
دفتر نقاشي خدا هميشه زيباست
اما فصل پاييز را براي دل خودت نگهدار
و تمامي رنگها را بخاطر بسپار
كه عشق لابلاي همين رنگهاي زيباست
ROOZERANGI

Niemann pick A/B

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PEDIATRIC ENDOCRINOLOGIST &

METABOLIC CONSULTANT

Agenda

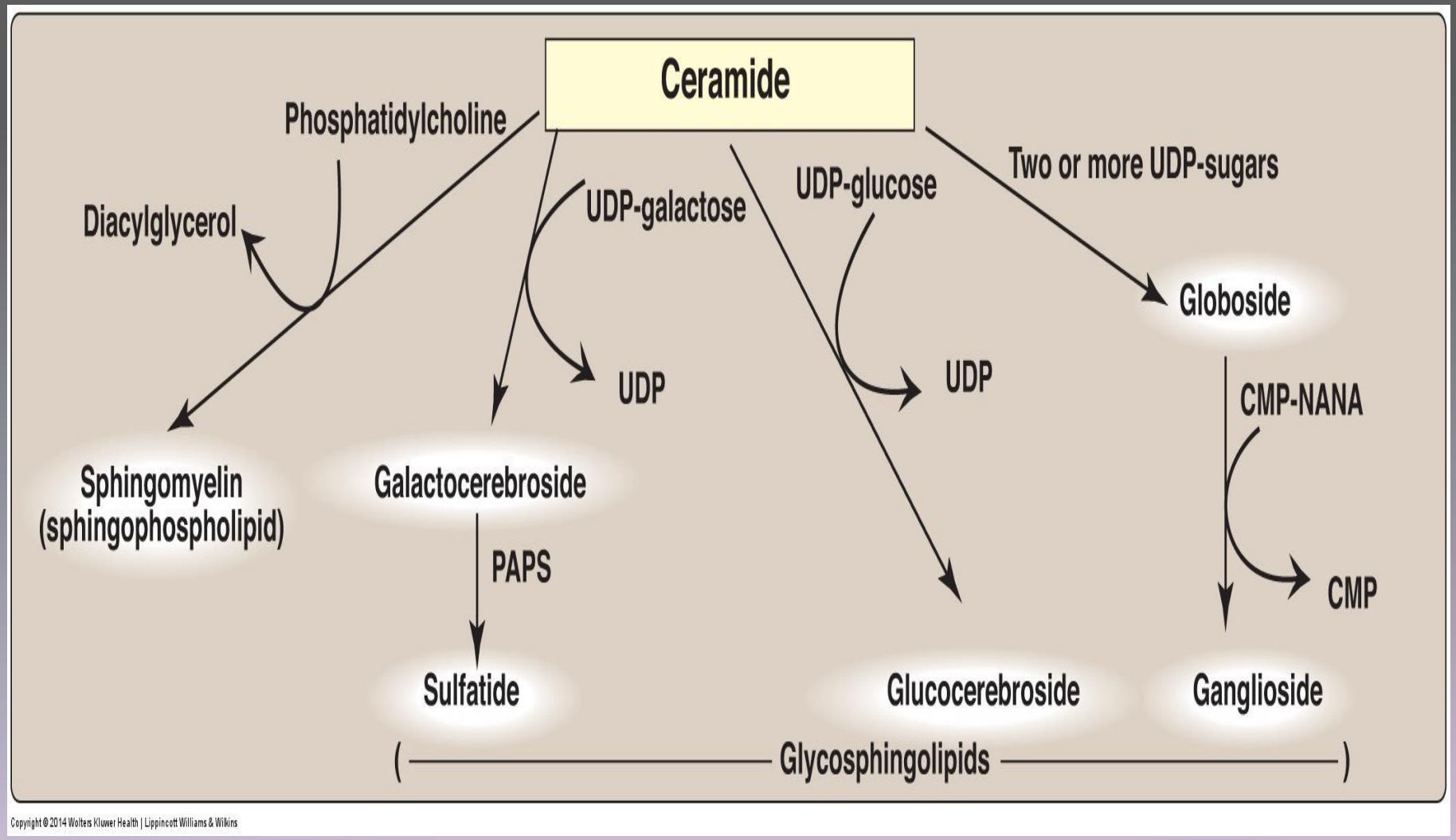
- 1- Lysosomes and Macromolecules
- 2- NPA/B Cases
- 3- History
- 4-Epidemiology
- 5-Genetic
- 6-Pathophysiology
- 7- Classification
- 8- Clinical presentations
- 9- Diagnosis
- 10-Treatment

Introduction

- The lysosomes, named after a Greek term that means “digestive bodies,” were discovered in 1955 by De Duve.
- Lysosomes contain hydrolytic enzymes that digest cell components and degrade complex cellular substrates such as glycoproteins, mucopolysaccharides (glycosaminoglycans), oligosaccharides, and lipids
- When a lysosomal pathway is blocked, there is progressive accumulation of intermediate metabolic products such as triglycerides, sterols, sphingolipids, sulfatides, sphingomyelin, gangliosides, and lipofuscins
- The concept of lysosomal disorders (LDs) was developed in 1963, following the discovery that Pompe disease was caused by a deficiency in a-glucosidase.
- LDs are inherited conditions that are caused by defects in enzymes, enzyme activator proteins, membrane proteins, transporters, or enzyme targeting to the lysosome with resulting abnormal storage of complex macromolecules

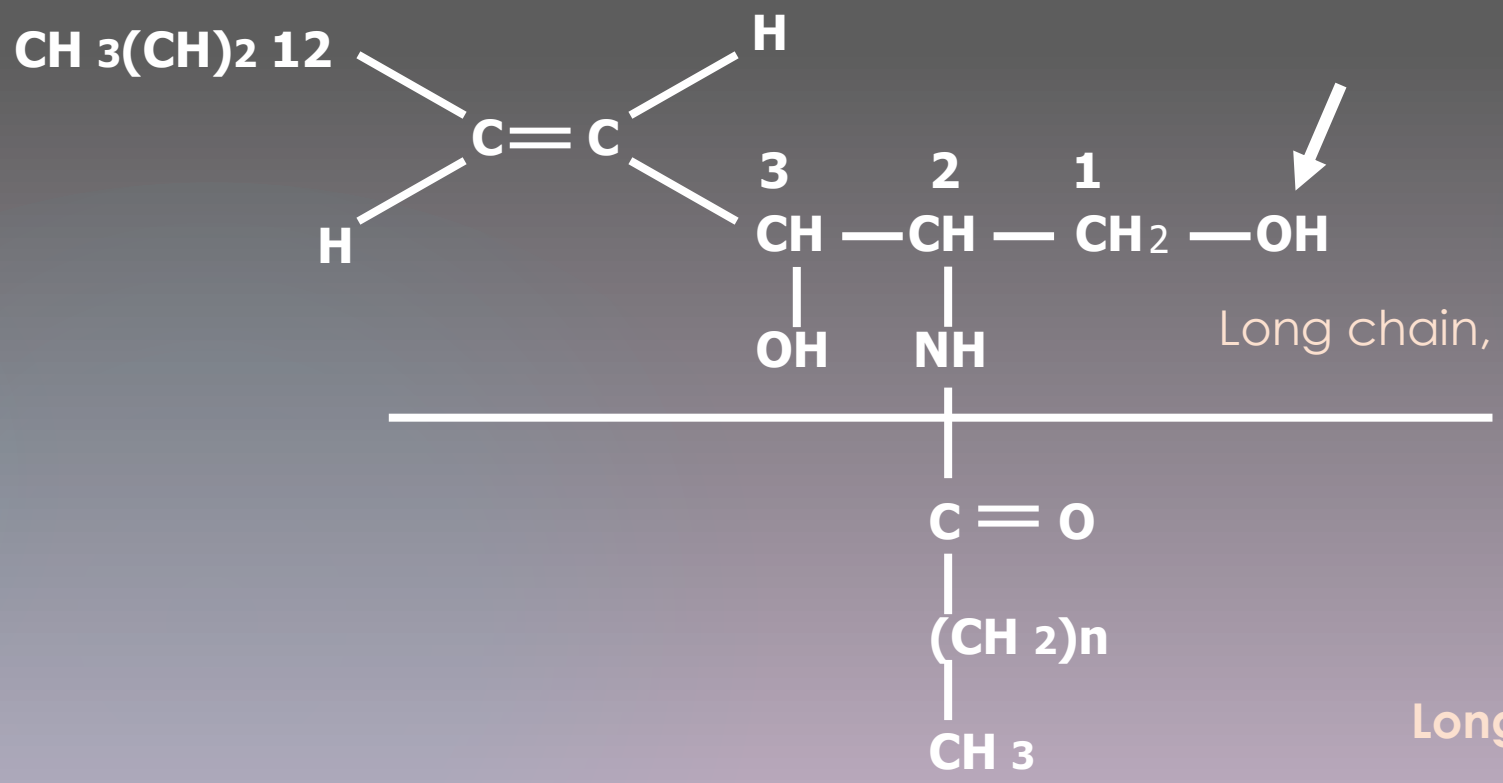
PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Sphingolipids' Synthesis



Ceramide

Basic structure of sphingolipids



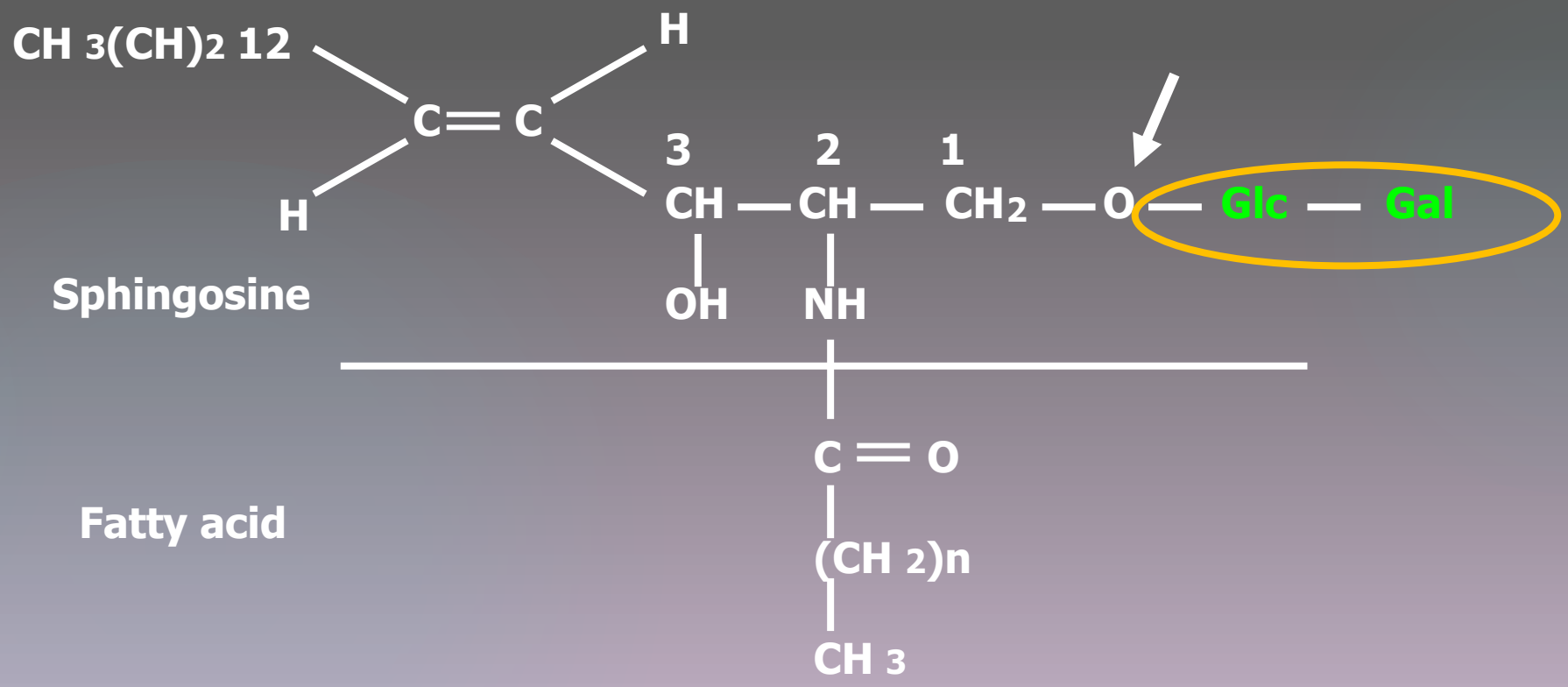
Sphingosine

Long chain, unsaturated amino alcohol

Fatty acid

Long chain fatty acid

Glycosphingolipids

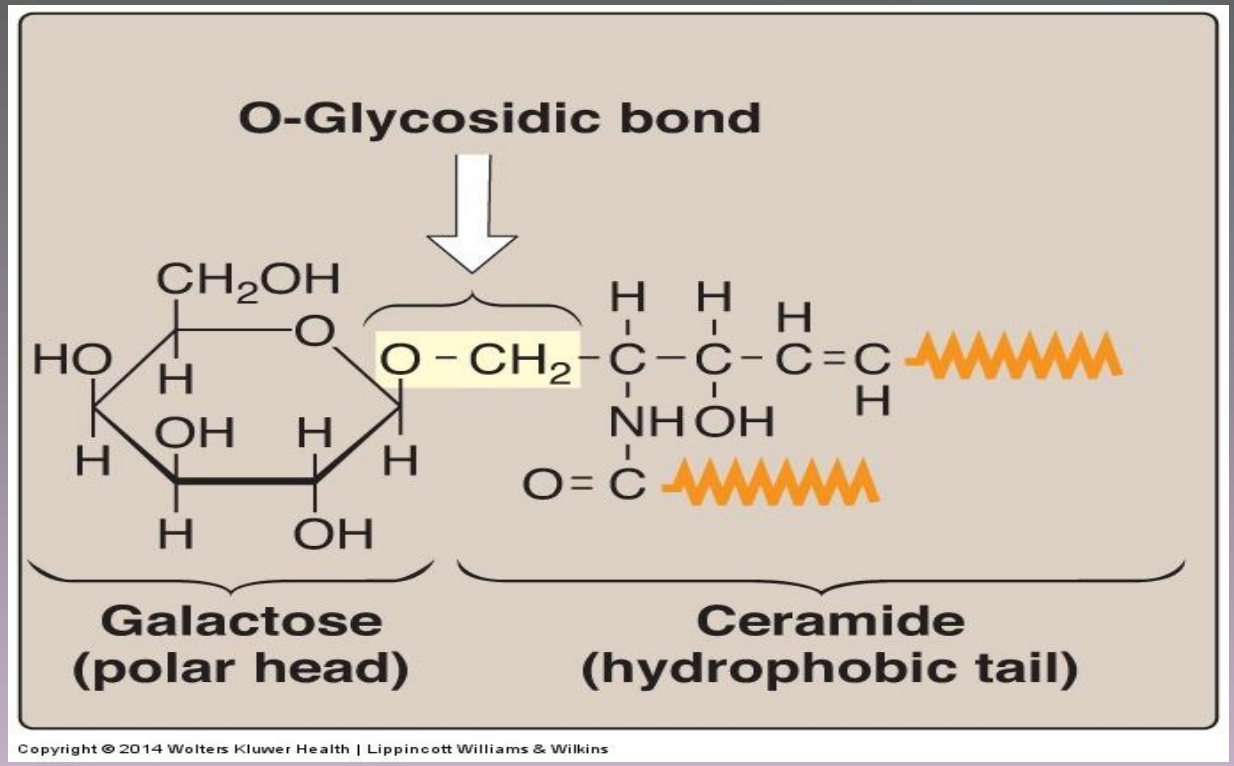


Ceramide+1 or more sugar

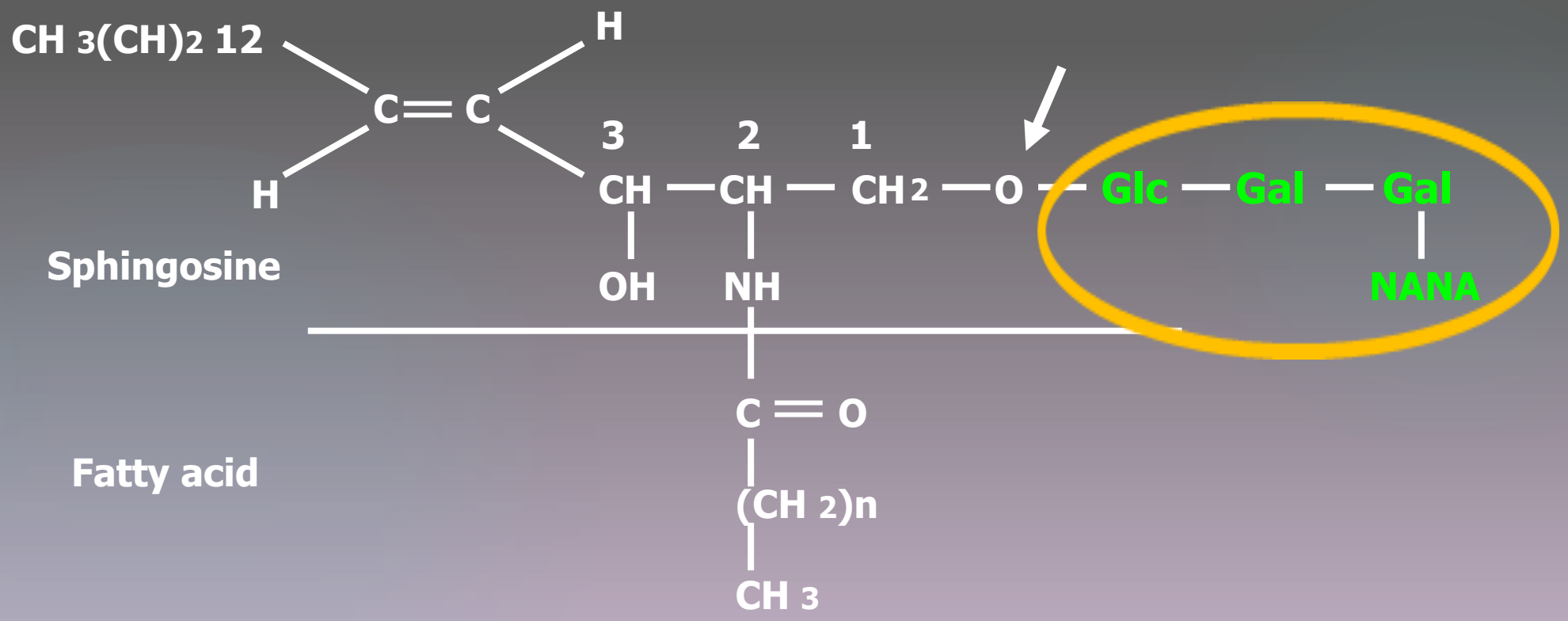
Cerebrosides

Cerebrosides = Ceramide + Monosaccharides

e.g. Galactocerebroside.

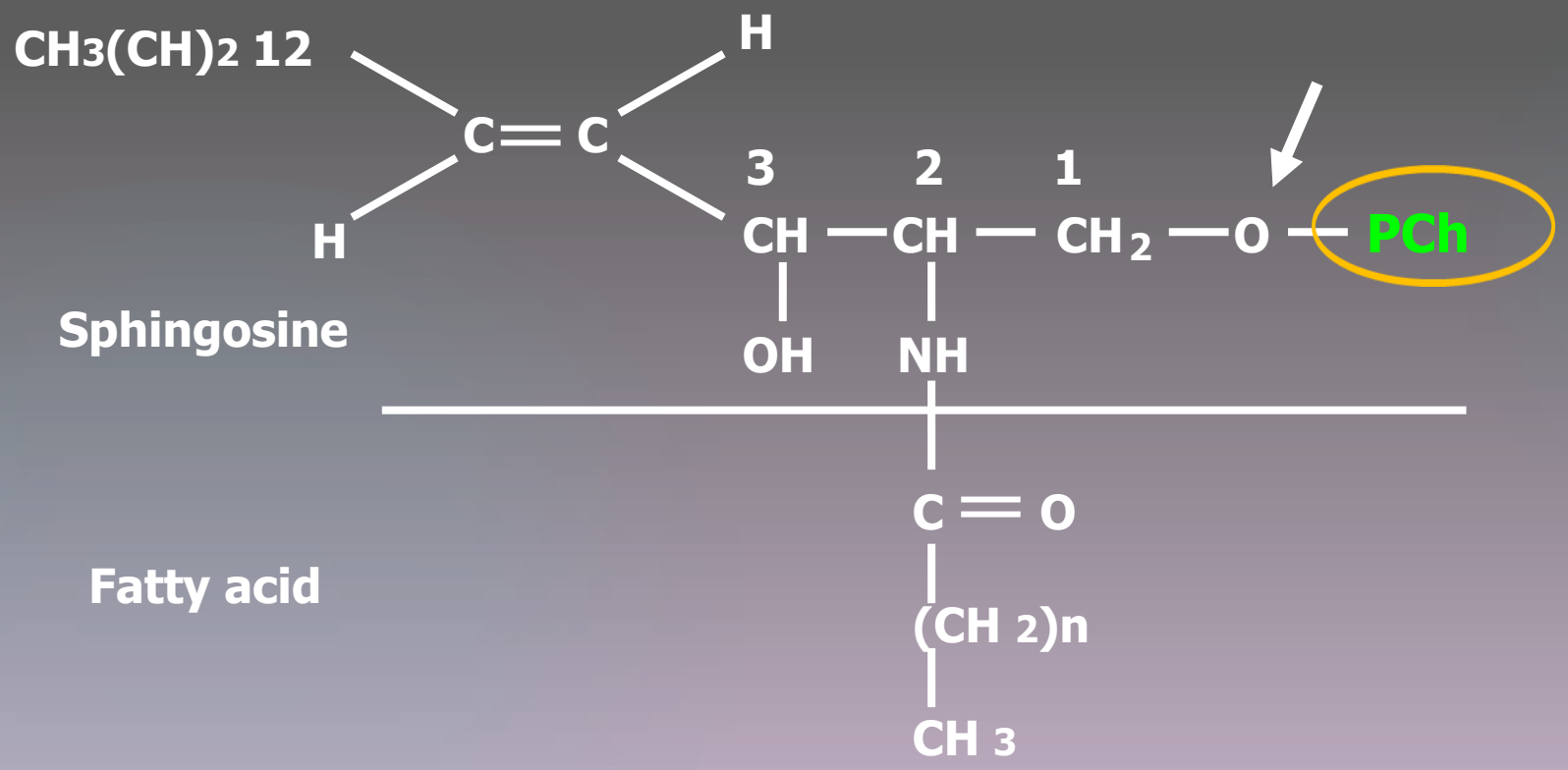


Gangliosides

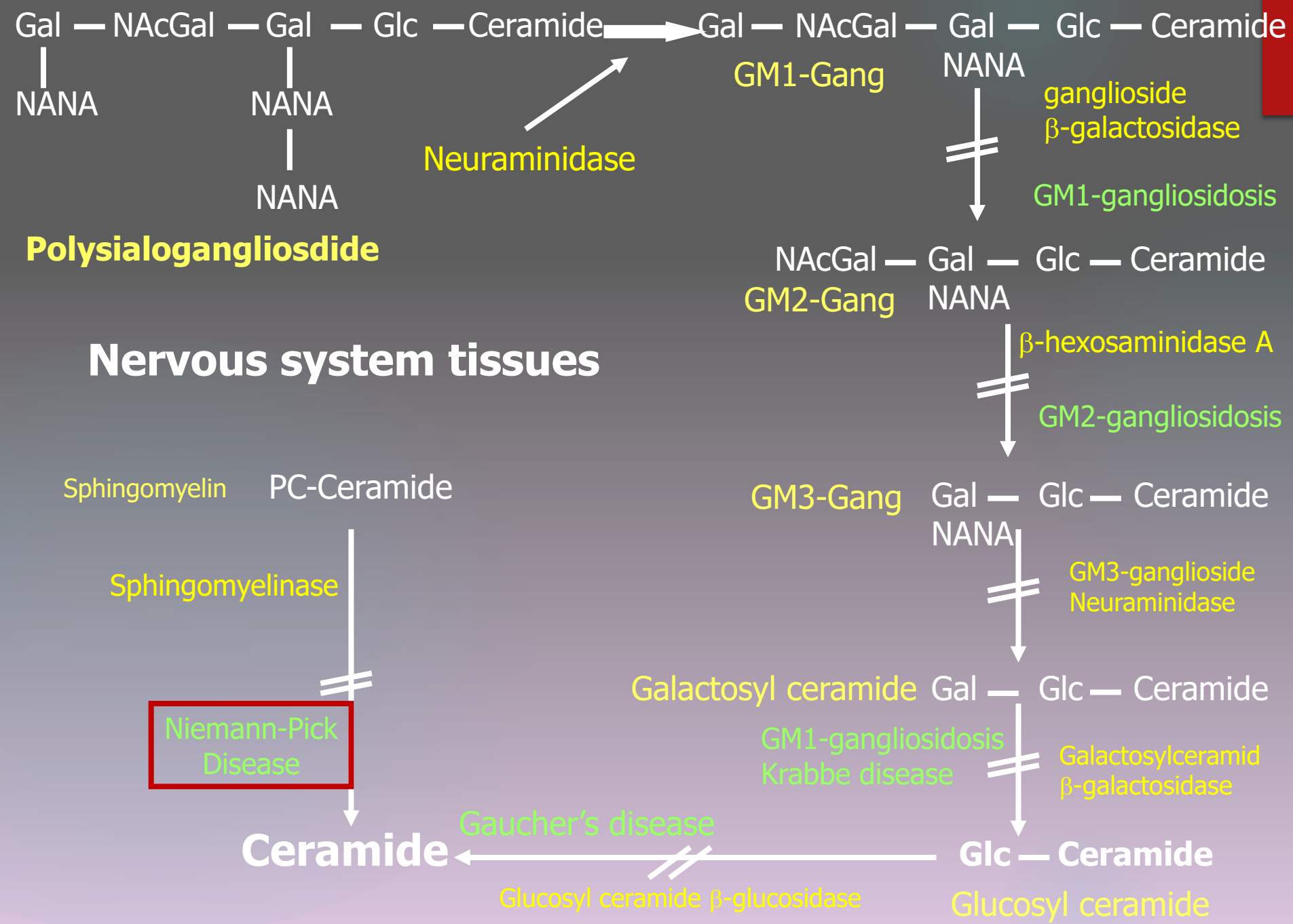


Glycosphingolipid+1 or more sialic acid residues (like GM2)

Sphingomyeline

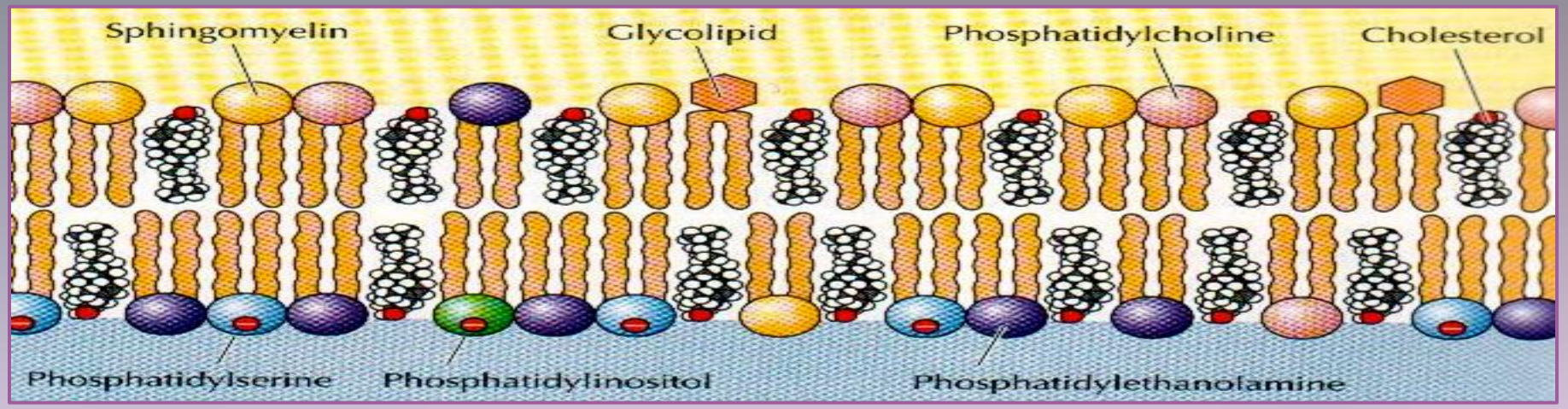


Ceramide+phosphorylcholine


Gal — NAcGal — Gal — Glc — Ceramide
NANA
NANA
NANA
Polysialogangliosdide
Neuraminidase
Gal — NAcGal — Gal — Glc — Ceramide
GM1-Gang
NANA
ganglioside
β-galactosidase
GM1-gangliosidosis
NAcGal — Gal — Glc — Ceramide
GM2-Gang
NANA
β-hexosaminidase A
GM2-gangliosidosis
Nervous system tissues
Sphingomyelin
PC-Ceramide
GM3-Gang
Gal — Glc — Ceramide
NANA
Sphingomyelinase
GM3-ganglioside
Neuraminidase
Niemann-Pick
Disease
Galactosyl ceramide
Gal — Glc — Ceramide
GM1-gangliosidosis
Krabbe disease
Galactosylceramid
β-galactosidase
Gaucher's disease
Ceramide
Glc — Ceramide
Glucosyl ceramide β-glucosidase
Glucosyl ceramide

glycosphingolipids (GSLs),

- GSLs are essential components of the outer leaflet of cell membranes.
- GSLs contribute to signaling processes.
- The ganglioside GM3, a complex GSL, modulate epidermal growth factor (EGF)-R -and insulin-R signaling .
- GSLs are also involved in pathogen recognition and can serve as entry point of virus and bacteria (GM1 acts as receptor for various viruses and bacteria) or can serve as toxin binding site.



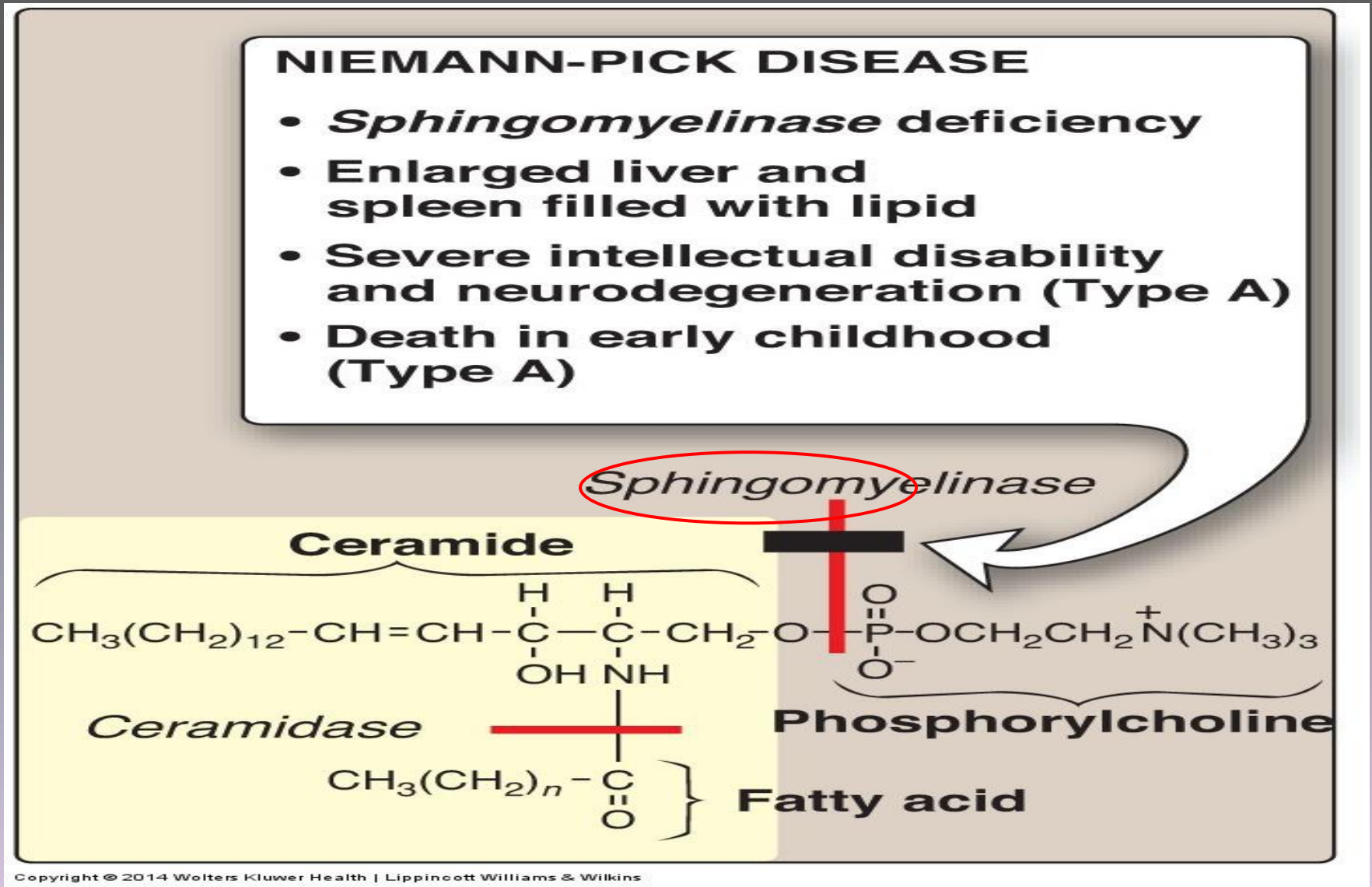
Essays in Biochemistry (2020) **64** 565–578

glycosphingolipids (GSLs),

- Complex GSLs have also been connected to CD4+ and CD8+ lymphocyte function.
- Mice lacking GM3 synthase show severely diminished CD4+ T-cell activation, without disturbance of CD8+ T-cell activation.
- Vice versa GM2 synthase deficient mice show absent CD8+ T-cell activation, with normal CD4+ T-cell activation
- GSLs are also part of the ABO blood group antigens that are critical mediators in transfusion medication.
- As key constituents of the myelin sheet galactosylceramide and sulfatides have been reported to contribute to its stability and continuity

Essays in Biochemistry (2020) **64** 565–578

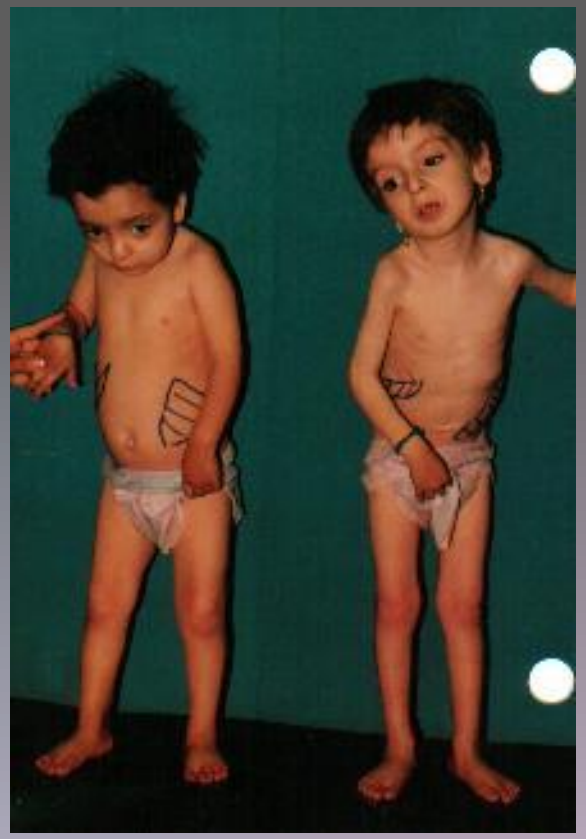
Niemann-pick disease

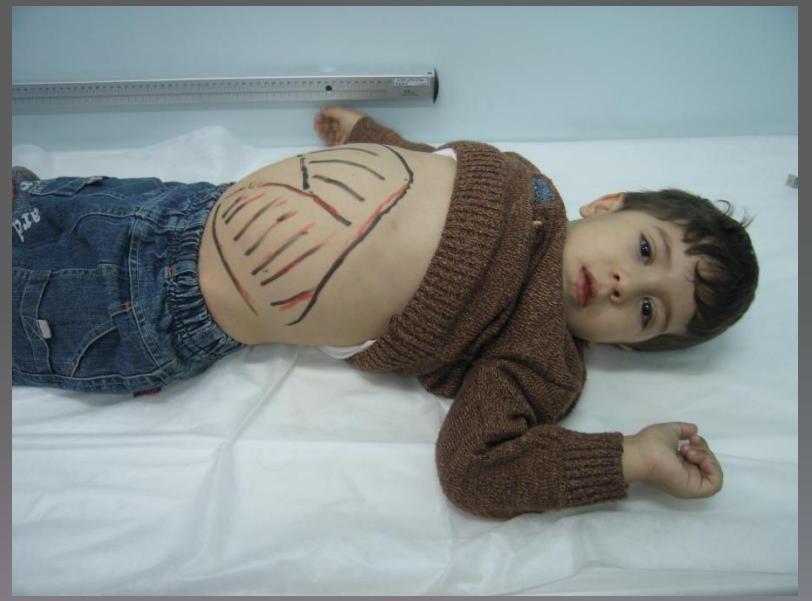


Case 1

Niemann-Pick A/B

Sphingomyelinase, 11p15





Case 2

- Soroush is a 3.5 year old boy (DOB=1398/9/9)
- He is the second child (G4P2Ab2Dc0) of a consanginous parents (first cousin)
- His perinatal and postnatal period were completely normal, with birth Wt=3.8 kg and Hc=35 cm
- Now his Wt AND Ht are 14 kg (25%) and 94 cm(25%) respectively
- His developmental milestones were normal
- He was refereed to clinic due to hepatosplenomegaly (liver span 12.5 cm and spleen=16 cm)
- In previous work up the LFTs were slightly increased and in liver biopsy severe fibrosis was reported.
- He also had mild thrombocytopenia
- The WES was requested for him and in SMPD1 gene homozygote mutation revealed
- Due to NPB diagnosis he introduced to the hematologist for HSCT

Case 2

SalehGohari Medical Genetic Laboratory
Medical Genetic PhDfrom Sheffield univercity

آزمایشگاه ژنتیک دکتر صالح گوهری
متخصص ژنتیک پزشکی از شفیلد انگلستان

Gene	NM- No	Nucleotide change	Aminoacid change	Zygosity	Variant classification	Disorder (OMIM#, inheritance)
SMPD1	NM_000543.5	c.1493G>A	p.Arg498His	Hom	Likely pathogenic	Niemann-Pick disease, type B (AR) [MIM:607616] Niemann-Pick disease, type A (AR) [MIM:257200]

Variant identified in SMPD1

Details about R498H (NM_000543.5) [Recessive HOM]

The homozygote G->A substitution at chr11:6415434 is predicted to result in abnormal protein translation of the SMPD1 protein at amino acid position 498.
Predicted effect(s) on the protein: Missense
The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
The maximal allele frequency of this specific variant in healthy control population was found in the ExAC database is 1.19e-5.

Clinical Significance of SMPD1

NIEMANN-PICK DISEASE, TYPE A [MIM:257200]

An early-onset lysosomal storage disorder caused by failure to hydrolyze sphingomyelin to ceramide. It results in the accumulation of sphingomyelin and other metabolically related lipids in reticuloendothelial and other cell types throughout the body, leading to cell death. Niemann-Pick disease type A is a primarily neurodegenerative disorder characterized by onset within the first year of life, mental retardation, digestive disorders, failure to thrive, major hepatosplenomegaly, and severe neurologic symptoms. The severe neurological disorders and pulmonary infections lead to an early death, often around the age of four. Clinical features are variable. A phenotypic continuum exists between type A (basic neurovisceral) and type B (purely visceral) forms of Niemann-Pick disease, and the intermediate types encompass a cluster of variants combining clinical features of both types A and B.

Dr. N. SalehGohari(MD, PhD)
Human Genetics

(فکس) ۰۳۴-۳۲۵۱۶۰۲۲ ۰۹۰۳۱۴۰۲۴۳۵ ،۰۳۴-۳۲۵۳۲۴۵۱
Salehgohari.lab@yahoo.com ۷۶۱۷۷۹۳۹۱۴(کد پستی) کرمان- استقلال ۱۶، نبش فرعی اول

History

- The disease was first described in 1914 an infant with hepatosplenomegaly who died at 18 months after progressive neurologic.
- While working as an intern at the children's hospital of the Charit´e in Berlin, Germany, the pediatrician Albert Niemann tried to diagnose a 17-months-old girl named Irene.
- The infant presented a "colossally swollen abdomen (circumference 50 cm)", apathy and a "quite miserable nutritional state".
- Niemann tested and treated the child for congenital syphilis–without success. Irene died within 4 weeks.
- In 1914, Niemann published a case report with the blatantly honest title "An unknown clinical picture

Progress in Lipid Research 90 (2023) 101225

History

- Niemann died in 1921 from tuberculosis, but his observations were followed up by other colleagues, notably the eminent German pathologist Ludwig Pick.
- He stated that the cases reported by Niemann belong to a distinct group of "lipoid cell splenohepatomegaly of infants"
- in 1926, Pick distinguishes the cases with "lipoid cell hepatosplenomegaly type Niemann" from Gaucher disease
- In the same year, when Pick published his review, the yet-to-become famous pediatrician Erwin Schiff was the first to use the term "type Niemann-Pick" for his diagnosis of a 17-months-old boy.

Progress in Lipid Research 90 (2023) 101225

History

- In 1927, Brahn and Pick reported several-fold increased levels of cholesterol in spleens of Niemann-Pick patients compared to normal controls.
- In the 1930s, Ernst Klenk discovered elevated levels of sphingomyelin in their spleen , liver and brain
- In 1961, when Allen C. Crocker working at the Children's Hospital of the Harvard Medical School (USA) distinguished four forms of the disease (A though D)
- Crocker already presumed distinct genetic causes for the different forms of the disease, and normal levels of ASM activity were detected in organs from Niemann-Pick Type C and D patients

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Epidemiology

- approximately 70 monogenic LSDs described to date, the majority follow an AR pattern, with the exception of three X-linked disorders; Mucopolysaccharidosis (MPS) type II, Fabry and Danon disease
- Classification of LSDs is based on the major type(s) of stored substances; include the MPS, sphingolipidoses, oligosaccharidoses, and…
- In isolation, individual LSDs are rare, however, combined they account for an overall prevalence reported to be as common as 1 per 4800 live births
- Niemann–Pick disease type A 1:250,000 *SMPD1* 11p15 275200
- Niemann–Pick disease type B ? *SMPD1* 11p15 607608
- Niemann–Pick disease type C ~1:200,000 *NPC1* 18q11-q12 257220

J Inherit Metab Dis. 2023;1–32.

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Genetic

- The disease is caused by pathogenetic variants in the SMPD1 gene (MIM# 607608), located in chromosome 11p15.4 and is inherited as a recessive trait.
- To date, more than 250 variants within the SMPD1 have been described in patients affected by ASMD
- The p.F333SfsX52, p.L304P and p.R498L, highly frequent among Ashkenazi Jewish patients, are associated to the severe ASMD A,
- p.H423Y, p.W393G and the p.Q294K variants seem to be associated with the intermediate phenotype
- The most frequently mutation is a three-base deletion which leads to the loss of the arginine residue p.Arg610del (p.R610del) and is associated with attenuated ASMD B phenotype.

Int. J. Mol. Sci. ***2021****, 22, 12870*

Genetic

- In general, mutations that create a premature stop codon, such as nonsense and small deletions or insertions that cause a shift of the open reading frame, would lead to be severe forms
- Besides these general correlations, it is worth noting that a phenotypic heterogeneity has been described among patients with the same genotype.
- This might be explained, at least in part, by epigenetic factors.
- Indeed, it has been reported that the SMPD1 locus is paternally imprinted , meaning that the gene is normally expressed by the maternal chromosome, as the paternal chromosome is inactivated.

Int. J. Mol. Sci. ***2021****, 22, 12870*

Pathophysiology

- 1-The release of acid hydrolases into the cytoplasm causes cellular damage
- 2-Defective transport of substrates into and out of lysosomes secondary to abnormal storage may play a role in disease pathogenesis,
- 3-Dysregulation of apoptosis
- 4-Impaired recycling of cellular components by autophagy
- 5-Diminished energy conversion in mitochondria
- 6-Enhanced oxidative stress.
- 8-the secondary accumulation of gangliosides (GGs) and glycosphingolipids (GSLs) in Niemann–Pick disease types A, B, and C and in mucopolysaccharidoses (MPSs) are well known.

Progress in Lipid Research 90 (2023) 101225

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Pathophysiology

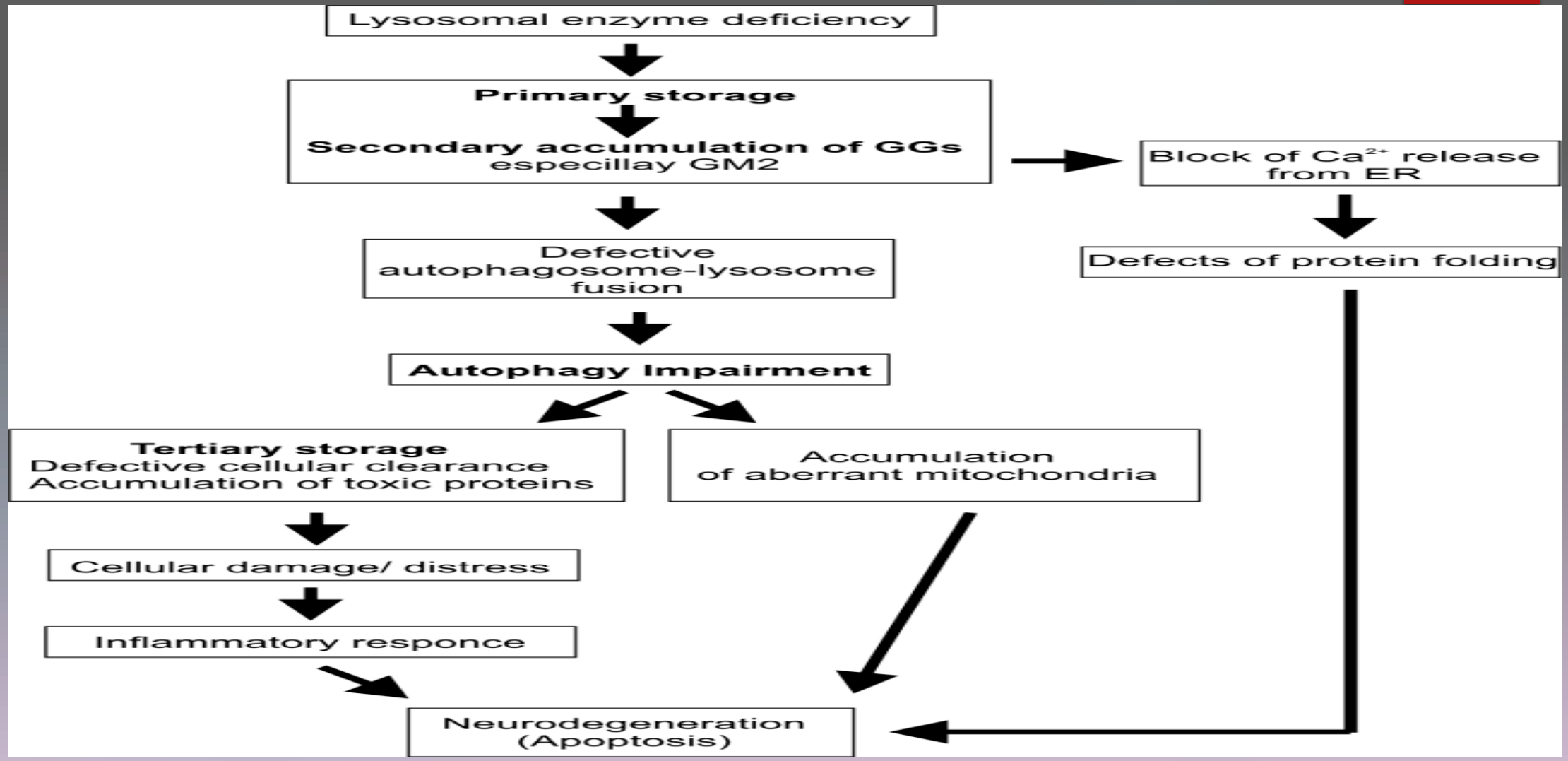
- Primary lysosomal storage compounds like sphingomyelin, cholesterol, and chondroitin sulfate were identified as inhibitors of GSL-catabolism triggering a secondary GSL-accumulation in Niemann–Pick diseases and in MPS

- 8- sphingomyelin is an effective inhibitor of cholesterol secretion from the late endosomal and lysosomal compartment explaining the secondary lysosomal cholesterol accumulation in Niemann–Pick disease types A and B

- 9-Lysosomal accumulation of metabolites can affect several functions of the organelle e.g., autophagy Ca2+-homeostasis , and signaling cascades

Int. J. Mol. Sci. **2020**, 21, 2566; doi:10.3390/ijms21072566

Pathophysiology



Int. J. Mol. Sci. **2020**, 21, 2566; doi:10.3390/ijms21072566

Classification

- Since the early 1980s, the heterogeneous group of "Niemann- Pick disease" has been divided in two separate entities: Acid sphingomyelinase deficiency (ASMD) , and NPC
- ASMD categorized into ;
- 1- Severe, acute neuronopathic or Infantile neurovisceral ASMD form (type A),
- 2- Non- neuronopathic or Chronic visceral form (type B) ,
- 3- A continuum ranging from mild to severe type B, and then from late-onset neurological type A or Chronic neurovisceral forms (NPD-A/B)
- Type A has its highest prevalence in Ashkenazim and is rare in other ethnic groups.
- Type B appears more frequent in southern Europe, North Africa, Turkey, the Arabian Peninsula, and in Chile.

Progress in Lipid Research 90 (2023) 101225

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

Clinical manifestations; Type A

- The neonatal period is usually normal, with vomiting and/or diarrhoea, appearing in the first weeks of life.
- Progressive hepatosplenomegaly and lymphadenopathy, in most cases before 3-4 months of age
- Neurological examination is essentially normal until the age of 5-10 months, when the child shows hypotonia, progressive loss of acquired motor skills, lack of interest in the surroundings and reduction of spontaneous movements
- Loss of motor function and intellectual deterioration continue to the point where patients become spastic and rigid.
- Seizures are rare.
- Death usually occurs between 1.5 and 3 years.

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

Clinical manifestations; Type A

Eye manifestations: A cherry-red spot in the retina is a typical feature but is often not present until an advanced stage

- Although ~ 50% of NPD type A patients will have a "cherry red spot"
- visual loss is rare.
- Lipid deposits may cause corneal and retinal opacification
- Niemann-Pick type A cause secondary optic atrophy
- The electroretinogram is abnormal

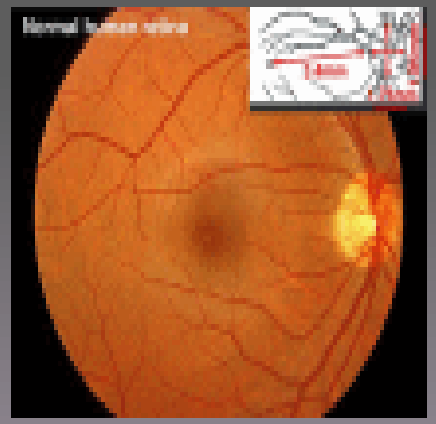
2)Pulmonary involvement

- Pulmonary involvement due to alveolar infiltration also may occur
- episodes of bronchitis and aspiration pneumonia may be severe.

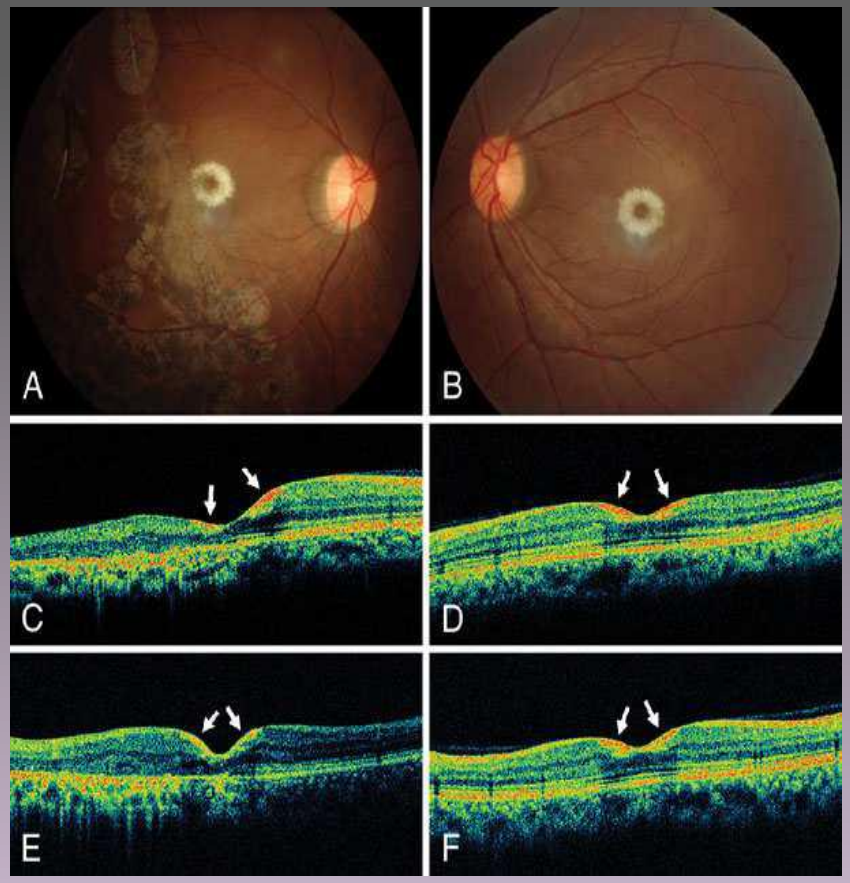
PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Cherry red spot

- The ganglion cells of the retina form a single cell layer, except in the macula, where they are present in multiple layers, and in the foveola, where they are absent.
- If significant lipid accumulation occurs in the ganglion cells, a white ring of lipid-laden neurons encircling the red, ganglion cell-free fovea can be observed, hence this characteristic finding is termed "macular halo" or "cherry red spot"



Normal retina



J Inherit Metab Dis (2010) 33:633–634

Clinical manifestations; Type A

- Some patients have neonatal edema and hydrops fetalis may occur.
- Transaminases AST and ALT are elevated. The alkaline phosphatase is also elevated.
- The cholesterol may be elevated in addition.
- There may be prolonged neonatal jaundice, and episodes of unexplained jaundice later.
- Patients who presented in early infancy with acute jaundice, abnormal liver function tests, and hepatomegaly, suggesting a diagnosis of acute hepatocellular disease rather than a lipid storage disease.
- At least one patient with Niemann-Pick disease was thought, on biopsy, to have glycogenosis
- Some patients have had noisy respirations and rhinorrhea from birth .
- Patients may also have unexplained fever

ATLAS OF INHERITED METABOLIC DISEASES
L. Nyhan, 4th ed. 2020

Clinical Presentations; Type B

- In type B typically, the presenting sign is splenomegaly or hepatosplenomegaly in late infancy or childhood but discovery may occur at any age from birth until late adulthood.
- Bruising and epistaxis are frequent.
- Hypersplenism occurs in a small proportion of patients. Splenectomy, seldom necessary
- In adults pulmonary involvement is often the main complaint, ranging from dyspnoea on exertion (frequent) to oxygen dependency.
- The most constant associated signs are radiographic abnormalities of the lung (diffuse, reticulonodular infiltrations) and interstitial lung disease with variable impairment of pulmonary function (low DLCO)

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

Clinical Presentations

- In children, retarded body growth is a common finding between the ages of 6 and 16 years. Skeletal age and puberty are often delayed
- Alterations of liver function are in general mild, but possibly underestimated; Fibrosis is common in the periportal and pericellular areas.
- Frank cirrhosis is not uncommon.
- Hyperlipidemia is common with elevated LDL cholesterol and decreased HDL.
- Other features associated with the disease are joint/limb pain, headache, abdominal pain, and diarrhoea.
- Some patients with NPD type B have been noted to have "cherry red" maculae.
- Niemann-Pick type B cause secondary optic atrophy

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Clinical manifestations; Type B

- True type B patients do not have neurological involvement and are intellectually intact,
- Some patients with a relatively mild phenotype may have some neurologic features.
- Extrapyramidal signs were reported in one family .
- Impaired mental development was reported in unrelated patients
- A number of patients has been reported with cerebellar ataxia
- Evidence of abnormal neural storage has been observed despite absence of neurologic abnormalities
- Two sisters without impaired mental development had inclusion bodies in exons and Schwann cells of rectal biopsies, and vacuolated macrophages in the cerebrospinal fluid (CSF)

ATLAS OF INHERITED METABOLIC DISEASES
L. Nyhan, 4th ed. 2020

Clinical manifestations; Type B

- Some others that have been included in type B have had quite severe, and early-onset disease (Saudi variant)
- Early symptoms are failure to thrive and huge splenomegaly.
- The liver may be just as huge or even more so.
- They have been said not to have neurodegenerative disease, but they all have cherry red macular spots
- Patients are hypotonic and developmentally delayed.
- Most of these patients die by three years of age.
- Terminal events include bleeding, anemia, and thrombocytopenia, often requiring daily transfusion of platelets, and hepatic failure
- Pulmonary infiltration is evident in roentgenograms as miliary nodular lesions and pulmonary function may be abnormal,

ATLAS OF INHERITED METABOLIC DISEASES
L. Nyhan, 4th ed. 2020

Niemann Pick disease

Four Saudi infants with Niemann-Pick disease illustrating some similarity of facial features. Patients tend to lose adipose tissue over the forehead and about the orbits; the nasal bridge is spared, giving the appearance of a crest of tissue.

Clinical manifestations

- Height and weight were usually low, and these correlated with large organ volumes
- Cardiomyopathy is very rare in Niemann pick A/B
- Mongolian spot and Xanthoma might be seen in NPA/B
- Rhizomelic chondrodysplasia punctate is also reported
- There is also a link between BCS (Budd Chiari Syndrome) and lipid storage diseases.
- Some researchers have found that lipid storage diseases should be included as a risk factor for BCS
- Osteoporosis is a common problem in this disease.

ATLAS OF INHERITED METABOLIC DISEASES
L. Nyhan, 4th ed. 2020

BMC Medical Genomics (2022) 15:196

A Clinical Guide to Inherited Metabolic Diseases
Joe T. R. Clarke. Second Edition 2004

Clinical manifestations; Type B

- A survey study of 59 pediatric and adult NPD-B patients revealed that 39 % complained of joint or limb pain suggesting that skeletal involvement may be a more common feature of NPD-B
- In a case series 43 % of all patients had a history of one or more skeletal fractures,
- The results reported here demonstrate that skeletal involvement occurs commonly in patients with NPD-B, as has been noted for other lipid storage disorders like Gausher and Fabry.
- The relationship between spleen size and decreased bone density in both pediatric and adult patients like other aspects of disease provides further evidence that spleen volume may be a useful surrogate marker of disease burden

J Inherit Metab Dis (2013) 36:123–127

Clinical presentations

- These findings suggest that examination of the skeleton including DEXA scan, should be part of the clinical evaluation of patients with NPD.
- In Gaucher disease, one study found that alendronate adjunctive therapy in combination with enzyme replacement therapy (ERT) incrementally improved osteopenia in affected adults
- To date, no clinical trials to assess the use of bisphosphonates have been carried out in children with Gaucher disease.
- However, this approach in NPD-B may be precluded by the finding that biphosphonates are inhibitors of ASM activity and have a prolonged half-life in bone which could potentially worsen the disease
- Newer treatments for osteoporosis, such as monoclonal antibodies (e.g., Denosumab) that inhibit the receptor activation of nuclear factor kappa-B ligand (RANKL) thus reducing osteoclast function may be worth consideration

J Inherit Metab Dis (2013) 36:123–127

Clinical Presentations

- **Intermediate Forms of ASMD**
- This is a heterogeneous category.
- Some patients are closer to type A with a late infantile, juvenile, or adult neurological onset and a slowly progressive disease
- They may show cerebellar ataxia, extrapyramidal involvement, or psychiatric disorders.
- Some others are closer to type B, with minimal nervous system involvement (often peripheral neuropathy) and/or mild mental retardation

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

Diagnosis

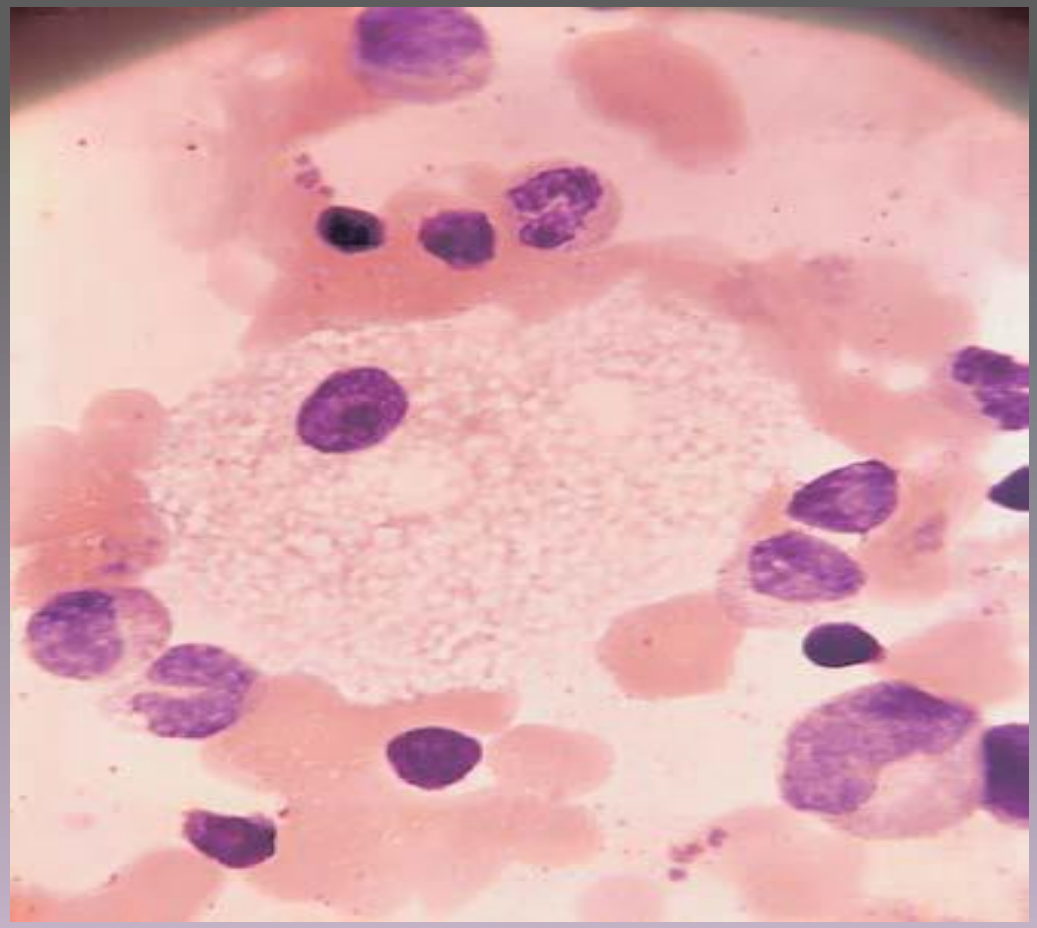
- The large macrophage is detected in bone marrow aspirate. the cells have a foamy appearance due to accumulation of lipid and sphingomyeline.
- The lipid droplets are uniform in size, and the appearance has been called honeycomb-like or mulberry-like.
- The cytoplasm of these cells stains blue with Wright stain, which gives rise to the sea-blue histiocyte designation (SBH)
- As a reticuloendothelial cell, it is found widely in the spleen, liver, lymph nodes, and lungs.
- There may be infiltration in the gastrointestinal tract, which might account for intestinal symptoms and failure to thrive.
- There is also storage of cholesterol and sphingomyelin in the liver of patients, and this tends to be more in tissues of type A than of type B patients.

Inborn Metabolic Diseases
Jean-Marie Saudubray
7TH ed. 2022

ATLAS OF INHERITED METABOLIC DISEASES
L. Nyhan, 4th ed. 2020

Blue Histiocyte

- In many diseases can also be secondary SBH including :
- NPA/B
- LPI
- LAL deficiency
- Primary thrombocytopenic purpura,
- Chronic myeloid leukaemia (CML)
- Myelodysplastic syndrome,
- Thalassemia,
- Lipoproteinemia,



BMC Medical Genomics (2022) 15:196

Diagnosis

- The pathognomonic feature of all patients with deficiency of sphingomyelinase
- Decreased ASM activity is present in peripheral blood leukocytes or fibroblasts and other nucleated cells.
- In general, in type A patients, there is less than 5 percent of control activity, and often activity is undetectable
- In type B disease, activity is variable and may be up to 10 percent of control, but it may also be zero in type B.
- Residual activity is not a reliable index of clinical severity.
- On the other hand, heterozygote detection may not be reliably excluded by enzyme assay, because of overlap with the normal range.

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Diagnosis

- Enzyme activity assessed on DBS by multiplexed tandem mass spectrometry (MS/MS) coupled to specific biomarkers as second-tier analysis,
- Enzyme activity was expressed as micromoles of substrate hydrolyzed per hour of incubation per liter of blood (μmol/l/h).
- Based on a pilot study on 3500 residual and known patient DBSs, a cutoff of 1,2 umol/l/h have been established for NB A/B activity, according to 0.2 multiple of median (MOM).
- Determination of biomarkers like LysoGb1 and Lyso SM in DBS is also helpful
- Lyso-SM are useful for diagnosis and follow up due to decrease with treatment, and their levels correlate with disease severity

Orphanet Journal of Rare Diseases (2023) 18:197

Diagnosis

- Biomarker candidates for ASMD measured in blood were :
- Cytokines,
- 7-ketocholesterol,
- Lysosphingomyelin (Lyso-SM) ,
- Sphingosylphosphorylcholine,
- Lysophingomyelin-509 (now more properly renamed N-palmitoyl-O-phosphocholineserine or PPCS)
- Among plasma bio-markers, only elevation of lysosphingomyelin is specific of ASMD, since abnormal levels of the oxysterols cholestane-3β,5a,6β-triol , 7- ketocholesterol, lysosphingomyelin-509 , are also elevated in Niemann-Pick C and for oxysterols, in acid lipase deficiencies (LAL def.) and some other conditions
-

Progress in Lipid Research 90 (2023) 101225

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

Diagnosis

- Chitotriosidase is a human chitinase with markedly elevated activity in a variety of lysosomal storage disorders (LSDs)
- Chitotriosidase is secreted by activated macrophages
- Chitotriosidase activities above 200 nmol/h per ml were predictive for GD, NP A/B or NPC.
- Activities above 4000 nmol/h per ml were predictive for GD.
- Plasma CCL18 was increased together with chitotriosidase.
- This suggests that NP storage cells, like Gaucher cells, also secrete the chemokine CCL18

J. Inherit. Metab. Dis. 28 (2005)

J Inherit Metab Dis (2006) 29:647–652

Genetic

- Private mutations typically are present in ethnic groups
- L137P, A196P, and R474W were also associated with mild disease.
- DR608 and other mutations found in milder type B phenotype
- Among the Saudi Arabian patients, some 85 percent of alleles carried the two mutations H421Y and K576N . These mutations led to early onset and early demise. All had pulmonary disease
- Niemann-Pick type B is relatively common in Turkish patients, in whom three mutations (L137P, fsP189, and L549P) accounted for about 75 percent of the alleles was consistent with quite mild disease.
- ***Prenatal Diagnosis*** is possible by measuring ASM activity in amniocytes or chorionic villi. If the mutations are known, DNA analysis is also possible.

Int. J. Mol. Sci. ***2021****, 22, 12870*

Inborn Metabolic Diseases
Jean-Marie Saudubray 7TH ed. 2022

ASMD diagnostic algorithm

- ***1) Increased transaminases***; 75% of patients had mildly increased ALT and 65% mildly increased AST
- ***2) Dyslipidemia***; hypertriglyceridemia and increased LDL-C in 62% and 67% of patients respectively and 100% of patients showed decreased HDL-C.
- ***3) Growth retardation***; In 30 pediatric patients reported height Z-scores ranging from − 4.88 to -2.14.
- the association between growth retardation and the degree of organomegaly was suggestive of causal relation in ASMD
- ***4) Respiratory involvement***. 20% of patients had generic respiratory symptoms at the presentation
- Abnormal diffusing capacity of the lungs for carbon monoxide (DLCO) test or radiological data consistent with interstitial lung disease

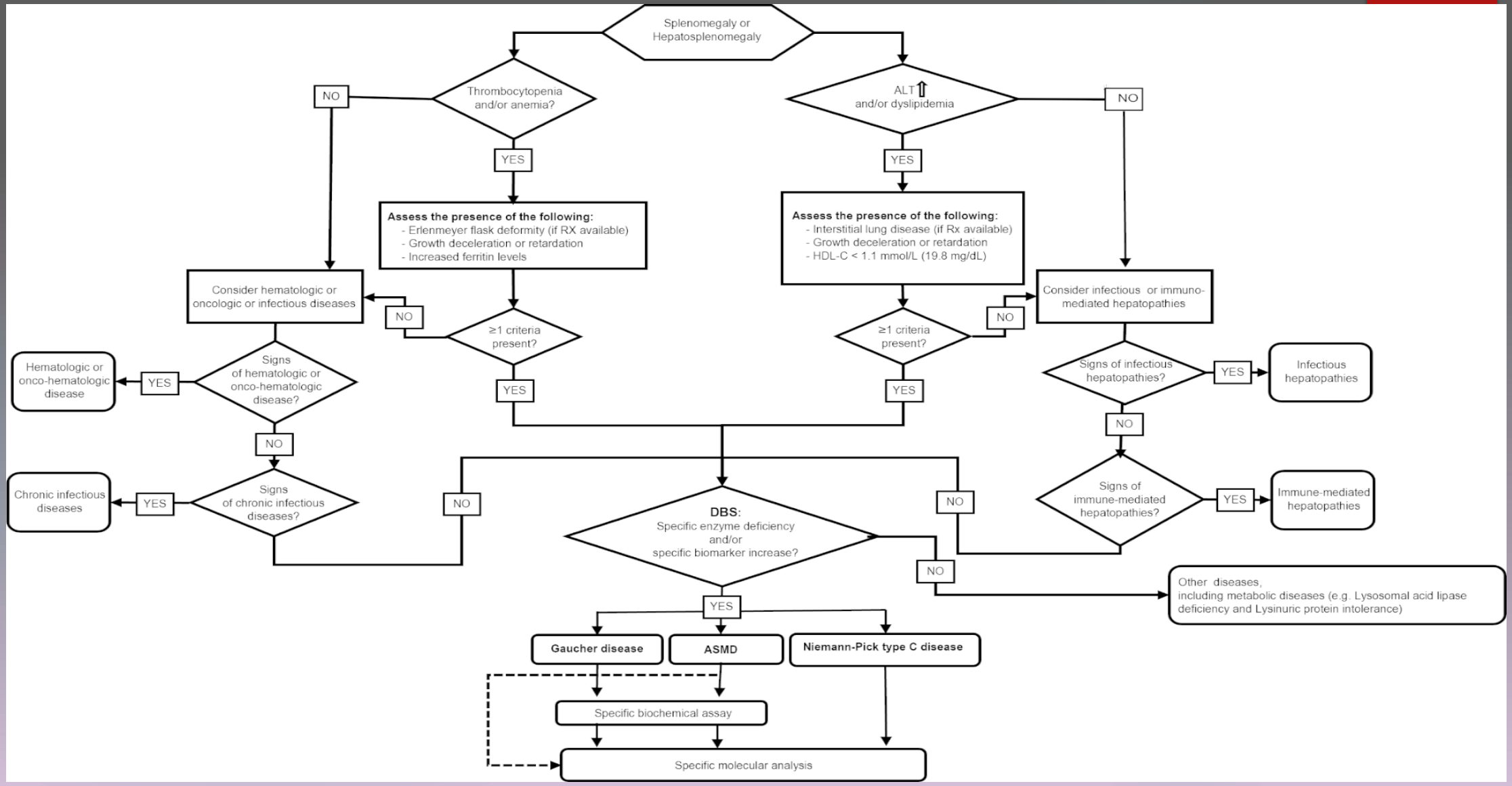
Orphanet Journal of Rare Diseases (2023) 18:197

ASMD diagnostic algorithm

- In cases with hepatosplenomegaly ALT levels and/or dyslipidemia should be assessed for the presence of at least 1 criterion among interstitial lung diseases, growth deceleration or retardation, and HDL-C < 1.1mmol/L (19.8 mg/dl).
- If ≥ 1 criteria are present, the patient is eligible for DBS screening.
- If none of the above criteria are met, the physician should rule out other differential diagnosis (such as infectious or immuno-mediated hepatopathies).
- Determination of acid β-glucocerebrosidase [ABG] enzyme activity coupled with the determination of LysoGb1 and Lyso-SM will allow for better identification of patients and reduction of false positives for Gaucher Disease and ASMD, eventually leading to the diagnostic confirmation with specific molecular analysis.

Orphanet Journal of Rare Diseases (2023) 18:197

ASMD diagnostic algorithm



Orphanet Journal of Rare Diseases (2023) 18:197

Treatment

- Supportive treatment should be used for all types of NPD.
- Supportive therapy to treat the pulmonary manifestations or liver disease is still the mainstay of treatment.
- Splenectomy is rarely done as it aggravates the liver and lung disease, but may be required in case of extensive enlargement and infarcts or rupture.
- Standard lipid-lowering agents are indicated for the treatment of ASMD-associated lipid abnormalities in adult patients, but it is not routinely recommended
- Broncho alveolar lavage has been tried in some cases of extreme pulmonary involvement to relieve symptoms, but its effect is unclear.

Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases
Nenad Blau 2ND ed. 2022

Treatment

- Liver transplantation has had long-term success in severe non-neuropathic cases.
- For ASMD, in the 1970s transplantation of liver samples and HSCT had performed from different sources
- Improvement of organomegaly following bone marrow transplantation has been observed in NPD type B.
- Enzyme replacement appeared as a promising approach for ASMD, and its preclinical development took off in the 1990s
- No change in the neurological course was noted in type A disease.
- Since NPD type B is a disorder with little or no neurologic involvement, it was considered that BMT might be an effective treatment .

Progress in Lipid Research 90 (2023) 101225

PEDIATRIC ENDOCRINOLOGY AND INBORN ERRORS OF METABOLISM
Sarafoglou, 2nd ed. 2017

Treatment

- Trehalose is a natural non reducing disaccharide in various organisms, from bacteria to animals, that exerts cell-protective effects under tensions, such as temperature, drought, and oxidative stress
- Trehalose has also been reported to prevent neuronal damage and attenuate neurodegenerative disorders caused by LSDs
- Anti-aggregant, anti-inflammatory, and antioxidant properties, along with autophagy inducer, might be proposed as mechanisms of neuroprotective
- The chaperone-like activity of trehalose could prevent protein misfolding and clearance of accumulated proteins through promoting autophagy in neurodegenerative diseases
- Trehalose is emerging as a novel therapeutic alternative to repressing oxidative stress and inflammation by decreasing the production of reactive oxygen species (ROS) and pro-inflammatory cytokines, such as IL-1 and TNF,

J. Clin. Med. ***2022****, 11, 247*

Treatment

- Trehalose can be used by either oral or intravenous (IV) administration; however, its absorption is decreased to 0.5% in the oral route
- Trehalose infusion (15 g/week) was tried for a period of 12 weeks in five NPA and NPB patients.
- At doses up to 50 g, trehalose is safe for humans, without no adverse effect
- Elevated levels of lysosphingolipids (lyso-SM and lyso-SM-509) which is seen in all types of NP (A/B and C), are decreased by Trehalose

J. Clin. Med. ***2022****, 11, 247*

ERT

- Olipudase alfa (Xenpozyme®) is a recombinant human ASM enzyme replacement therapy (ERT) approved for the treatment of the non-central nervous system manifestations of ASMD in children and adults.
- The study included patients with ASMD types B or A/B and no patients with ASMD type A were enrolled.
- 36 adults and 20 children were enrolled in this clinical trial.
- Two clinical trials, one phase 2 and one phase 2/3 (NCT02004704; NCT02004691), was ongoing with olipudase alfa treatment once every two weeks
- In addition, three studies have been completed, one in phase 1/2 (NCT02292654) and the other two in phase 1 (NCT00410566; NCT01722526)

Int. J. Mol. Sci. ***2021****, 22, 12870*

Orphanet Journal of Rare Diseases (2022) 17:437

ERT

- A phase 1 single-ascending-dose study of olipudase alfa, aiming to address the safety of ASM ERT in adult patients, identifies 0.6 mg/kg as the maximum tolerated first dose (NCT00410566)
- Eleven adult patients participated in other study and divided into five groups hat were infused with different doses of olipudase alfa (0.03, 0.1, 0.3, 0.6 or 1.0 mg/kg).
- No serious adverse drug reactions occurred during the study.
- Acute-phase reaction-type adverse drug reactions arose 12–24 h following doses higher or equal to 0.3 mg/kg.
- The regimen was first evaluated in a 6-month Phase 1b study in five adults who were administered initial doses of 0.1 mg/kg of olipudase alfa followed by stepwise biweekly increases to reach the target dose of 3.0 mg/kg

Int. J. Mol. Sci. ***2021****, 22, 12870*

ERT

- In a similar way, a study in phase 1/2 was conducted in pediatric patients in order to evaluate the safety and tolerability of olipudase alfa with ascending doses (NCT02292654)
- Twenty patients between 1.5 and 17.5 years were enrolled
- All patients underwent individualized dose escalation over a minimum of 16 weeks in the ASCENDPeds trial
- The first infusion started at 0.03 mg/kg and followed by 0.1 mg/kg two weeks after.
- Latter, escalating doses were given: 0.3, 0.6, 1 and 2 mg/kg, reaching, at last, the maintenance dose of 3 mg/kg by week 64.
- All patients reported at least one mild adverse event, such as pyrexia, cough, vomiting, nasopharyngitis, diarrhea, headache, nausea, rhinitis, oropharyngeal pain, ear pain and rhinorrhea
- However, five patients reported a serious adverse events related to the treatment, one of which led to a temporarily discontinuation.

Int. J. Mol. Sci. ***2021****, 22, 12870*

ERT

- After the 52-week (efficacy)/64-week (safety) primary analysis periods, all 20 patients have continued olipudase alfa treatment in a long-term study
- Recently, the outcomes of phase 2/3 clinical trial with olipudase alfa were published in a press release from Sanofi (NCT02004691; NCT02292654).
- The outcomes from the past 30 months show improvements in relevant disease clinical measures; including significant reductions on liver (31%) and spleen (39%) volumes and an increase of 35% in lung diffusion capacity.
- Lipid profiles improved in all patients: triglycerides decreased by 43%, total cholesterol by 13%, LDL-C decreased by 23% and HDL-C increased by 138%.
- In terms of safety, there were no serious or severe events during treatment.

Int. J. Mol. Sci. ***2021****, 22, 12870*

Orphanet Journal of Rare Diseases (2022) 17:437

ERT

- The clinical and biochemical end points including:
- Spleen size and platelet count
- Percent predicted diffusing capacity of the lung for carbon monoxide DLCO] adjusted for hemoglobin,
- Volumetric lung function tests (FVC , TLC)
- High-resolution computed tomography [HRCT] lung imaging scores,
- Liver function,
- Plasma lipid profiles
- Height Z-scores
- BMD and skeletal fractures
- Biomarkers (plasma chitotriosidase activity [μmol/L/hr], plasma lyso-sphingomyelin [μg/L])

Orphanet Journal of Rare Diseases (2022) 17:437

ERT

- Splenomegaly is a prominent clinical manifestation of ASMD and contributor to disease burden.
- Olipudase alfa improved splenomegaly in all study participants and was accompanied by increases in platelet counts, indicating the correction of secondary hypersplenism contributing to thrombocytopenia
- Mean spleen volume decreased from 19.0 ± 8.8 MN at baseline to 7.2 ± 3.3 MN at 24 months
- Individual decreases in spleen volume ranged from 41.6 to 76.2%.
- All pediatric patients had reductions from baseline in spleen and liver volumes of greater than 30% by 24 months.

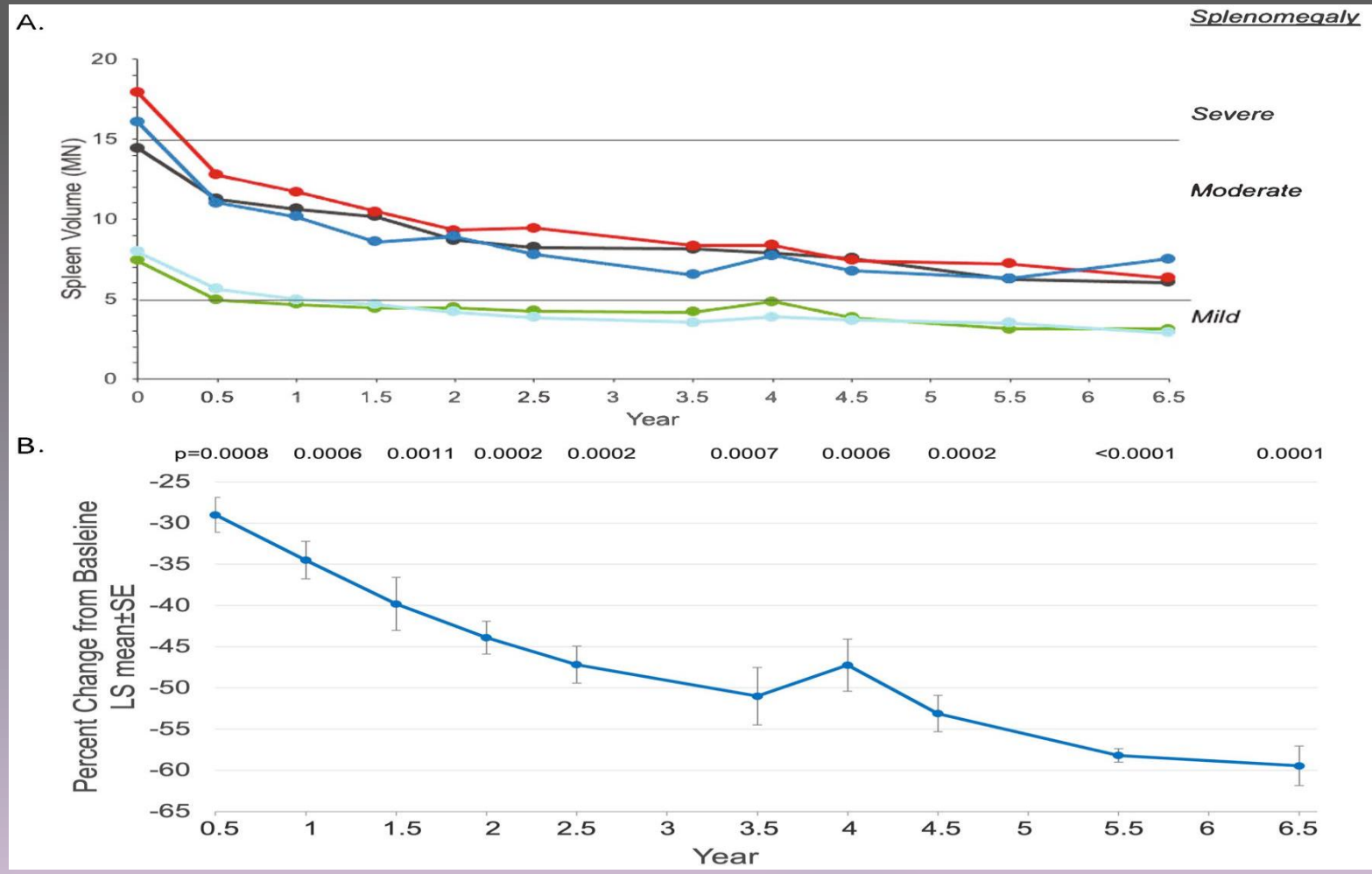
Orphanet Journal of Rare Diseases (2022) 17:437

Orphanet Journal of Rare Diseases (2023) 18:94

ERT

Spleen volumes were calculated by MRI images and expressed as multiples of normal (MN) where normal spleen volume is 0.2% of body weight .

Severe and moderate splenomegaly were defined as >15 and > 5 to ≤ 15MN, respectively



Orphanet Journal of Rare Diseases (2023) 18:94

ERT

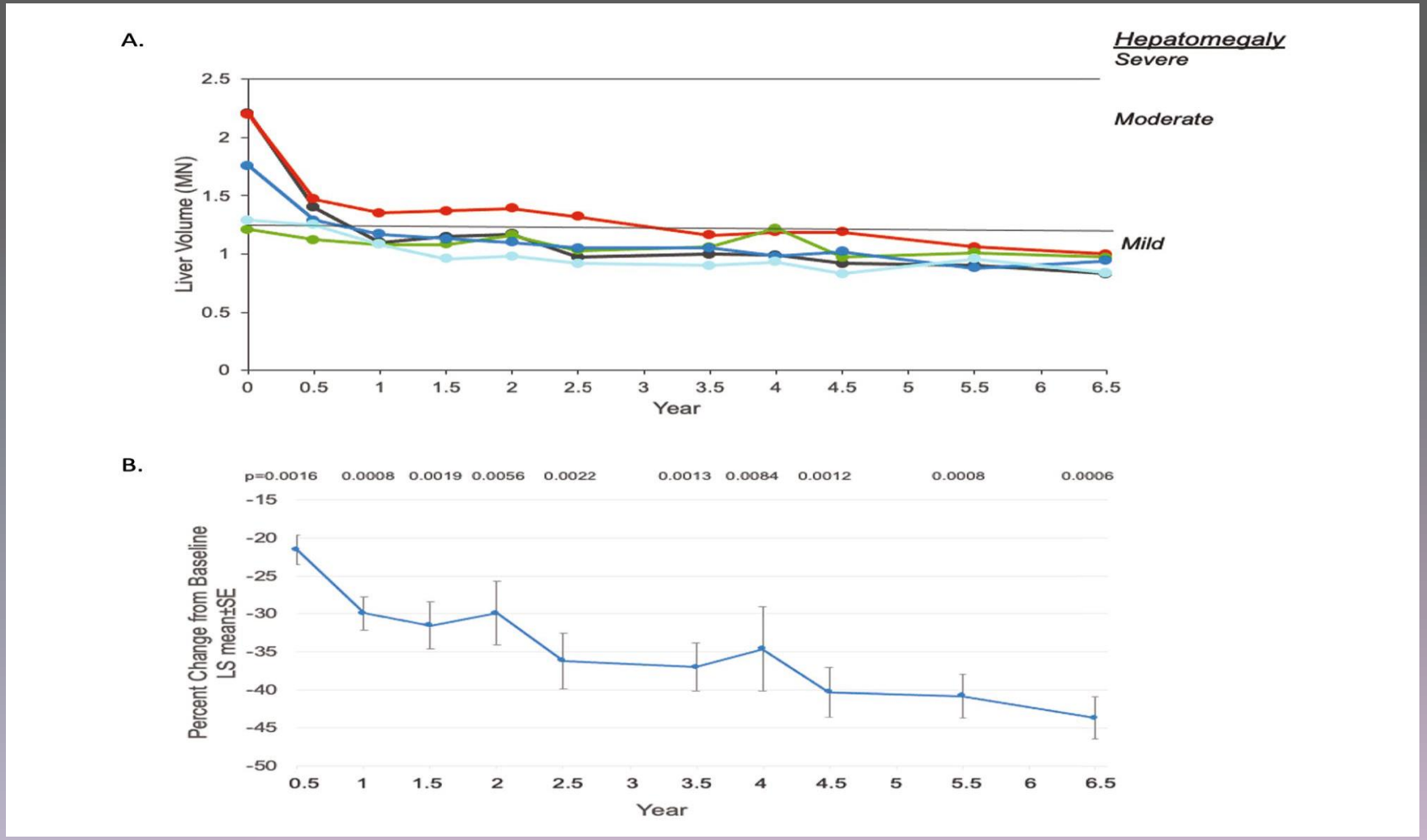
- Mean liver volume decreased from 2.7 ± 0.7 MN at baseline to 1.3 ± 0.2 MN at 24 months with individual decreases ranging from 30.5 to 66.5%.
- The five adults showed significant and sustained improvements in liver sphingomyelin burden within the first year of olipudase alfa treatment, and the clearance of excess sphingomyelin in hepatocytes and Kupfer cells through year 3.5 of treatment
- Elevated liver transaminases reflecting ASMD-associated liver pathology in pediatric patients normalized beginning in the first few weeks of treatment and remained within normal limits through 24 months
- The severity of hepatomegaly steadily decreased over 6.5 years of treatment in all participants.

Orphanet Journal of Rare Diseases (2023) 18:94

ERT

Normal liver volumes are considered to be 2.5% of body weight

hepatomegaly were defined as > 2.5 and > 1.25 to ≤ 2.5MN , respectively.



Orphanet Journal of Rare Diseases (2023) 18:94

ERT

- It is important to note that there are two components of ILD in ASMD:
- Alveolar infiltration and infiltration of the intra-alveolar septum (as is seen in other interstitial lung diseases such as pulmonary fibrosis).
- DLCO improved in all nine patients with baseline data by 24 months, Individual changes from baseline ranged from 17% to 85.3%, no or mild impairment after 6.5 years,
- The mean percent predicted value improved from 77.4 ± 16.3% at baseline to 89.6 ± 23.4% at 24 months for FVC and from 86.8 ± 23.3% to 122.6 ± 22.8% for TLC
- Lung function and ILD improved in all pediatric patients receiving olipudase alfa.
- In parallel, radiographic imaging of lung parenchymal features over time indicated resolution of ground glass appearance and improvement in ILD scores.

Orphanet Journal of Rare Diseases (2023) 18:94

ERT

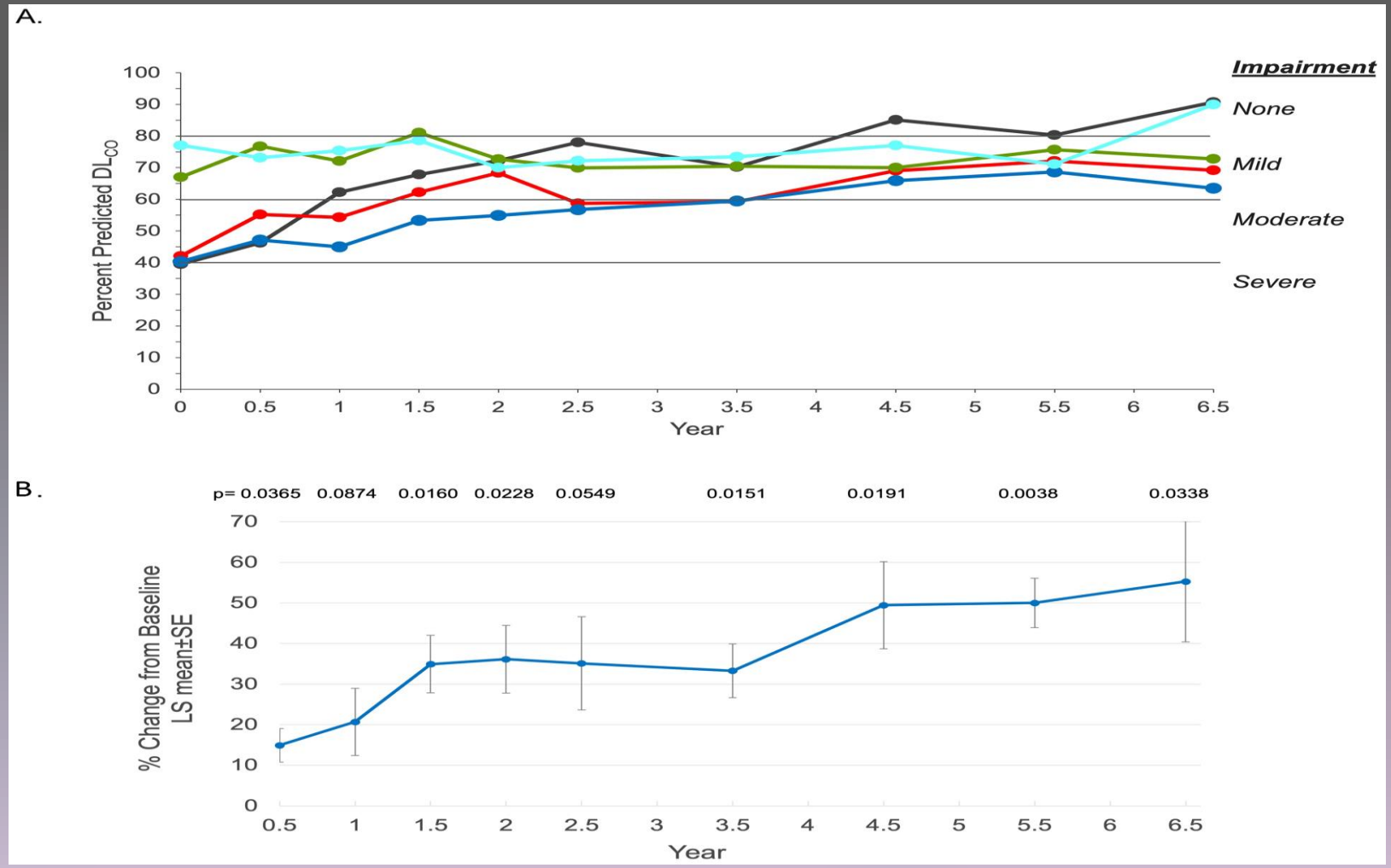
Cutoffs for impairment are:

> 80% normal/no impairment,

> 60% to ≤ 80% mild impairment

40–60% moderate impairment

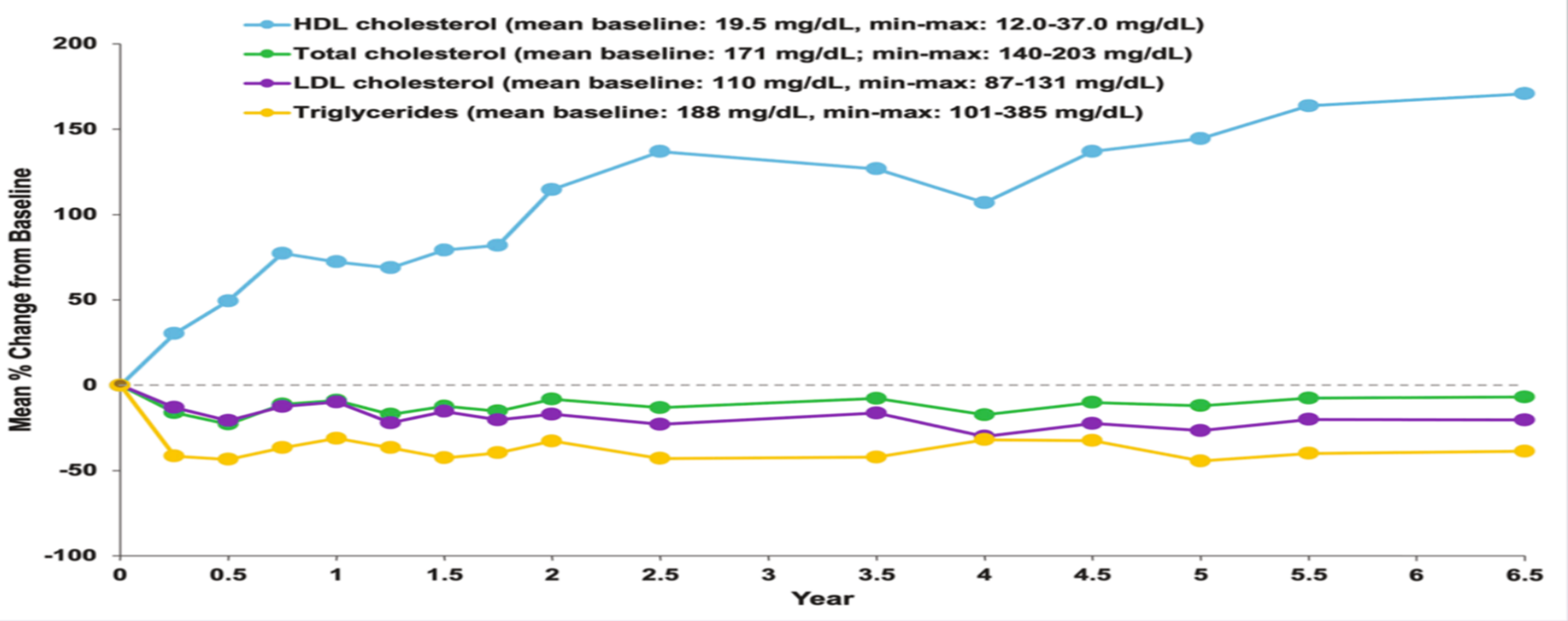
< 40% severe impairment



Orphanet Journal of Rare Diseases (2023) 18:94

ERT

- Lipid profiles improved in all patients: triglycerides decreased by 43%, total cholesterol by 13%, LDL-C decreased by 23% and HDL-C increased by 138%.
- Lipid profiles significantly improved over 12 months of olipudase alfa treatment and showed additional improvements and normalization by 24 months of treatment and sustained over the 6.5 years of treatment



Orphanet Journal of Rare Diseases (2022) 17:437

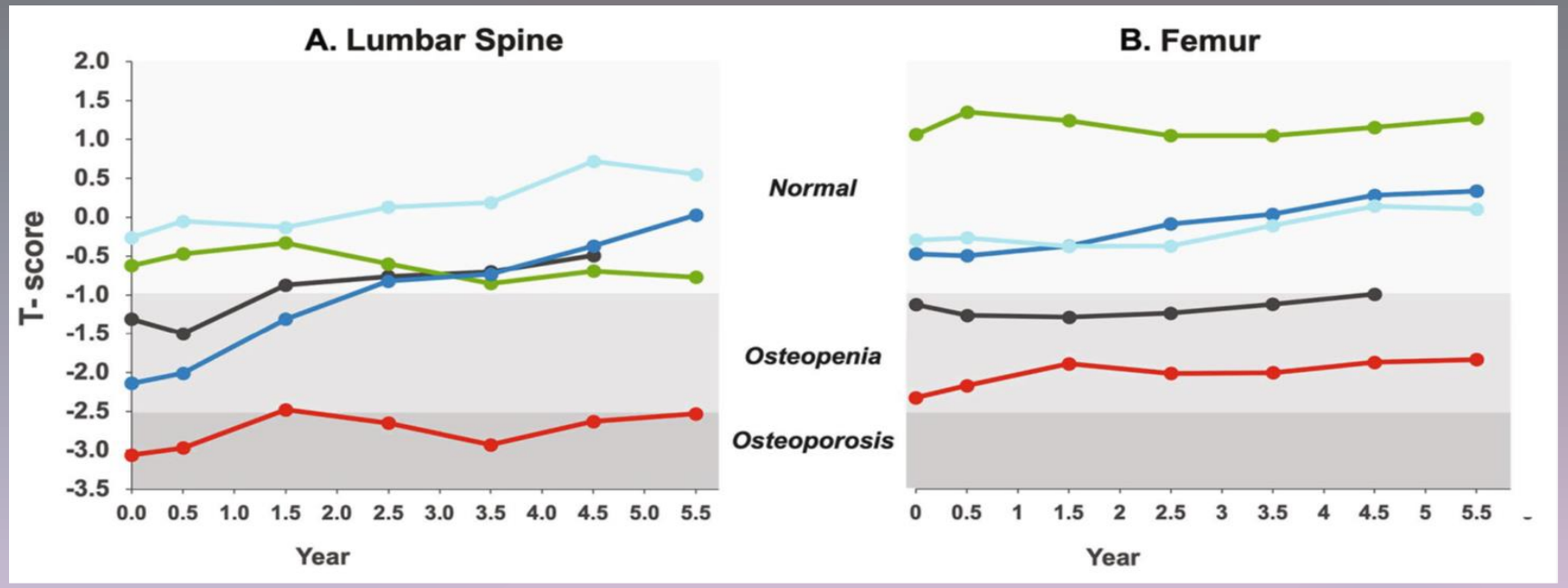
ERT

- Mean height Z-score improved from − 2.14 ± 0.84 at baseline to − 0.99 ± 0.88 at 24 months
- Improvements in Z-scores occurred in all patients, and the percentage of children with short stature decreased from 50% at baseline to 19% at 24 months of treatment
- of sphingomyelin and plasma chitotriosidase activity, were elevated at baseline (mean values > 60 and > 6 times the upper limit of normal.
- Plasma chitotriosidase activity was also close to the ULN at 24 months, reflecting a 76% reduction from baseline
- Plasma levels of the lyso-sphingomyelin levels shown to decrease over the first three months in pediatric patients remained stable at near normal values through 24 months of treatment (up to 87%)
- The biochemical markers lyso-sphingomyelin and chitotriosidase declined in the first 1–3 years of treatment, and remained within, or close to, normal levels through 6.5 years.

Orphanet Journal of Rare Diseases (2022) 17:437

ERT

- Most patients with ASMD have osteopenia or osteoporosis, with the degree of splenomegaly correlating inversely with lumbar spine bone mineral density Z-scores .
- Skeletal fractures are reported for 53% of adults and 25% of children
- T-scores improved modestly over time; however, the small sample size precludes any definitive conclusions on the impact of olipudase alfa on skeletal outcomes



Orphanet Journal of Rare Diseases (2023) 18:94

ERT

- The improvements in multiple clinical endpoints reported after 2.5 years of olipudase alfa treatment remained stable or were further improved after 6.5 years of treatment.
- FDA an EMA Approval was based on the outcomes of a 1-year placebo-controlled trial in 36 adults with ASMD and a 1-year open-label study in 20 children .
- The recommending dosage is :
- **Children:** starting dose of 0.03 mg/kg w/dose escalation over at least 16 weeks to maintenance goal of 3 mg/kg
- **Adults:** starting dose of 0.1 mg/kg w/dose escalation over at least 14 weeks to maintenance goal of 3 mg/kg

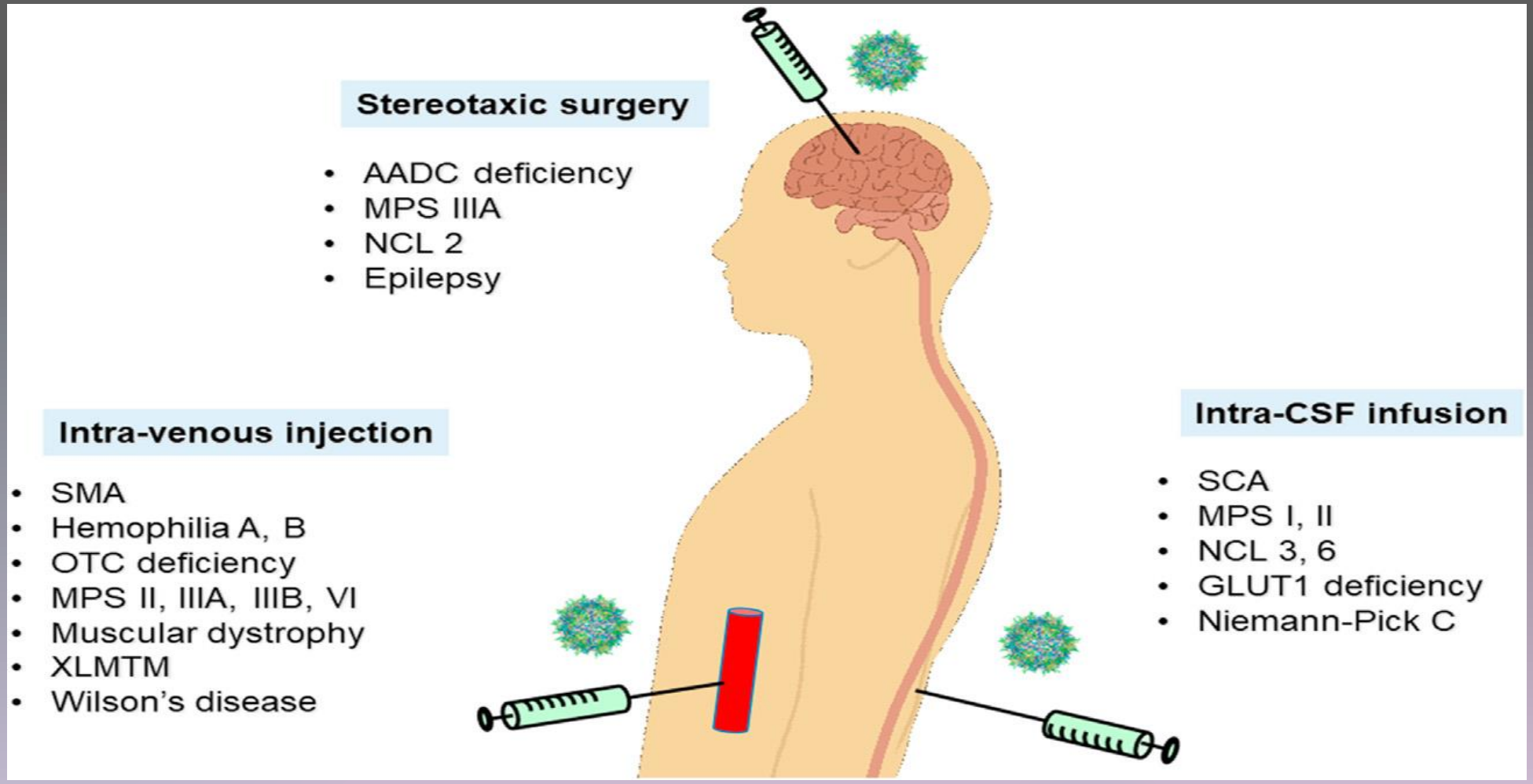
Orphanet Journal of Rare Diseases (2023) 18:94

Gene therapy

- The concept of gene therapy was proposed over 50 years ago.
- Therapeutic gene can be delivered directly to the brain, liver, and muscles (in vivo) or to hematopoietic stem cells (HSCs) cultured outside the body and then returned to the body (ex vivo).
- In in vivo gene therapy, adeno-associated virus (AAV) vectors are used, and lentiviral vectors have been applied in ex vivo gene therapy.
- Developments in ex vivo gene therapies to manage neurological diseases include metachromatic leukodystrophy and adrenoleukodystrophy
- Clinical trials using AAV vectors are underway mainly in the United States for mucopolysaccharidosis types I, II, IIIA, and IIIB, as well as for ceroid lipofuscinosis types 2, 3, and 6.
- Because hematopoietic stem cell transplantation is a primary therapeutic option for MPSs, ex vivo gene therapy is also under development

Gene therapy

Various routes of administration in AAV vector-based gene therapy



Pediatrics and Neonatology 64 (2023) S3eS9

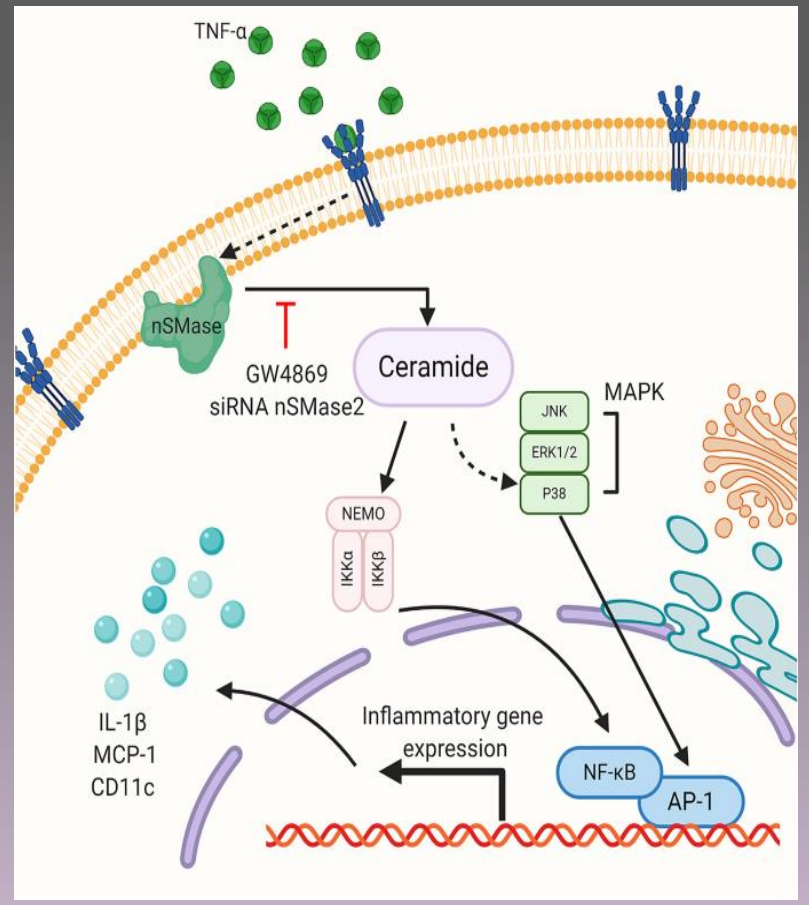
Gene therapy

- Several characteristics make NPD-A especially suitable for gene therapy.
- A low residual activity of the ASM enzyme in patients (~5 to 10% of normal activity) seems to be enough to prevent the neurological symptoms of NPD
- This suggests that modest restoration of the missing ASM activity in the brain might have therapeutic effects in patients with NPA
- Direct brain injection of adeno-associated viral vector (AAV) carrying a competent copy of the human ASM gene .
- Infusion of rhASM into the lateral ventricle resulted in reduced cortical distribution and no subcortical transduction due to a limited parenchymal permeation
- Diagnosis is generally made on the basis of symptoms in children 3 to 6 months of age when disease has already progressed

Sci Transl Med. 2019 August 21; 11(506)

Gene therapy

- The liver and spleen are severely affected by NPD-A and, may be far from a fully corrective effect, thereby necessitating ERT in addition to gene therapy
- Metabolites of SM, like ceramide and its downstream products, sphingosine and sphingosine-1-P, can trigger calcium imbalance, aberrant intracellular signaling, inflammation, and cell death
- However, these adverse effects were likely due to reaching the maximum-tolerated dose and may be eliminated by dose de-escalation.
- The serotype of the AAV vector and the route of delivery are key determinants in meeting these goals



Sci Transl Med. 2019 August 21; 11(506)


Thank you