Metabolic disorders involving the CNS: A case-based discussion

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Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

1. Describe how inborn errors of metabolism present clinically and are diagnosed
2. Identify specific histologic patterns observed in lysosomal storage disorders, organic acidemias, and mitochondrial disorders
3. Outline the appropriate steps for tissue handing in the setting of a suspected metabolic disorder

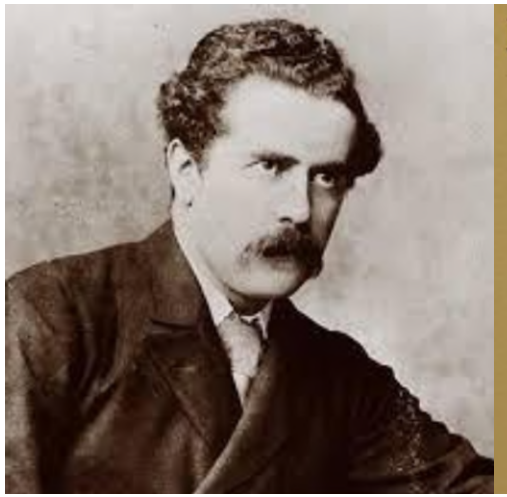
Outline

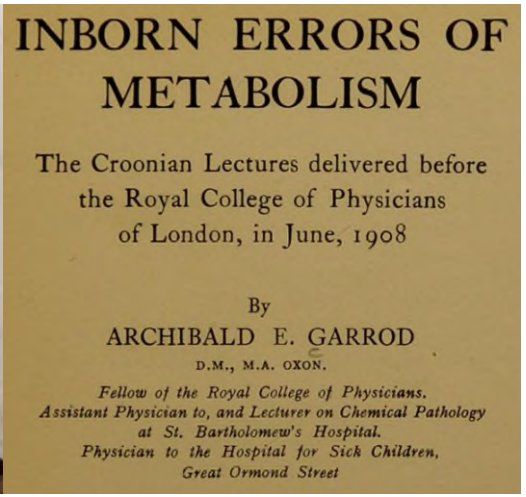
- Background
- Amino acid and organic acid disorders
- Storage disorders
- Mitochondrial disorders
- Glycogen metabolism disorders
- Practical considerations

Background: breadth of the topic

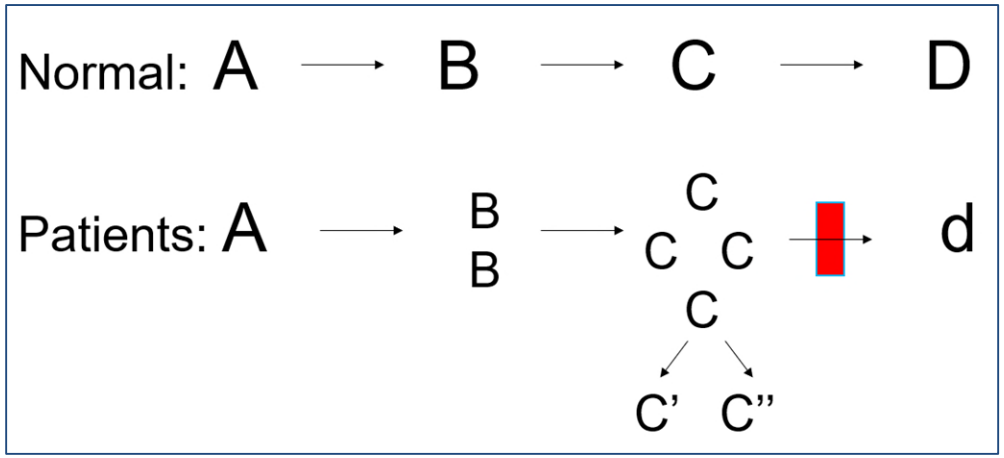
- *Metabolic disorder* can encompass anything not considered structural/anatomic and occurs at the intracellular level
- Definition is arbitrary
  - Mitochondrial enzyme vs. respiratory chain deficiency?
  - Disorders of trace metal metabolism? Wilson's, Menkes'
  - Disease secondary to maternal metabolic changes? hypothyroidism
  - Acquired or nutritional disorders?
  - Ion channel disorders? cystic fibrosis, Dravet
- Today will focus on inborn errors of metabolism (IEM), with a focus on cases encountered in real neuropathology practice

Inborn errors of metabolism (IEM)





- Term first used by Archibald Garrod in 1908
  - Blocks in metabolic pathways
- At least 7,000 hereditary metabolic disorders are known
  - Important to recognize early to treat early
  - Genetic implications for family
- Rare diseases (1:4,000 to 1:250,000)
- Increased awareness and carrier/prenatal screening has lowered incidence of many IEM
  - e.g., Tay Sachs
- Total modern birth prevalence for all IEM is **~50:100,000** live births *(Waters et al., J Glob Health 2018)*



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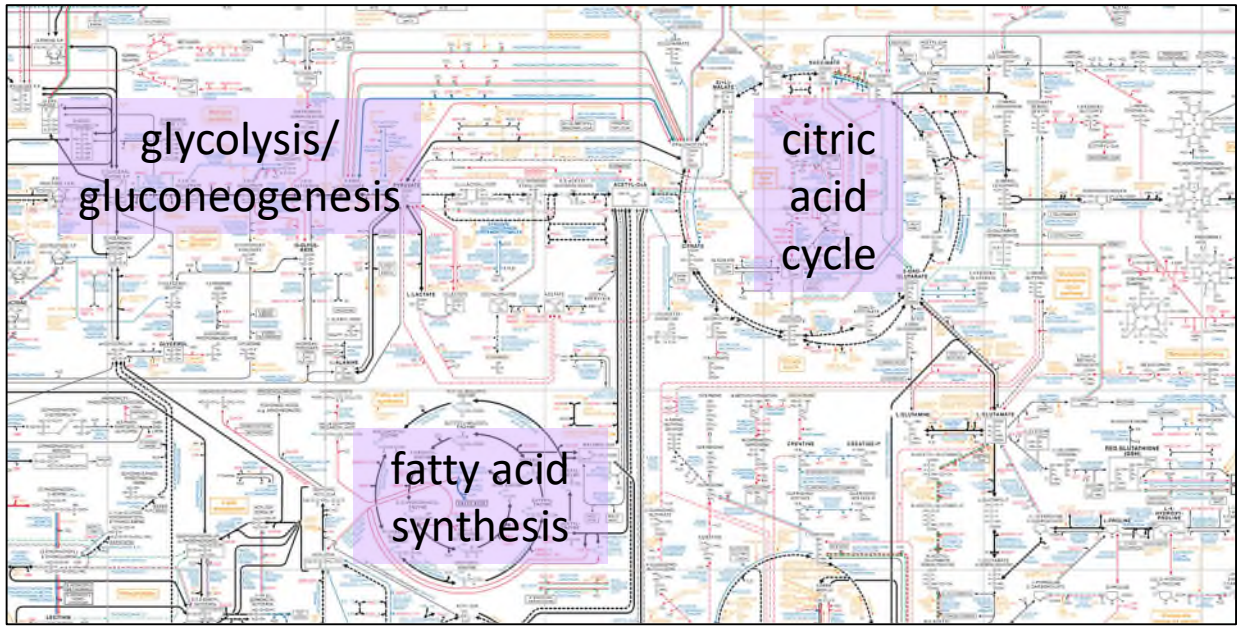
Mapping out metabolic disorders



- Nearly every author uses a different system to “organize” IEM
- Intoxication
  - Amino acid, organic acidurias
  - Urea cycle disorders
  - Sugar intolerance
- Energy deficiencies
  - Congenital lactic acidemia, fatty acid oxidation disorders, mitochondrial respiratory chain disorders
- Disorders of complex molecules
  - Lysosomal storage, peroxisomal, glycosylation

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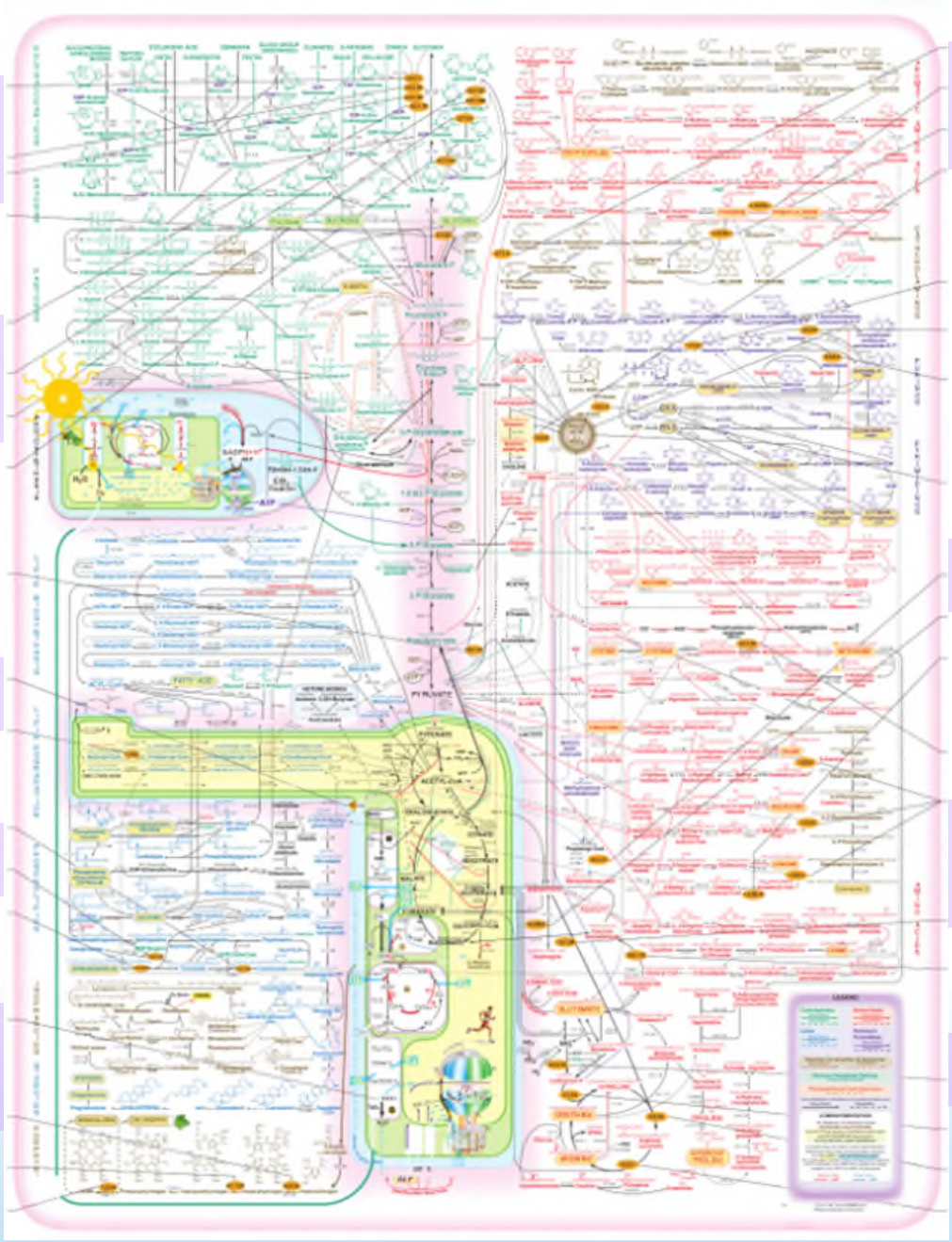
Glycogen storage diseases

Mono- and disaccharides

Lipid metabolism

Sphingolipidoses

Respiratory chain defects



Amino acid metabolism

Organic acidurias

Amino acid metabolism

Urea cycle defects

Inborn errors of metabolism

- Inherited biochemical defects
  - Carbohydrates
  - Amino acids
  - Purines/pyrimidines
  - Metals
  - Lipids
  - Mucopolysaccharides
- Each disorder has a very low incidence but cumulatively contribute to morbidity and mortality in pediatrics
- Usually manifest during childhood and often immediately after birth

Newborn Screening (NBS)

- Initiated in 1960s with screening for phenylketonuria (PKU)
  - "Guthrie card"
- Now includes 80 disorders (as of 2022)
- Heel stick blood spots screened by electrospray tandem mass spectrometry
  - More recent use of extracted DNA (e.g., for *SMN1*)
- High throughput, fast turnaround time
- Expedited diagnosis and initiation of therapy

Recommended Uniform Screening Panel[1] (RUSP)
Core Conditions[2]
(As of October 2020)

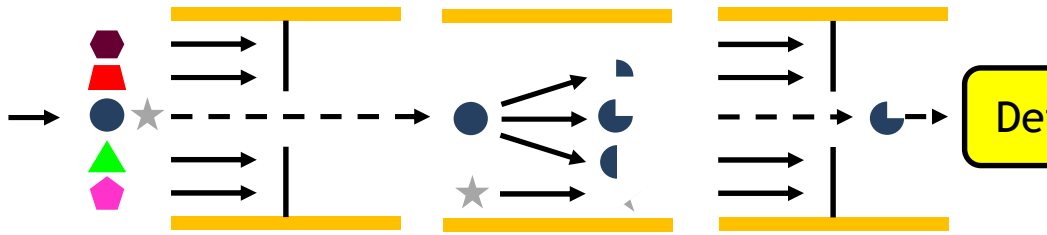
Category	Condition	Included in California Newborn Screening
Organic Acid Disorders	Propionic Acidemia	✓
	Methylmalonic Acidemia (Methylmalonyl-CoA Mutase)	✓
	Methylmalonic Acidemia (Cobalamin Disorders)	✓
	Isovaleric Acidemia	✓
	3-Methylcrotonyl-CoA Carboxylase Deficiency	✓
	3-Hydroxy-3-Methylglutaric Aciduria	✓
	Holocarboxylase Synthase Deficiency	✓
	β-Ketothiolase Deficiency	✓
	Glutaric Acidemia Type I	✓
Fatty Acid Oxidation Disorders	Carnitine Uptake Defect	✓
	Medium-chain Acyl-CoA Dehydrogenase Deficiency	✓
	Very Long-chain Acyl-CoA Dehydrogenase Deficiency	✓
	Long-chain L-3-Hydroxyacyl-CoA Dehydrogenase Deficiency	✓
	Trifunctional Protein Deficiency	✓
Amino Acid Disorders	Argininosuccinic Aciduria	✓
	Citrullinemia Type I	✓
	Maple Syrup Urine Disease	✓
	Homocystinuria	✓
	Classic Phenylketonuria	✓
	Tyrosinemia Type I	✓
Endocrine Disorders	Primary Congenital Hypothyroidism	✓
	Congenital Adrenal Hyperplasia	✓
Hemoglobin Disorders	S,S Disease (Sickle Cell Anemia)	✓
	S, β-Thalassemia	✓
	S,C Disease	✓
Other Disorders	Biotinidase Deficiency	✓
	Cystic Fibrosis[3]	✓
	Classic Galactosemia	✓
	Glycogen Storage Disease Type II (Pompe)	✓
	Mucopolysaccharidosis Type I	✓
	Severe Combined Immunodeficiencies	✓
	X-linked Adrenoleukodystrophy	✓
	Critical Congenital Heart Disease[4]	
	Hearing Loss[4]	
	Spinal Muscular Atrophy	✓

Tandem Mass Spectrometry (MS/MS)

Separation by liquid chromatography or gas chromatography

Molecule

Ionizer: convert to gas phase ion

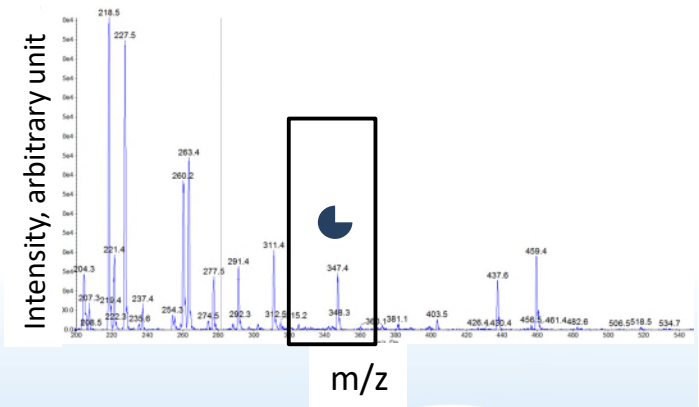


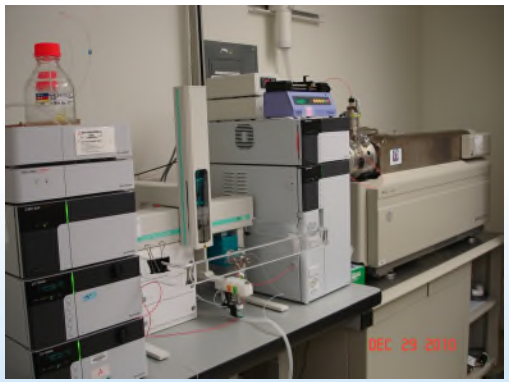
select precursor ion based on mass-to-charge ratio (*m*/*z*)

collision cell break ions apart

select product ion based on mass-to-charge ratio (*m*/*z*)

Detector





LC-MS/MS at CHLA

Challenges of defining the neuropathologic features of a given metabolic disorder

- Rarity of diseases
- Complexity of illness resulting from IEM
- Difficulty distinguishing early from late changes in patients who survive to older ages

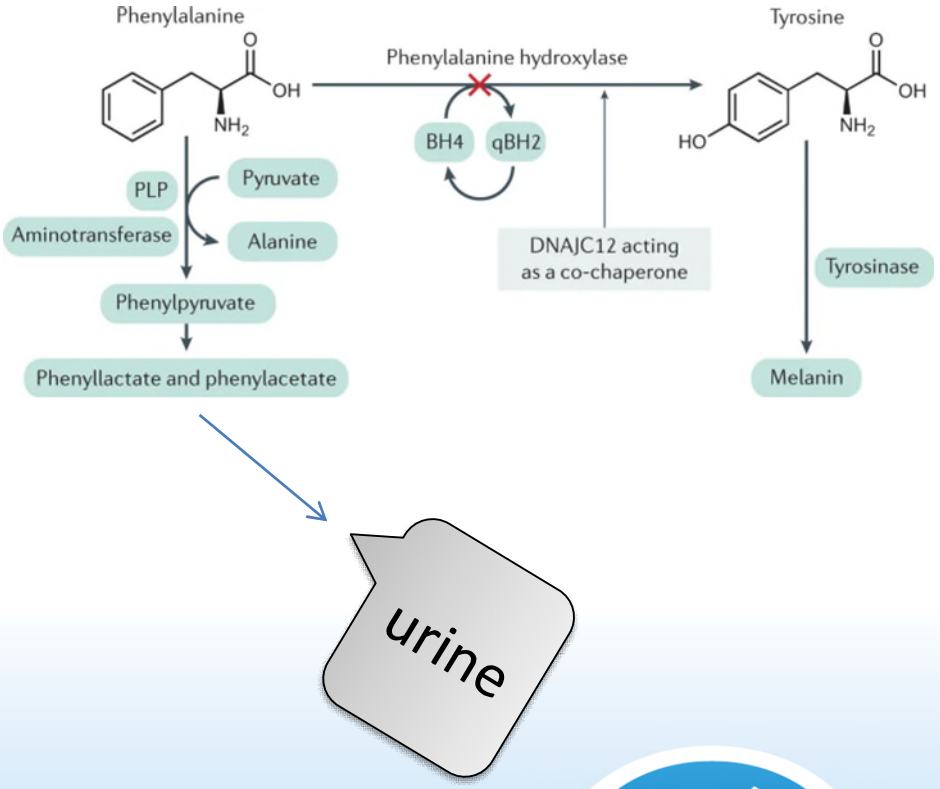
Common (but not universal) features in IEM

- AR inheritance
  - can appear sporadic due to small family size
- “Spongy myelinopathy” – common to AA disorders
  - Vacuoles between myelin lamellae
  - Except urea cycle disorders and homocystinuria
- “catastrophic severe neonatal illness”
- Dysmorphic features
- Manifestations in liver
  - LM and EM usually performed

Phenylketonuria (PKU)

a.k.a. phenylalanine hydroxylase (PAH) deficiency

- AR disorder of phenylalanine (Phe) metabolism
  - Pathogenic variants in *PAH* cause lack of enzymatic function
  - “hyperphenylalaninemia” (HPA)
  - Deamination of Phe forms phenylketone bodies readily excreted in the urine
- Profound intellectual disability/brain dysfunction
- One of the earliest identified IEM, strong intervention effect
  - Dietary restriction of phenylalanine (1953) – low protein diet
  - Untreated/late-treated children often required permanent institutional care (Weller et al. 1983)
  - Treated kids were as healthy at age 7 as their unaffected siblings
- In 1960s transition to blood screening was recommended
  - First disease taken to population-based neonatal screening



van Spronsen FJ et al. *Nature rev dis prim*. 2021 PMID 34017006

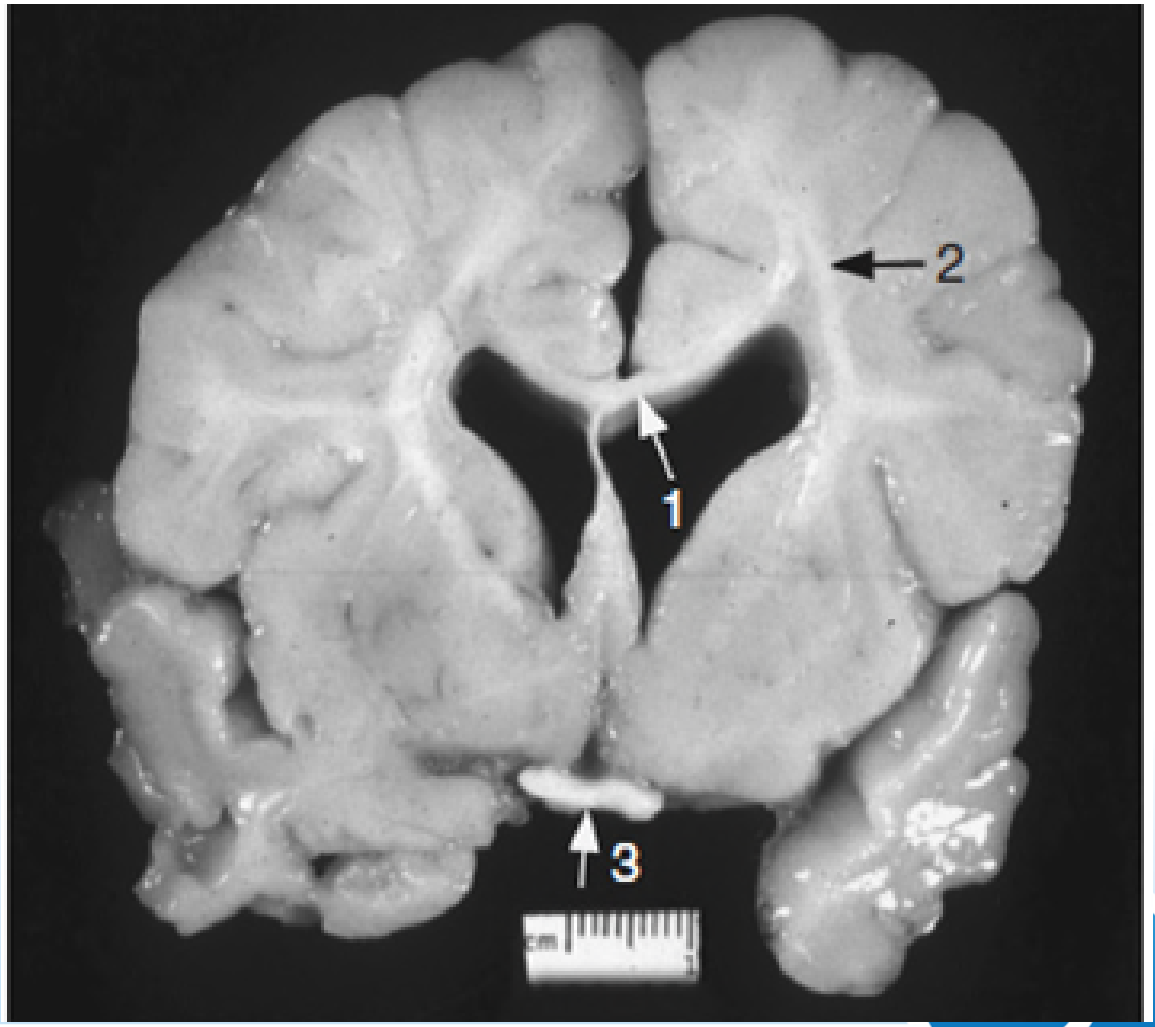
Presentation of PKU

- Incidence in US 1:8,000-15,000
- Normal appearance at birth, first signs @ months
  - Musty/mousy odor from skin and urine
  - Fair skin/hair (lack of Tyr => lack of melanin)
  - Eczema, seizures, tremors
- Lab: Elevated blood Phe, decreased Tyr
- Genetics: >1000 mutations can result in PKU, cause protein misfolding/instability
  - Spectrum of severity
  - Most patients are compound heterozygotes
- Treatment: lifelong restrictive diet with target blood Phe range

https://www.sciencehistory.org/distillations/on-the-scent-the-discovery-of-pku

Neuropathology of PKU

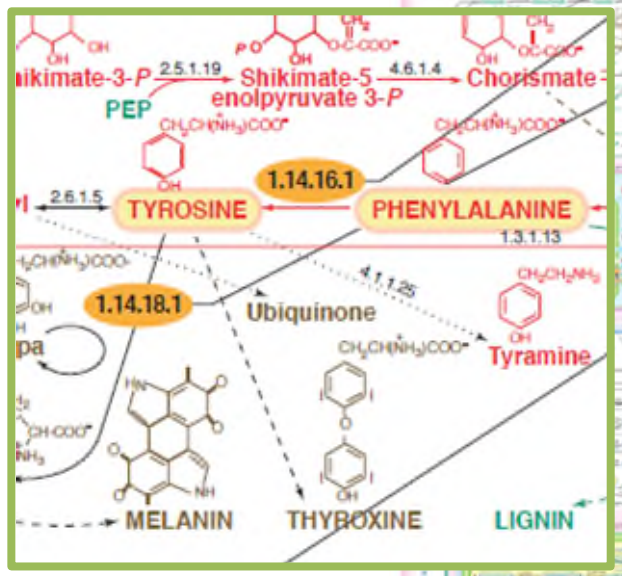
- Hypothesized to be due to toxic effects of Phe
- Limited human neuropathology studies
  - Small brain (80%)
  - Abnormal myelination of late-myelinating structures
    - "spongy change", pallor
  - ?Cortical developmental delay



Koch R et al. *Dev Med and Child Neurol.* 2008.

Where PKU fits on the map

- Amino acid disorder
- PAH fails to convert Phe to Tyr
  - One gene, one protein



Class of error	Examples
Amino acid disorders	PKU, homocystinuria
Organic acid disorders	Propionic aciduria, methylmalonic aciduria
Fatty acid disorders	Short/Medium chain acyl coenzyme A dehydrogenase deficiency, carnitine deficiency
Lysosomal disorders	Fabry, Farber, Gaucher, Niemann-Pick
Carbohydrate metabolism disorders	Galactosemia, Pompe, Lafora
Urea cycle disorders	Citrullinemia, argininemia
Mitochondrial disorders	Leigh
Peroxisomal disorders	Zellweger, Refsum

Adapted from Waters D et al. *J Glob Health* 2018 PMID 30479748

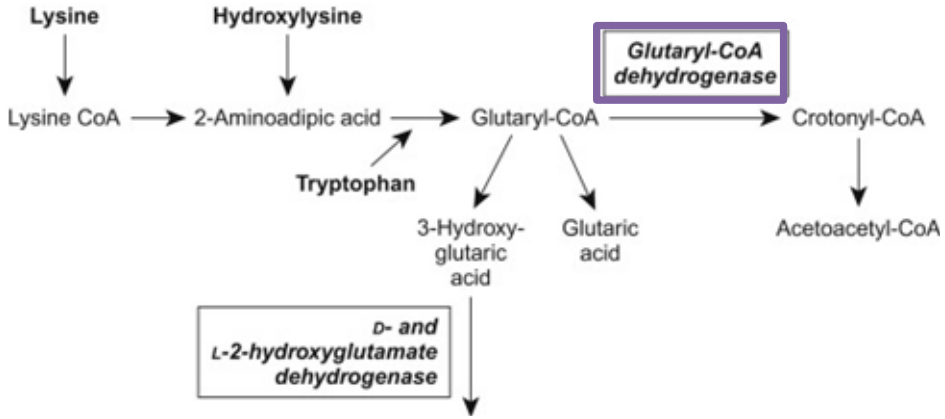
Amino acidemias/urias and white matter impact

"During the past decade or two, a new group of hereditary diseases with amino-acidemia or amino-aciduria of various types has become recognized… Relatively few have been subjected to neuropathological examination… but one observation is relevant to the purposes of this chapter – that **the white matter appears to bear the brunt of the pathological process during the period of active myelination**, and further, that the changes in the white matter are nonspecific."

– Roizin, Haymaker, and D'Amelio, Disease states involving the white matter of the CNS, in Histology and Histopathology of the Nervous System (Haymaker and Adams), vol. 1 1982.

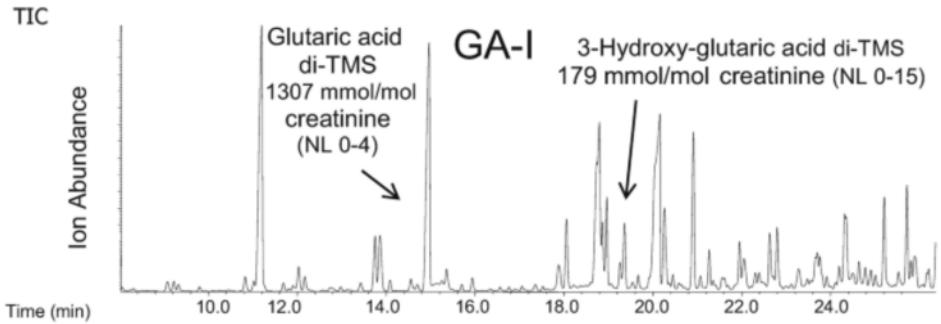
Case 1

- 18 month old F presents with progressive dystonia and seizures
- Found to have macrocephaly and metabolic acidosis
- Diagnosed with glutaric acidemia type 1
- Sibling with same disease
- *GCDH* gene mutation
  - Loss of glutaryl-coA dehydrogenase function
  - Inability to metabolize lysine, hydroxylysine, and tryptophan
  - Accumulation of glutaric acid, 3-OH-glutaric acid, and glutaconic acid



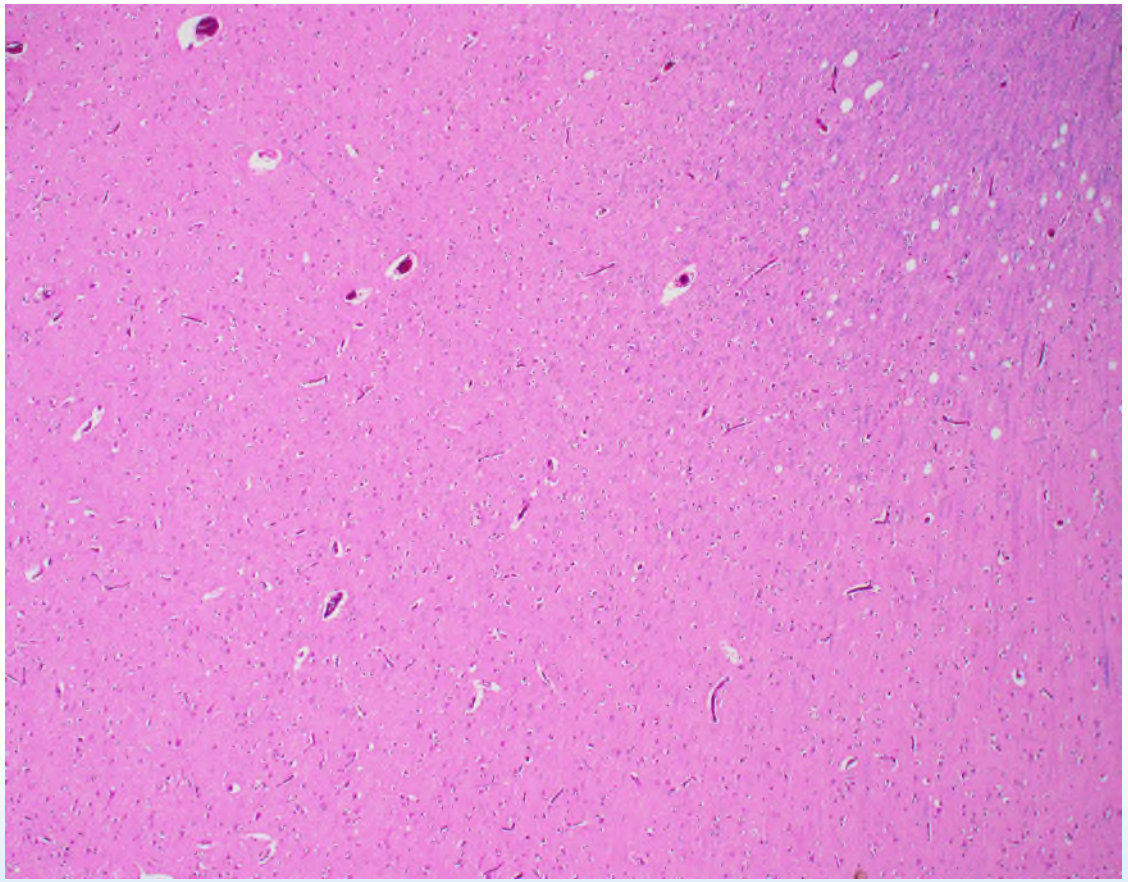
Case example, glutaric acidemia type 1, continued

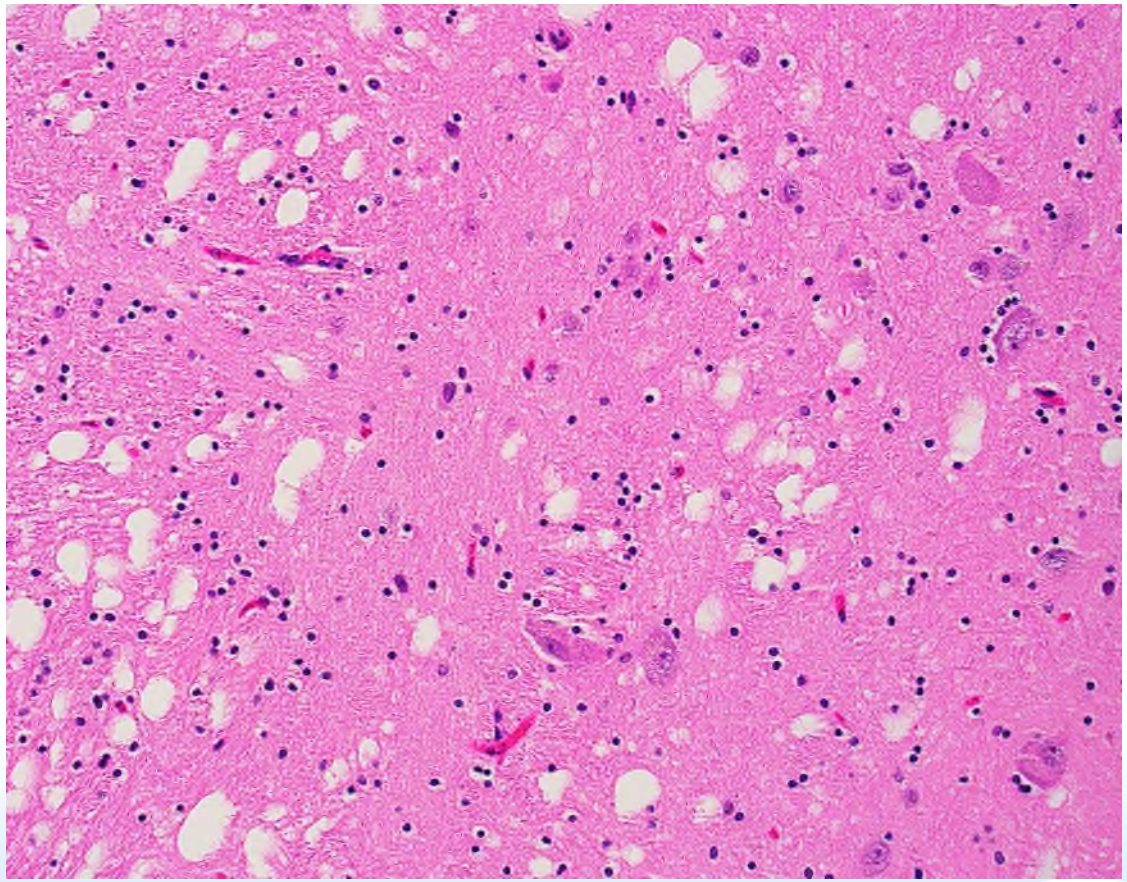
- Treated with dietary restriction of lysine and tryptophan
- Supplementation of carnitine and riboflavin
- Experienced urinary tract infection and consequent metabolic decompensation
- Progressive neurologic deficits and death at age 14



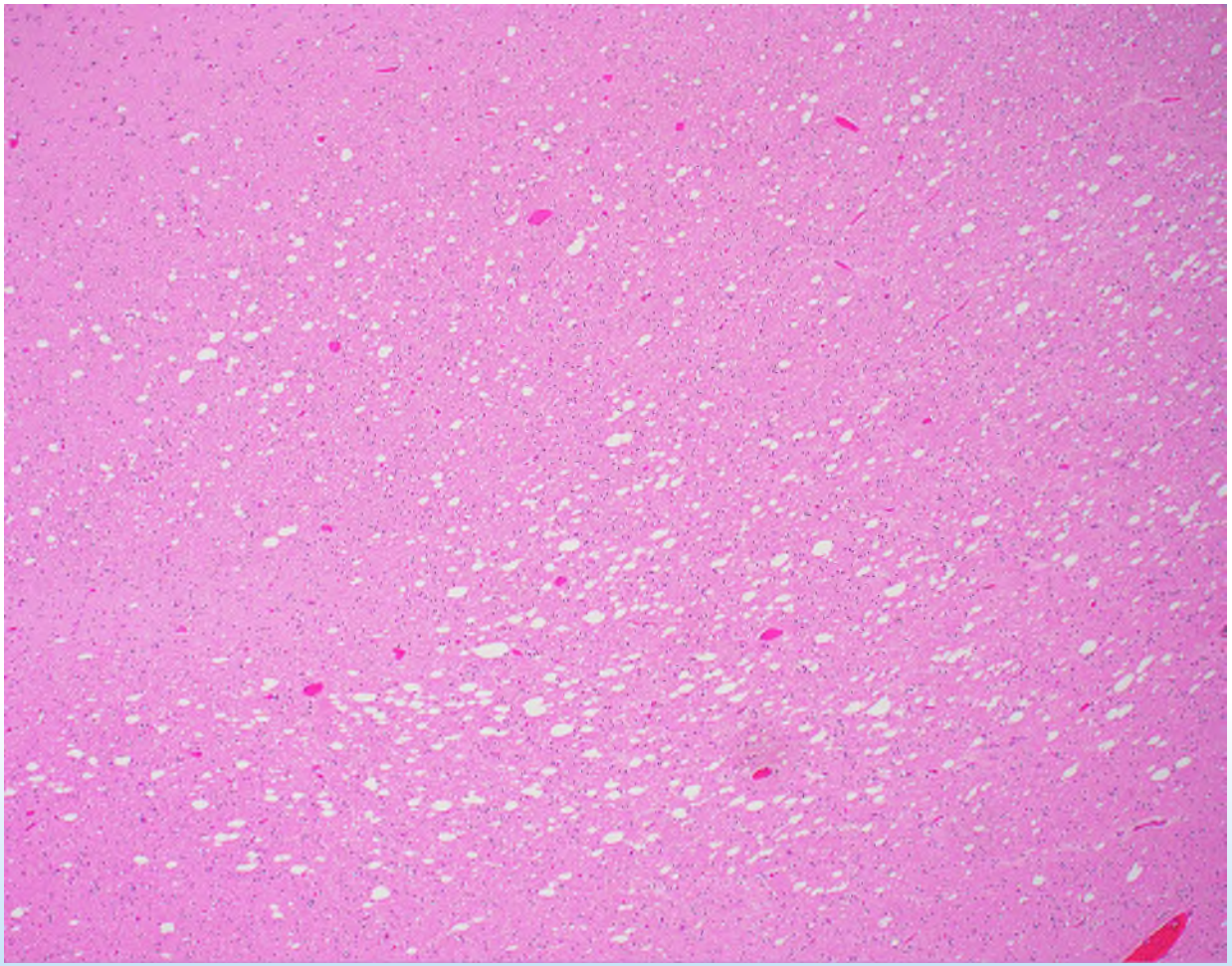
Urine organic acid by GC-MS. From Stanley Lo et al., Clin Appl of Mass Spectrometry in Biomolecular Analysis, 2022

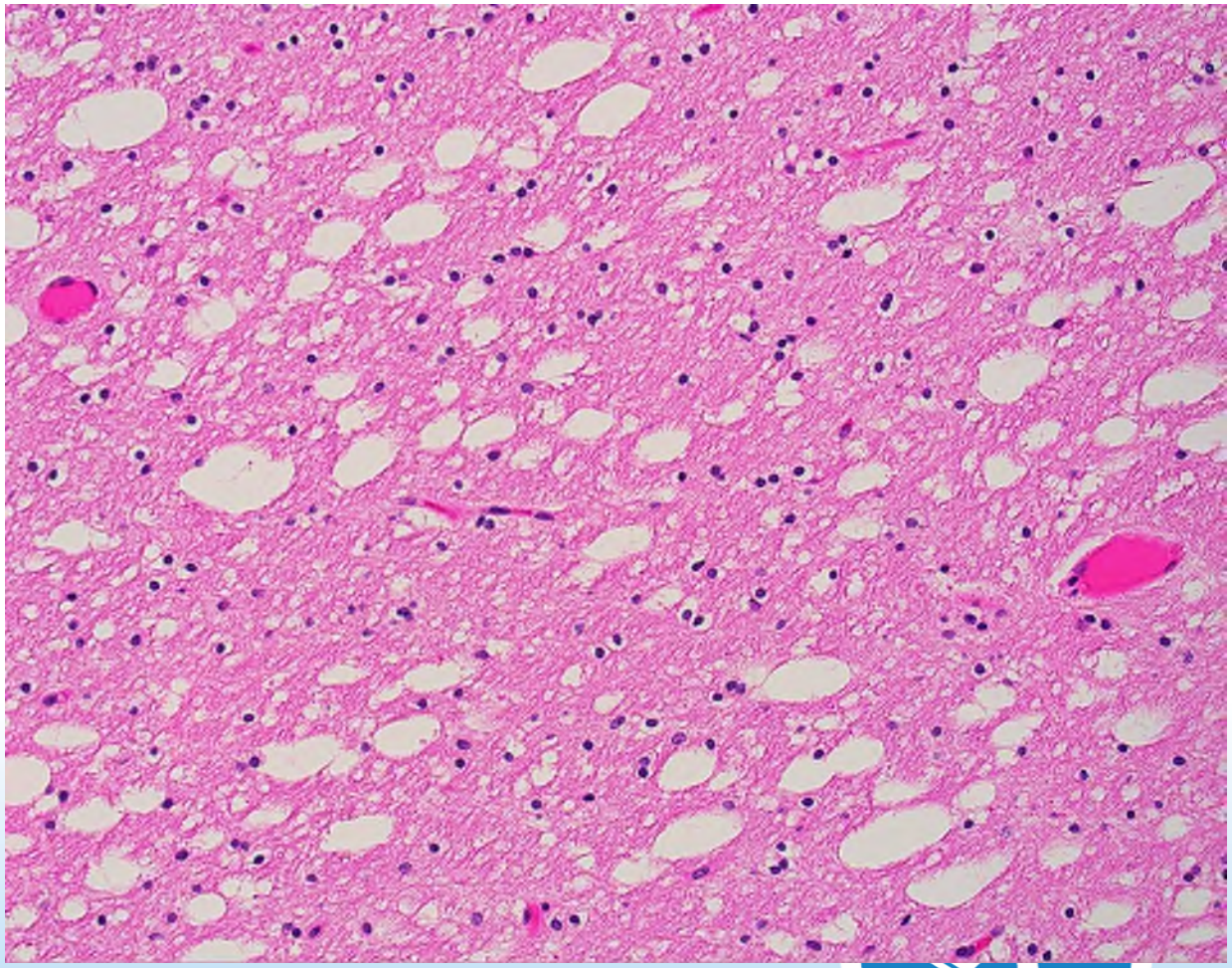
Glutaric acidemia, type 1 – gray/white junction, temporal lobe





Glutaric acidemia, type 1 – white matter, temporal lobe





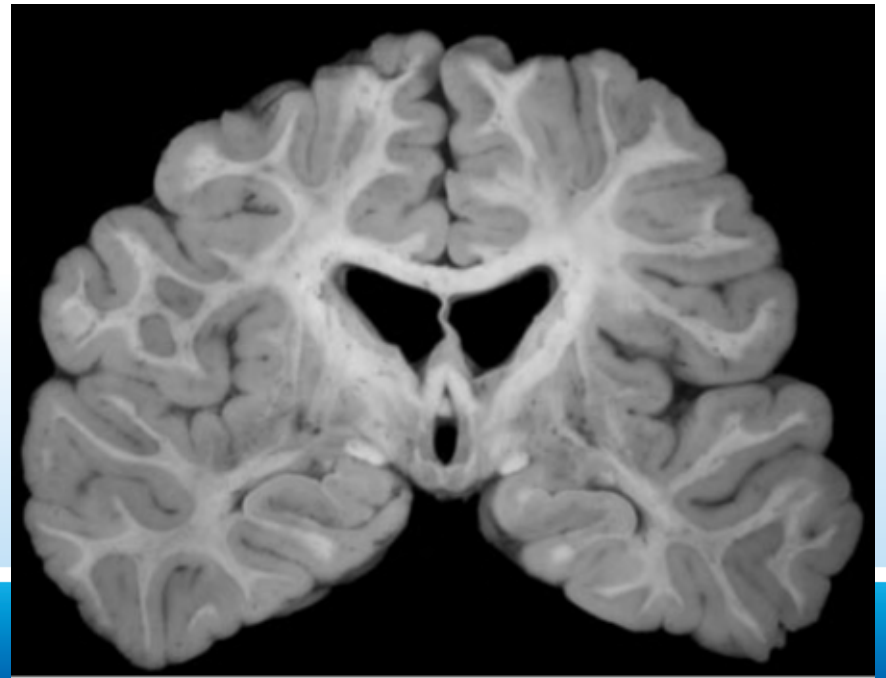
Brain findings – glutaric acidemia type 1

- Simplified gyral pattern/broad gyri
- Macrocephaly
- Spongy myelin particularly in temporal stem and striatum
- Small basal ganglia (may be a common feature of this dx*)
- Neuronal loss and gliosis

doi:10.1093/brain/awh401 *Brain* (2005), **128**, 711–722

Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort

Christopher B. R. Funk,[1,5] Asuri N. Prasad,[6] Patrick Frosk,[3] Sven Sauer,[7] Stefan Kölker,[7] Cheryl R. Greenberg[3,4] and Marc R. Del Bigio[1,2,5]

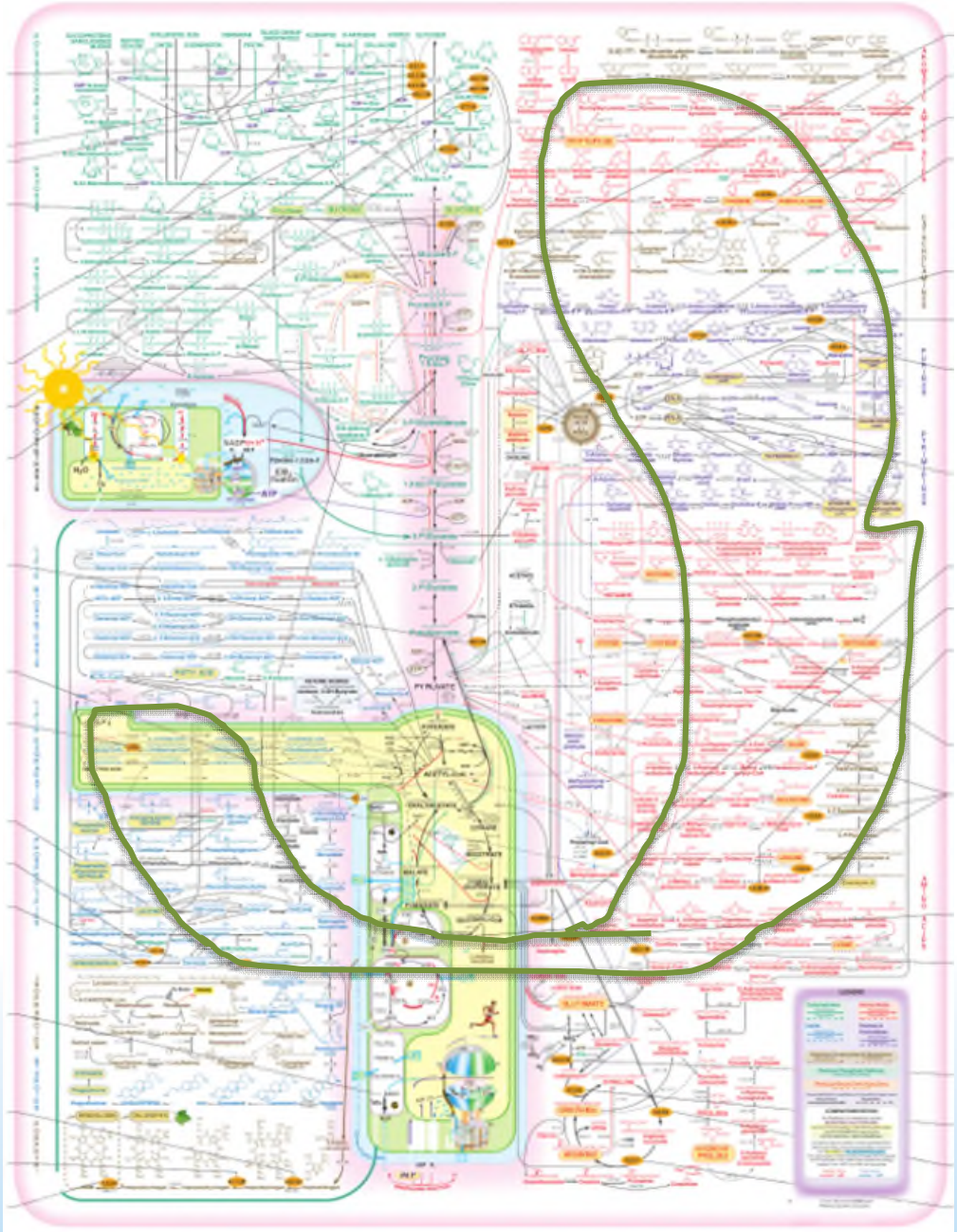


Glutaric acidemias

- Type I (case shown), can present with encephalopathy
  - deficient metabolism of L-lysine, L-OH-lysine and L-tryptophan
  - 1:110,000
- Type II, “multiple acyl coA dehydrogenase deficiency” (MADD)
  - Enzyme primarily active in mitochondria
  - Deficient metabolism of fatty acids, amino acids, and choline

Putting glutaric acidemias on the map

- Loss of function of glutaryl-coA dehydrogenase
  - Key step in lysine and tryptophan metabolism
  - Glutaryl CoA dehydrogenase operates within the mitochondria
  - Feeds forward to Krebs Cycle
- Shows the close relationship between
  - amino acid disorders
  - organic acid disorders
  - mitochondrial disorders



Canavan disease (aspartoacyclase/ASPA deficiency)

- 1:6,000-14,000 among Ashkenazi Jewish community
- 1:100,000 in general population
- progressive psychomotor delay
- progressive epileptic encephalopathy
- macrocephaly
- leukodystrophy with spongiform appearance, predilection for subcortical U-fibers
  - *"mass of lacy oedema with glia cells fairly well preserved, but not in excess"*

    -Dr. Myrtelle M. Canavan, *Arch NeurPsych* 1931

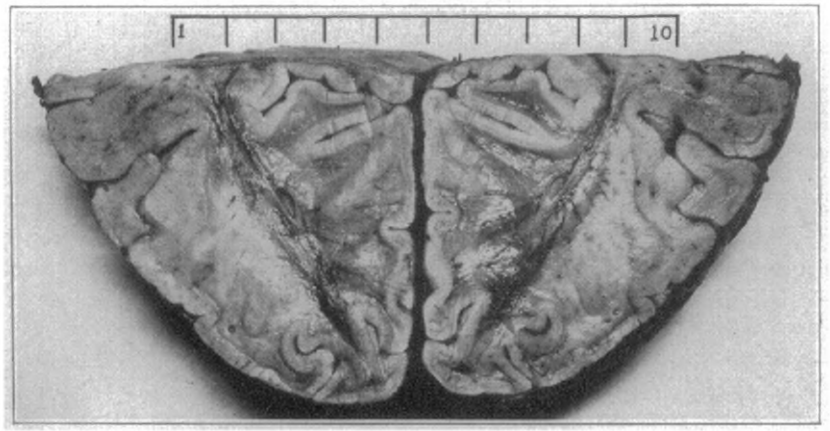


Fig. 4.—Horizontal sections of the occipital lobes. Note the complete softening of the white matter as evidenced by its retraction from the cortex.

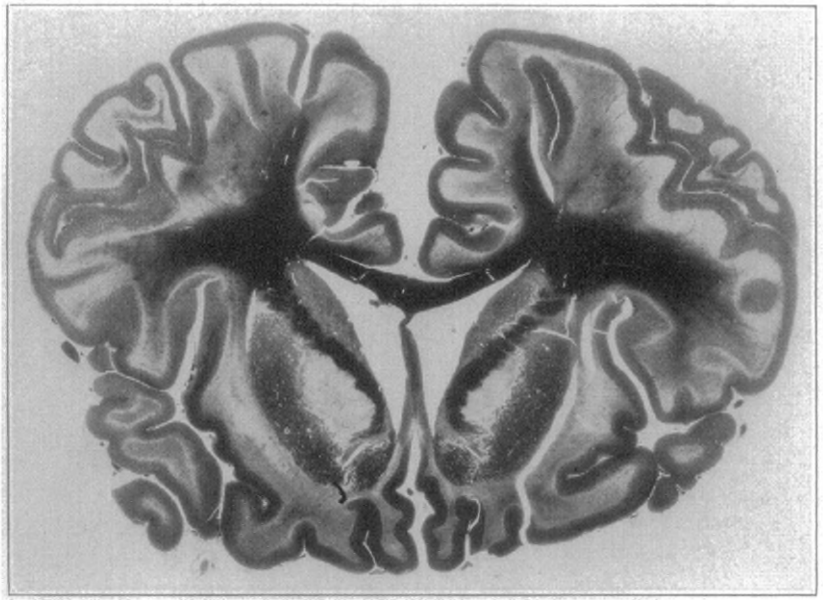
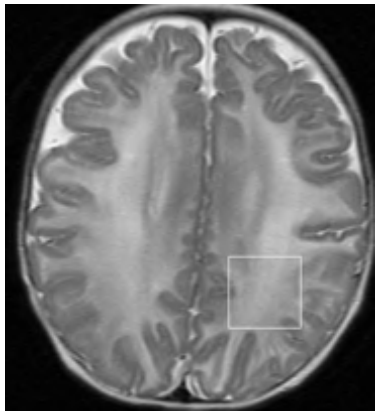
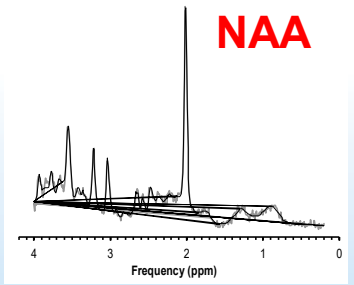


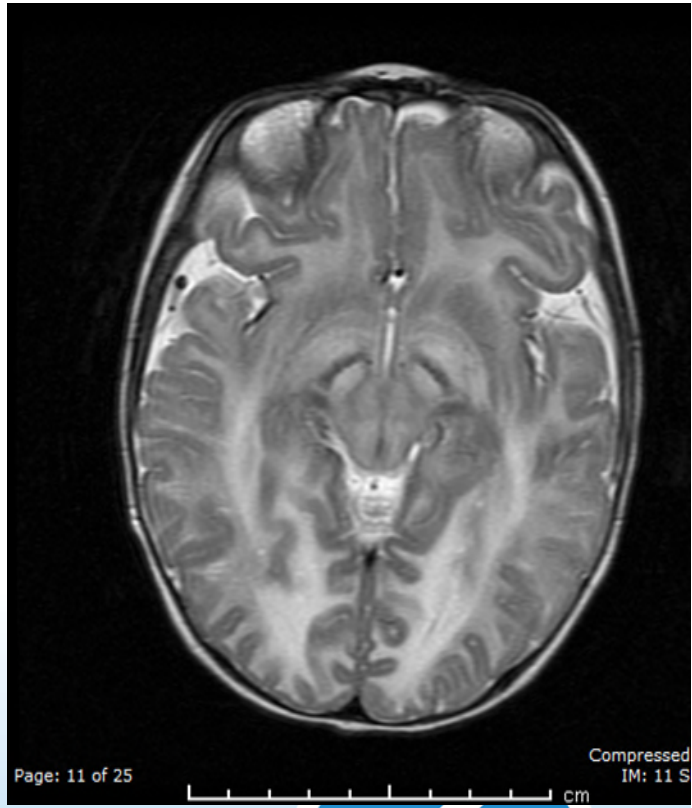
Fig. 8.—Weigert section showing loss of myelin sheaths at the periphery of the white matter and preservation within.

MRS in diagnosis of Canavan disease

- N-acetylaspartate (NAA) accumulates due to the absence of aspartoacylase (ASPA), the enzyme that breaks down NAA.
  - MRS: prominent NAA in both GM and WM

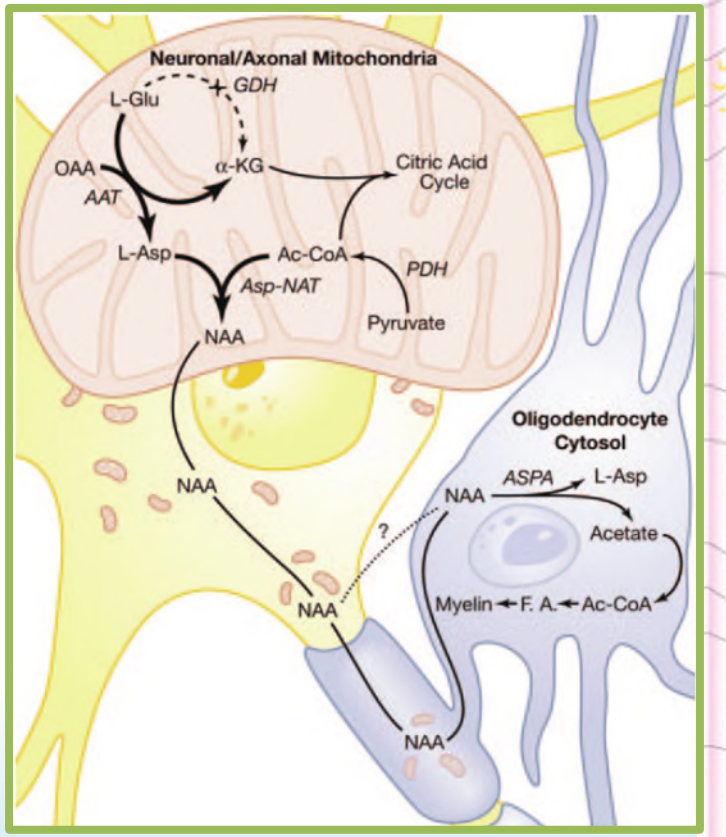




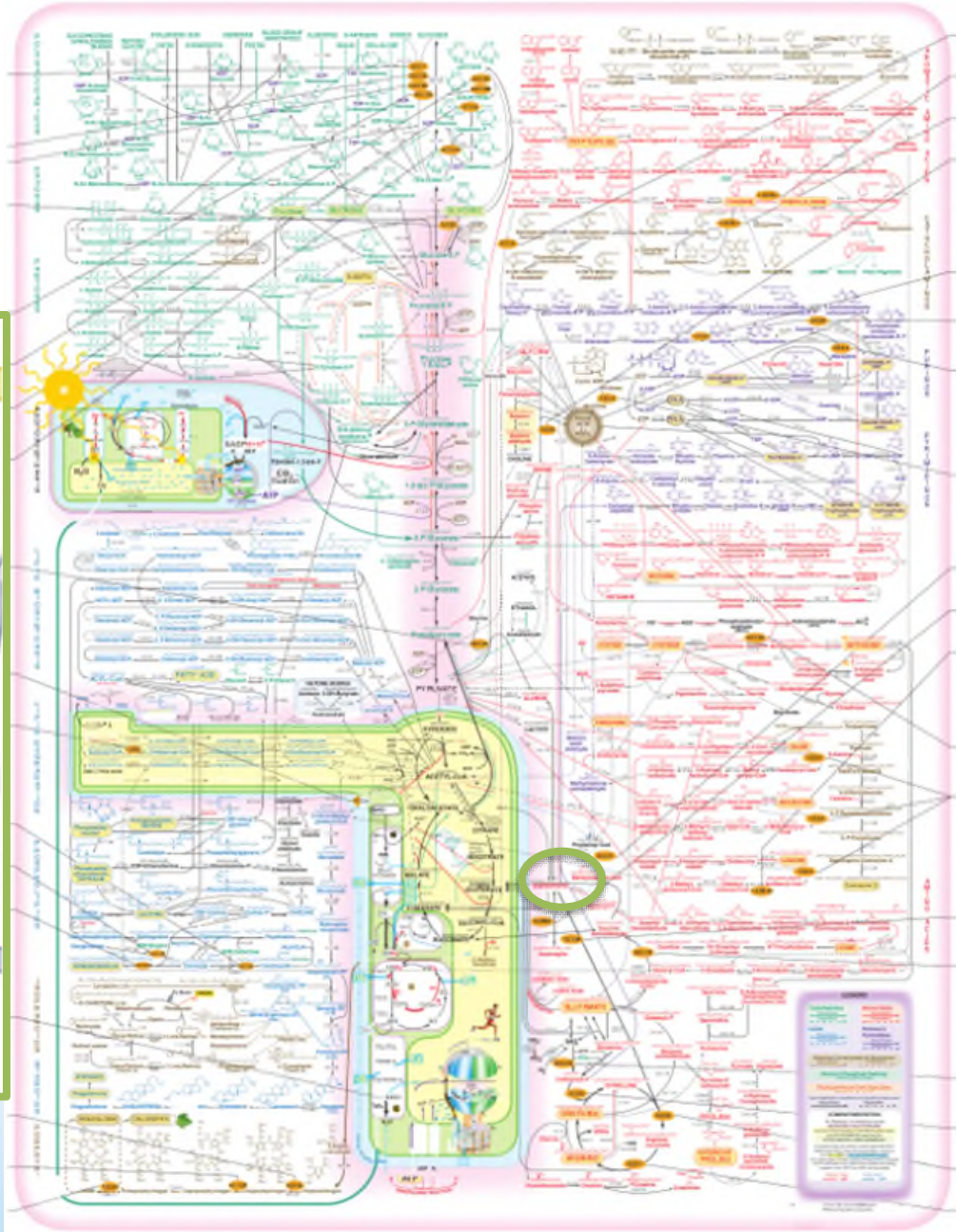


Putting Canavan on the map (aspartate is circled)

- NAA is particularly important in CNS and is transferred from neurons to glial cells
- Key enzyme in myelin formation by oligodendrocytes

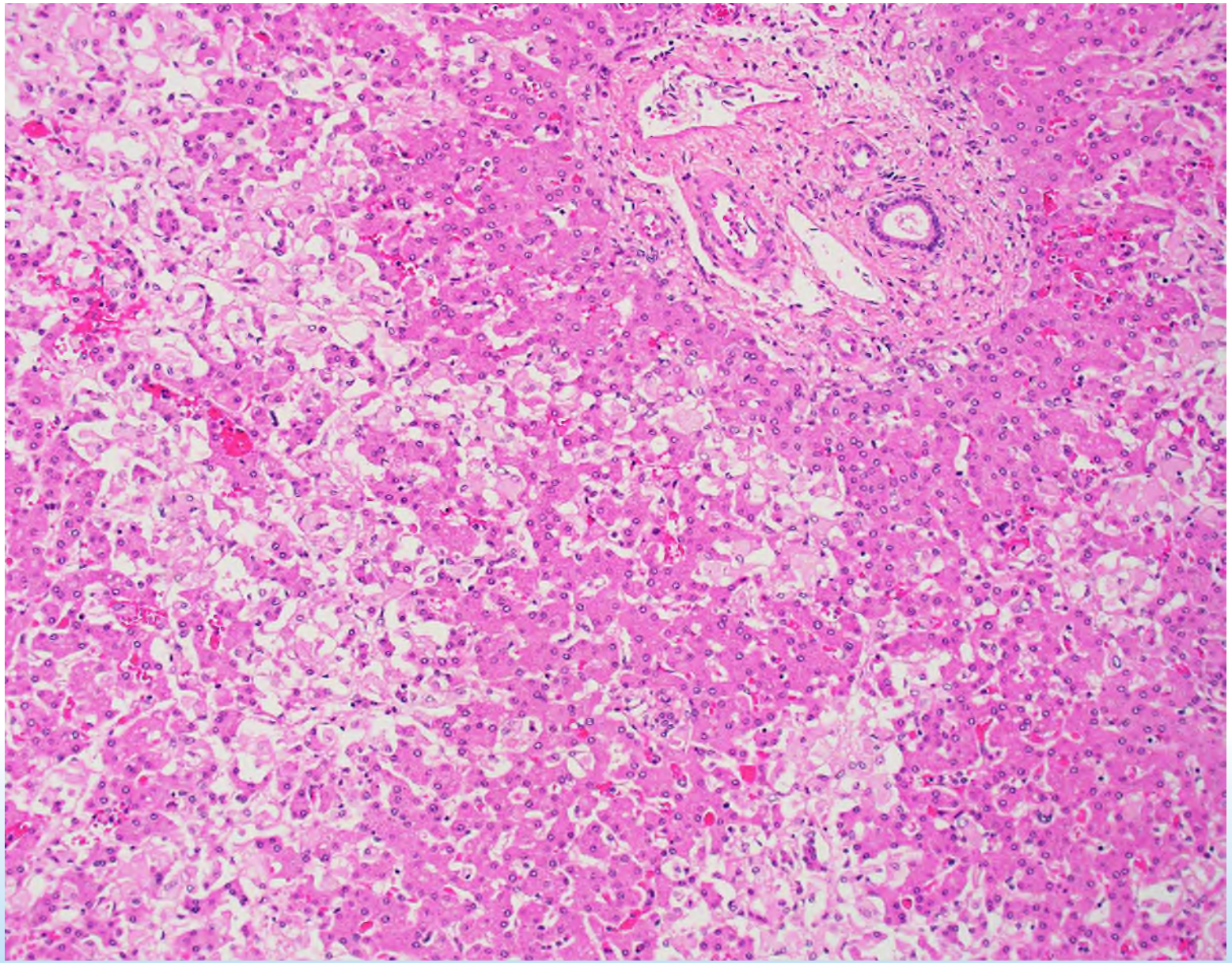


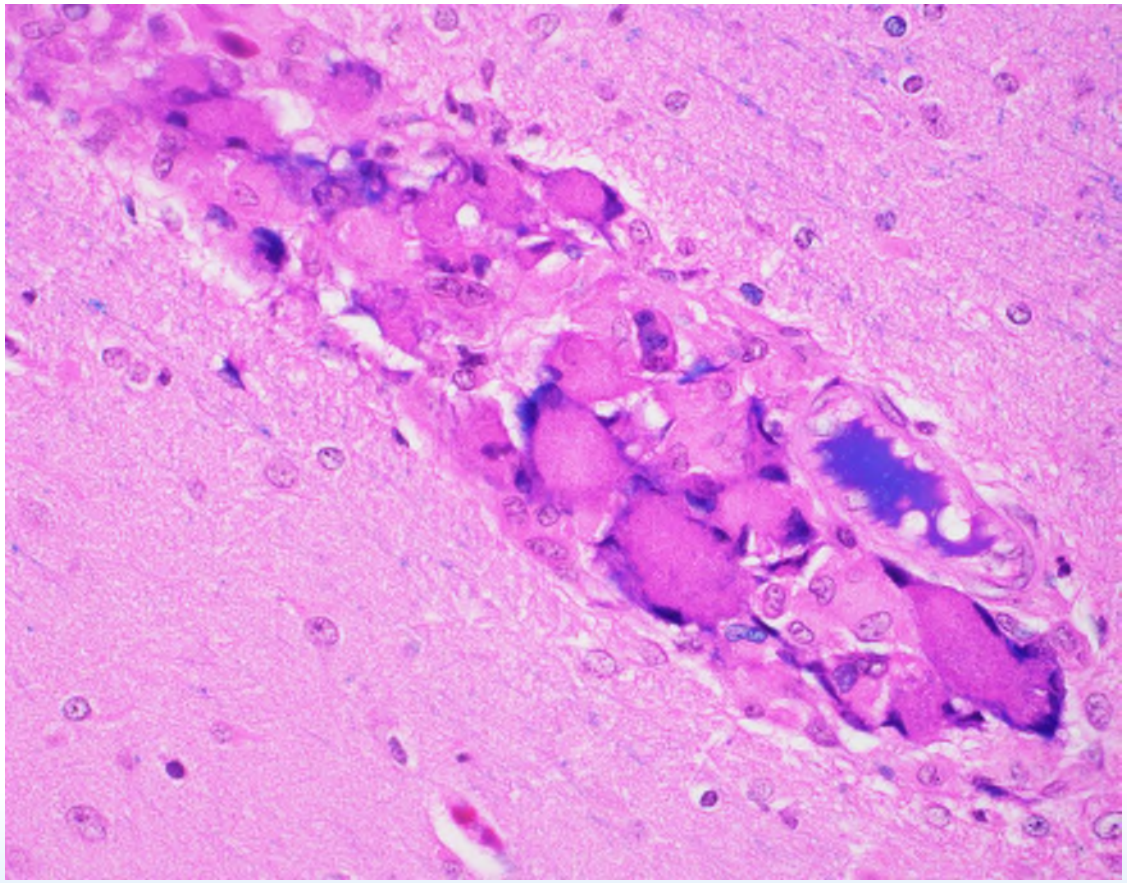
Proposed model for NAA synthesis and degradation (Madhavarao et al., 2005)

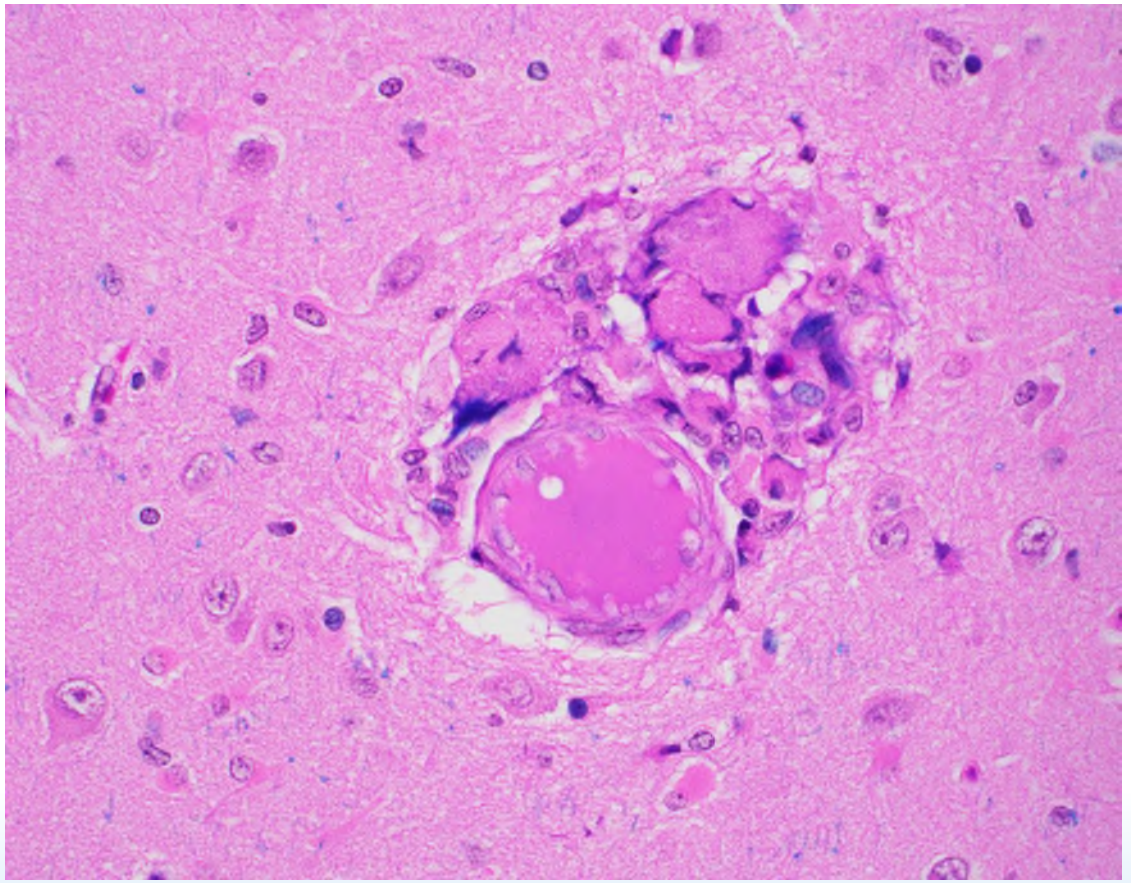


Case 2

- 8 month old girl with developmental delay and failure to thrive
- Hepatosplenomegaly
- Progressive deterioration



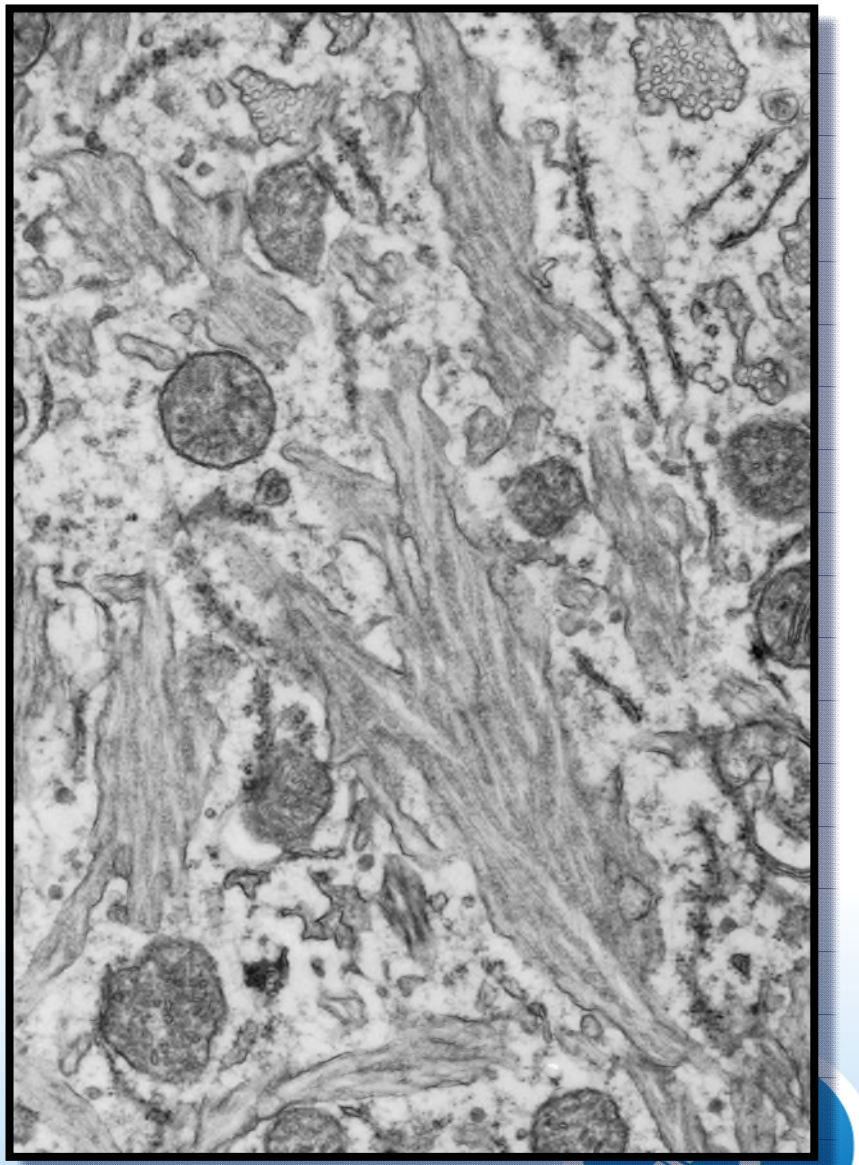


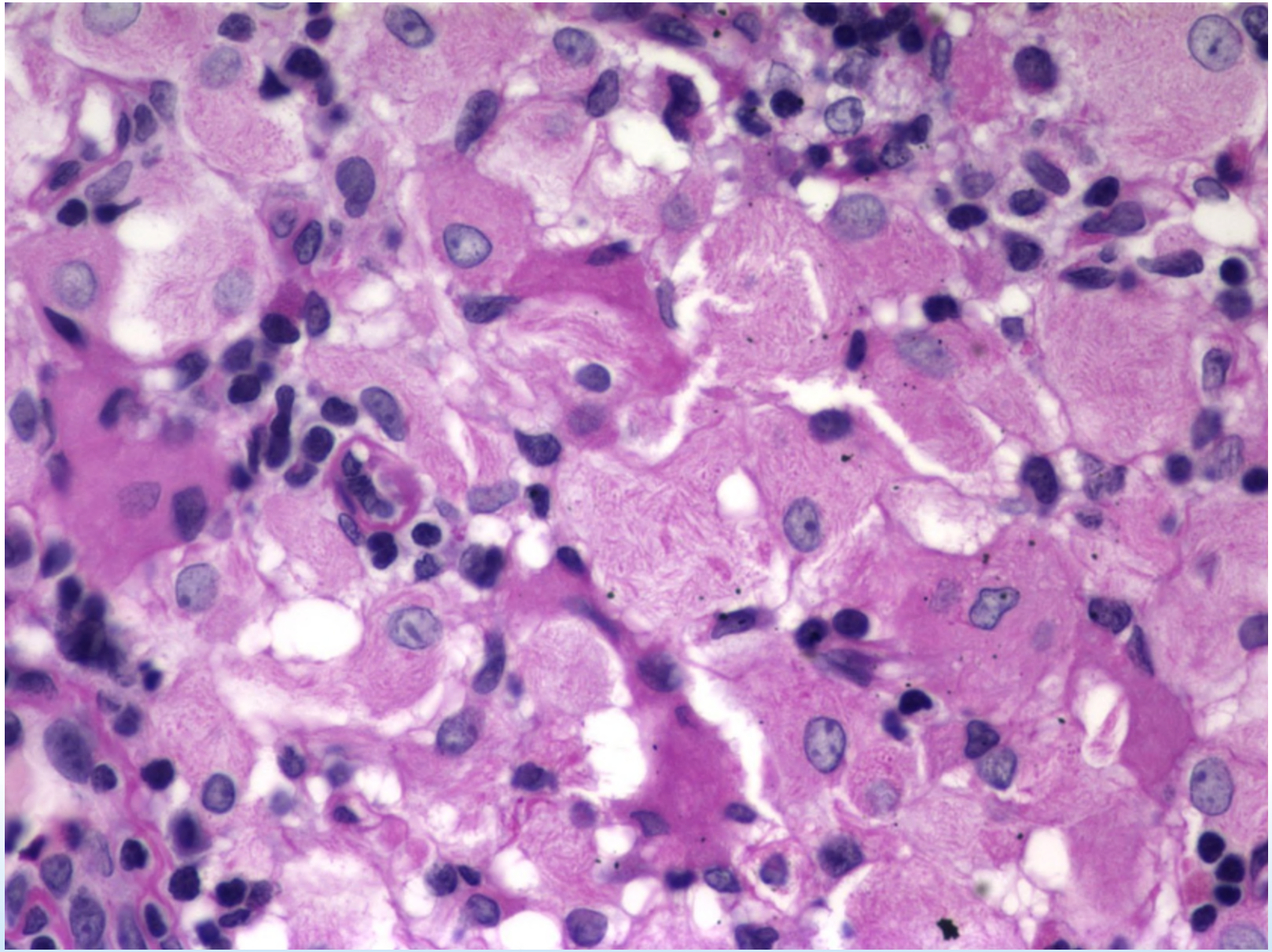


Gaucher disease

- Absence of lysosomal acid B-glucosidase (glucocerebrosidase)
- Accumulation of glucocerebroside
- Accumulation in reticuloendothelial system
- Large numbers of membrane-bound inclusions containing tubular structures

Spleen (Histiocyte)





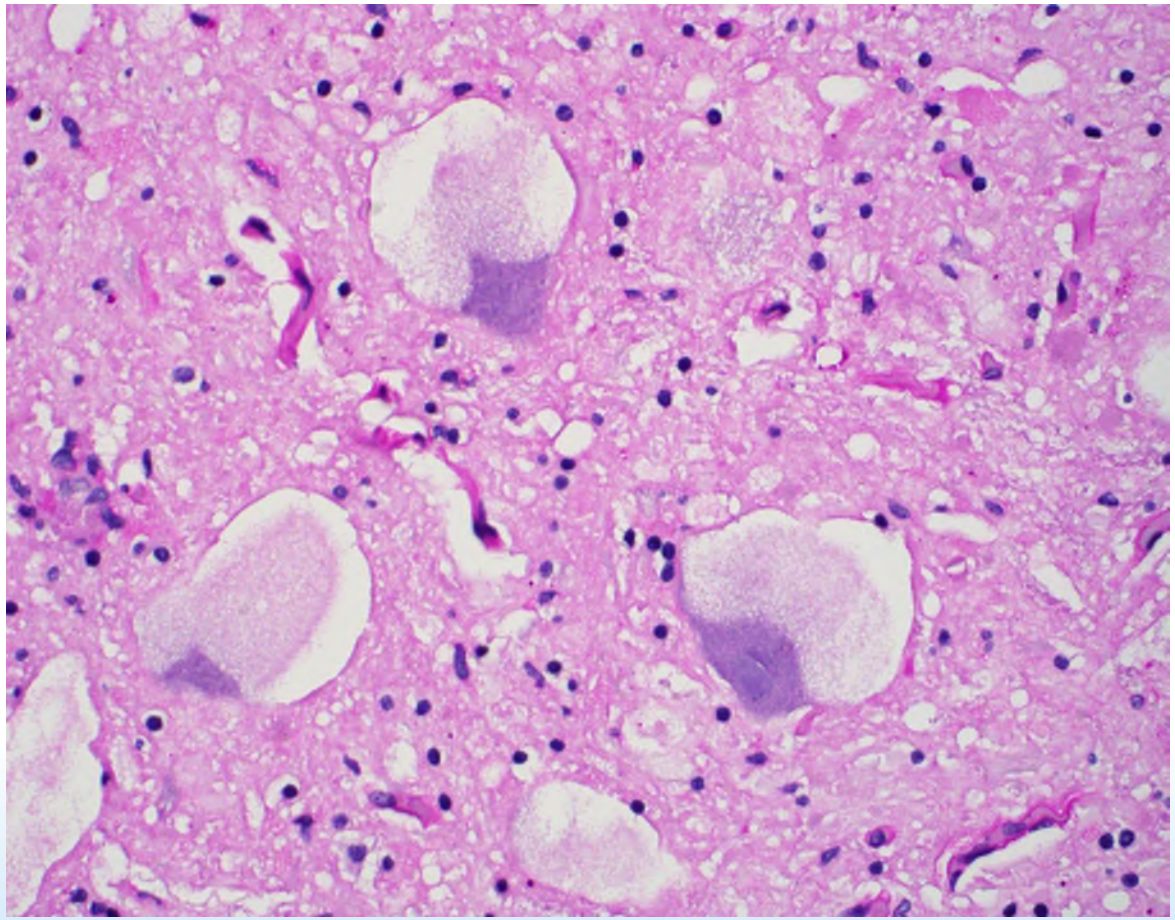
Gaucher Lymph node, PAS-D

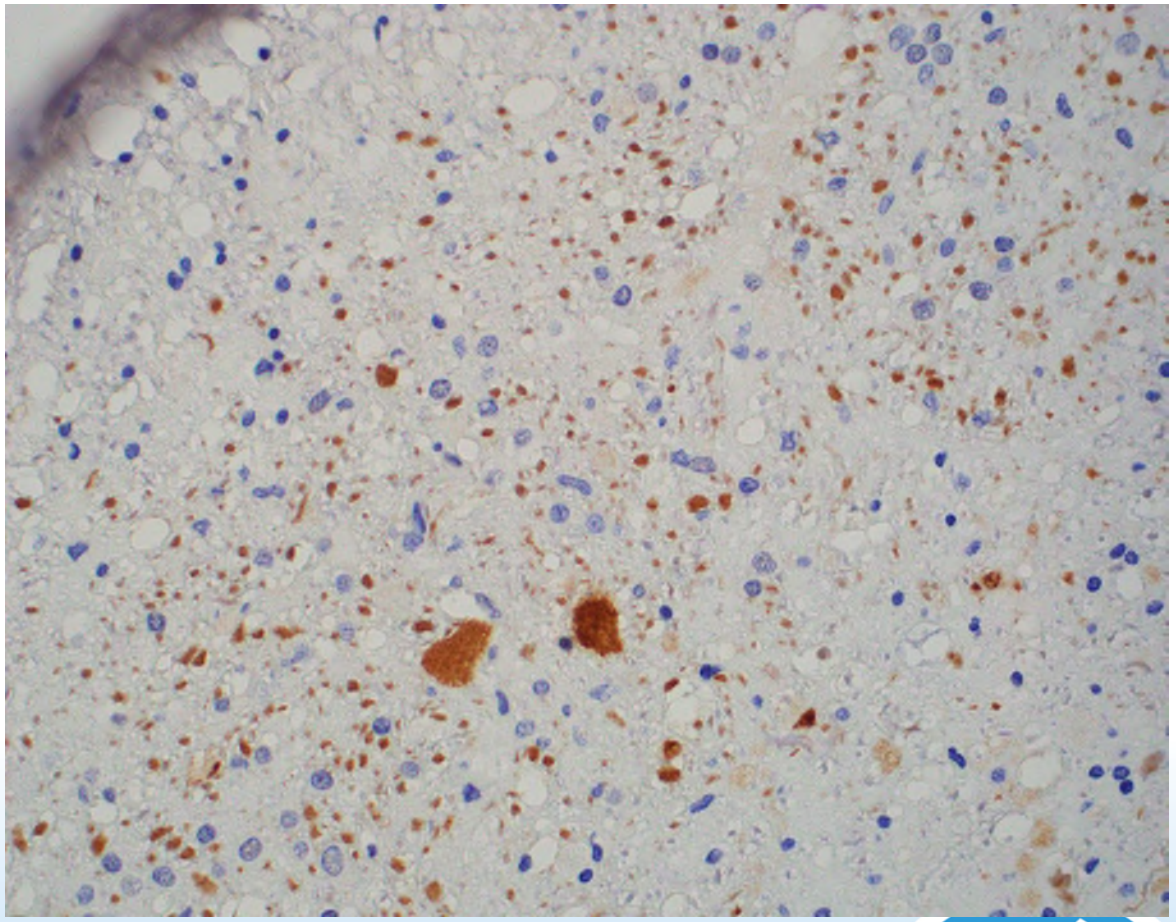
Image from Dr. Bruce Pawel

Case 3

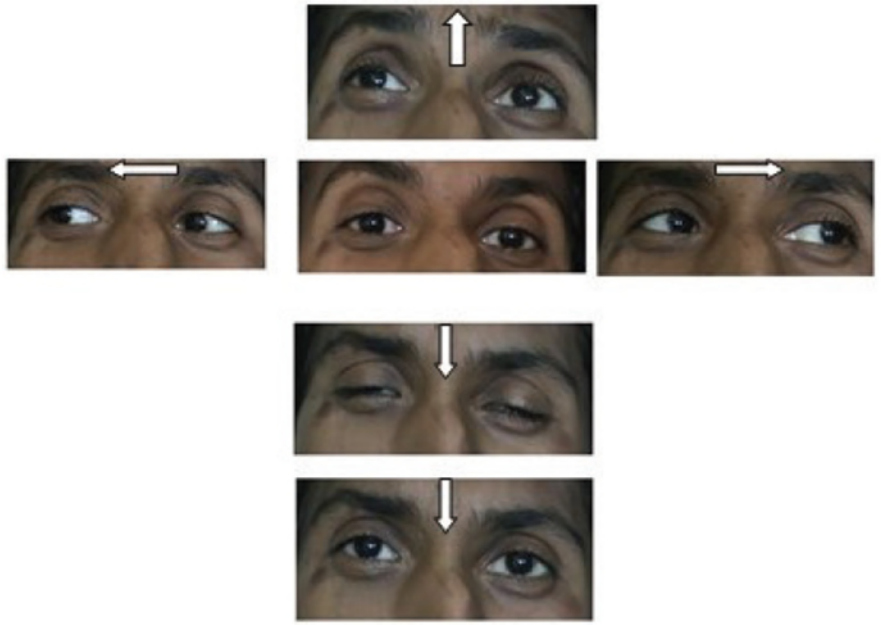
- 4 year old girl with hepatomegaly
- Decreased strength and motor delay
- Difficulty sustaining upward gaze

- Virtual slide: spinal cord





Niemann-Pick type C

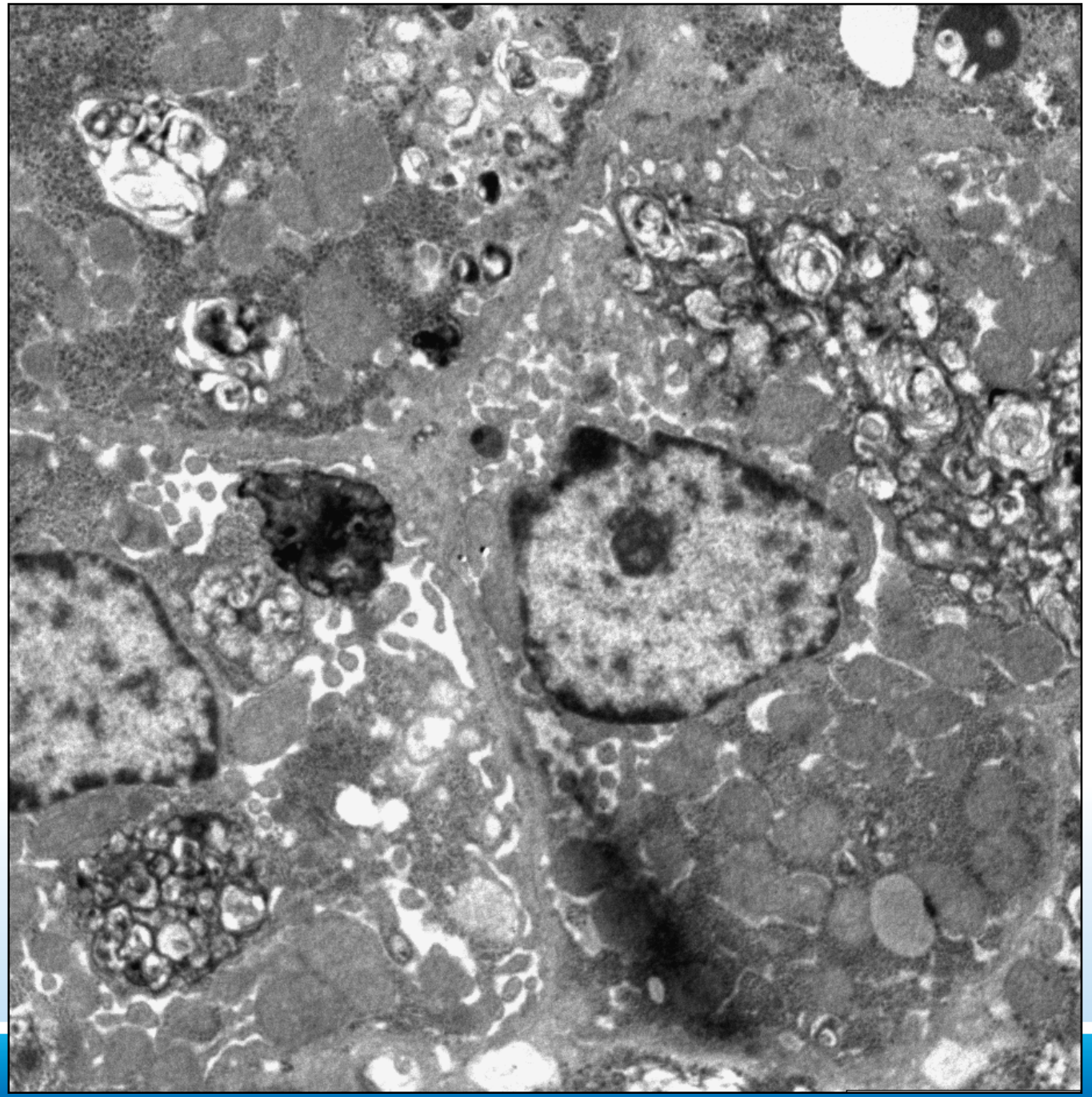


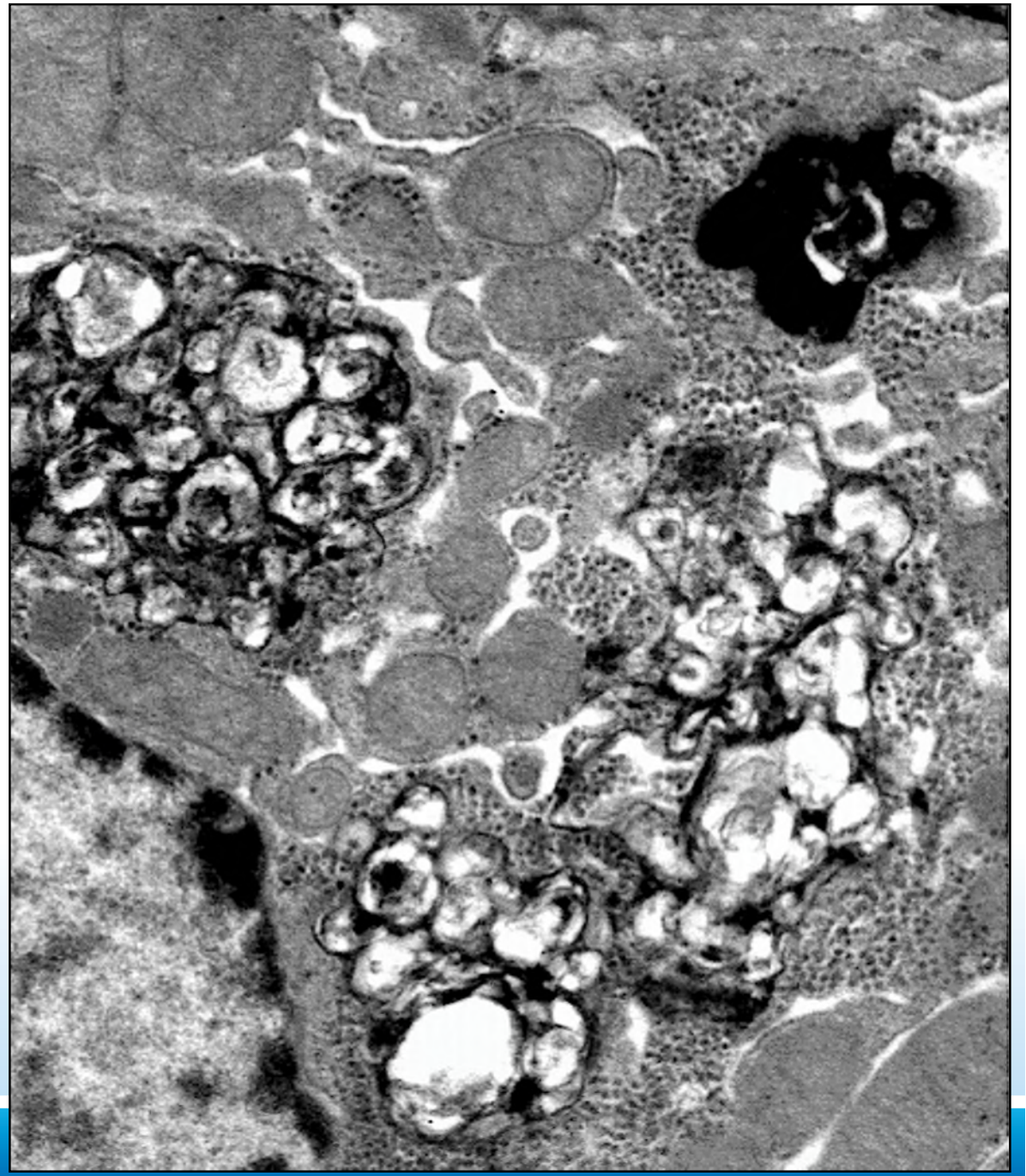
- 1:150,000
- Failure of transport of cholesterol and lipids
  - Lysosomal storage disorder
- Rapid neonatal form recognized
- Most cases detected in childhood and lead to early death
- Hepatosplenomegaly common presenting sign
- Impaired vertical eye movements
  - ?dorsal midbrain involvement

Beedasy et al., Afr Vision Eye Health 2019

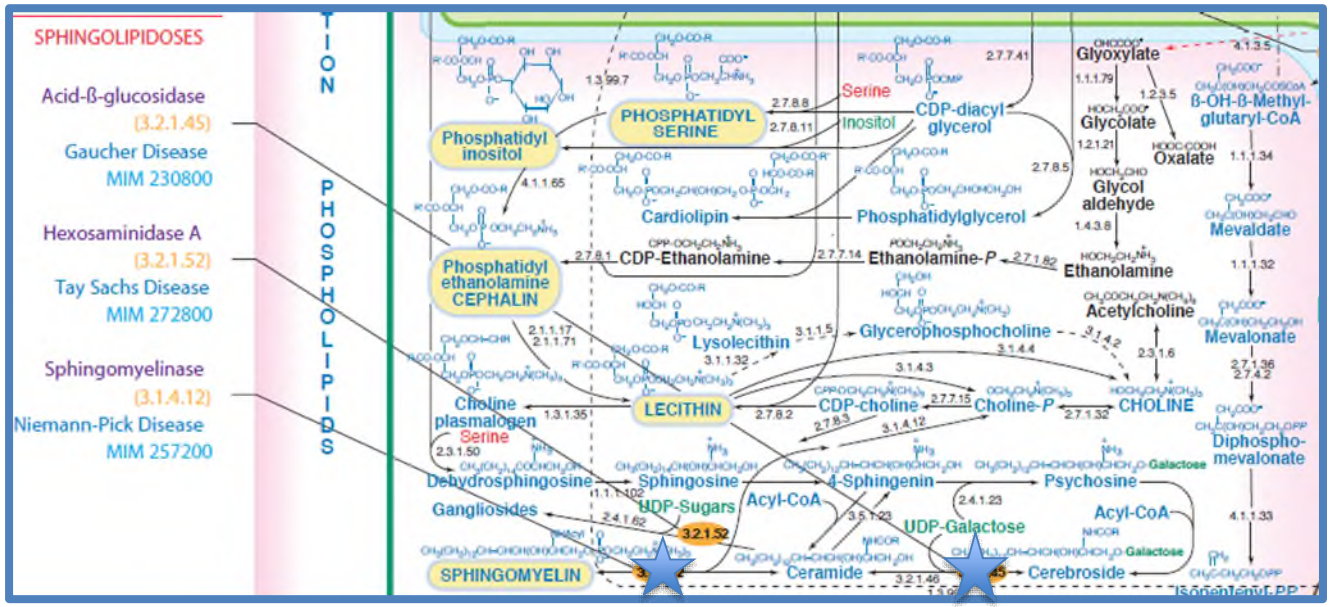
Niemann-Pick type C

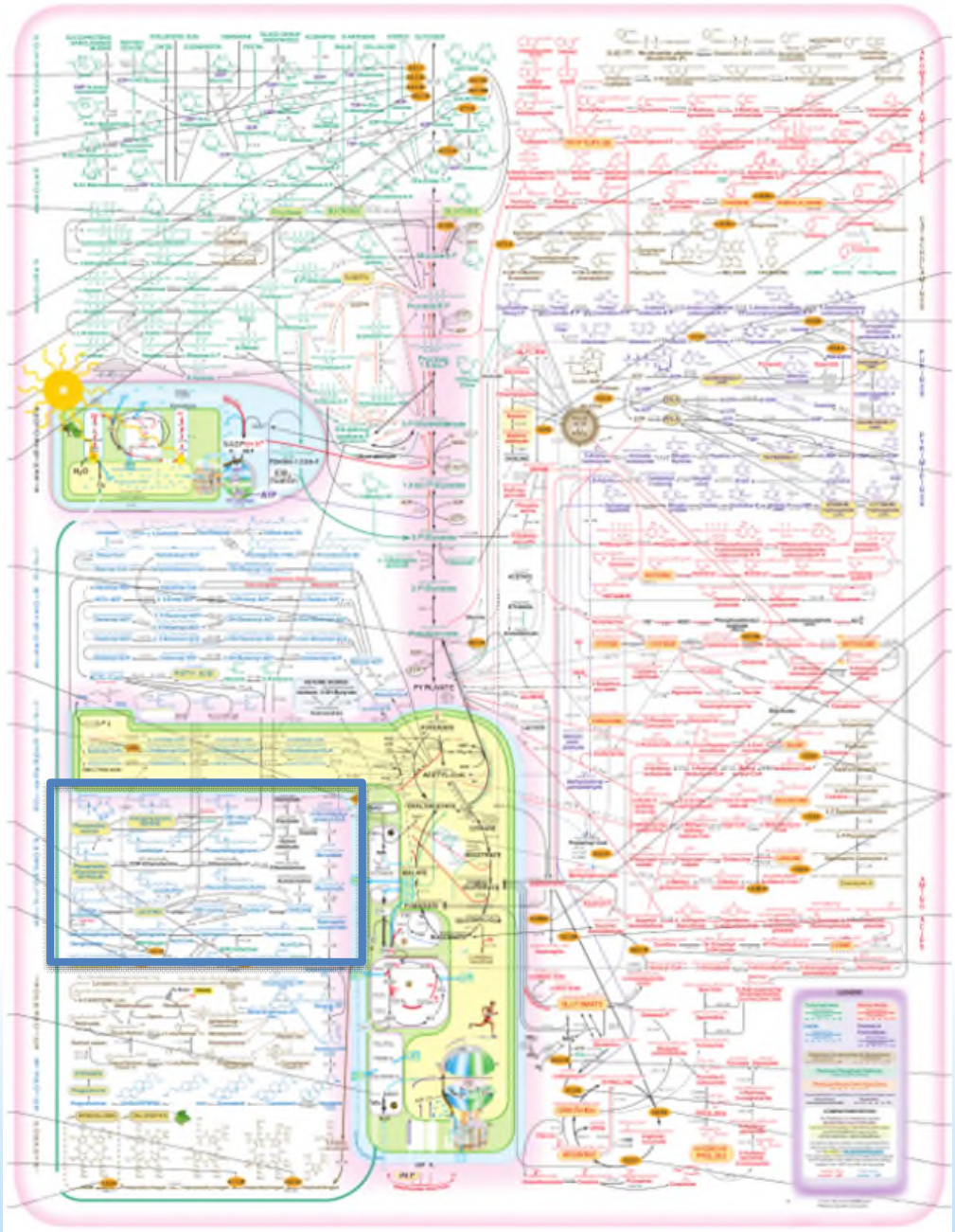
- Genetics: Mutation of *NPC1* or *NPC2*
- Visceral pathology: accumulation of foamy macrophages
- CNS pathology: cerebral atrophy, expanded neurons
  - PAS-negative or weakly positive
  - Loss of Purkinje cells with axonal spheroids
- Ultrastructure: pleomorphic inclusions with electron-lucent vacuoles, electron-dense curved short membranous structures





Finding Gaucher and Niemann-Pick on the map





Note that Niemann Pick type C (NPC) is distinct from A and B types, which are acid sphingomyelinase deficiencies.

NPC is a <u>cholesterol trafficking defect</u>

Krabbe disease (globoid cell leukodystrophy)

- "brain sclerosis" described 1916 by Knud Krabbe: small, firm brain
- Metabolic disorder of lipids (neural membranes)
  - Galactocerebroside-beta-galactosidase deficiency
    - Lipids accumulate in globoid macrophages
- Demyelination phenotype
- EM: crystalline clear inclusion bodies
- Genetics: *GALC* deletion/point mutation

A NEW FAMILIAL, INFANTILE FORM OF DIFFUSE BRAIN-SCLEROSIS.

BY KNUD KRABBE, M.D. COPENHAGEN.

From Queen Louise's Hospital for Sick Children [Professor MONRAD], *and from the Children's Department of the University Hospital, Copenhagen* [Professor BLOCH].

IN a previous paper [12], three years ago, I described a case of a peculiar affection in the brain of a child. This case I regarded as an early stage of the disease named "diffuse sclerosis of the brain," and in

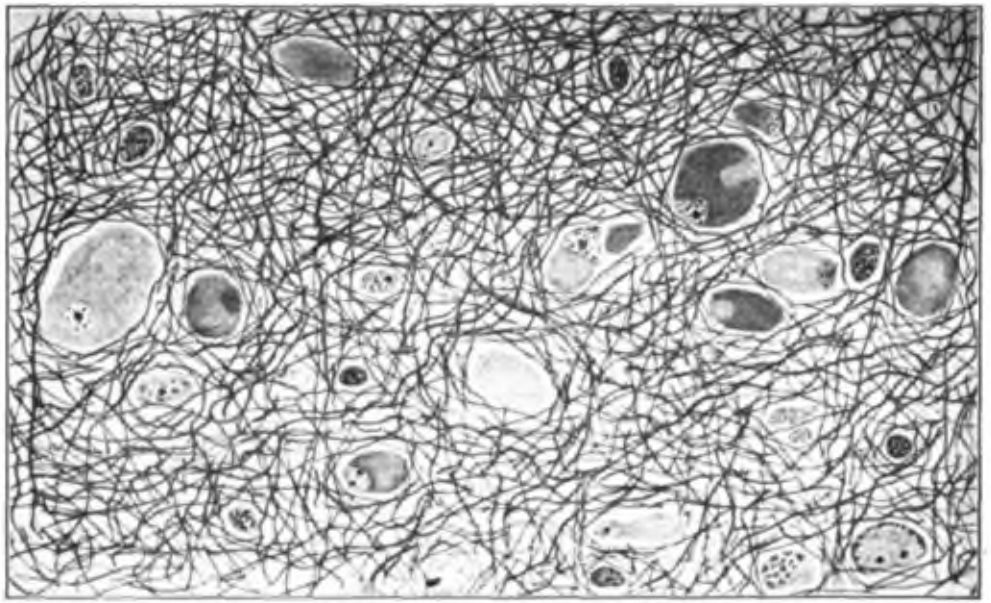


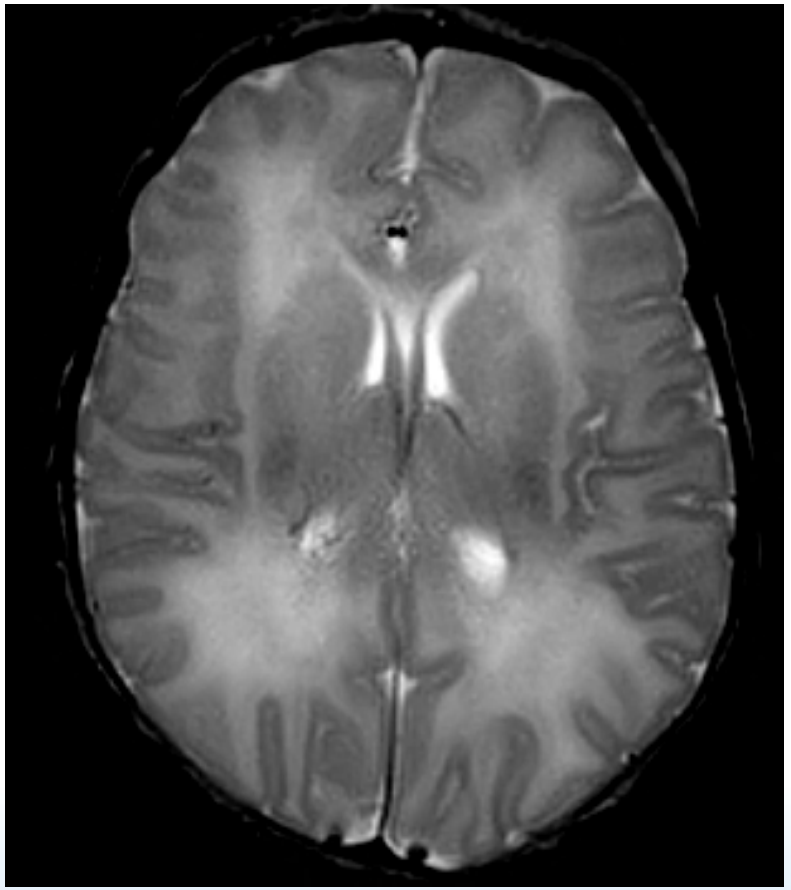
FIG. 12.—White substance of the hemispheres. The whole white substance is replaced by neuroglia in which may be seen many different types of neuroglial cells, small and large.

ANATOMO-PATHOLOGICAL CONSIDERATIONS OF THE CASES.

The most characteristic feature of the above cases, as far as their pathological anatomy is concerned, is the complete destruction of the axis-cylinders and medullary sheaths, the replacement of the destroyed tissue by neuroglia and the relative intactness of the nerve-cells. The destruction shows a peculiar distribution, as may be seen from the description of Cases 1, 2 and 4; the processes of all the nerve-cells of cortex cerebri and cerebelli are most affected; destruction of the processes from the basal ganglia represents the next stage and of those from the spinal centres the last stage of the disease.

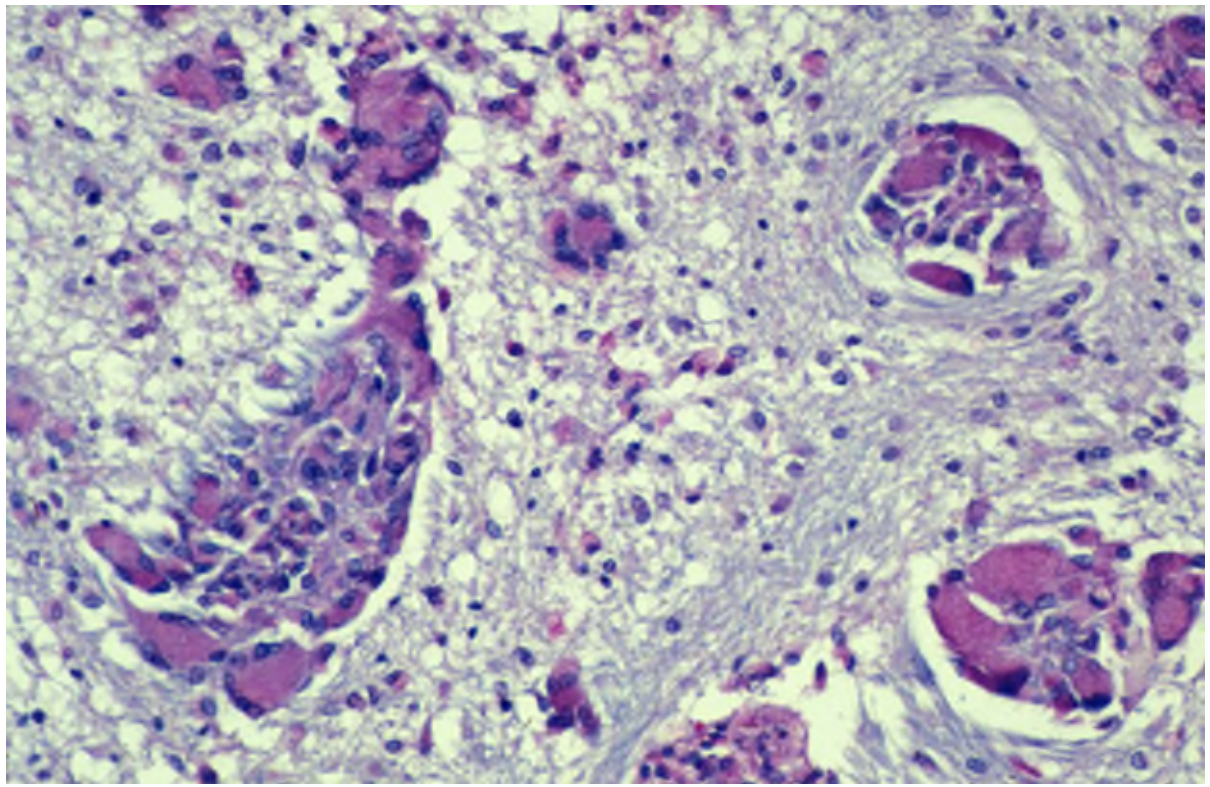
Krabbe disease

- 1-2:100,000 live births
- Rapidly progressive infantile CNS disease with peripheral nerve involvement
  - Delayed nerve conduction
- Lab: elevated CSF protein, decreased GBG activity (definitive)
- MRI: white matter abnormalities



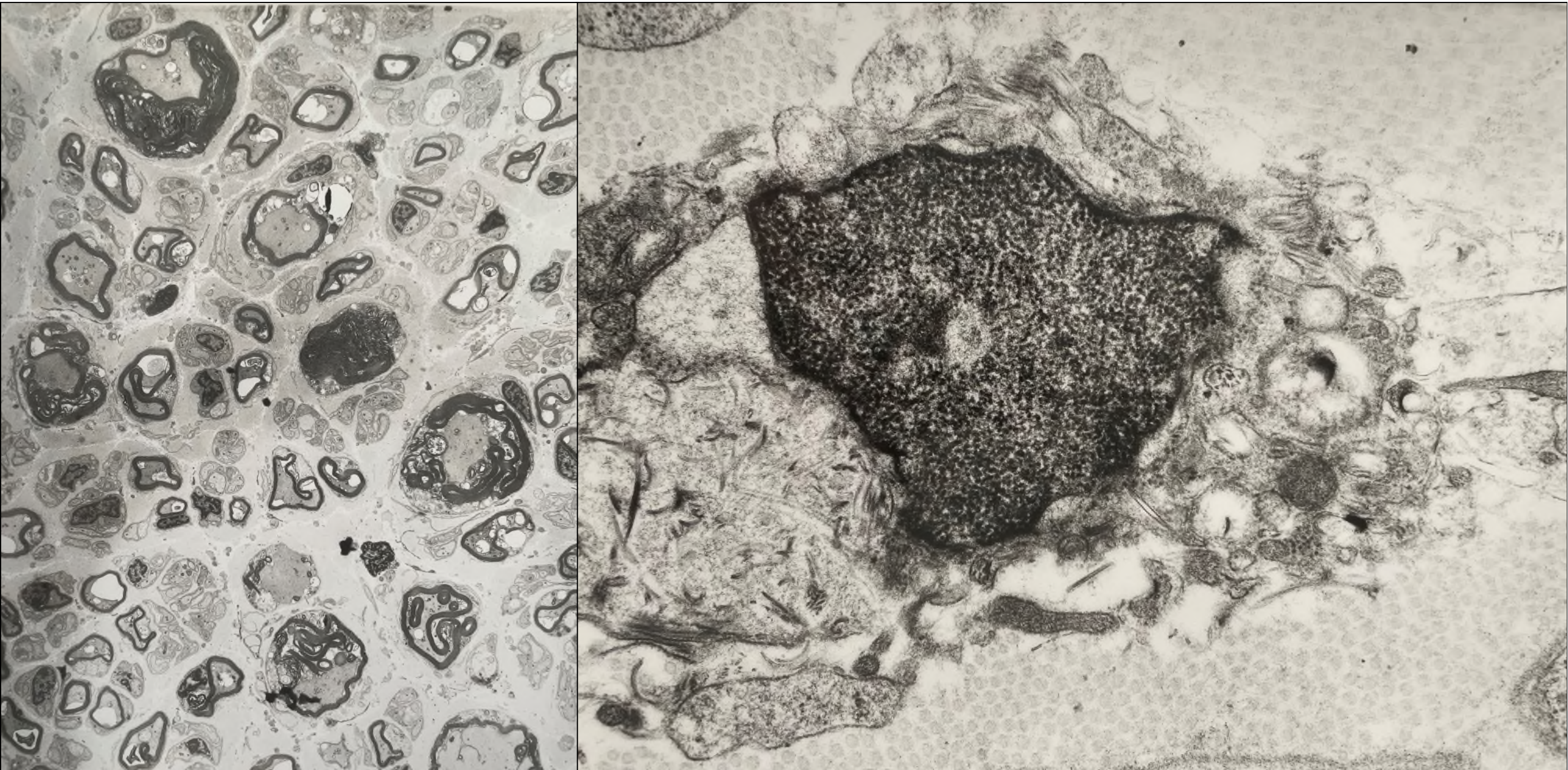
CNS findings

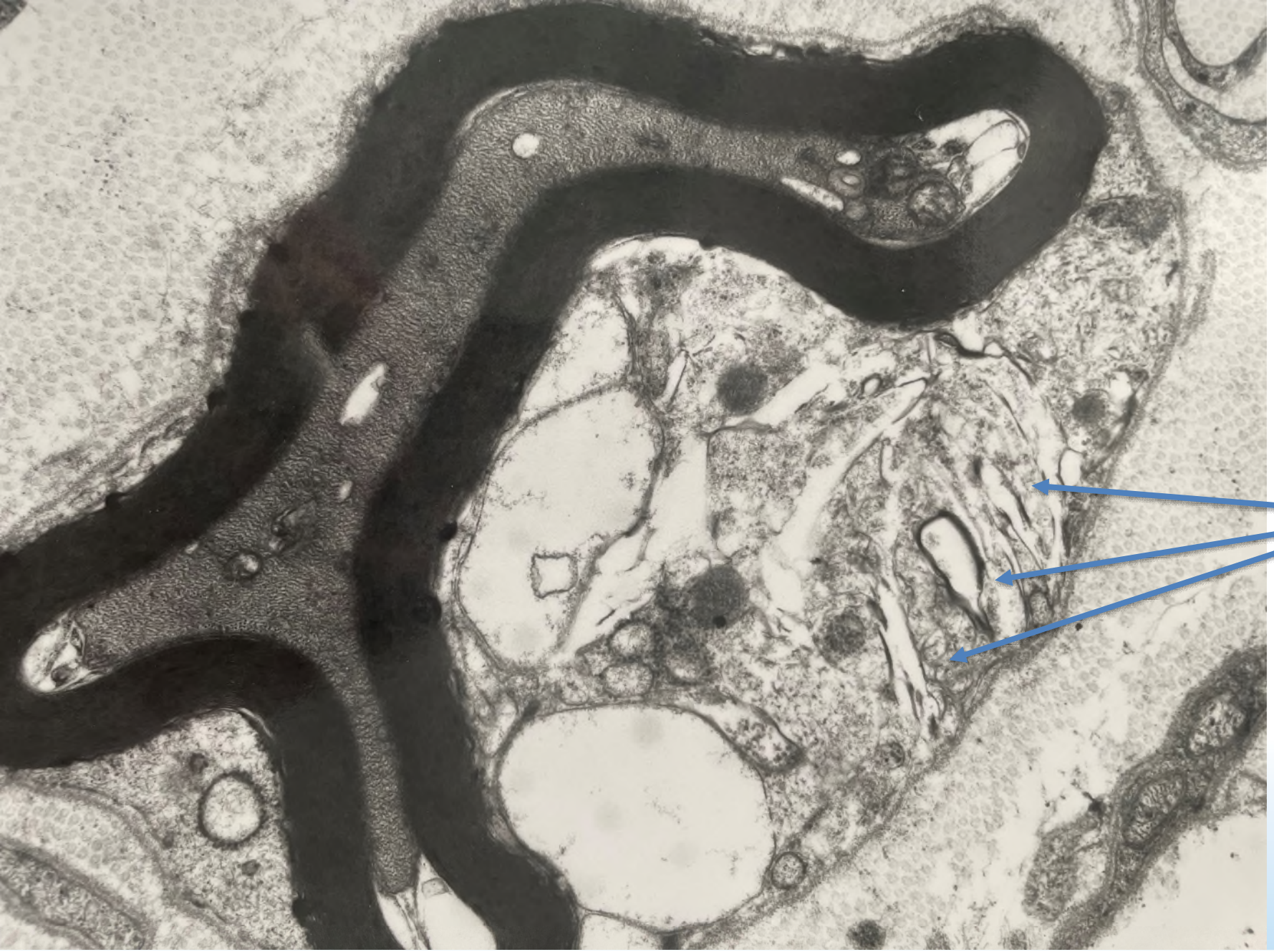
- Brain macrophages filled with PAS-positive material
- Perivascular aggregates
- Demyelination with gliosis
- Neuronal loss



neuropathology-web.org

Krabbe – ultrastructural findings (sural nerve, 1 yo F)



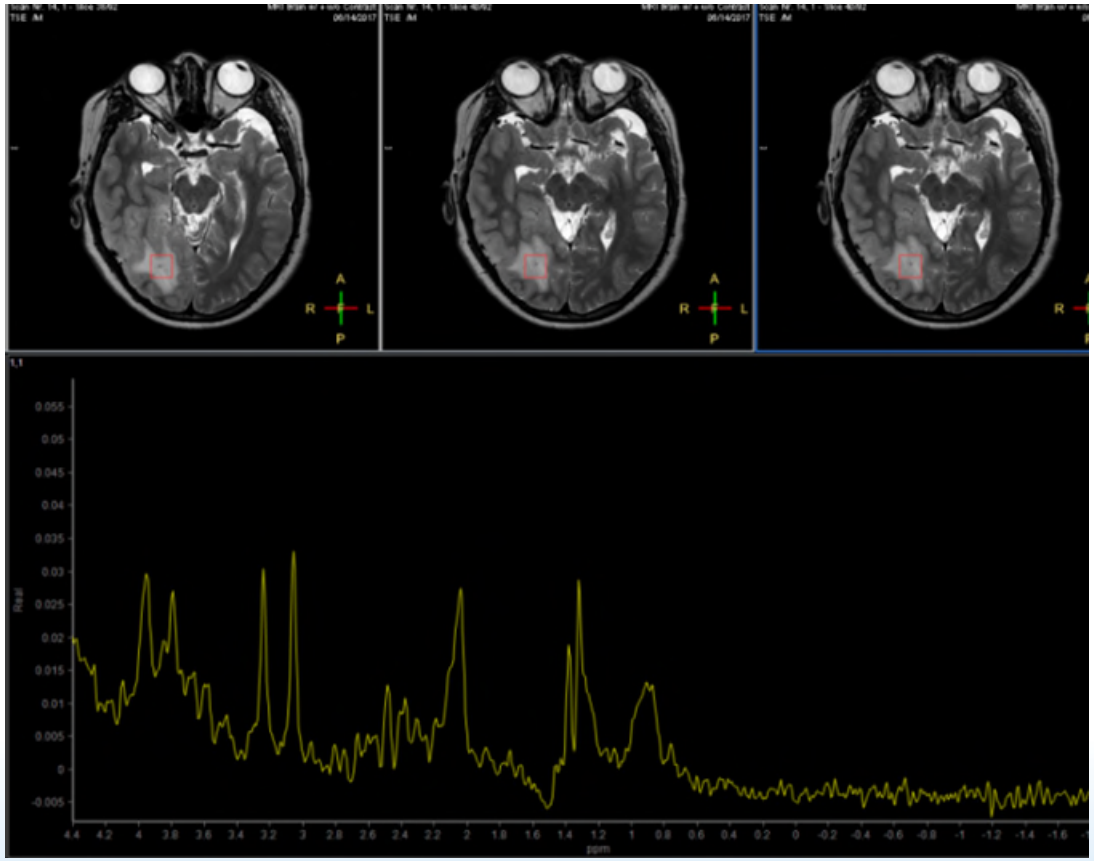


Krabbe ultrastructural findings (sural nerve, 1 yo F)

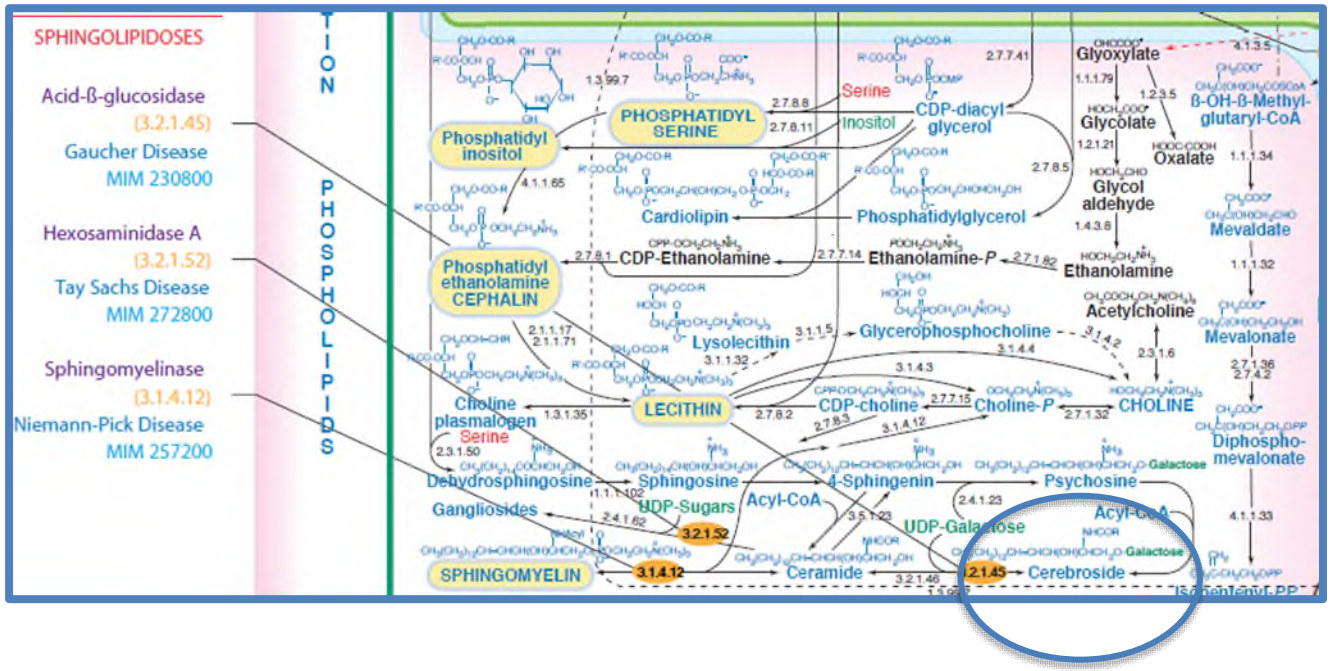
Elongated clear crystalline inclusions in Schwann cells (galactocerebroside)

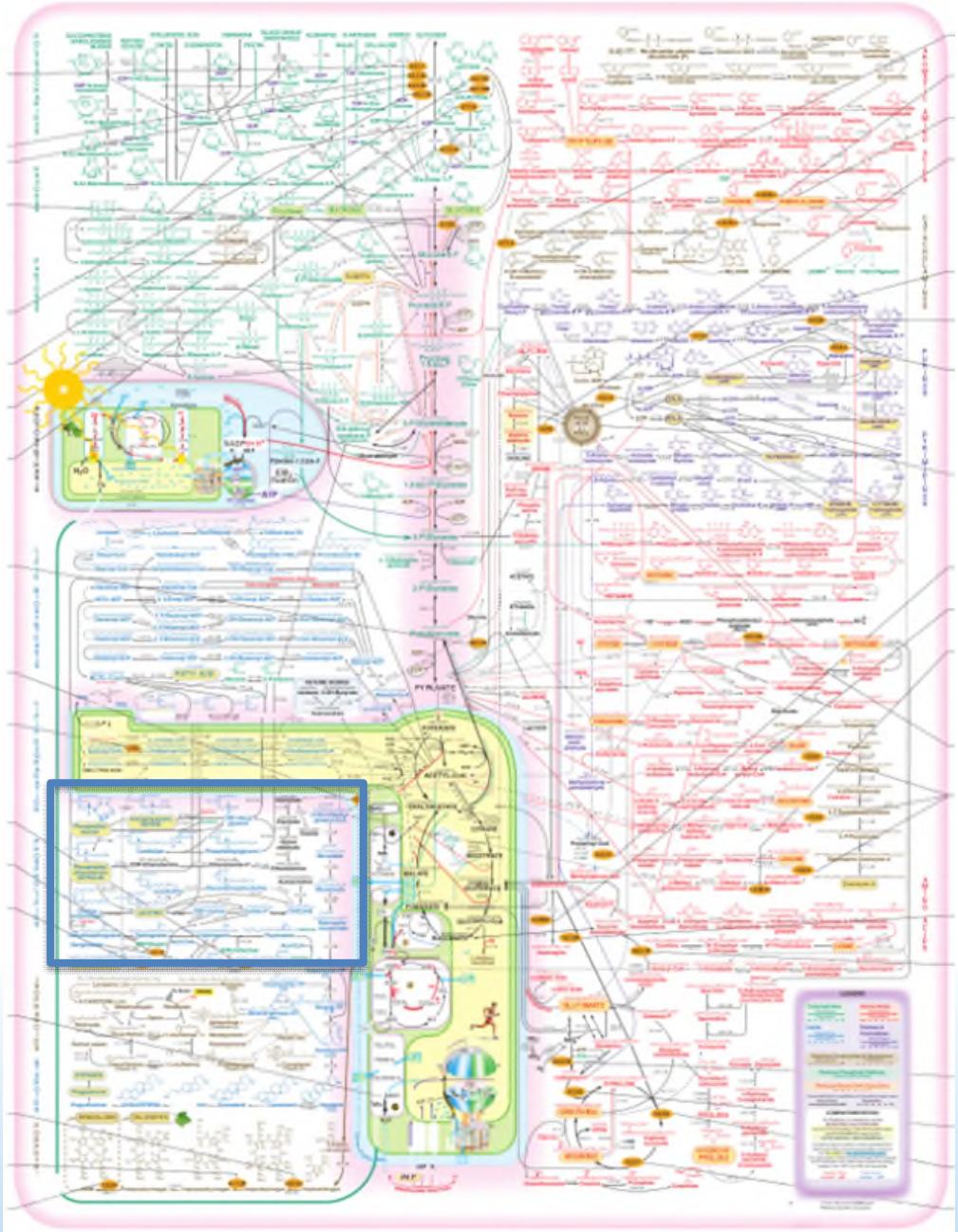
Another lysosomal leukodystrophy: Metachromatic Leukodystrophy

- 1:40,000
- Deficiency of arylsulfatase A (ARSA gene)
  - Inability to degrade sulfated glycolipids
  - Sulfatides stain brown on cresyl violet (metachromasia)
- Causes diffuse demyelination
  - Usually central to peripheral, sparing U fibers
- MRS: lipids and lactate elevated
  - Consistent with acute demyelination



Where Krabbe and MCL fit on the map





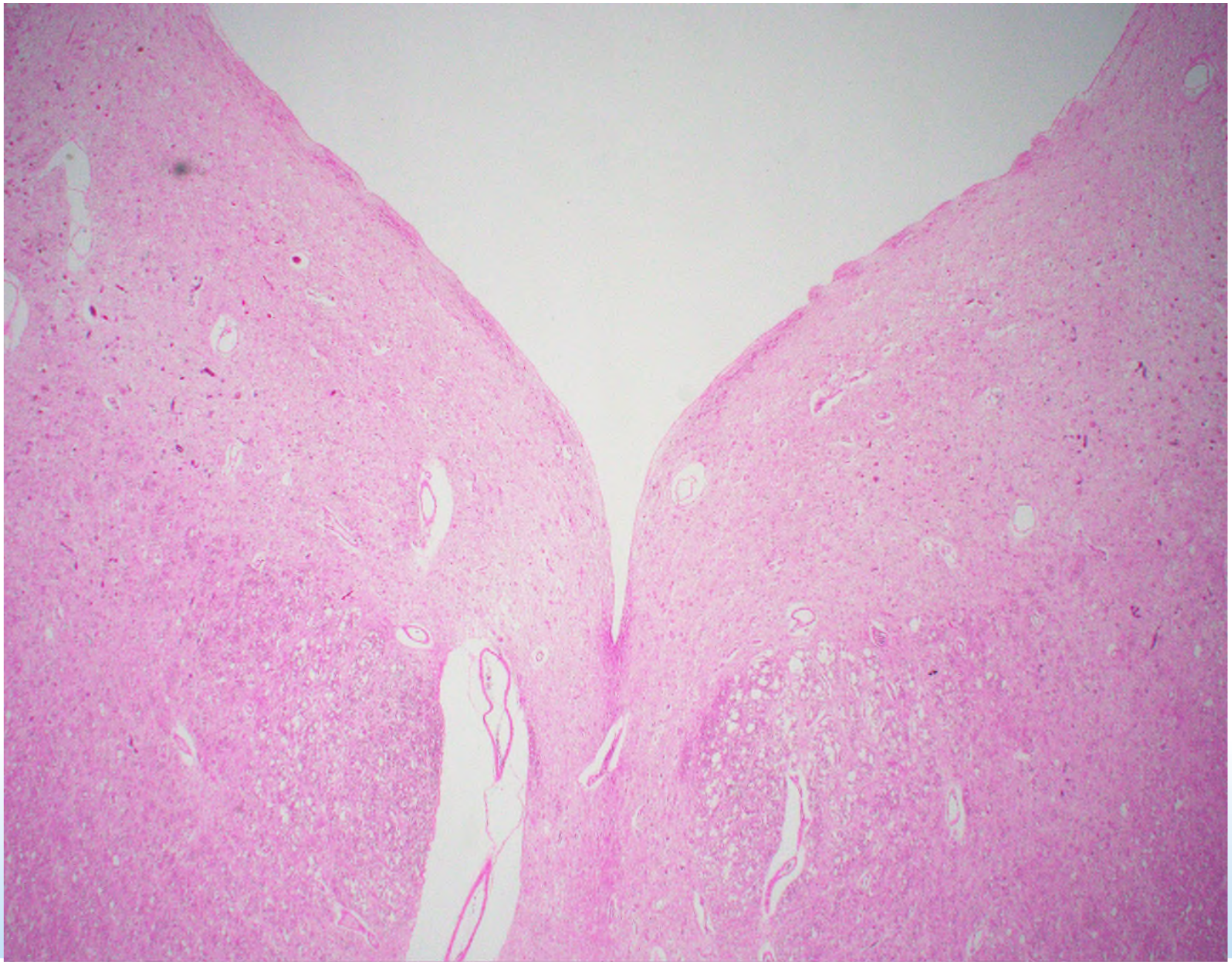
- MCL: breakdown of cerebroside sulfatase (no galactocerebroside generated)
- Krabbe: breakdown of galactocerebroside (no ceramide generated)

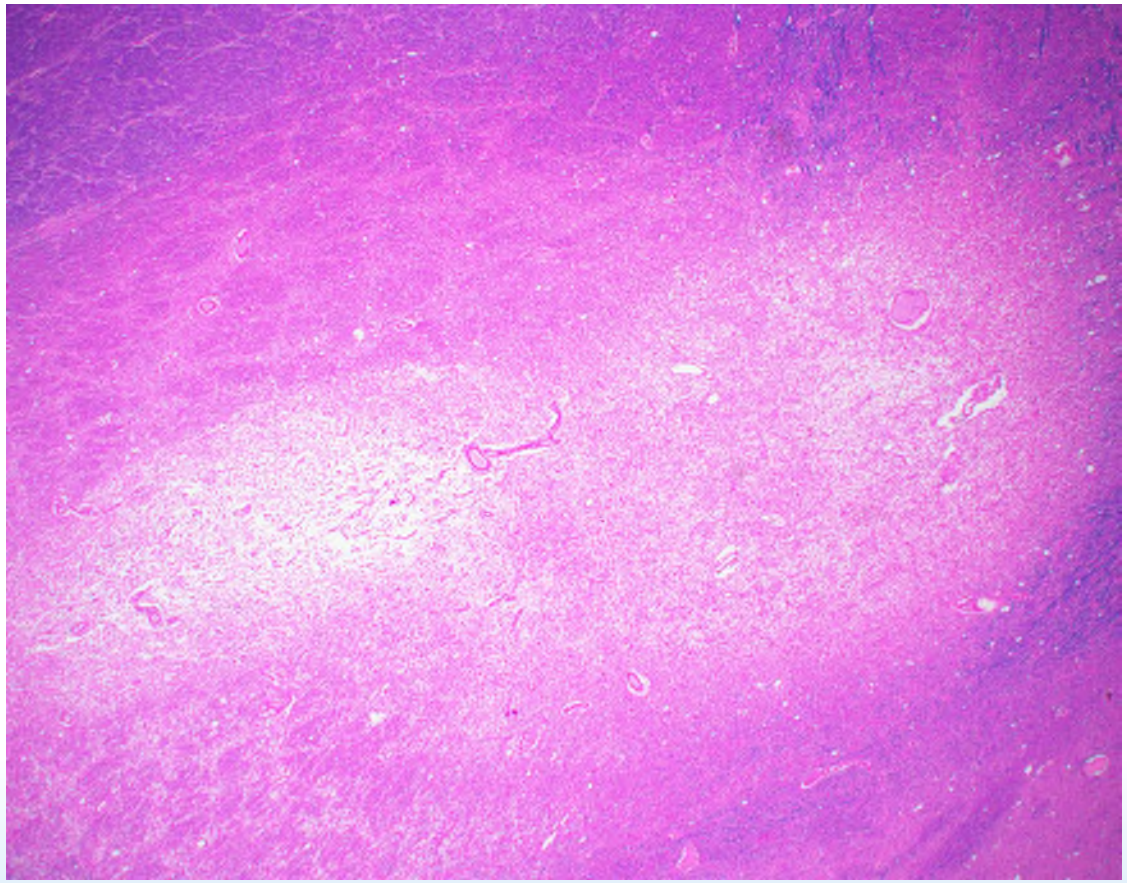
Case 4

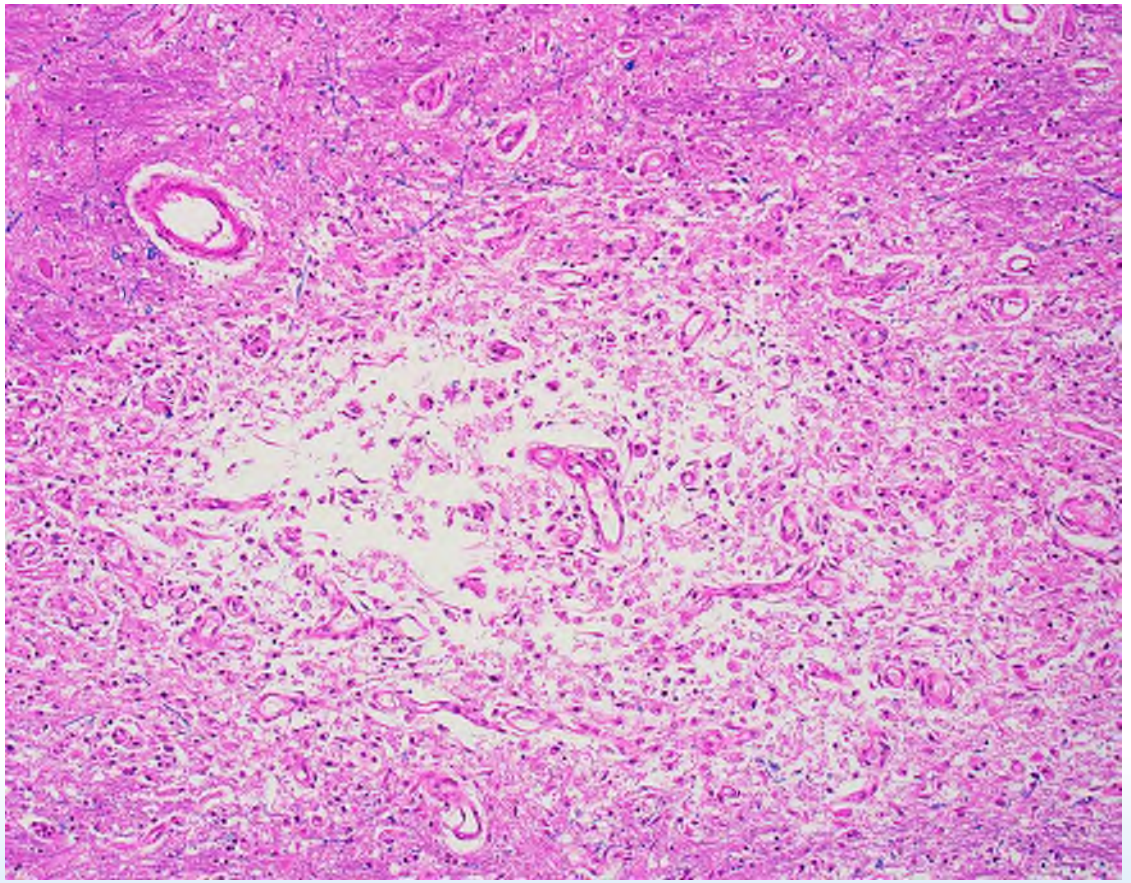
- 8 year old girl, child of third cousins
- Younger sibling with history of “encephalitis”
- Small for age, problems with balance/coordination
- Started losing milestones at age 3.5, poor fine motor skills
- Admitted at age 8 with weakness and respiratory distress, MRI showed T2 hyperintensity in putamen/globus pallidus, and midbrain
- Terminal pneumonia and sepsis
- Mitochondrial *ATP6* gene mutation (codon 8993 T>C)
  - 90% in blood and 95% in muscle

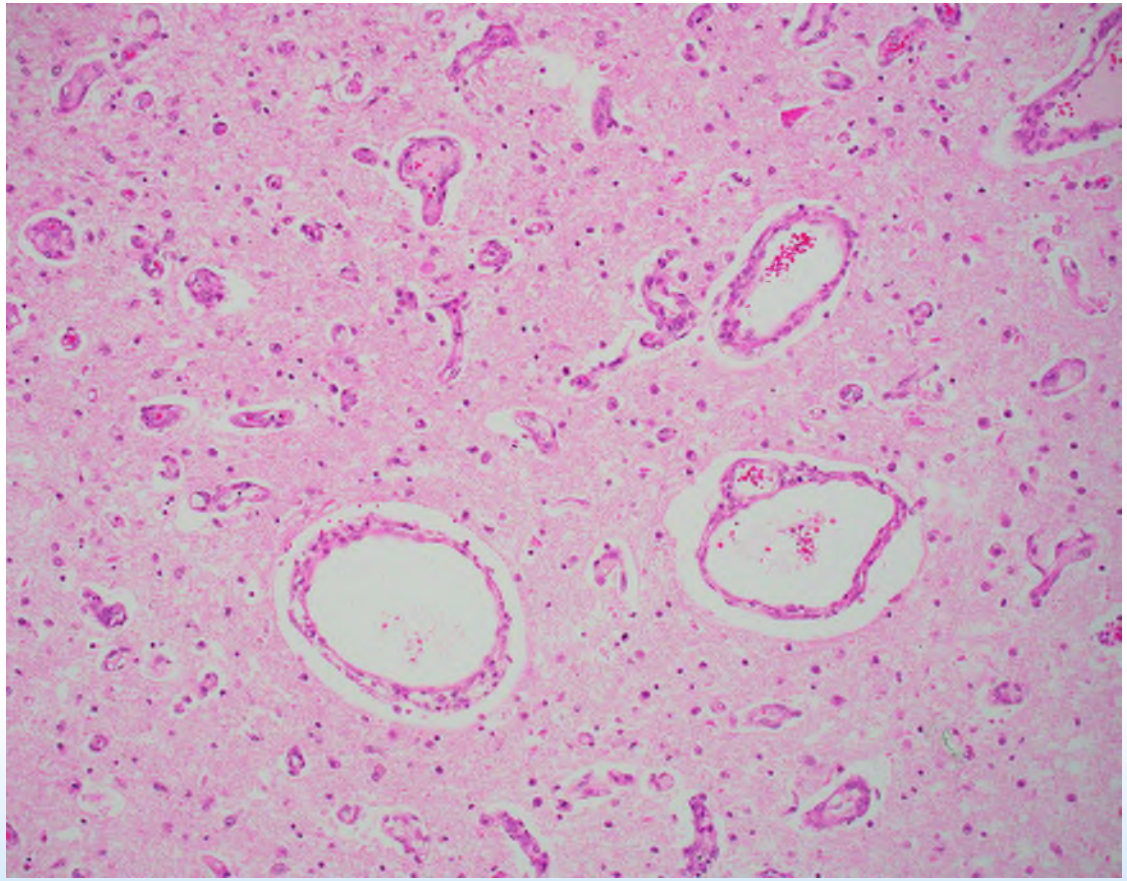
Virtual slides

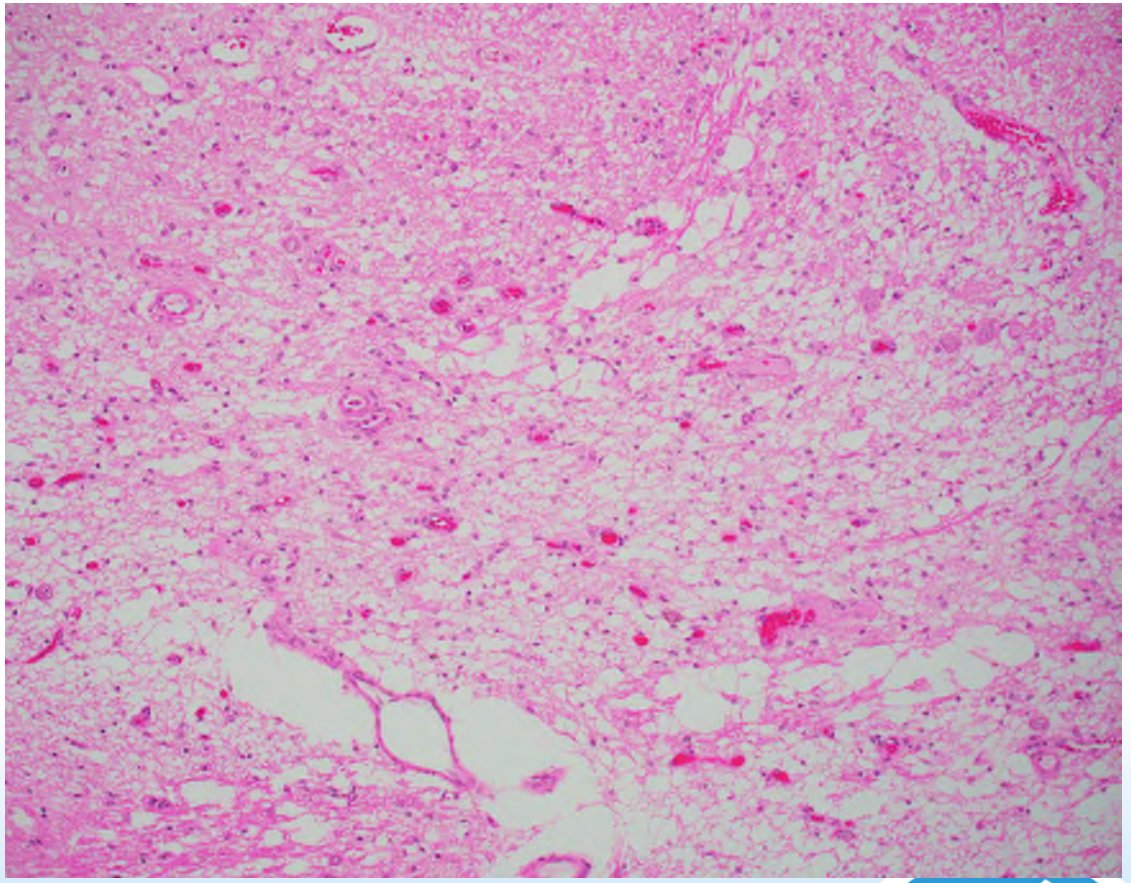
- Midbrain





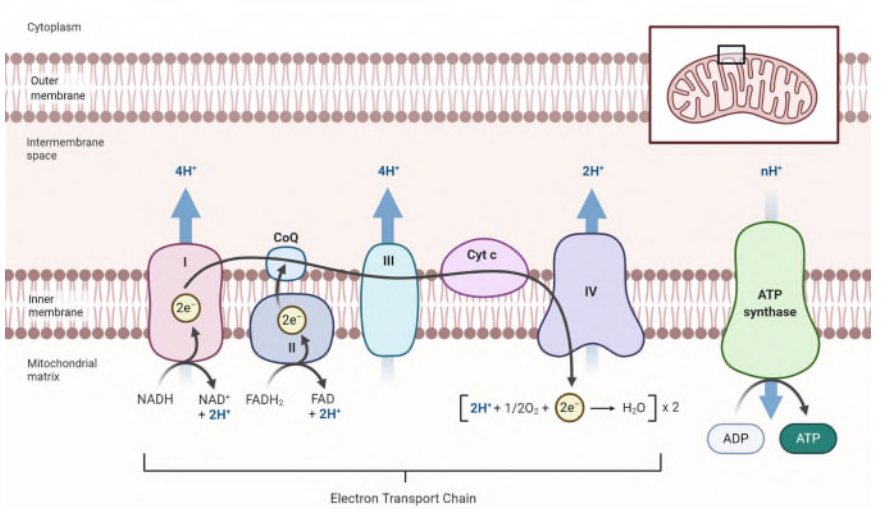


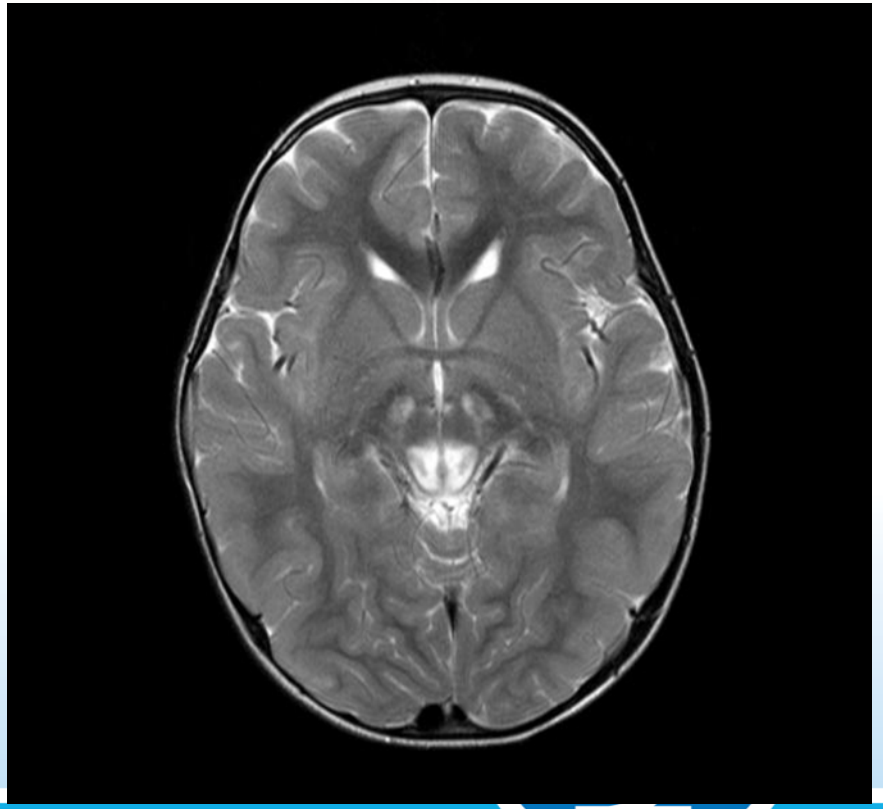




Leigh syndrome

- Subacute necrotizing encephalomyelopathy
  - Described 1951 by Denis Leigh
- 1:36,000-40,000 live births
- Deficiency in mitochondrial production of ATP
  - Electron transport chain
- Focal bilaterally symmetric spongy lesions
  - Particularly in brain stem and thalamus
- Treatment limited, supportive
- Survival poor (20% at 20 years)





Leigh syndrome

- Symptoms between 3 months – 2 years
- Progressive deterioration (loss of milestones), vomiting, seizures
- Lab: high CSF lactate, sometimes aciduria
- Genetics: Defects of mitochondrial energy production
  - Pyruvate hydrogenase deficiency
  - Pyruvate decarboxylase deficiency
  - Respiratory chain complex deficiency
  - May be from nuclear DNA or mitoDNA (heteroplasmy)
    - MT-ATP6 mutation is associated with the majority of LS cases (seen in this case)
  - **Inheritance pattern varies – AR, X-linked, maternal**

More frequent mitochondrial disease “classic syndromes”

Syndrome	Relative frequency	Features	Inheritance	Genetic findings
Kearns-Sayre Syndrome	Frequent	Ocular myopathy (ptosis, ophthalmoparesis)	Sporadic	Single large-scale deletion of mtDNA
Leber hereditary optic neuropathy	Very frequent	Optic neuropathy	Maternal	Various mtDNA mutations
Leigh syndrome	**Frequent**	**Severe encephalopathy**	**AR, XL, maternal**	**Various nuclear or mtDNA mutations**
Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)	Frequent	Stroke-like episodes	Maternal	mtDNA mutation (m.3243A>G)
Myoclonic encephalopathy with ragged red fibers (MERRF)	Frequent	Myoclonus	Maternal	m.8344A>G
Nonsyndromic hearing loss (NSHL)	Frequent	Hearing loss	Maternal	m.1555A>G
Progressive external ophthalmoplegia (PEO)	Very frequent	Ocular myopathy	AD, AR, maternal, sporadic	Various nuclear genes with secondary mtDNA deletions/mutations

Adapted from Orsucci et al., J Clin Med. 2021

Case 5

- 8 week old girl with failure to thrive
- Elevated liver enzymes, lactate, and ammonia
  - Ketogenic diet did not improve clinical course
- MRI not performed
- Died with respiratory failure and acidosis
- Compound heterozygous *EARS2* mutations
  - Combined OXPHOS deficiency 12
  - Leukoencephalopathy with ragged red fibers

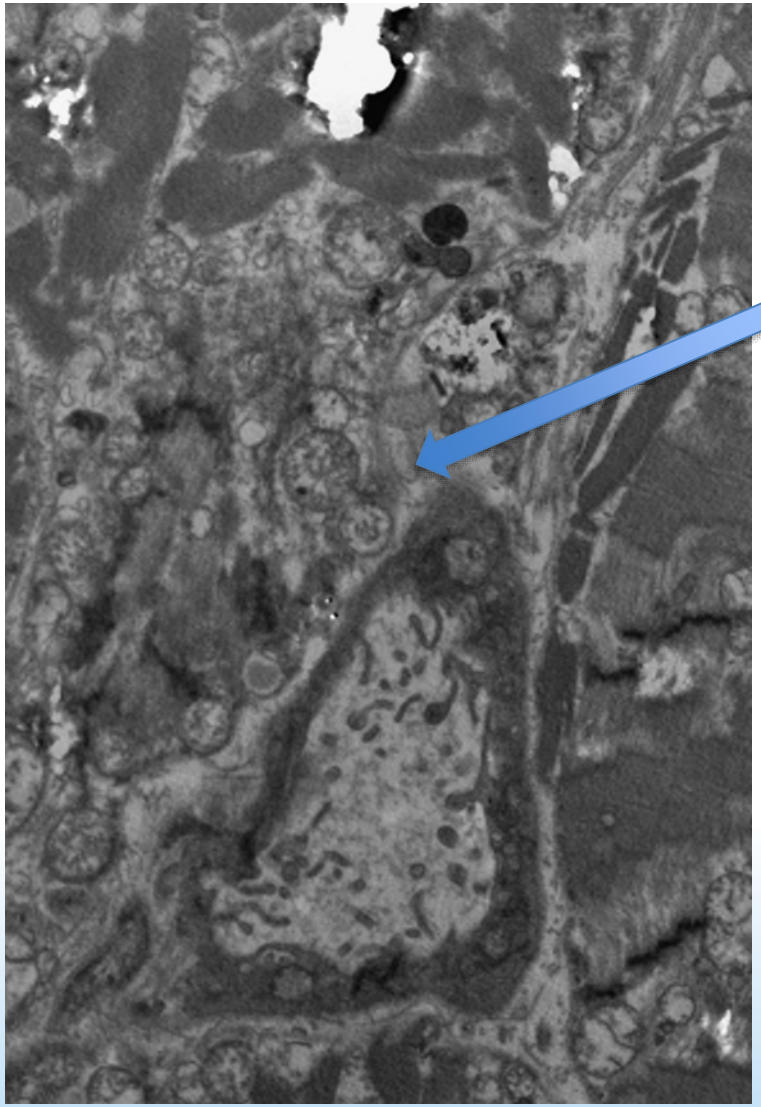
Virtual slide

- Medulla

Different pattern of mitochondrial encephalopathy: LTBL

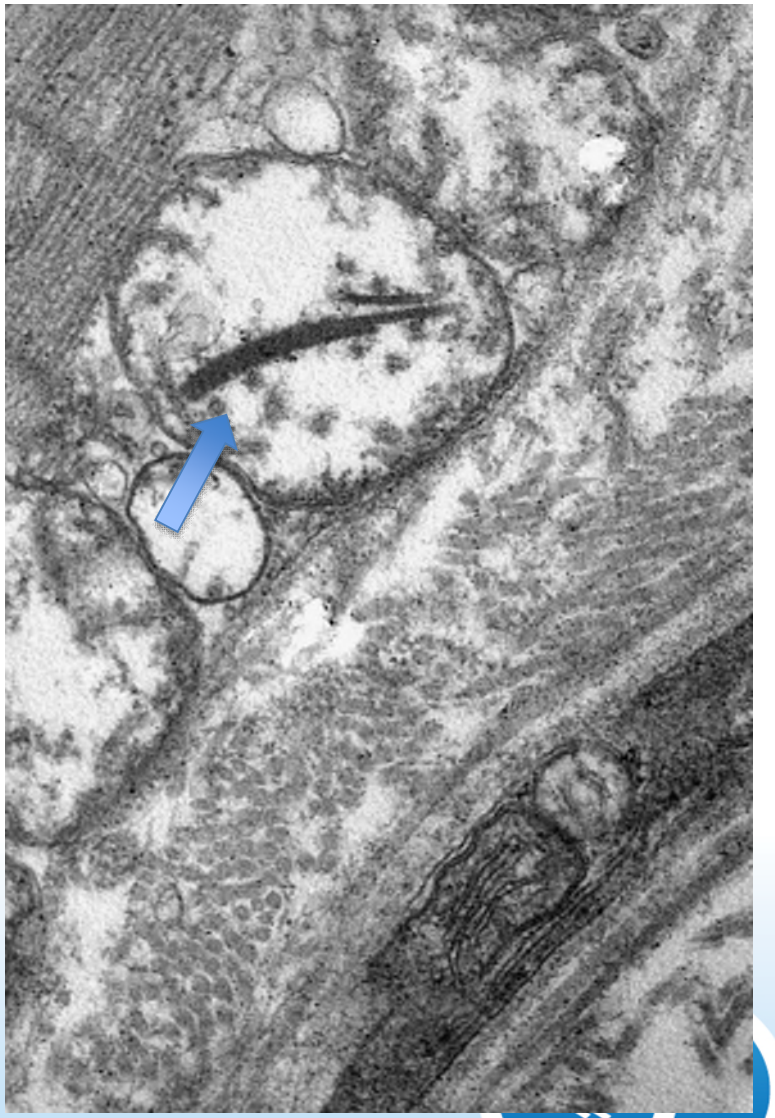
- leukoencephalopathy with thalamus and brainstem involvement and high lactate
- Symmetric white matter abnormalities
- Infantile onset, rapidly progressive
- Associated with *EARS2* mutations

EARS2-associated mitochondriopathy - ultrastructure

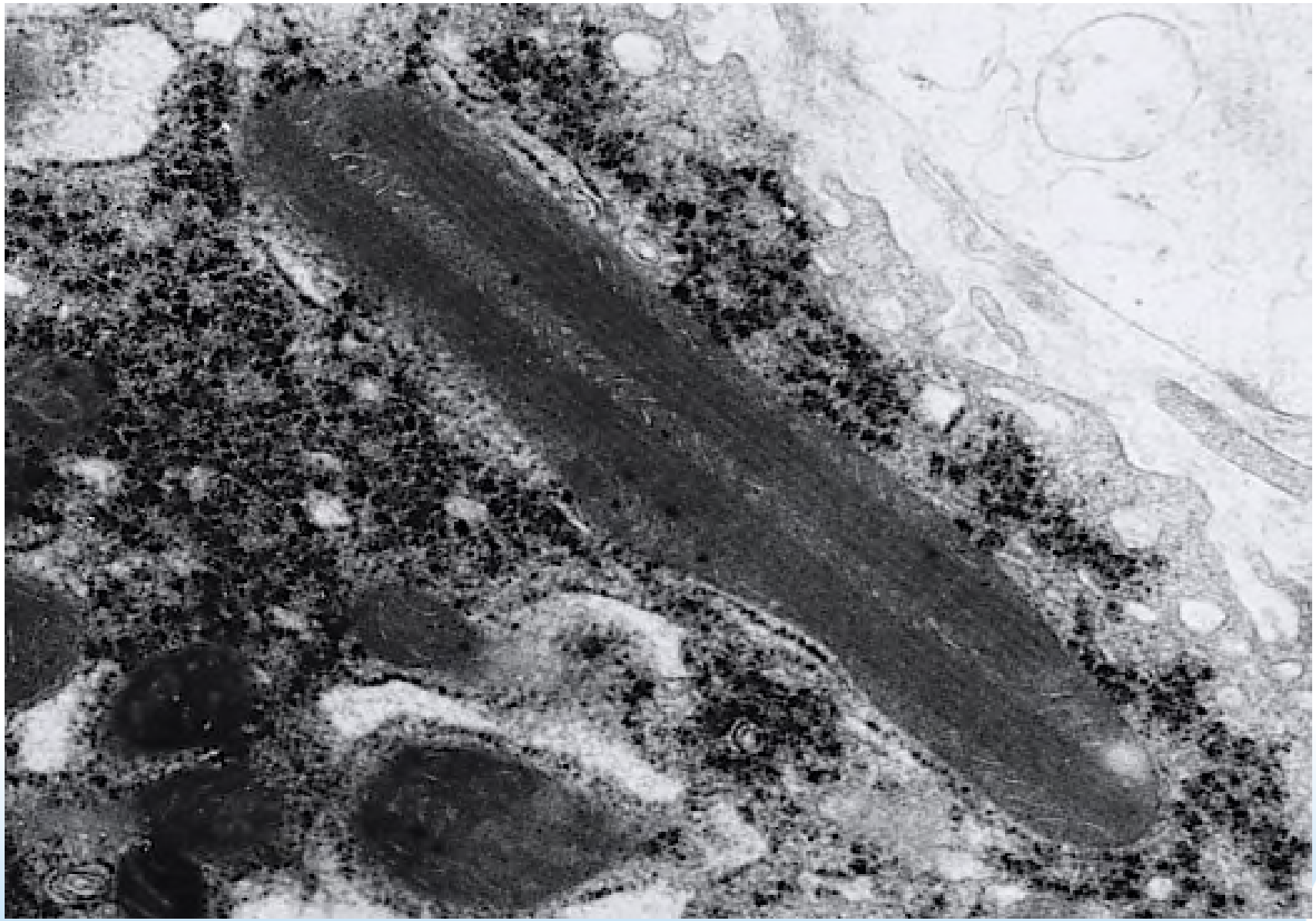


- Markedly increased number of mitochondria particularly in subsarcolemmal space

- Inclusions in mitochondria noted despite poor preservation from autopsy



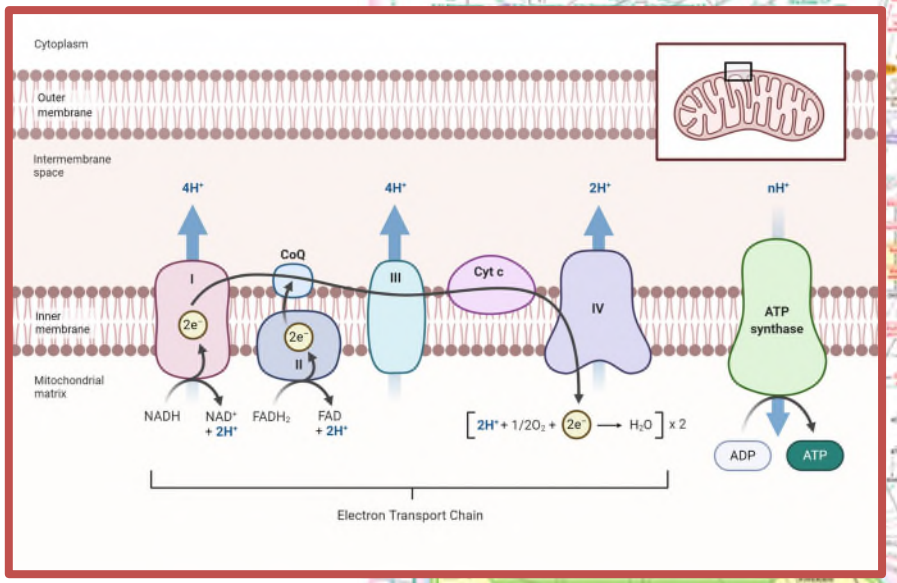
Mitochondrial disorder



Courtesy of Dr. Mika Warren

Where mito disorders fit on the map

- Defects of energy production
- Numerous genes implicated
- Variable degrees of severity
- Variable patterns of inheritance

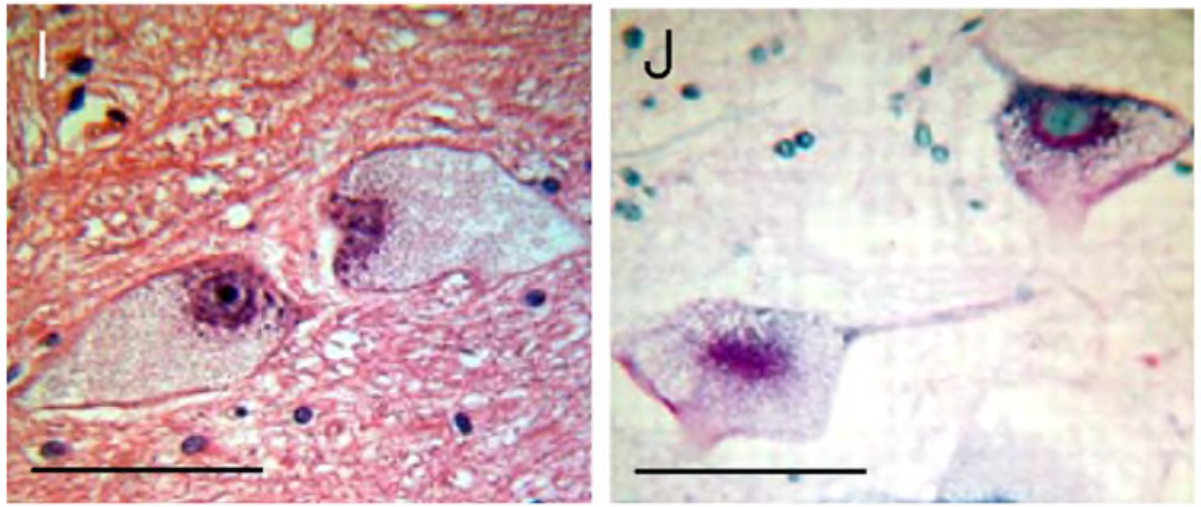


Pompe disease (Glycogen storage disease type II)

- Glycogen accumulation disorder (lysosomal aggregates)
- Acid alpha-glucosidase deficiency ("GAA," lysosomal enzyme)
  - a.k.a. acid maltase
  - AR inheritance, *GAA* pathogenic variants
- 1:40,000 births
- Infantile and late-onset types
  - Onset age associated with severity of deficiency
  - White matter hyperintensity and hypertrophic cardiomyopathy common in infantile type
  - Slowly progressive myopathy typical of late-onset type
- Enzyme replacement therapy available

CNS Neuropathology features in Pompe

- Glycogen accumulation in brainstem, cortex, dentate nuclei, Purkinje cells (case reports)
- Glycogen accumulation in anterior horn cells (common)
- Neuronal loss with areas of gliosis

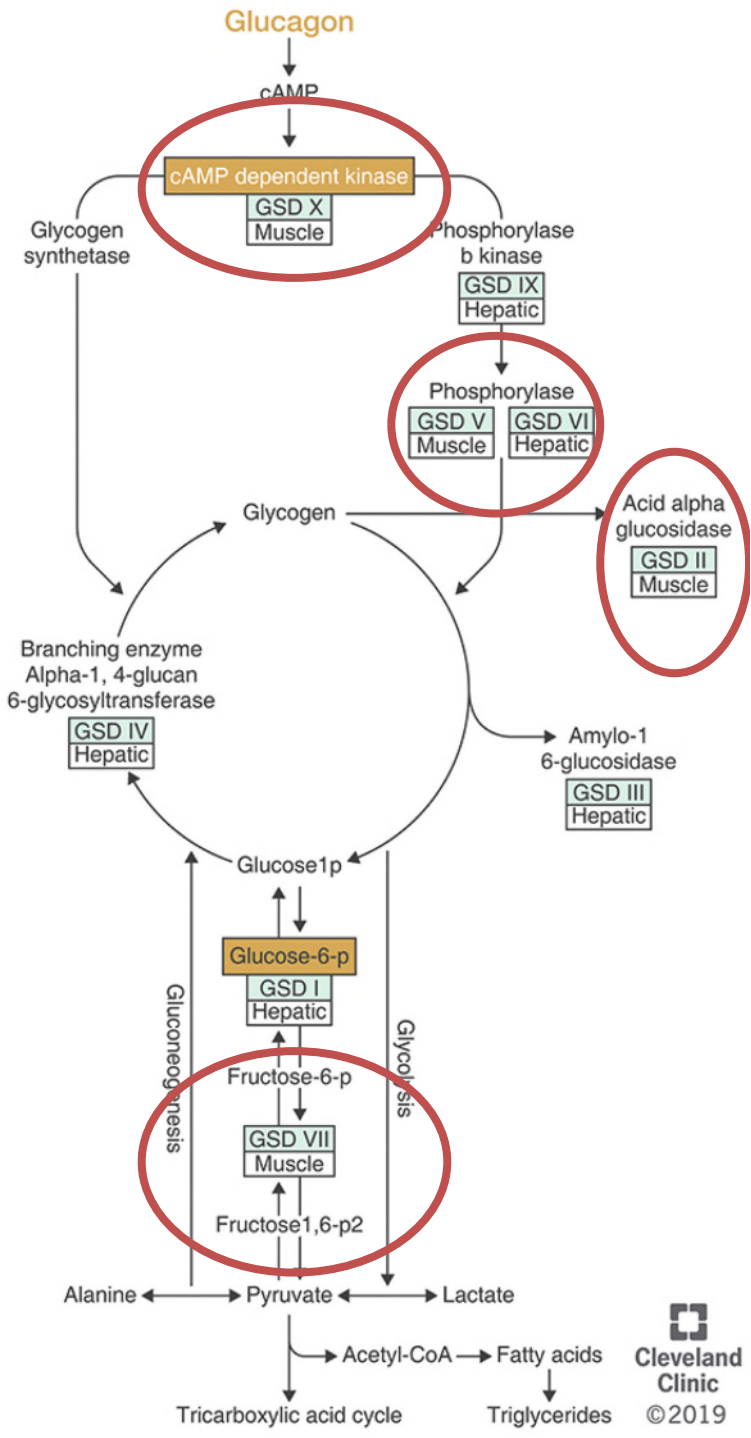


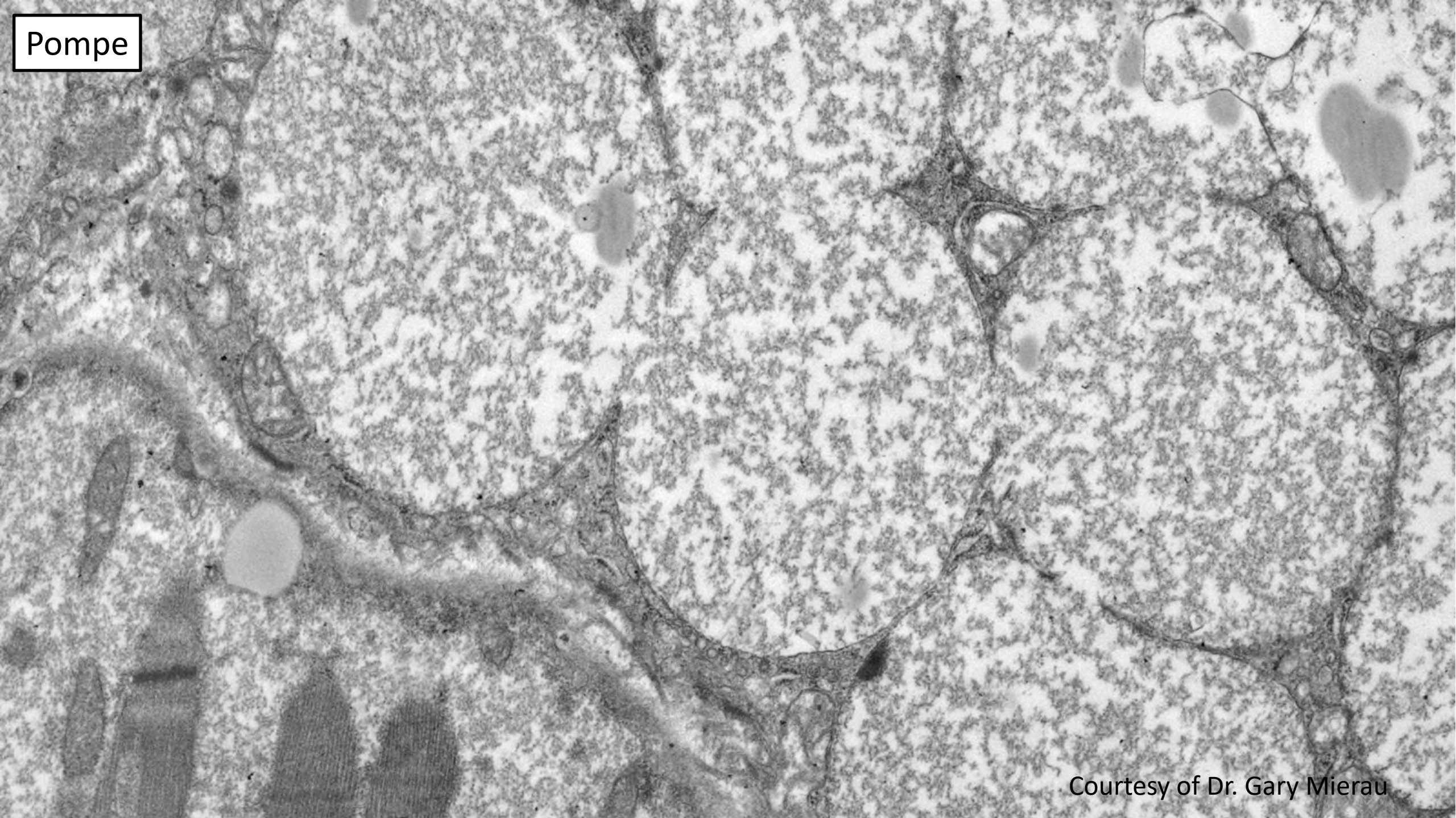
H&E PAS

DeRuisseau et al. PNAS 2009

Glycogen storage diseases that affect muscle

- Type II (Pompe, GAA)
- Type V (McArdle, phosphorylase)
- Type VII (Tarui, phosphofructokinase)
- Type IX (phosphorylase b kinase)
  - Muscle involvement only rarely
- Type X (Dimauro, phosphoglycerate mutase)



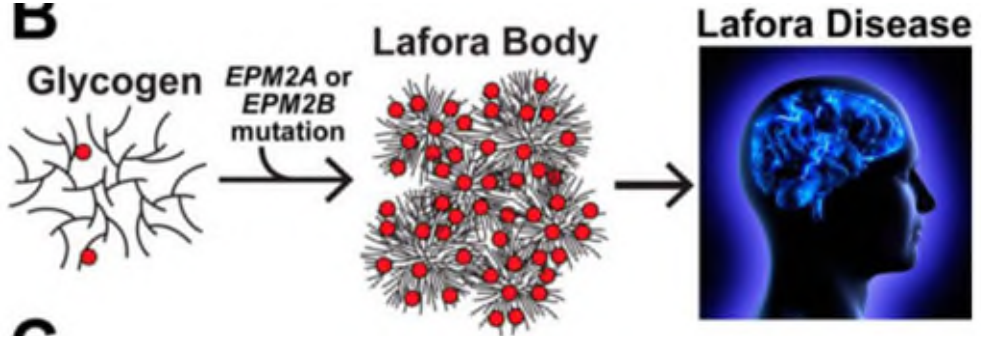

Pompe
Courtesy of Dr. Gary Mierau

Case 6

- 14 year old F with intractable epilepsy
- Axillary biopsy (target eccrine duct cells)
- *NHLRC1* mutation (homozygous)

Lafora disease

- Estimated prevalence 0.4:100,000
- Glycogen metabolism disorder
- Accumulation of polyglucosan (poorly branched glycogen)
- Progressive myoclonic epilepsy, starting in teenage years
- Genetics: mutations of
  - *EPM2A* laforin, glycogen phosphatase
  - *NHLRC1 (EPM2B)* malin, E3 ubiquitin ligase (ubiquitinates glycogen metabolism enzymes)
  - Either result in excess of hyperphosphorylated glycogen with disrupted glucose chain branching

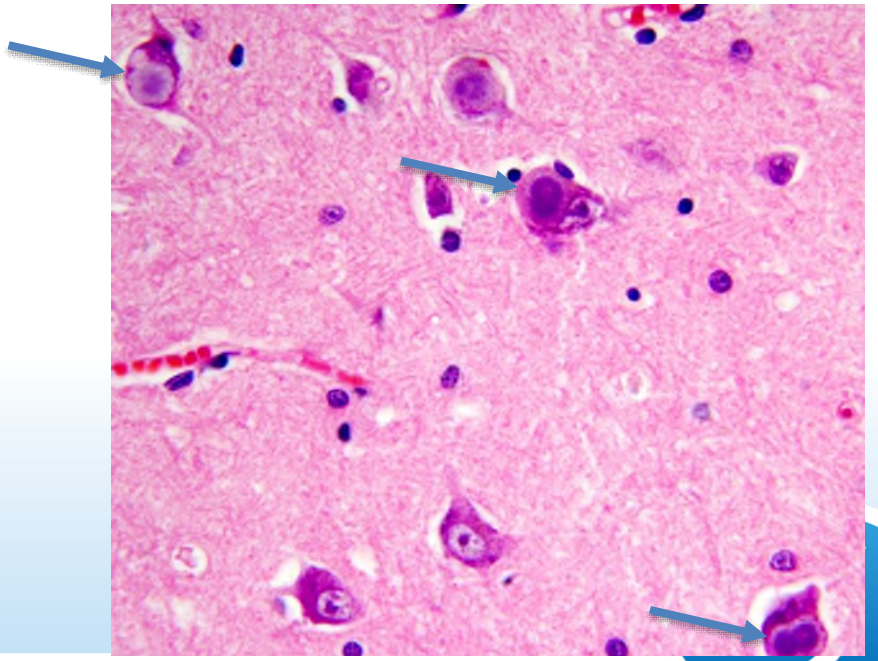


JBC THEMATIC MINIREVIEW

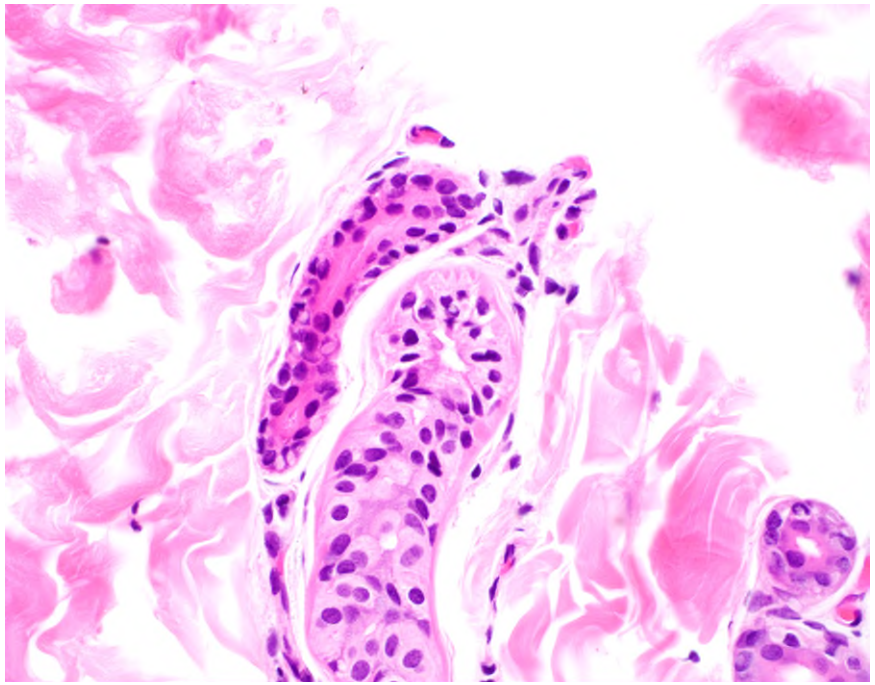
Lafora disease offers a unique window into neuronal glycogen metabolism

Published, Papers in Press, February 26, 2018, DOI 10.1074/jbc.R117.803064

Matthew S. Gentry,[a,b,c,1] Joan J. Guinovart,[a,d,e,f] Berge A. Minassian,[a,g,h] Peter J. Roach,[a,i] and Jose M. Serratosa[a,j,k]



https://chelseashope.org/overview-of-lafora/



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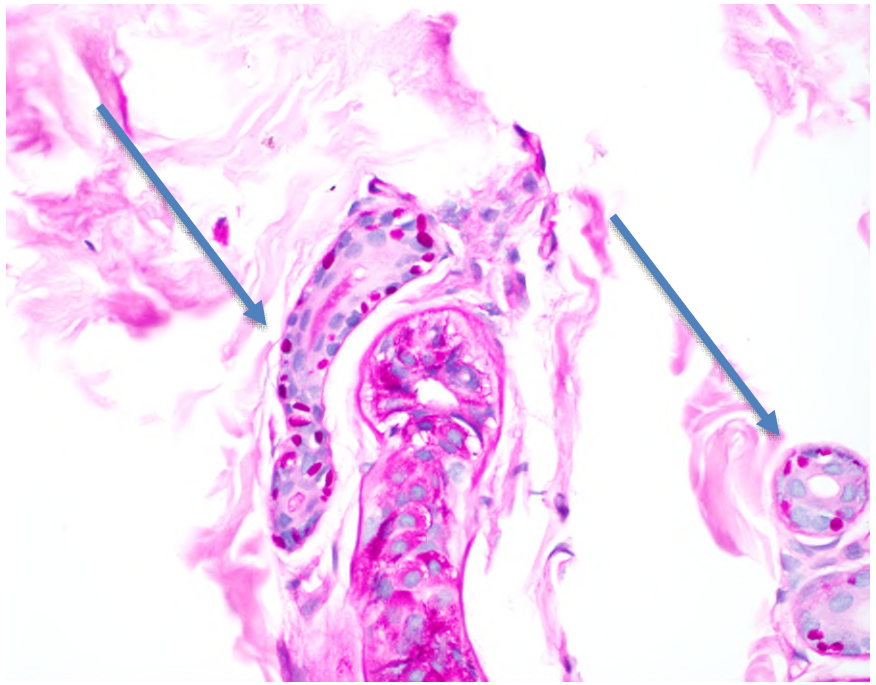
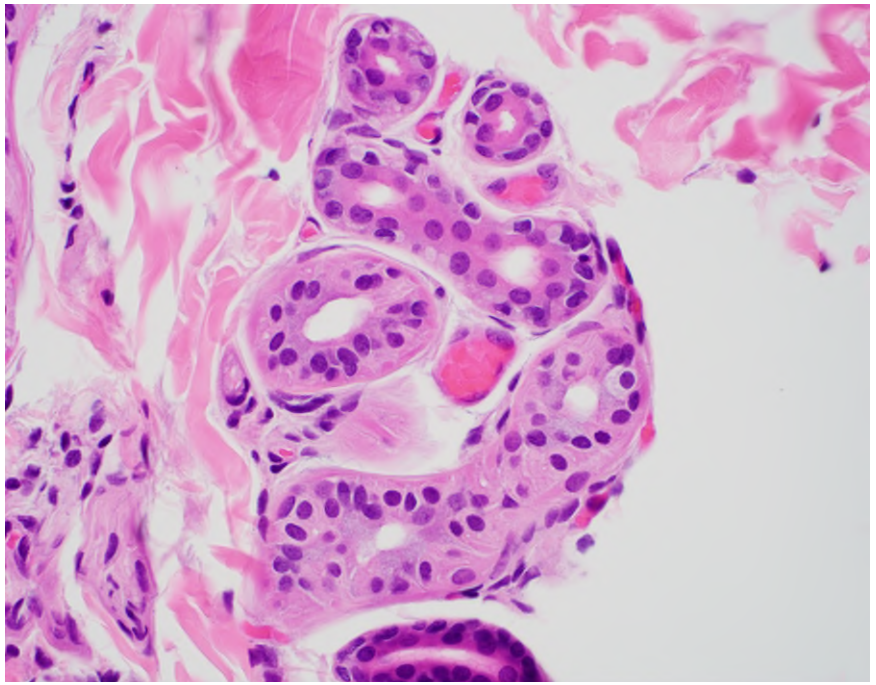


PAS 40x



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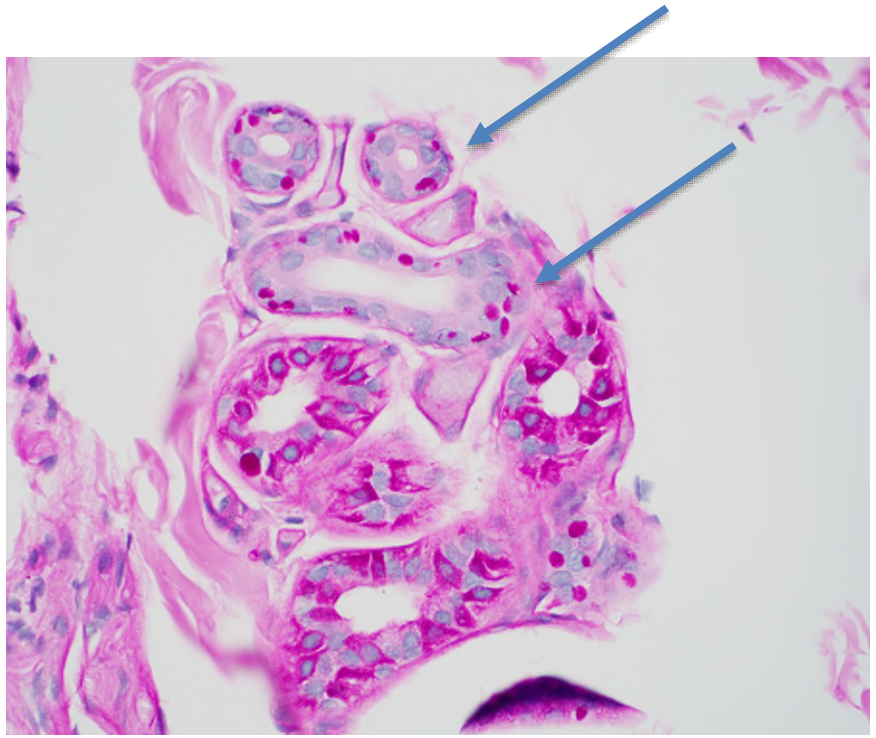

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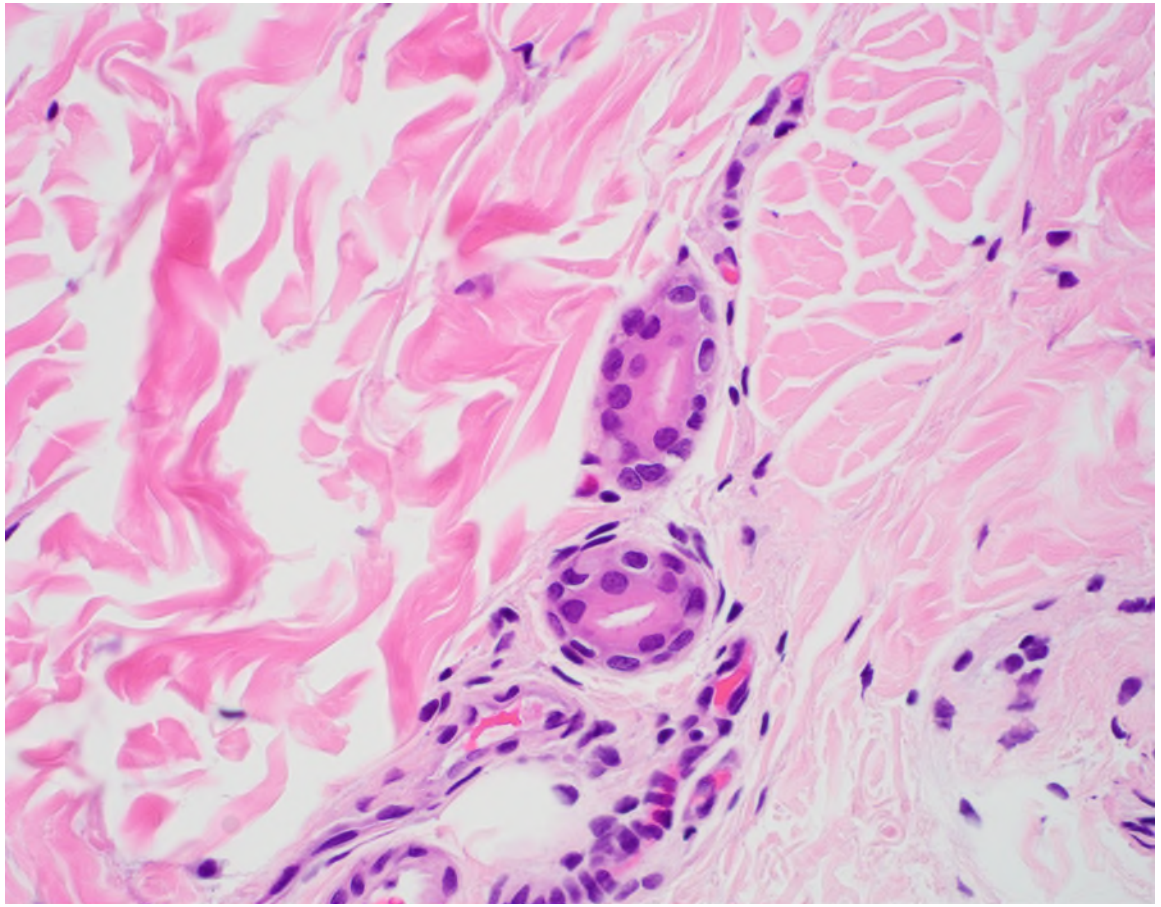

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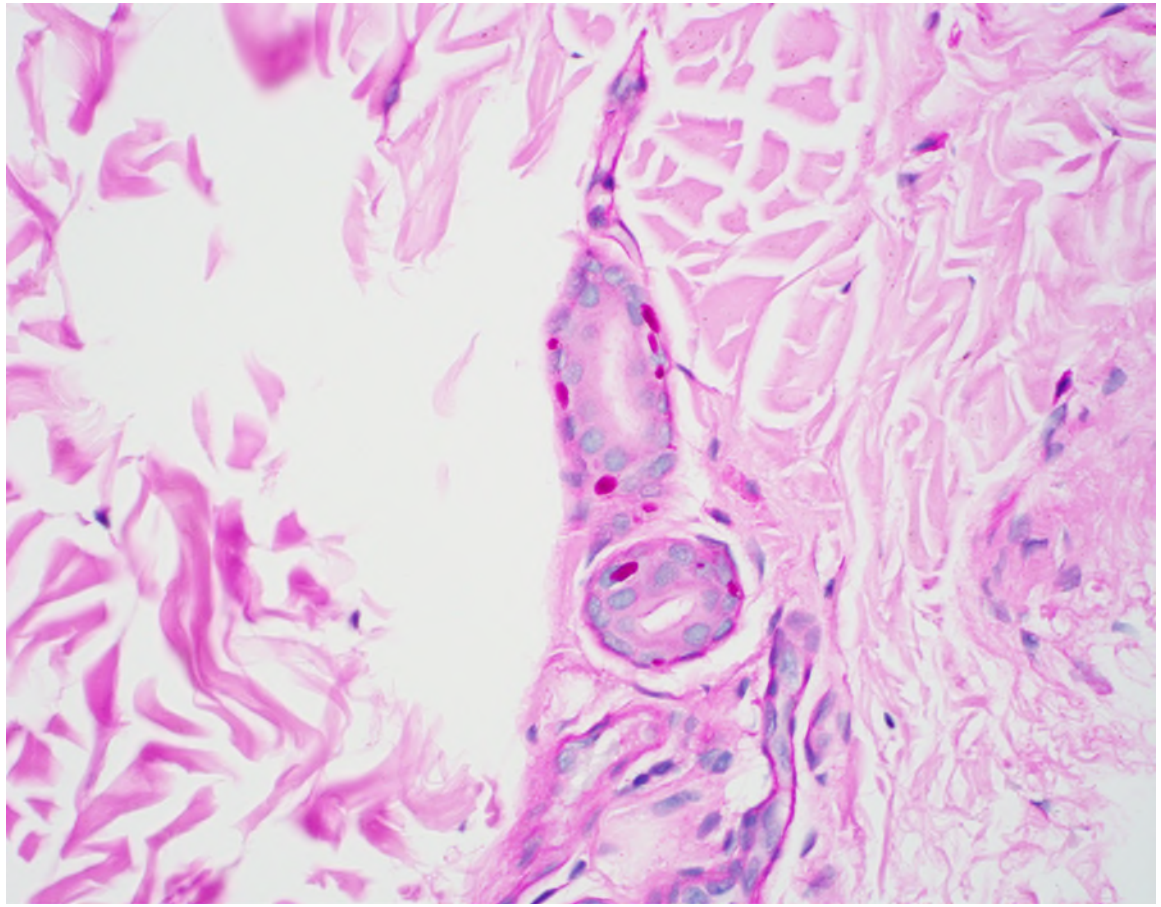


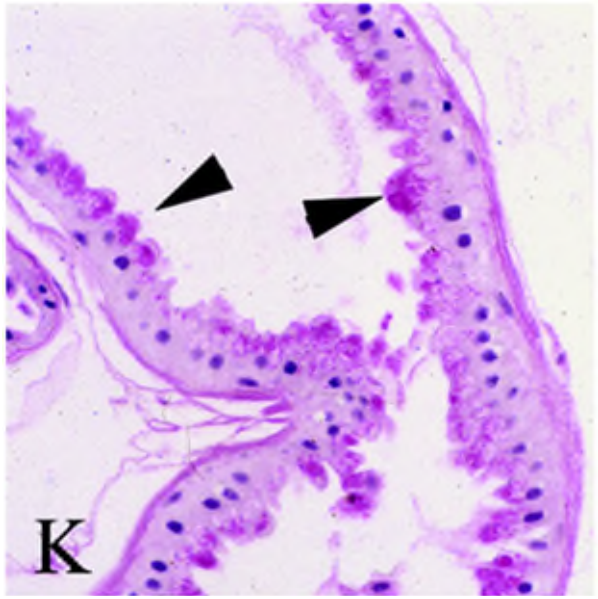
PAS 40x

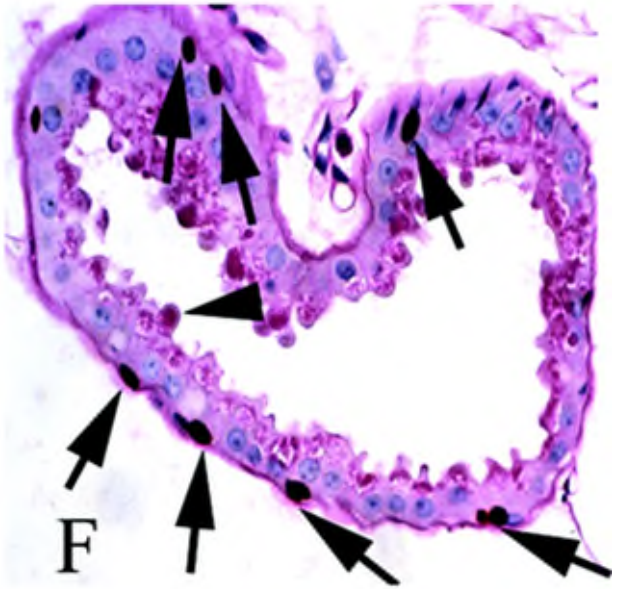
CME

Skin biopsy in Lafora disease

Genotype–phenotype correlations and diagnostic pitfalls

D.M. Andrade, MD; C.A. Ackerley, PhD; T.S.C. Minett, MD; H.A.G. Teive, MD; S. Bohlega, MD; S.W. Scherer, PhD; and B.A. Minassian, MD

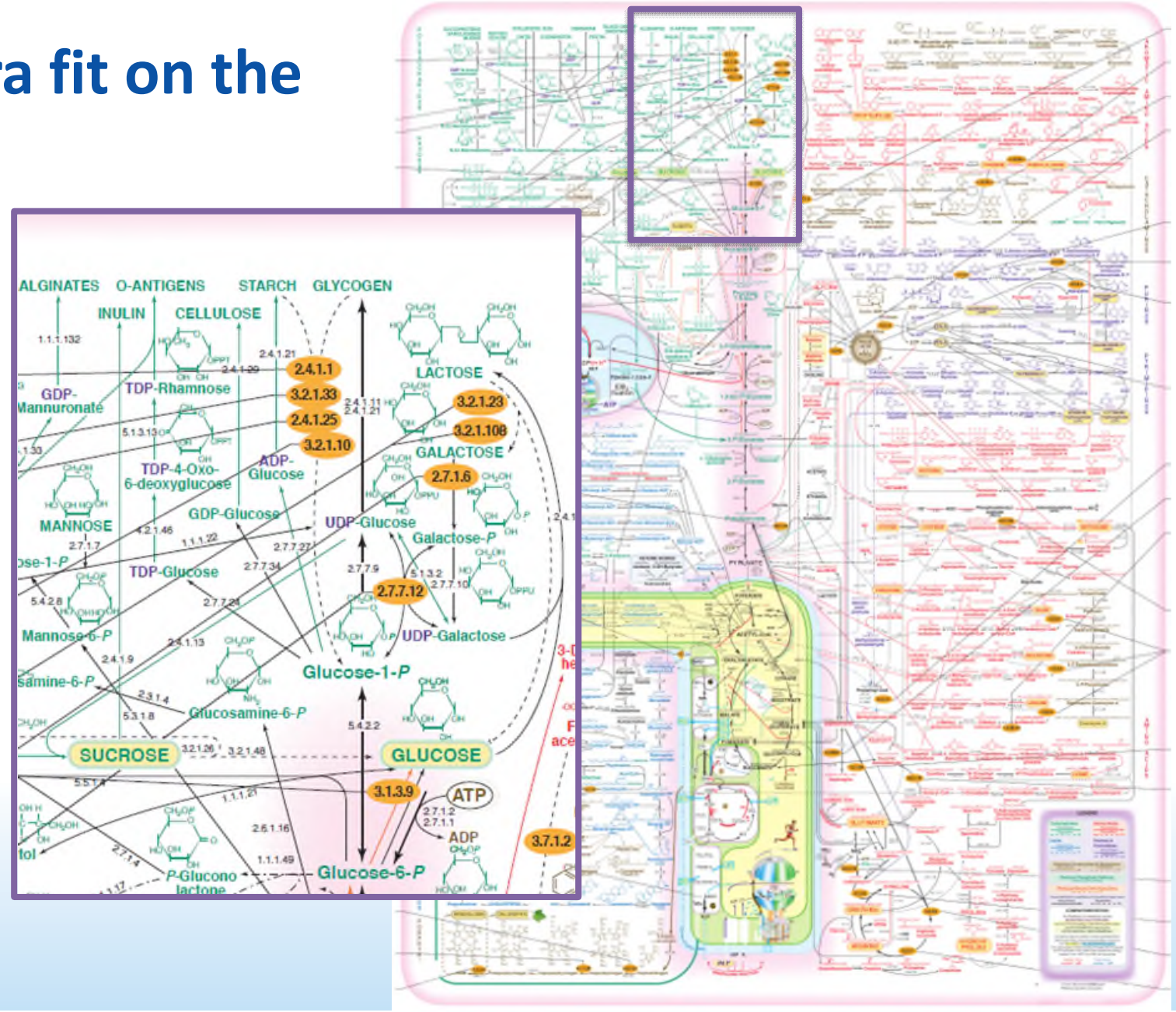




- Note that apocrine glands can normally have prominent PAS-positive inclusions in their apical regions
  - Arrowheads – normal
  - Full arrows – Lafora bodies
- Diagnostic inclusions should be basal/myoepithelial
- Some advise avoiding axillary skin for this reason

Where Pompe and Lafora fit on the map

- Glycogen to G-1-P cycle errors
  - Classical GSD
- Glycogen branching errors
  - Lafora disease



Disease	Category	Gene(s)	Molecule(s) accumulated	Neuropathology
PKU	Amino acid disorder	PAH	Phenylalanine	Small brain, spongy WM
GA-1	Amino acid/organic acid disorder	GCDH	glutaric acid, 3-OH-glutaric acid, glutaconic acid	Small striatum, spongy WM
Canavan	Amino acid disorder	ASPA	NAA	Spongiform WM, U-fibers involved
Gaucher	Lysosomal storage		glucocerebroside	Perivascular storage PAS+ Mϕ
NPC	Lysosomal storage	NPC1/2	cholesterol, lipids	Cerebral atrophy, neurons with storage material (PAS+/-)
Krabbe	Lysosomal storage	GALC	Galactocerebroside	Small firm brain, demyelination
MCL	Lysosomal storage	ARSA	Sulfatides	Diffuse demyelination, U-fibers spared
Mito (LS, LTBL)	Energy deficiency	Various		Symmetrical subacute focal necrosis (with vascular proliferation)
Pompe	Glycogen metabolism/ Lysosomal storage	GAA	Glycogen	Myopathy
Lafora	Glycogen metabolism	EPM2A, NLHRC1	Hyperphosphorylated glycogen	Intracellular inclusions

Outline

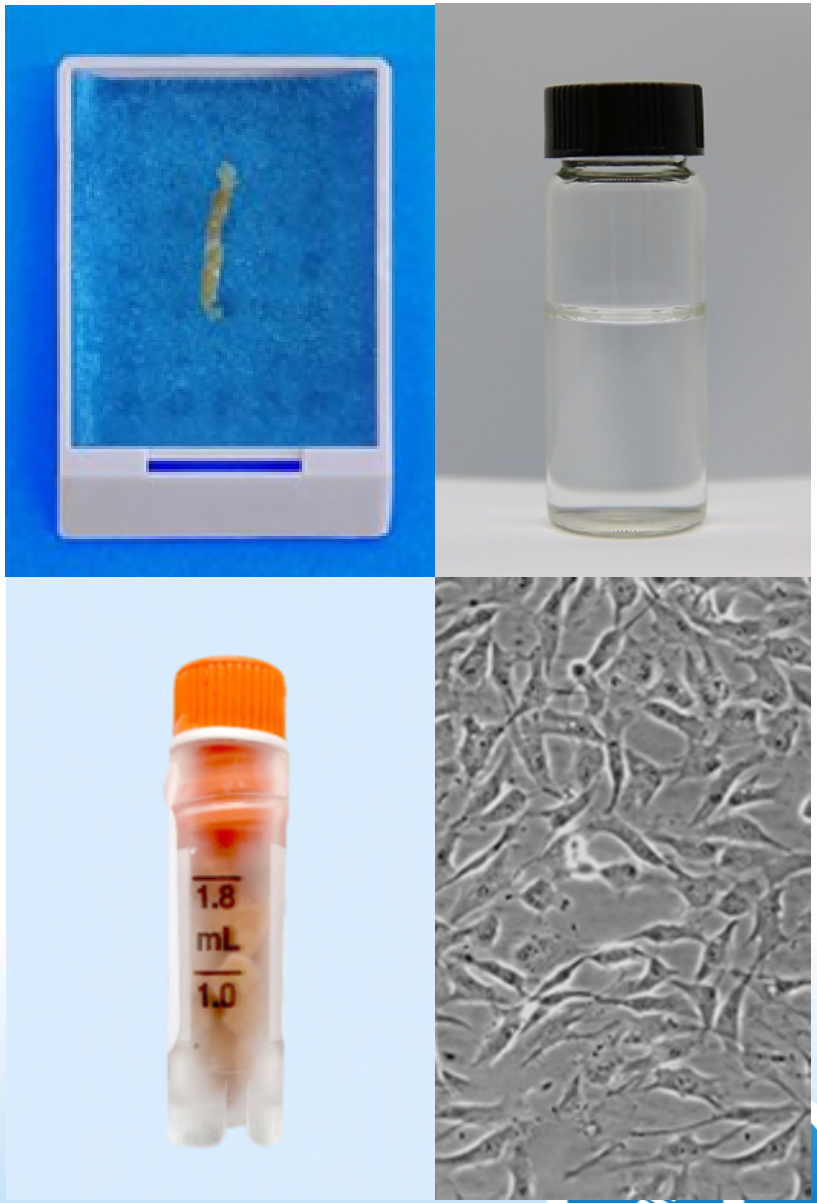
- Background
- Amino acid and organic acid disorders PKU, GA1
- Storage disorders Gaucher, Niemann-Pick type C, Krabbe
- Mitochondrial disorders Leigh syndrome, LTBL
- Glycogen metabolism disorders Pompe, Lafora
- Practical considerations

Clinical suspicion for metabolic disorder

- History of parental consanguinity
- History of unexplained death, multiple spontaneous abortions
- Critical illness with nonspecific findings refractory to normal treatments
  - Dehydration
  - Acidosis
  - Vomiting
  - Seizures
- Acute encephalopathy
- Hydrops fetalis or placental abnormalities

Biopsies for metabolic disorders

- Liver, muscle, intestinal, skin biopsies more common
- Any tissue should be divided for
  - morphology
  - biochemical analysis
  - probably EM
  - skin for fibroblast culture



“Metabolic autopsy” (Ernst et al., *J. Peds* 2006)

- Rapid tissue collection required
- Suggested procurement:
  - Snap frozen tissue (liver, muscle, heart, kidney, brain)
  - Tissue in glutaraldehyde for EM
  - Blood
  - Urine
  - Vitreous fluid
  - Bile
  - Skin

THE VALUE OF THE METABOLIC AUTOPSY IN THE PEDIATRIC HOSPITAL SETTING

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Emergence of rapid exome/genome sequencing for NICU (2012-present)

- Can be fast but not yet cheap
- Raises ethical challenges not present in traditional mass spec screening
  - How to manage uncertain or unrelated genetic findings
  - Status of parental consent in medical crisis
  - Whether to use result to redirect/withdraw care
- Could shorten time to definitive diagnosis
- Shift towards genomic diagnosis for **newborn screening** is being studied in many countries; cost and variant calling are issues

Learning Objectives

1. Describe how inborn errors of metabolism present clinically and are diagnosed
2. Identify specific histologic patterns observed in lysosomal storage disorders, organic acidemias, and mitochondrial disorders
3. Outline the appropriate steps for tissue handing in the setting of a suspected metabolic disorder

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Q&A