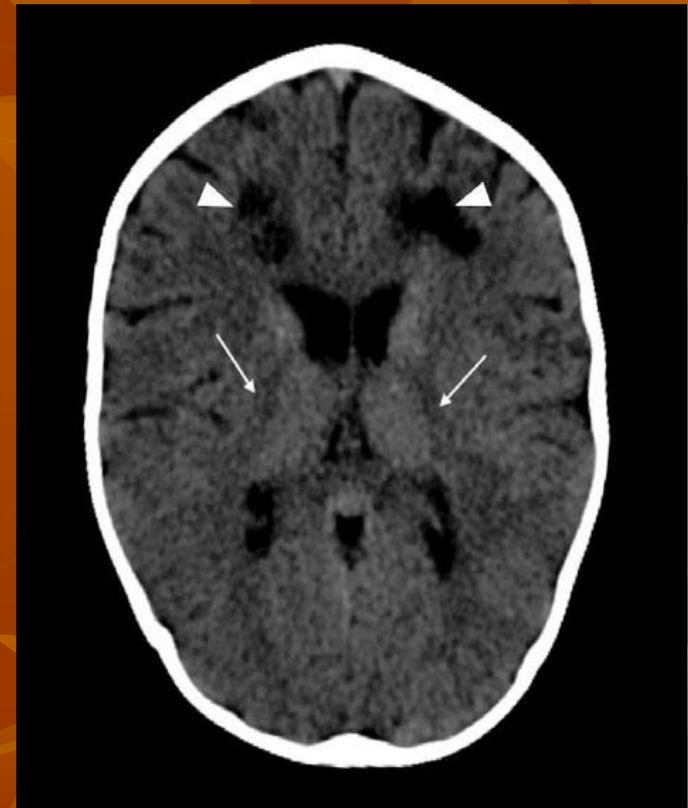
CT Findings of LSD

Leukodystrophy Pattern

Globoid Cell Leukodystrophy (GLD)

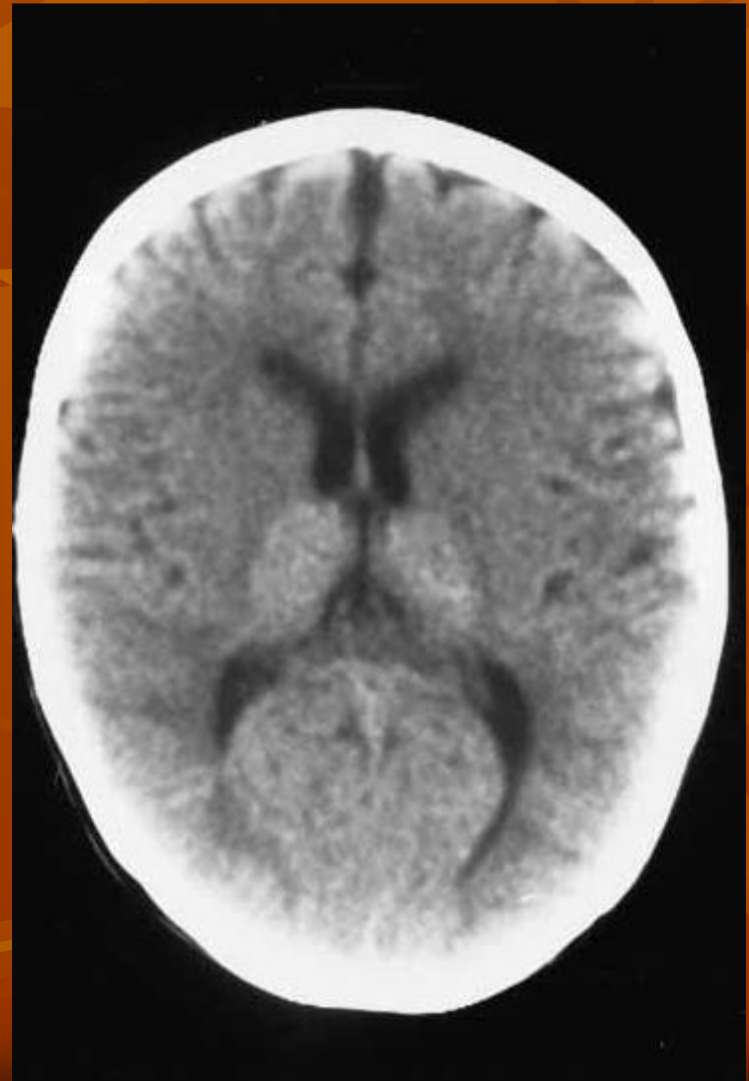
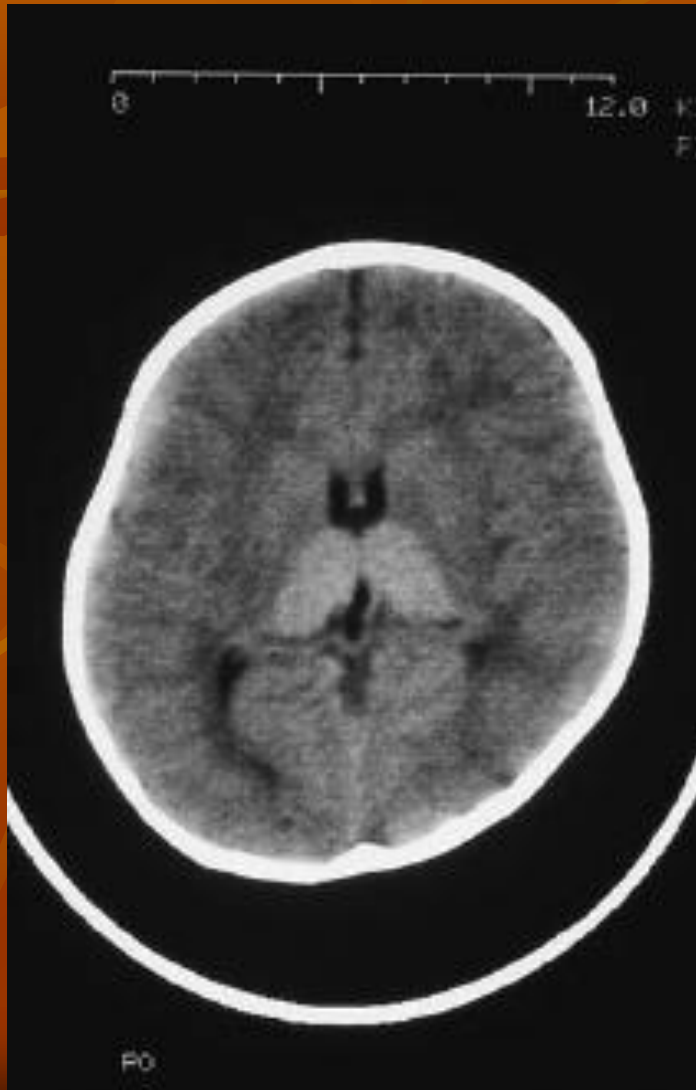
Krabbe Disease

- * Axial non-contrast-enhanced CT image at the level of the thalami in a 4-year-old boy with Krabbe's disease.
- * An imaging finding in KD is increased attenuation within the bilateral thalami (arrows) early in the course of the disease .
- * In addition, there is decreased bifrontal preriventricular density (arrow heads) from demyelination.



CT Findings of LSD

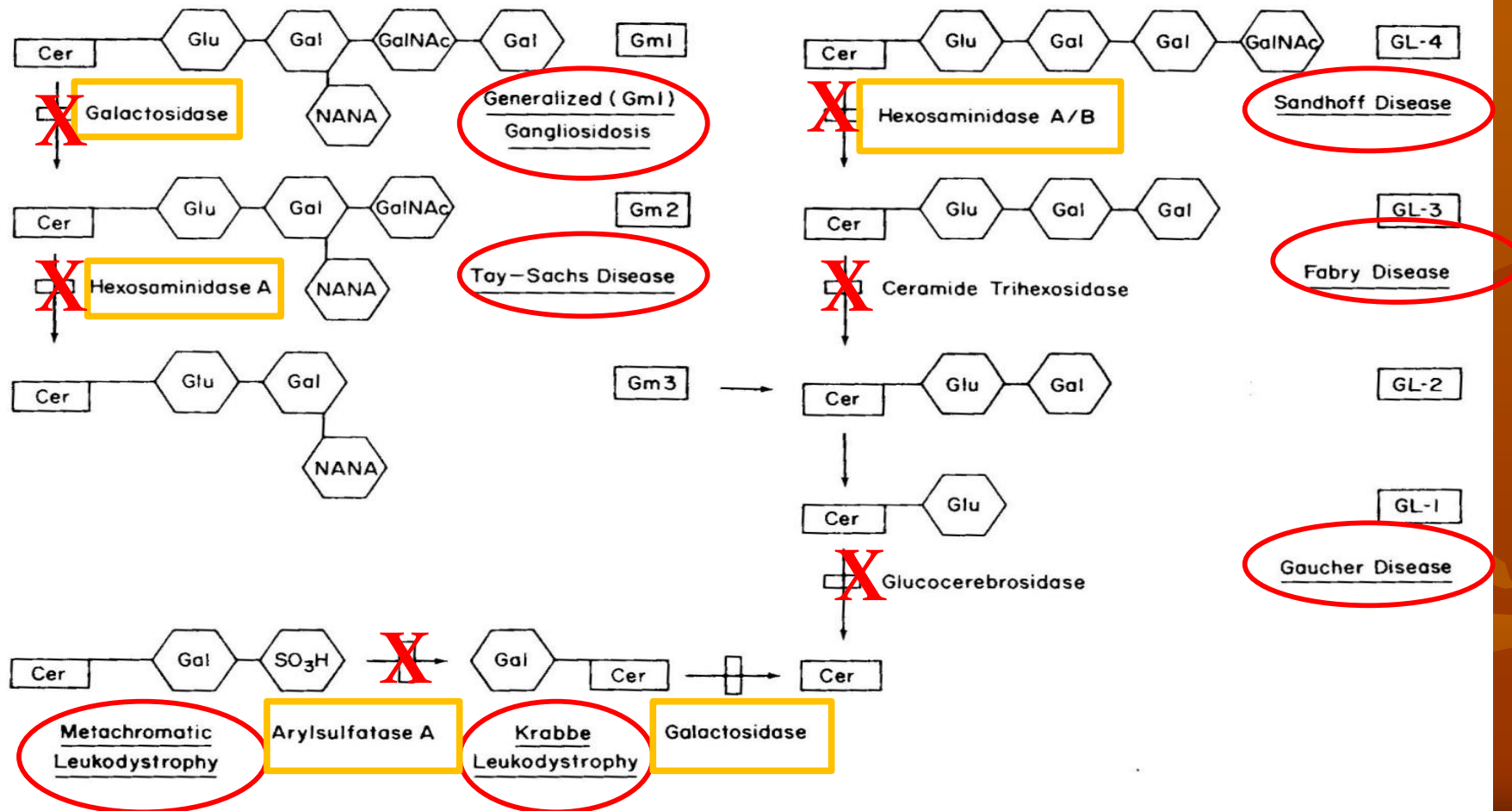
Turkish Mustache & Bright thalami sign
Tay-sachs & Sandhoff Disease



Lysosomal Storage Disorders

Enzyme Analysis

GLYCOSPHINGOLIPID METABOLISM



Concluding Remarks

- The LSDs are a heterogeneous group of disorders that are individually rare but collectively common.
- This storage process leads to a broad spectrum of clinical manifestations depending on the specific substrate and site of accumulation.
- While clinical features vary amongst the disorders, they all share a progressive course.

Concluding Remarks

- Diagnosis of LSDs is often a challenge for clinicians, owing to the **rarity of single disorders** and to the **non-specificity of signs and/or symptoms**, often attributed to other neurological and/or systemic diseases.
- Before the spread of expanded newborn screening, individuals were diagnosed years after sign and/or symptom onset, when the disease was already advanced and interventions proved less efficacious .



LSDs in the genomic era



Thank you for your Attention

