Neonatal manifestations of lysosomal storage diseases

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2nd Oman international pediatric and neonatal conference
13th-15th April 2017 Muscat
• Which of the following could be manifestation of neonatal LSD diseases?
  1- Thrombocytopenia
  2- Hepatosplenomegaly
  3- Lobar emphysema
  4- Congenital adrenal hyperplasia
Outline

1-Introduction lysosomal function
2-Systemic manifestation of neonatal presentations of LSD
3-Principle of management in lysosomal storage diseases
4-Neonatal screening of LSD world experience
Introductions

• Lysosomal storage disorders are rare inborn errors of metabolism, with a combined incidence of 1 in 1500 to 7000 live births.

• A significant number of the >50 different lysosomal storage disorders, do manifest in the neonatal period and should be part of the differential diagnosis of several perinatal phenotypes.
Introd ... 

• Autosomal recessive diseases
• Cause death in early to late childhood (after normal infancy)
• Varying involvement of the nervous system
• All ‘store’ material in the lysosome due to defects in substrate degradation or biogenesis of the lysosome
• Considered the ‘gut’ or garbage disposal unit of cell

• Material for degradation trafficked to lysosome via endocytosis or autophagy

• Lysosomal enzymes trafficked to lysosome via M6P receptor pathway
History of the LSDs

• Symptoms of some LSDs were described as early as the 1880s,

• Many had been described and classified before the lysosome was discovered in 1955 and before their biochemical and genetic basis was fully understood

• This is why they received common names (i.e.: Gaucher disease, name of discovering physician).

• Later, an additional, more clinically descriptive name often came into use (glucocerebrosidase deficiency)
History of the LSDs

Ernest GAUCHER (1854-1919)

Gaucher cell 1882
• When a lysosomal enzyme (or another protein that directs it) is deficient or malfunctioning, the substrate it targets accumulates, interfering with normal cellular activity.
Complex substrate → Normal lysosomal degradation → Small diffusible end products → Stored nonmetabolized products

Complex substrate → Lysosomal enzyme deficiency → Stored nonmetabolized products
Biochemical and Cellular basis of LSDs

1 catalytic activity
2 activator
3 misfolding
4 multienzyme complex
5 glycosylation
6 M-6-P targeting
7 other transport steps
8 membrane transporters
9 membrane regulators

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LSD Sub-Categories
LSD Sub-Categories

- Lipid storage disease (Gaucher, Wolmen, Niemann Pick, Fabry).
- Mucopolysaccharide
- Oligosaccharide
Neonatal presentations of LSD

- It is very likely that the incidence of perinatal manifestations of LSDs is vastly underestimated.
- Greater physician awareness of these early presentations has important clinical implications.
- The recent development and availability of enzyme-replacement therapy (ERT) for several of the LSDs makes diagnosis early in the clinical course particularly important.
Frequent clinical manifestations in the neonatal period

- Most newborns with LSDs appear normal at birth, because many of the toxic metabolites cross the placenta during pregnancy and are cleared by the mother during gestation.

- Presentation can take hours to months.
Neurology manifestations

Neuromuscular (hypotonia)

Glycogen storage disease type 2
• Acute neuropathic form, type 2

• Krabbe disease (galactocerebrosidase)

• I-cell disease (mucolipidosis type 2)
• I-cell disease (mucolipidosis type 2) is a rare lysosomal disorder that presents at birth or in the first few months of life with profound developmental delay and microcephaly.
Respiratory manifestation

- Congenital lobar emphysema
- Impaired cough
- Recurrent infections
- Respiratory infections Hoarseness
  (Niemann-Pick disease type A and B)
Endocrine

- Osteopenia
- Metabolic bone disease
- Secondary hyperparathyroidism
Cardiology

- Cardiomegaly
- Congenital heart failure
- Arrhythmias
- Cardiomyopathy
Dysmorphology Head & neck

- Microcephaly (NCL)
- Enlarged nuchal translucency
- Microstomia Micrognathia/microretro gnathia philtrum
- Coarse facial features
Gastrointestinal

- Hepatosplenomegaly
- Neonatalcholestasis (lipid storage)
- Wolman, severe form of Gaucher
Bone and joint disease

• Lytic bone lesions
• Joint contractures
• Dysostosis multiplex Hyperphosphatasemia
  Vertebral breaking Broadening of tubularbones
  Punctuateepiphysis Craniosynostosis Painful
  jointswelling
Skin

- Congenital ichthyosis
- Collodion infant
- Hypopigmentation Telangiectasias
- Extended Mongolianspots
Ocular

- Corneal clouding
- Megalocornea Glaucoma
- Cherry-red spots
- Fundi hypopigmentation
- Bilateral cataracts
- Hematologic Anemia Thrombocytopenia
- Hydrops fetalis NIHF
- Congenital ascites Recurrent fetal loss
Investigations

• Details history and family pedigree
• Looking for other evidences (eye exam, US, Echo, skeletal survey)
• Cbc, U&E, LFT, bone profile
• Peripheral blood film
• Biochemical (urine GAG)
• Metabolic consult
Therapeutic Modalities

• Supportive care and treatment for disease complications

• Therapies for type 1 Gaucher, Fabry, MPS types I, II, and VI, and Pompe diseases have been approved by the US Food and Drug Administration
Replacement Therapies for Lysosomal Diseases

**BMT** = Bone Marrow Transplantation
**ERT** = Enzyme Replacement Therapy
**SRT** = Substrate Reduction Therapy
**SCT** = Stem Cell Therapy
**CCT** = Chemical Chaperone Therapy (enzyme enhancement therapy)
**GT** = Gene Therapy

Prevention through carrier testing, and potentially with newborn screening
Early diagnosis is critical. Based on the availability of therapy and development of a screening method, 6 of the more than 40 known LSDs are candidates for newborn screening in the US: Gaucher disease, Pompe disease, Fabry disease, Niemann-Pick disease, mucopolysaccharidosis I, and Krabbe disease.
Newborn screening
Newborn screening of LSD

• National program locally?
Newborn screening for Krabbe's disease.

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Abstract

Live newborn screening for Krabbe's disease (KD) was initiated in New York on August 7, 2006, and started in Missouri in August, 2012. As of August 7, 2015, nearly 2.5 million infants had been screened, and 443 (0.018%) infants had been referred for followup clinical evaluation; only five infants had been determined to have KD. As of August, 2015, the combined incidence of infantile KD in New York and Missouri is ~1 per 500,000; however, patients who develop later-onset forms of KD may still emerge. This Review provides an overview of the processes used to develop the screening and followup algorithms. It also includes updated results from screening and discussion of observations, lessons learned, and suggested areas for improvement that will reduce referral rates and the number of infants defined as at risk for later-onset forms of KD. Although current treatment options for infants with early-infantile Krabbe's disease are not curative, over time treatment options should improve; in the meantime, it is essential to evaluate the lessons learned and to ensure that screening is completed in the best possible manner until these improvements can be realized. © 2016 Wiley Periodicals, Inc
Newborn screening for six lysosomal storage disorders in a cohort of Mexican patients: Three-year findings from a screening program in a closed Mexican health system.

OBJECTIVE:
To evaluate the results of a lysosomal newborn screening (NBS) program in a cohort of 20,018 Mexican patients over the course of 3 years in a closed Mexican Health System (Petróleos Mexicanos [PEMEX] Health Services).

RESULTS:
From July 2012 to April 2016, 20,018 patients were screened; 20 patients were confirmed to have an LSD phenotype (99.9 in 100,000 newborns). Final distributions include 11 Pompe disease, five Fabry disease, two MPS-I, and two Niemann-Pick type A/B patients. We did not find any Gaucher or Krabbe patients. A final frequency of 1 in 1001 LSD newborn phenotypes was established.

DISCUSSION:
NBS is a major public health achievement that has decreased the morbidity and mortality of inborn errors of metabolism. The introduction of NBS for LSD presents new challenges. This is the first multiplex Latin-American study of six LSDs detected through NBS.
The LSDs are rare diseases that are caused by deficient lysosomal enzyme activity or by a deficient lysosomal protein that interferes with enzyme activity.

Neonatal manifestation of lysosomal storage diseases are variable.

Early suspicion will help in initiation of proper treatment and avoiding unnecessary investigations.

Prompt diagnosis may enable both early treatment to prevent irreversible clinical sequelae and timely genetic counseling.