Metabolic Disorders Overview

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Disclosures:
Nothing to disclose

Objectives

1. To review common inborn errors of metabolism presenting with neurological symptoms
2. recognize clinical features
3. recognize laboratory findings
4. understand approach to treatment

Outline

- Introduction
- Overview of disorders of small molecule metabolism
- Overview of disorders of complex molecule metabolism

Inborn Errors of Metabolism (IEMs)

- Genetic disorders that disrupt biochemical processes in the body
  - enzyme activity, cellular transport, or mitochondrial bioenergetics
- >500 described to date
- Individually rare, but collective incidence of 1/1000

Categories of IEMs

1. Disorders of small molecule metabolism
2. Disorders of complex molecule metabolism
3. Disorders of energy metabolism
4. Miscellaneous inborn errors of metabolism

Categories of IEMs

1. **Disorders of small molecule metabolism**
2. **Disorders of complex molecule metabolism**
3. Disorders of energy metabolism
4. Miscellaneous inborn errors of metabolism

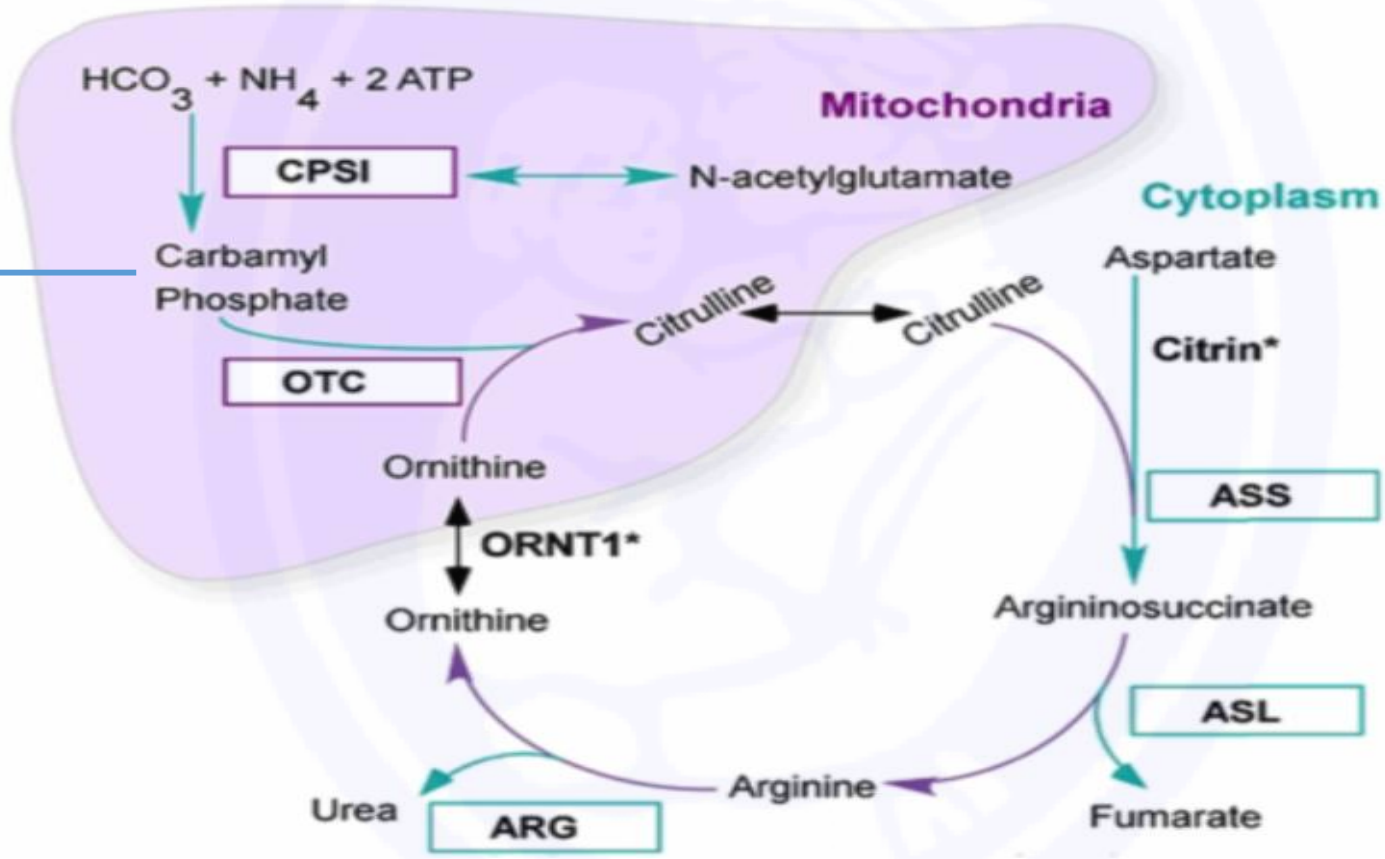
Disorders of small molecule metabolism

- Includes
  - Urea cycle disorders
  - Fatty acid oxidation and carnitine disorders
  - Organic acidemias
  - Amino acidopathies
- Most present with **acute/episodic** decompensations
- Most are associated with **basic biochemical abnormalities**
  - Acid-base disturbance, hypoglycemia, hyperammonemia, or ketosis
  - Exceptions: “cerebral” organic acidemias, aminoacidopathies
- Most are amenable to **specific treatments**

Urea Cycle Disorders

Urea Cycle

Orotic acid
Orotidine



Mourad M., et al. Int. J. Neonatal Screen. 2016

Urea Cycle Disorders

- Inheritance
  - Autosomal recessive, except ornithine transcarbamylase deficiency (x-linked)

- Clinical presentation
  - Onset from neonatal period to 6th decade
  - Episodic hyperammonemic encephalopathy
    - Neuro signs: headache, ataxia, seizures, psychiatric symptoms, altered mental status
    - nausea and vomiting
    - hyperventilation
  - Episodes provoked by illness, fasting, protein load, medications (eg. **valproic acid**)

Urea Cycle Disorders

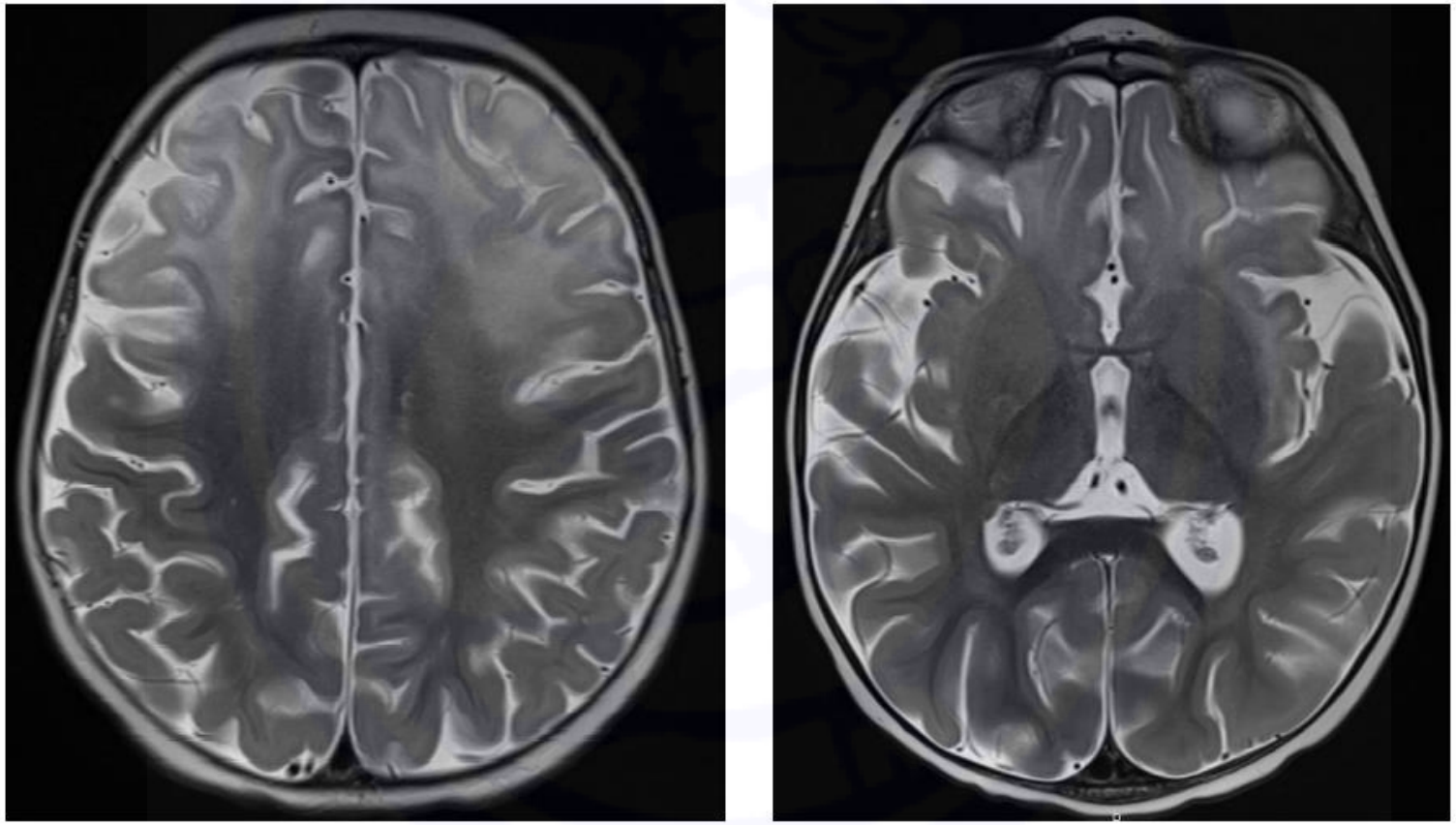
- General laboratory studies
  - Ammonia elevated > 80 umol/L (> 110 umol/L in neonate)
  - Primary respiratory alkalosis

- Diagnostic metabolic labs
  - Plasma amino acids: abnormal citrulline or arginine
  - Urine organic acids: orotic acid or arginosuccinic acid

Urea Cycle Disorders: plasma amino acids & urine organic acids

Disorder	Plasma amino acids	Urine organic acids
N-acetylglutamate synthetase deficiency	Low citrulline	Low orotic acid
Carbamoyl phosphate synthetase deficiency	Low citrulline	Low orotic acid
Ornithine transcarbamylase deficiency	Low citrulline	High orotic acid
Argininosuccinate synthetase deficiency	High citrulline	High orotic acid
Argininosuccinate lyase deficiency	High citrulline	Normal orotic acid, argininosuccinic acid
Arginase deficiency	High arginine	High orotic acid

MRI in hyperammonemic encephalopathy



14 mo F with ornithine transcarbamylase deficiency presenting with hyperammonemia

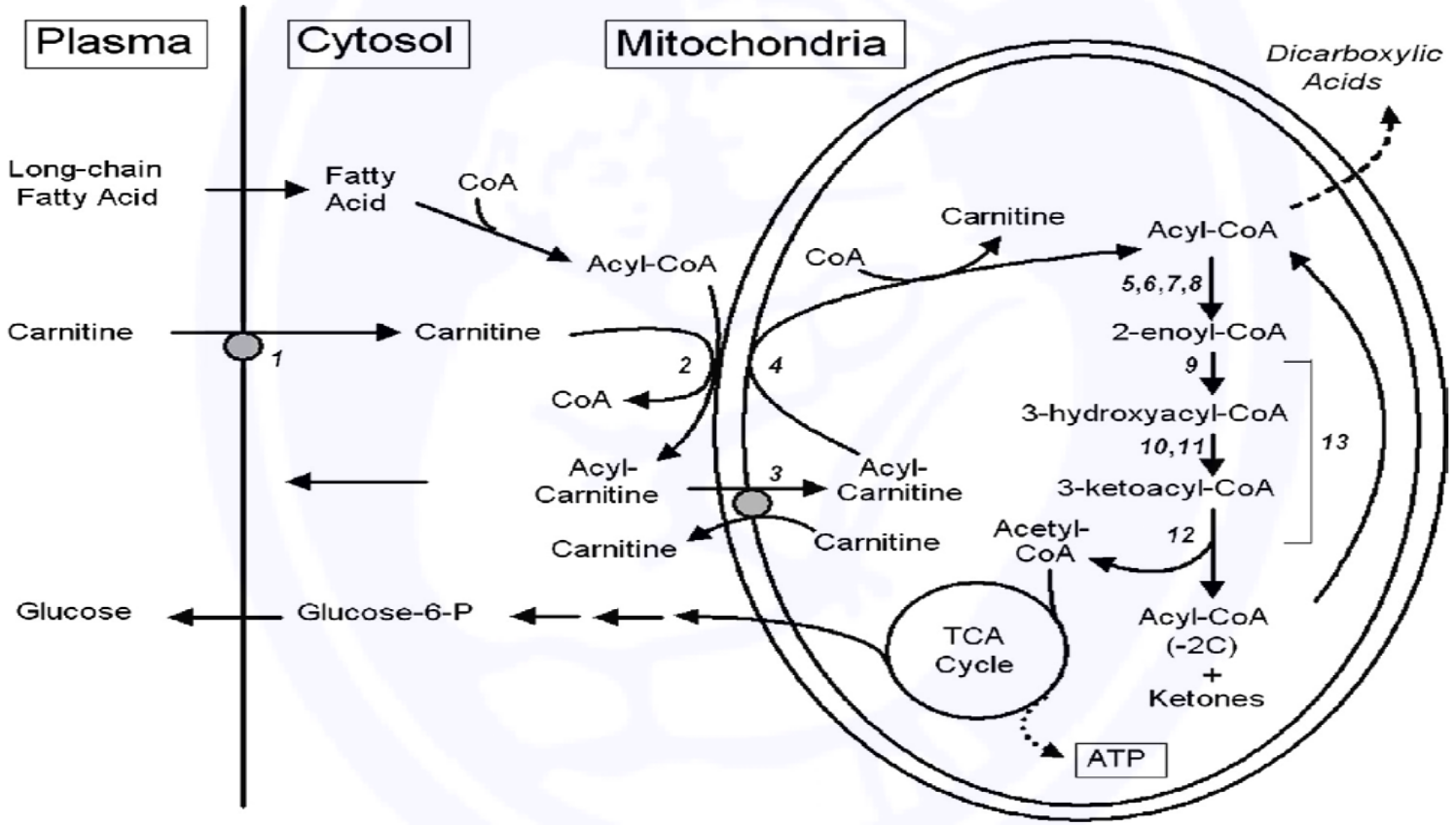
Urea Cycle Disorders: Treatment

- Acute
  - Stop protein
  - Provide protein-free calories via high dextrose infusion +/- intravenous lipid
  - IV ammonia scavenger Ammonul (sodium phenylacetate/benzoate)
  - IV arginine (except in arginase deficiency)
  - In severe/refractory cases, hemodialysis
  - In NAGS deficiency: N-carbamylglutamate

- Chronic
  - Protein restriction
  - Oral ammonia scavengers, (N-carbamylglutamate in NAGS deficiency)
  - Oral L-citrulline/L-arginine (except in arginase deficiency)
  - Liver transplant in severe cases or if significant liver disease

Fatty Acid Oxidation & Carnitine Disorders

Mitochondrial Fatty Acid Oxidation



Kompare et al. 2008

Fatty Acid Oxidation & Carnitine Disorders

- Fatty acid oxidation disorders
  - Medium chain acyl-CoA dehydrogenase deficiency (MCADD)
  - Very long chain acyl-CoA dehydrogenase deficiency (VLCADD)
  - Long chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
  - Mitochondrial Trifunctional Protein Deficiency (MTPD)

- Carnitine Disorders
  - Carnitine transporter deficiency
  - Carnitine palmitoyl-transferase 1 deficiency (CPT1)
  - Carnitine palmitoyl-transferase 2 deficiency (CPT2)
  - Carnitine-acylcarnitine translocase deficiency (CAT)

- Inheritance: autosomal recessive

Fatty Acid Oxidation & Carnitine Disorders

- Clinical presentation
  - Onset ranging from neonatal period to adulthood
  - Episodes provoked by illness and/or fasting (less often: high fat intake, meds like **valproate**)
  - Signs and symptoms
    - **Hypoglycemia**
    - **Hepatopathy**
    - **Encephalopathy**
    - SIDS, Reye-like syndrome
  - Additional symptoms in long chain disorders (VLCADD, LCHADD, MTPD, CPT2):
    - **Skeletal myopathy/rhabdomyolysis (episodic, exercise or illness-induced)**
    - **Cardiomyopathy**
    - Retinopathy & axonal polyneuropathy (only in LCHADD/MTPD)

Fatty Acid Oxidation & Carnitine Disorders

- General laboratory studies
  - **Hypoglycemia**
    - **Hypoketotic:** inappropriately low plasma beta-hydroxybutyrate (BHB), increased FFA:BHB ratio
  - **Abnormal LFTs**
  - **Elevated CPK (1000's)** (in long chain disorders)

- Diagnostic metabolic studies
  - **Plasma acylcarnitine profile** (may normalize when asymptomatic)
  - Free/total carnitine (increased in CPT1 deficiency; can be decreased in all others)

Plasma Acylcarnitines

Disorder	Plasma acylcarnitine abnormalities
Fatty acid oxidation disorders	
MCAD	C8 > C6 > C10
VLCAD	C12, C14, C14:1, C16, C18
LCHAD	C14OH, C16OH, C18OH, C18:1OH
MTP	C14OH, C16OH, C18OH, C18:1OH
Carnitine disorders	
Carnitine transporter	All acylcarnitines **decreased**
CPT1	**Decreased** C16, C18, C18:1
CAT	C16, C18, C18:1
CPT2	C16, C18, C18:1

Fatty Acid Oxidation & Carnitine Disorders: Treatment

- Acute
  - High dextrose infusion
  - MCT supplementation in long chain disorders

- Chronic
  - Avoidance of prolonged fasting (age dependent)
  - Carnitine supplementation if low
  - Long chain disorders
    - limit % calories from long chain fats (8-20%), monitor for essential fatty acid deficiency
    - MCT supplementation

Organic Acidemias

Organic Acidemias

- Disorders associated with the impaired metabolism of organic acids derived from amino acid oxidation (protein), resulting in accumulation and toxicity

- Can be divided into “classic” and “cereberal” organic acidemias
  - ***Classic organic acidemias***: neurological symptoms + acidosis, ketosis, hyperammonemia, (eg. methylmalonic and propionic acidemia)

  - ***Cerebral organic acidemias:*** neurological symptoms with no/minimal systemic metabolic abnormalities (eg. Glutaric aciduria type 1)

Methylmalonic & Propionic Acidemia

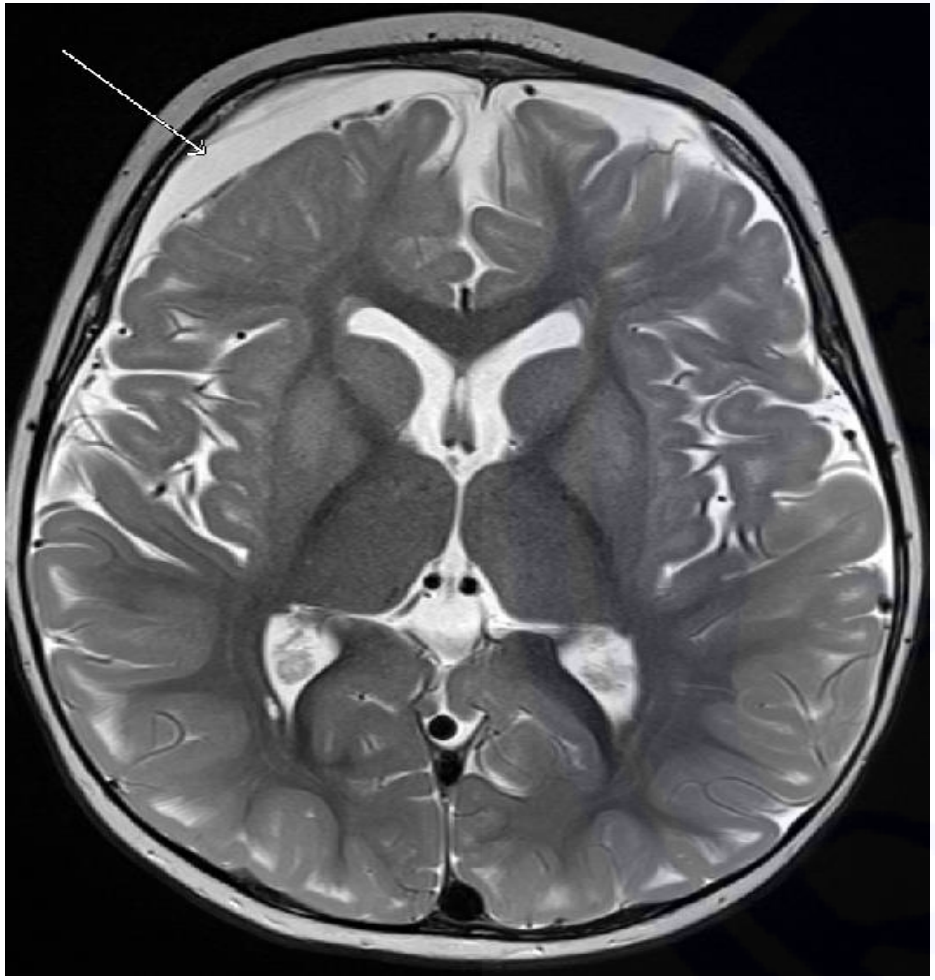
- Prototypical “classic” organic acidemias
- Enzymes in oxidation pathway of valine, isoleucine, methionine, and threonine
- Inheritance: autosomal recessive
- Presentation
  - Episodic decompensations provoked by illness, fasting, high protein intake
  - **Acute presentation:** acute encephalopathy, seizure, hyperventilation, metabolic stroke, pancreatitis
  - **Chronic complications:** DD/ID, failure to thrive, movement disorder, diabetes, cytopenia
  - deafness & cardiomyopathy/long QT in propionic acidemia
  - optic atrophy & renal disease in methylmalonic acidemia

Methylmalonic & Propionic Acidemia

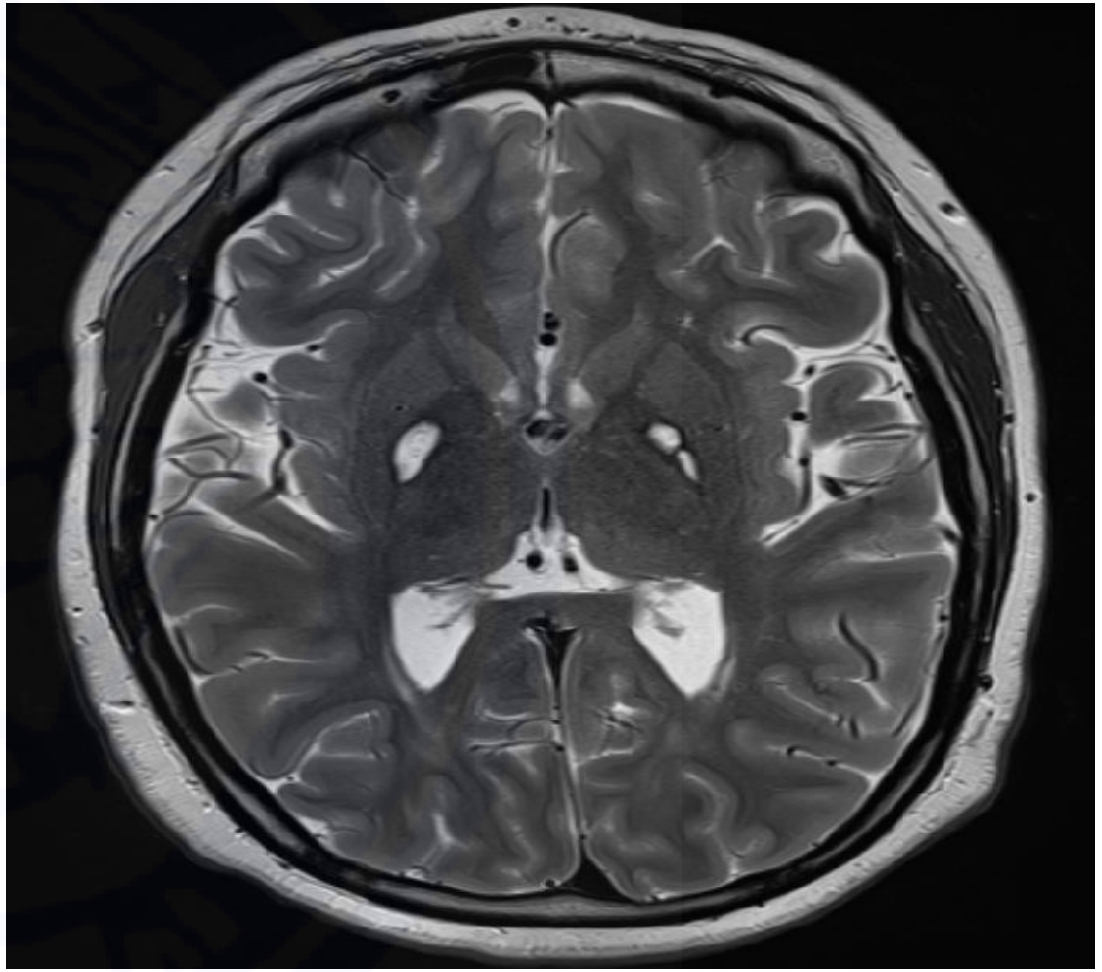
- Basic Labs
  - Increased gap metabolic acidosis
  - Ketonemia/ketonuria* (*Urine ketones are always abnormal in the neonate)
  - Hyperammonemia
  - +/- lactic acidosis

- Diagnostic metabolic labs
  - **Plasma acylcarnitine profile**: Increased propionylcarnitine (C3)
  - **Urine organic acids:** diagnostic metabolites
  - (plasma amino acids: increased glycine, reduced glutamine)

Methylmalonic & Propionic Acidemia



13 month old M with propionic acidemia



14 year old M with methylmalonic acidemia

Methylmalonic & Propionic Acidemia: Treatment

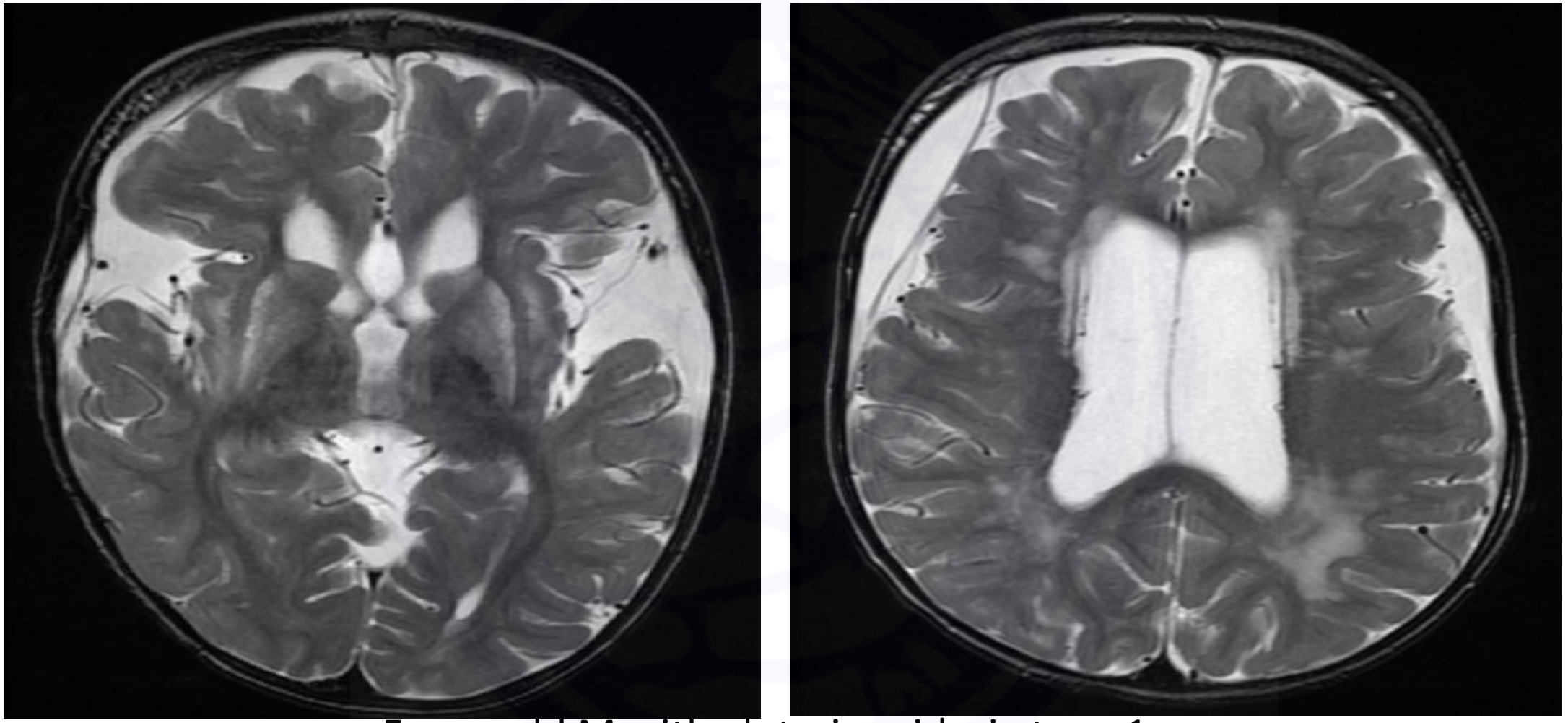
- Acute
  - Stop protein
  - High dextrose +/- lipid infusion
  - Base therapy if acidemic
  - L-carnitine if deficient
  - Methylmalonic acidemia may be B12 responsive (IM hydroxocobalamin)

- Chronic
  - Protein restriction
  - May require chronic base therapy
  - L-carnitine
  - B12 therapy in methylmalonic acidemia if responsive
  - Liver transplant in severe cases

Glutaric Acidemia Type 1

- Enzyme in oxidation pathway of lysine, hydroxylysine, and tryptophan
- Inheritance: autosomal recessive
- Presentation
  - Macrocephaly
  - Development initially normal
  - At risk for metabolic stroke during illness, especially in first 6 years of life
  - **Following stroke, often severe disability with dystonia and spasticity**
  - **May mimic non-accidental injury with subdural and retinal hemorrhage**
  - Late-onset cerebral white matter disease in many, but clinical significance unclear
  - May be increased risk of developing malignant brain tumors (Russi et al. 2018)

Glutaric Acidemia Type 1



5 year old M with glutaric aciduria type 1

- Treatment
  - Lysine and tryptophan restricted, arginine-enriched diet
  - If significant illness/high fever, restrict protein/lysine and increase calories
  - L-carnitine supplementation

Amino Acidopathies

Amino Acidopathies

- Heterogenous group of disorders involving amino acid degradation, synthesis, or transport

- **Some present with acute encephalopathy**
  - Maple syrup urine disease
  - Sulfite oxidase deficiency
  - Molybdenum cofactor deficiency
  - Classic glycine encephalopathy
  - Homocystinurias (rarely)
  - Tyrosinemia (rarely, porphyric crises)

- **Some present with more static neurodevelopmental abnormalities +/- epilepsy**
  - Phenylketonuria
  - Homocysteinurias (usually)
  - Serine deficiency syndromes
  - Attenuated glycine encephalopathy

Amino Acidopathies

- Inheritance: autosomal recessive
- Diagnosis
  - Plasma amino acids
  - Additional metabolic studies required for diagnosis in some (see next slide)
- Many have specific & effective treatments
  - Maple syrup urine disease, homocysteinurias, phenylketonuria, tyrosinemia, serine synthesis disorders, attenuated NKH, molybdenum cofactor def

Disorder	Clinical features	Diagnosis
Maple syrup urine disease	Acute encephalopathy, ataxia,cerebral edema, maple syrup odor	Elevated BCAA in plasma, elevated alpha-ketoacids in urine
Non-ketotic hyperglycinemia	Seizures (early myoclonic encephalopathy), myoclonus, hiccups, hypotonia, brainstem dysfunction	Elevated CSF/plasma glycine ratio (>0.08)
Homocysteinemias	DD/ID, thrombosis, marfanoid features (in CBS deficiency)	Elevated total homocysteine, abnormal methionine
Phenylketonuria	Developmental delay, autism, pale skin/eczema if untreated	Elevated phenylalanine, elevated phe/tyr ratio
Tyrosinemia type 1	Liver and renal disease, acute intermittent porphyric crises	Elevated tyrosine, elevated urine & plasma succinylacetone
Sulfite oxidase/molybdenum cofactor deficiency	Mimics neonatal HIE after well period, epilepsy	Elevated urine sulfocysteine and urine sulfites, low urate (molybdenum cofactor deficiency)
Serine deficiency disorders	Epilepsy, DD/ID, congenital microcephaly, multiple congenital anomalies	Low CSF serine +/- low plasma serine

Maple Syrup Urine Disease

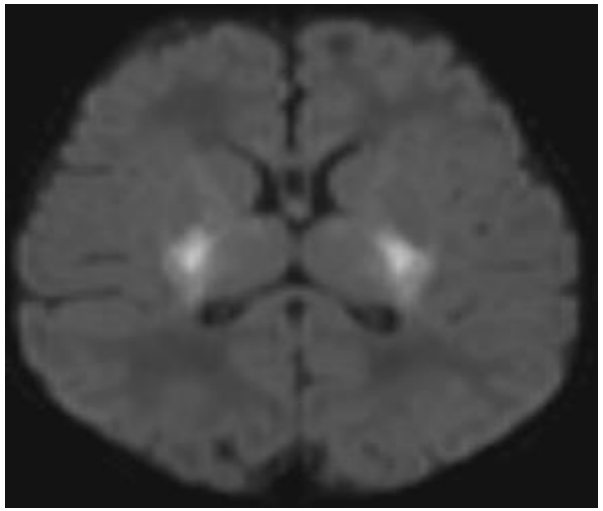
- Deficiency of enzyme in the oxidation of branched chain amino acids (leucine, isoleucine, valine)

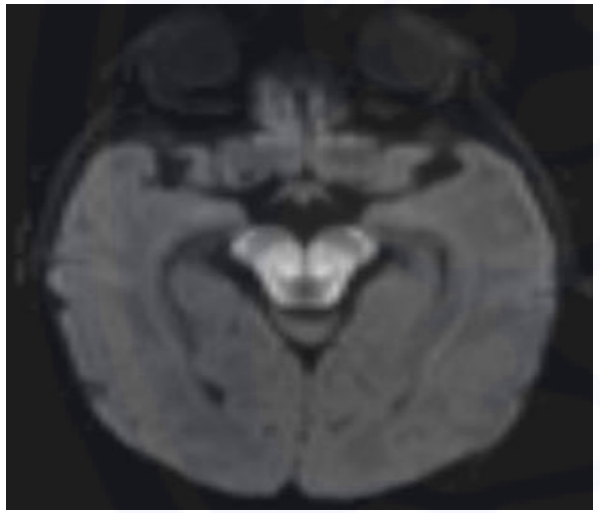
- Pathophysiology
  - Accumulation of leucine, isoleucine, and valine and their ketoacids
  - Very high levels of leucine are neurotoxic and causes cerebral edema
  - Leucine competes with other large neutral amino acids across shared CNS transporter (including neurotransmitter precursors tyrosine and tryptophan)

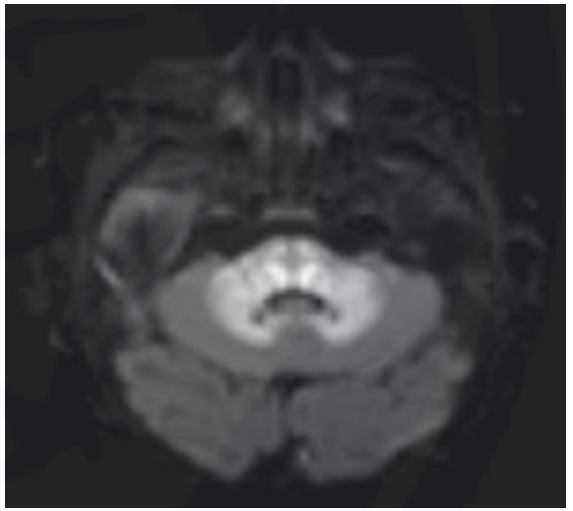
Maple Syrup Urine Disease

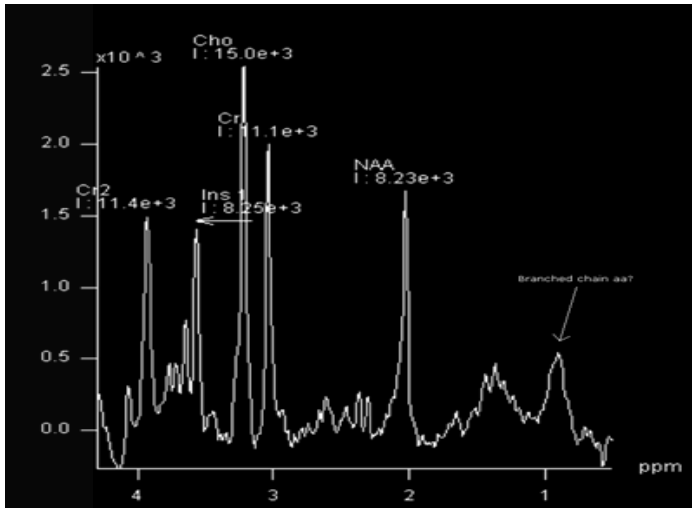
- Clinical presentation (classic form)
  - Neonatal-onset encephalopathy
  - May have seizures
  - Maple syrup odor to urine and ear wax (from sotolone, ddx: fenugreek)
- Laboratory diagnosis
  - Urine ketones +ve
  - May have ketoacidosis
  - Plasma amino acids: increased leucine, isoleucine, valine, **alloisoleucine**
  - May have hyponatremia (leucinosis causes SIADH)

Maple Syrup Urine Disease









Neonate with MSUD

Maple Syrup Urine Disease

- Acute management
  - **Requires immediate consultation with Metabolic specialist**
  - Stop all intact protein
  - Provide branched-chain amino acid free metabolic formula
  - Supplement with calculated amounts of isoleucine and valine (NO leucine)
  - If cerebral edema: standard ICU protocols, may consider hemodialysis

- Chronic management
  - Most of diet consists of branched-chain free amino acid metabolic formula
  - Small amount of intact protein (calculated according to mg of leucine)
  - Some patients respond to supplementation with cofactor thiamine

“Small Molecule” Screen

- Basic labs
  - Chemistry panel (bicarbonate, anion gap, glucose)
  - Urine ketones
  - Ammonia (free flowing, no tourniquet, on ice)
  - Lactic acid (free flowing, no tourniquet, on ice)

- Metabolic labs
  - Plasma amino acids
  - Urine organic acids
  - Plasma acylcarnitine profile
  - Free/total carnitine
  - Total homocysteine

Disorders of complex molecule metabolism

- Includes
  - Peroxisomal disorders
  - Lysosomal disorders
  - Congenital disorders of glycosylation
  - Cholesterol biosynthesis disorders

- **Associated with mostly chronic (static or slowly progressive) neurological abnormalities**

- **Most associated with dysmorphic features or multisystem involvement**

Peroxisomal Disorders

Peroxisomes

- Peroxisomes are small intracellular organelles found in all nucleated cells

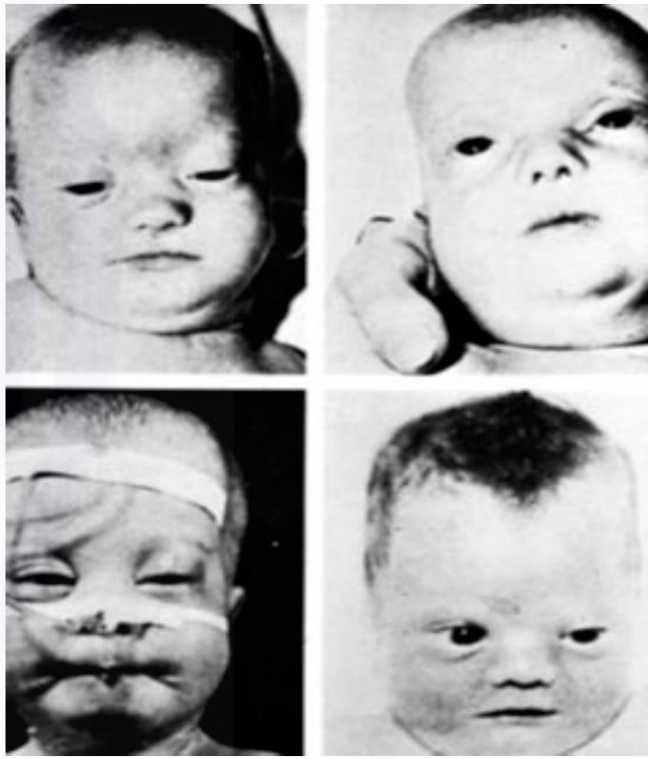
- Many functions facilitated by 50+ enzymes
  - Oxidation reactions
    - Beta-oxidation of very long chain fatty acids (VLCFA)
    - Alpha-oxidation of branched chain fatty acids
    - Omega-oxidation of fatty acids
  - Synthesis of ether phospholipids (plasmalogens)
  - Synthesis of cholesterol (mevalonate kinase)
  - Detoxification of Glyoxylate
  - Other: lysine catabolism (pipecolic acid), glutaryl-CoA metabolism, H_2O_2 metabolism

Peroxisomal Disorders - classification

- **Biogenesis disorders**
  - Abnormalities affecting importation of multiple enzymes into the peroxisome
  - eg. Zellweger syndrome
- **Single enzyme disorders**
  - eg. Refsum disease, x-linked adrenoleukodystrophy (X-ALD)
- All autosomal recessive, except X-linked ALD

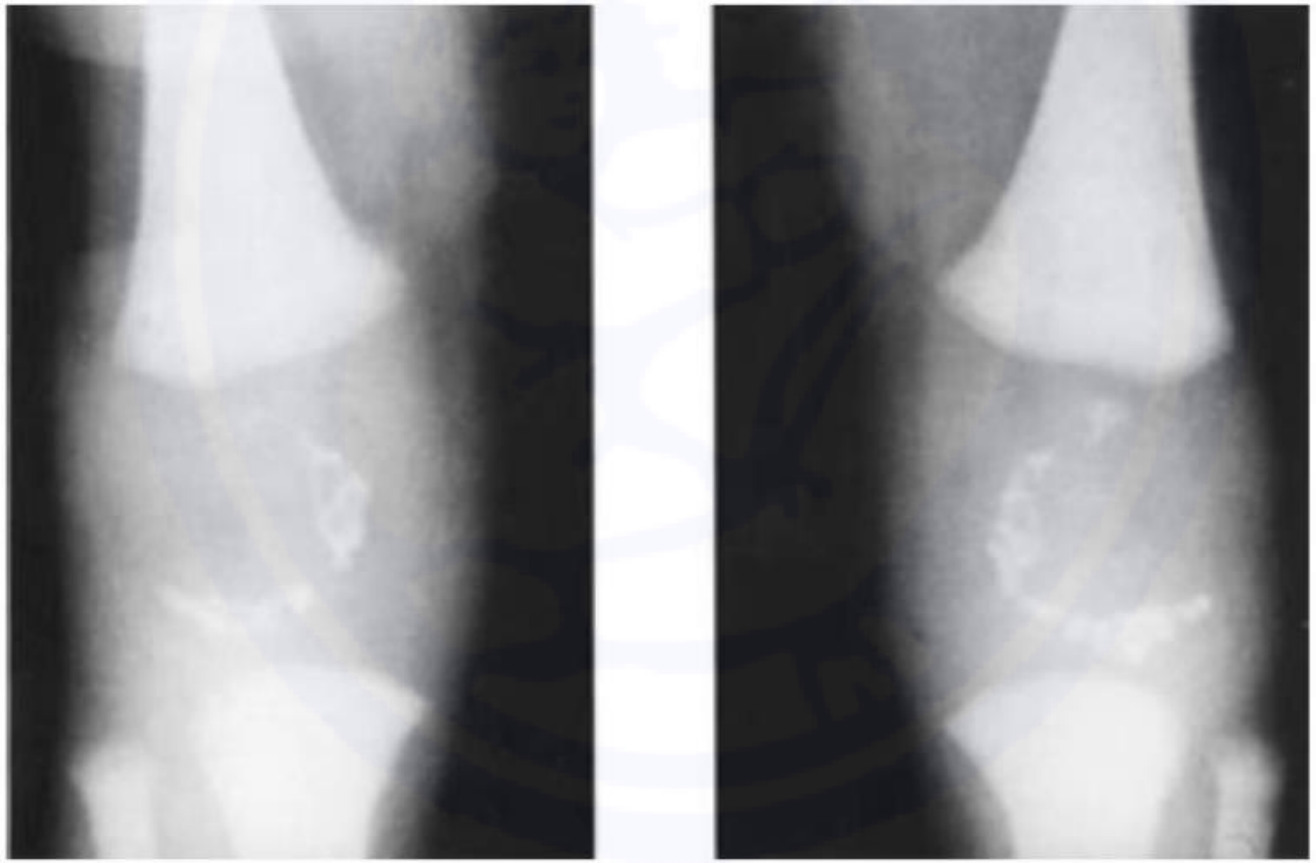
Zellweger Syndrome

- Clinical features
  - Craniofacial dysmorphism
  - Cataracts/corneal clouding
  - Retinopathy
  - Sensorineural hearing loss
  - Severe hypotonia
  - Seizures
  - Hepatopathy/cholestasis
  - Renal cysts
  - Chondrodysplasia punctata
- Average life expectancy 1-2 years

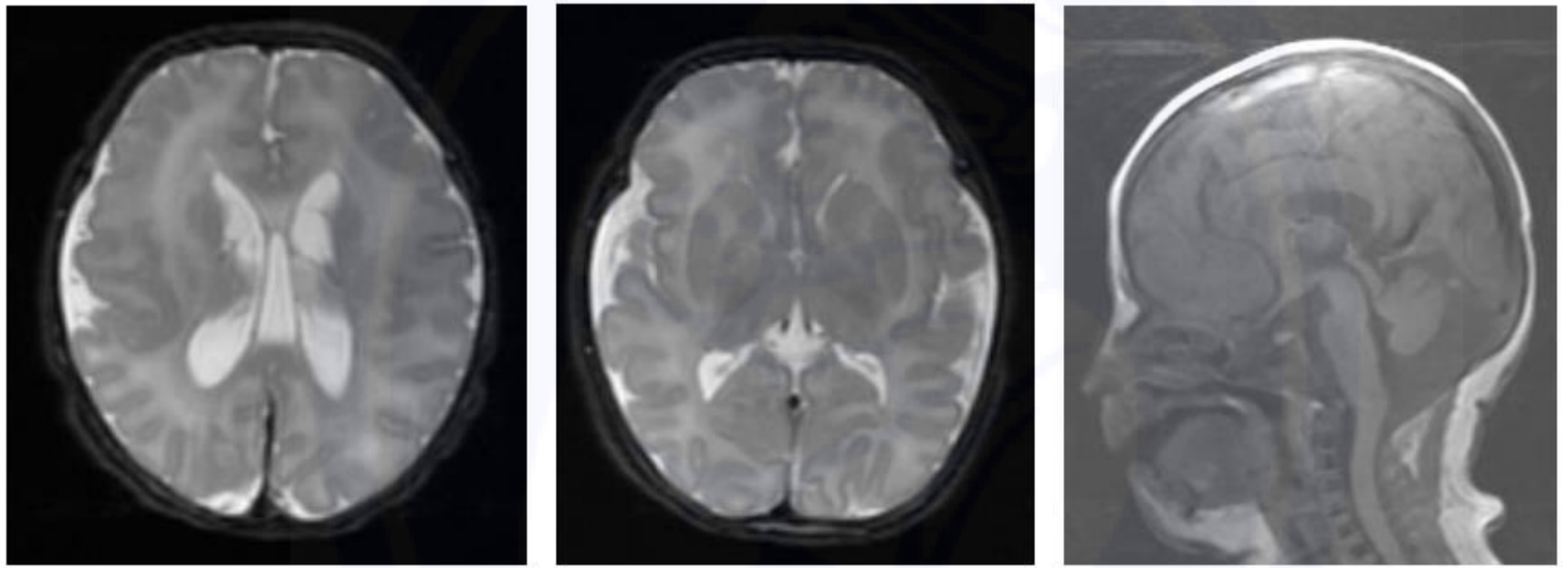


Patel D, et al. IJARPB. 2014.

Zellweger syndrome: chondrodysplasia punctata



Zellweger Syndrome: Imaging



3 day old

- Cortical malformations
  - perisylvian polymicrogyria, fronto-parietal pachygyria, heterotopias, germinolytic cysts
- Delayed myelination
- Later in childhood, demyelination including cerebellum and corticospinal tracts

Laboratory Evaluation for Zellweger syndrome

- Increased
  - plasma very long chain fatty acids
  - plasma pipecolic acid
  - plasma phytanic/pristanic acid (diet dependant, normal in neonate)
  - Urine and blood bile acid intermediates

- Decreased
  - RBC plasmalogens
  - cholesterol
  - fat soluble vitamins

Management of peroxisomal biogenesis disorders

- Supportive management
  - Eg. G-tube, anticonvulsants, etc.
- Restriction of dietary pristanic and phytanic acid
  - butter, cheese, beef, lamb, and some fish
- Cholic acid for cholestatic liver disease

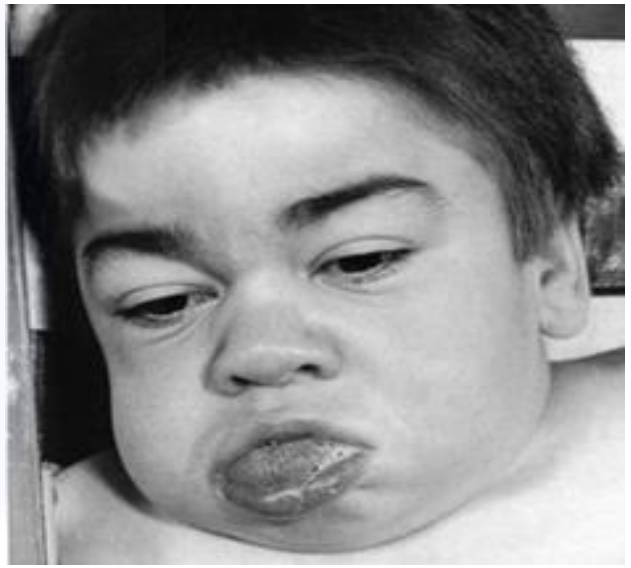
Lysosomal Disorders

Lysosomal Disorders

- Majority are disorders of intra-lysosomal hydrolytic enzymes, and several are transport disorders
- Varied disease phenotypes determined by the specific accumulating metabolite and the tissue it occupies (eg. muscle, connective tissue, myelin, vascular endothelium)
- Most are autosomal recessive, except X-linked Fabry Disease, Danon Disease, and Hunter syndrome
- Common presentations
  1. “Hurler-phenotype”
  2. Leukodystrophy
  3. Progressive myoclonus epilepsy (PME)

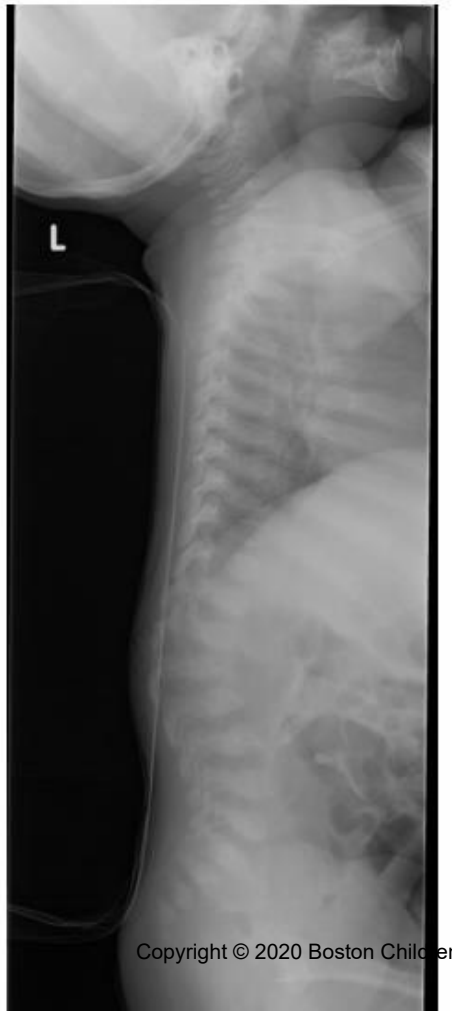
Common Presentations (1): “Hurler” Phenotype

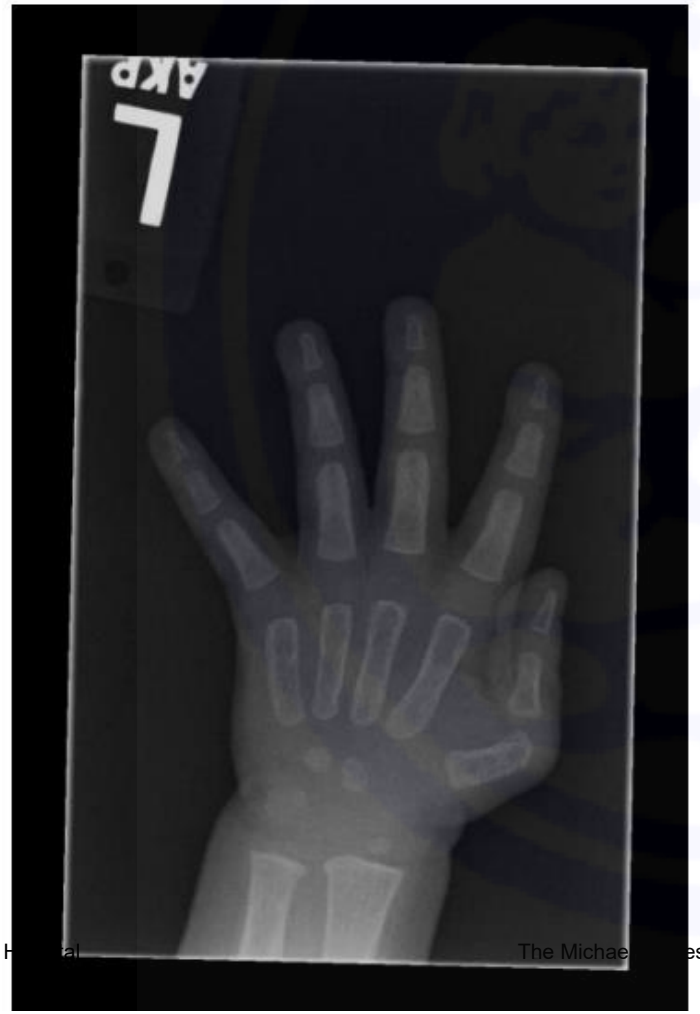
- Consists of
  - Coarse facial features
  - Dysostosis muliplex (bony deformities) with short stature
  - Hernias (umblilical/inguinal)
  - Hepatosplenomegaly
  - Corneal opacities
  - Deafness
  - Cardiac: valvular defects, coronary artery occlusion
  - Neuroimaging: prominent virchow-robin spaces (“honeycomb” sign)

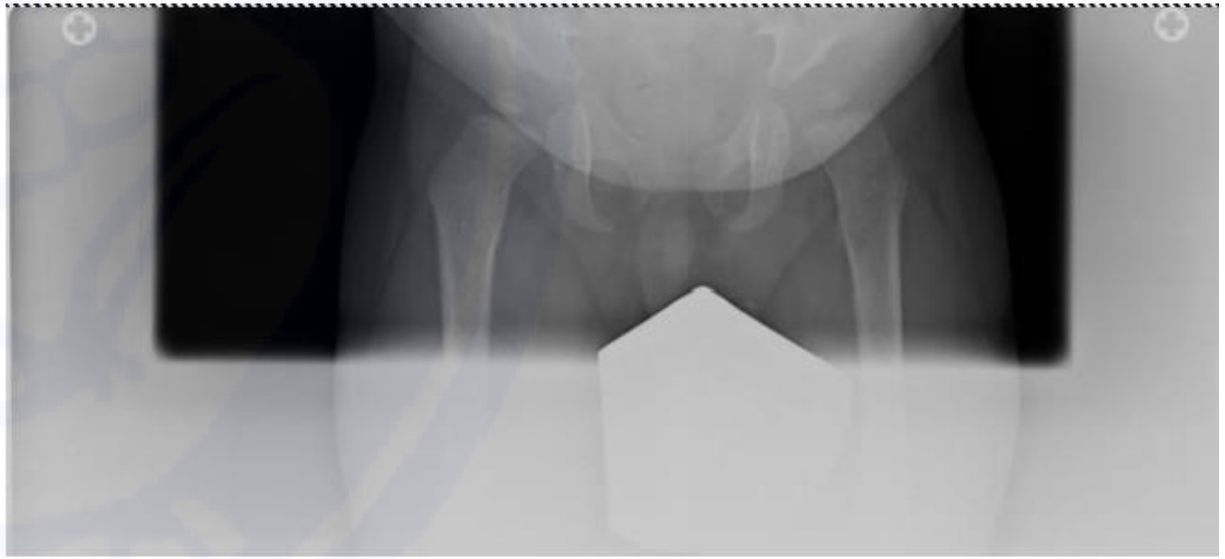


- Complications
  - Peripheral neuropathy, spinal stenosis, communicating hydrocephalus from storage

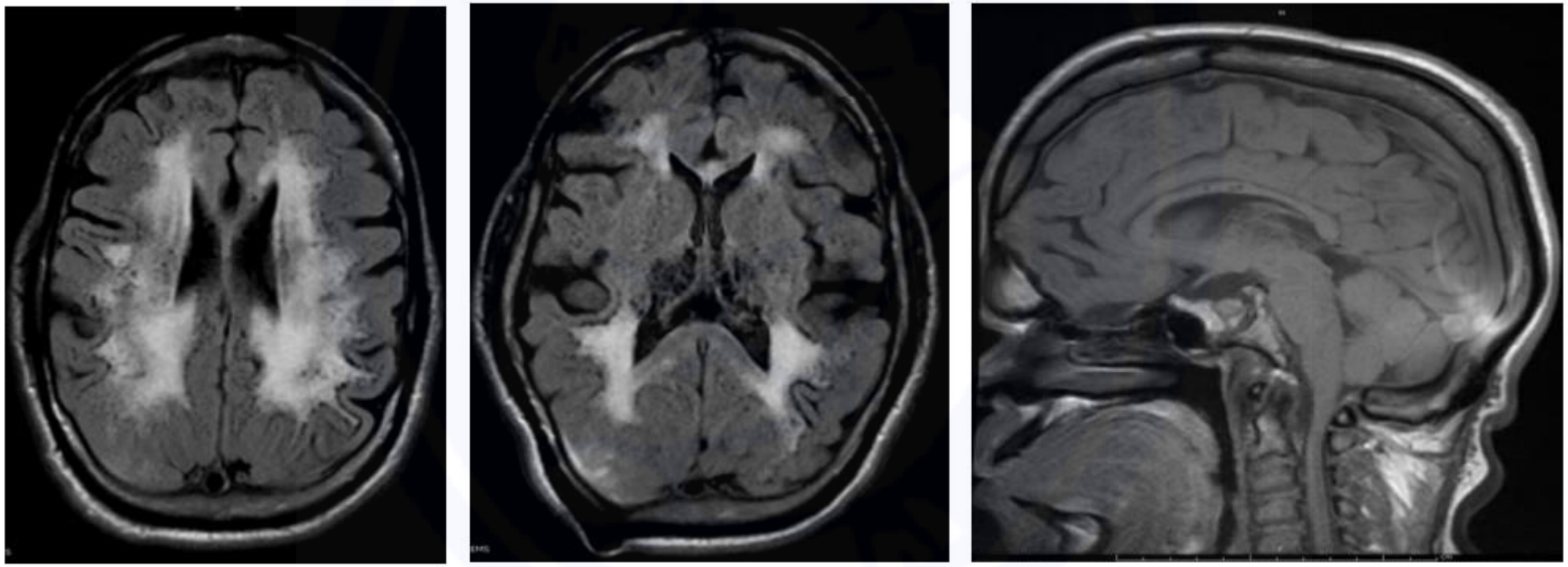
Dysostosis multiplex in Hurler syndrome







“Honeycomb” sign

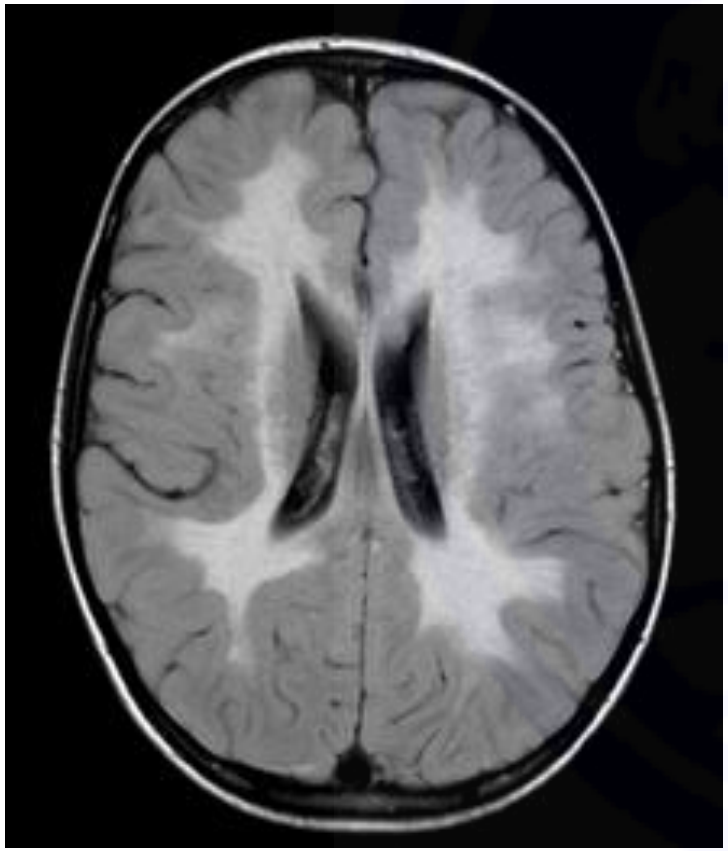


20 year old male with Hunter syndrome

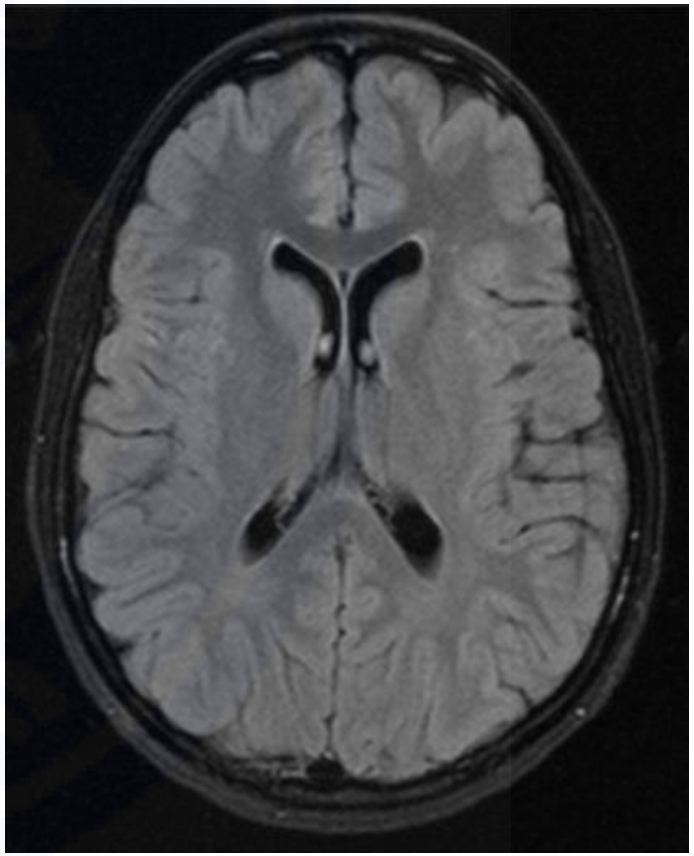
Common Presentations (2): Leukodystrophy

- Demyelination pattern: Krabbe disease, metachromatic leukodystrophy
- Hypomyelination pattern: Salla disease, fucosidosis
- Diagnosis facilitated by MRI pattern recognition

Metachromatic Leukodystrophy

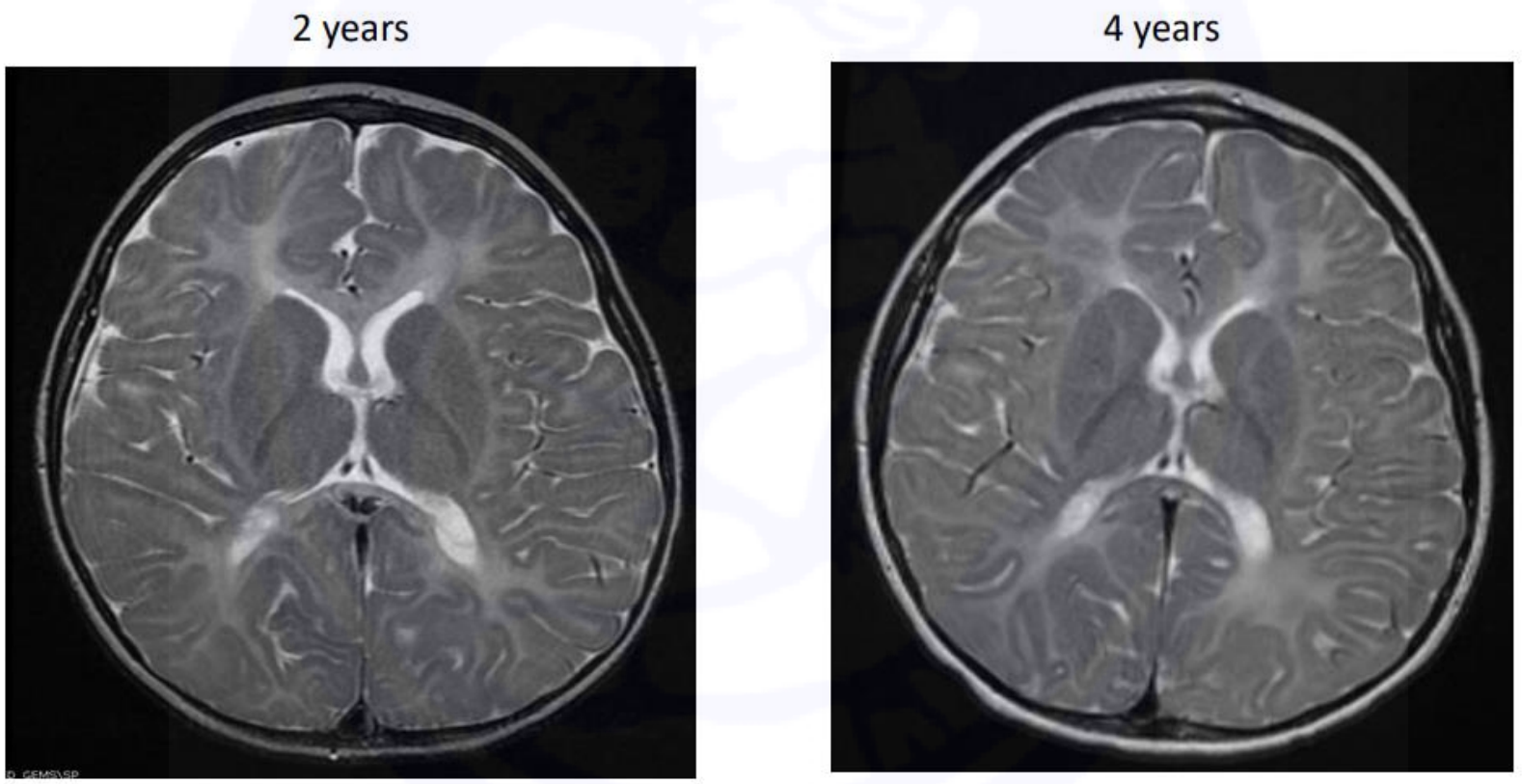


5 year old M with MLD



Normal MRI

Salla Disease - hypomyelination



Common Presentations (3): Progressive myoclonus epilepsy (PME)

- Constellation of
  - Epilepsy
  - Myoclonus
  - Ataxia
  - Dementia

- **Lysosomal disorders are an important cause of PME**

Lysosomal Disorders: presentation

Leukodystrophy	Hurler phenotype	PME
Krabbe Disease	Mucopolysacharidoses	Neuronal ceroid lipofuscinoses
Metachromatic leukodystrophy	Mucolipidosis 2 & 3	Gaucher 3
Austin's disease	Oligosaccharidoses	Sialidosis type 1
Fucosidosis	GM1 gangliosidosis	Sialidosis type 2
Salla Disease	Sialidosis Type 2	Galactosialidosis
	Galactosialidosis	GM2 gangliosidosis (rarely)
	Austin's disease	Sandhoff (rarely)
	Salla disease	

Lysosomal Disorders: Additional Clinical Cues

- Cherry red retinal spot
- T2 hypointense thalami on MRI
- vacuolated lymphocytes
- Infantile hydrops
- Hepatosplenomegaly
- Supranuclear gaze palsy

Disorder	Laboratory Evaluation
Mucopolysaccharidoses	Enzymology, urine glycosaminoglycans
Oligosaccharidoses (eg. Fucosidosis)	Enzymology, urine oligosaccharides
Mucolipidosis 2 & 3	Enzymology (multiple increased enzymes)
Metachromatic leukodystrophy, Austin disease, Saposin B deficiency	Arylsulfatase A activity, urine sulfatides (required to dx Saposin B deficiency)
Krabbe disease	Galactocerebrosidase activity
Gaucher	Glucocerebrosidase activity
Neimann-Pick type A	Sphingomyelinase activity
Neimann-Pick type C	Plasma oxysterols, skin bx for filipin staining and cholesterol esterification studies
Fabry disease	Alpha-galactosidase activity in males, (genetic studies required in females)
Pompe disease	Alpha-glucosidase activity
Danon disease	Genetic testing, muscle biopsy
Neuronal ceroid lipofuscinosis	Genetic testing, skin/conjunctival biopsy for inclusions, enzymology in several
Free sialic acid storage disease/Salla disease	Urine free sialic acid

Lysosomal Disorders: Treatment

- Enzyme replacement therapy
  - Fabry, Pompe, MPS I/II/VI, type I Gaucher, CLN2
- Bone marrow transplant
  - Krabbe, metachromatic leukodystrophy, MPS1
- Substrate reduction therapy
  - Neimann-Pick type C, Gaucher disease

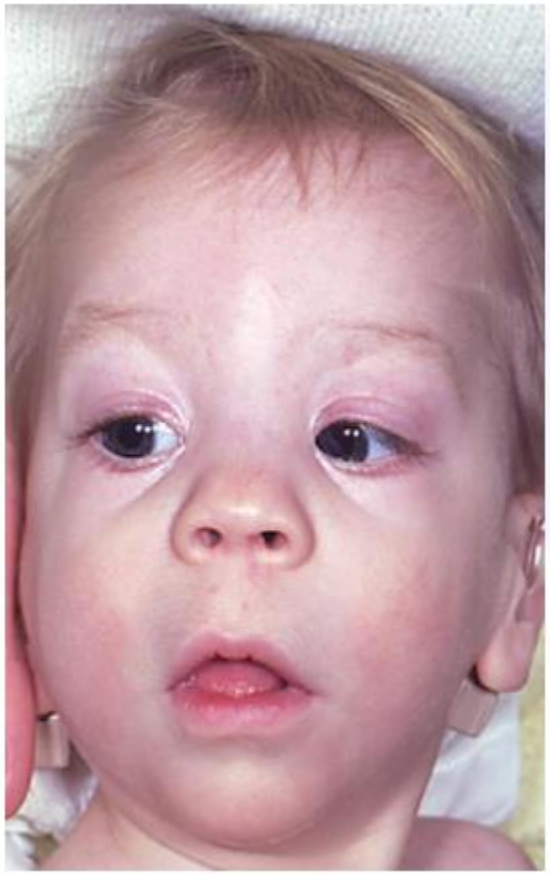
Cholesterol Biosynthesis Disorders

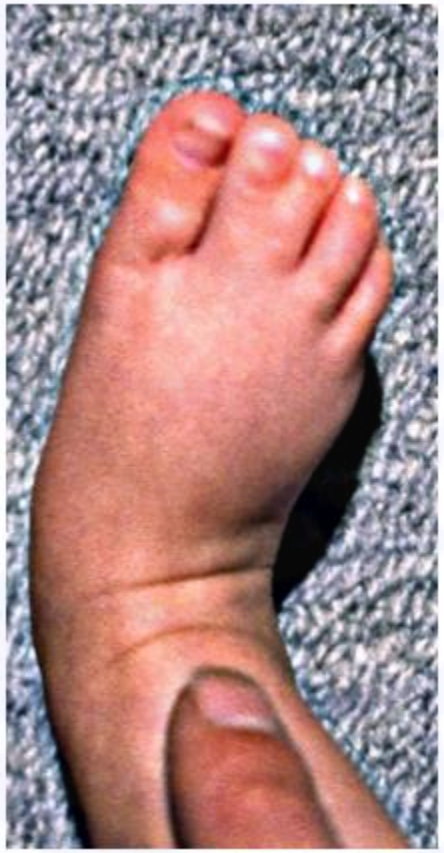
- Genetic disorders in the biosynthesis of cholesterol
- Cholesterol plays a number of vital roles
  - Steroid precursor
  - Bile acid synthesis
  - Hedgehog signaling pathway (SHH = holoprosencephaly)
  - Lipid membranes
- Prototypical disorder is Smith-Lemli-Opitz syndrome

Smith-Lemli-Optiz Syndrome

- Deficiency of 7-dehydrocholesterol reductase, the final enzyme of steroid synthesis
- AR inheritance
- Presentation
  - Static developmental delay → MR, autism
  - Behavioral and sleep difficulties
  - Hypotonia
  - IUGR
  - Congenital microcephaly
  - Dysmorphic features
  - Multiple congenital anomalies
  - Poor feeding

Smith-Lemli-Opitz dysmorphology





Smith-Lemli-Opitz syndrome

- Diagnosis
  - Cholesterol precursor measurements:
    - Elevated 7-dehydrocholesterol (and to lesser degree 8-dehydrocholesterol)
  - Low total cholesterol (<100)
  - Genetic testing

- Management
  - Cholesterol supplementation
  - Goal total cholesterol >100
  - May help with growth (cholesterol doesn't cross BBB)
  - Typically treat with stress dose hydrocortisone if severely ill (little evidence)

Congenital Disorders of Glycosylation (CDGs)

- Genetic disorders affecting the synthesis, attachment, or modification of carbohydrate side chains to proteins
- >50 disorders reported to date
- Most have autosomal recessive inheritance
- Disorders of glycosylation are often multisystemic and have highly variable clinical presentations
  - “great mimicker” in metabolism
  - common: developmental delay, epilepsy, hematologic, immunologic, and hepatic manifestations

Congenital Disorders of Glycosylation (CDGs)

- Divided into
  - Disorders of N-glycosylation (glycan amide linked to N- of asparagine)
    - Further divided into type 1 (synthesis) and type 2 (processing) defects
  - Disorders of O-glycosylation (link to O- of serine or threonine)
    - Disorders of alpha-dystroglycan
  - Combined disorders of N- and O-glycosylation

Congenital Disorders of Glycosylation (CDGs)

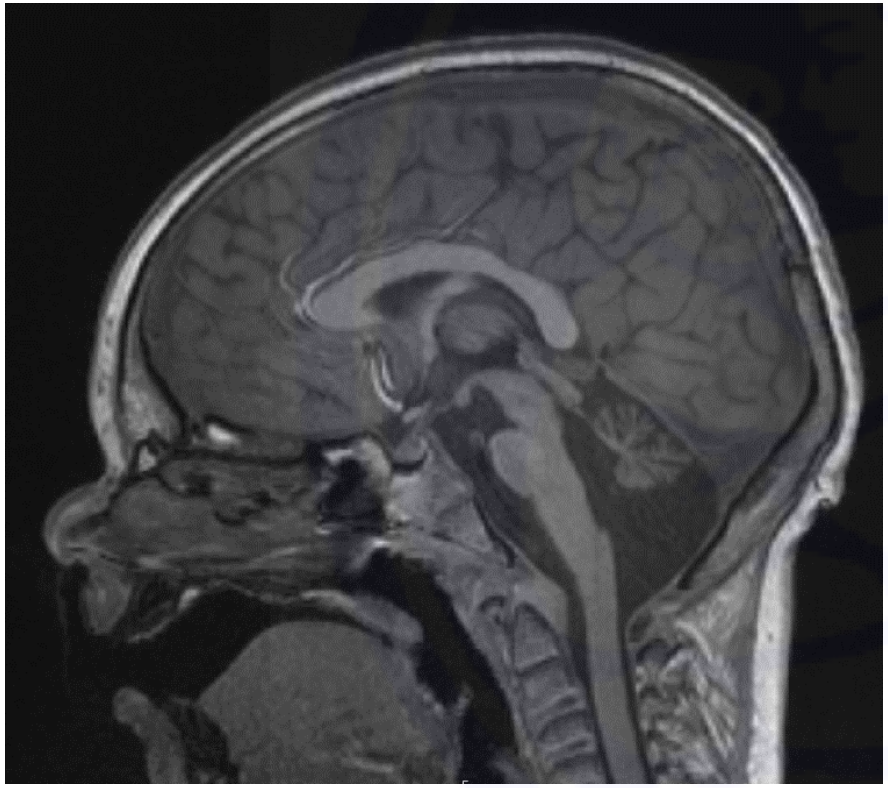
- Diagnosis
  - **Transferrin analysis – distinguishes N-glycosylation disorders between types 1 and 2**
  - Can further refine diagnosis: N and O-glycan analysis, urine oligosaccharides and free glycans
  - Gene panels/exome
- Management
  - Supportive in most
  - CDG IIb - Mannose

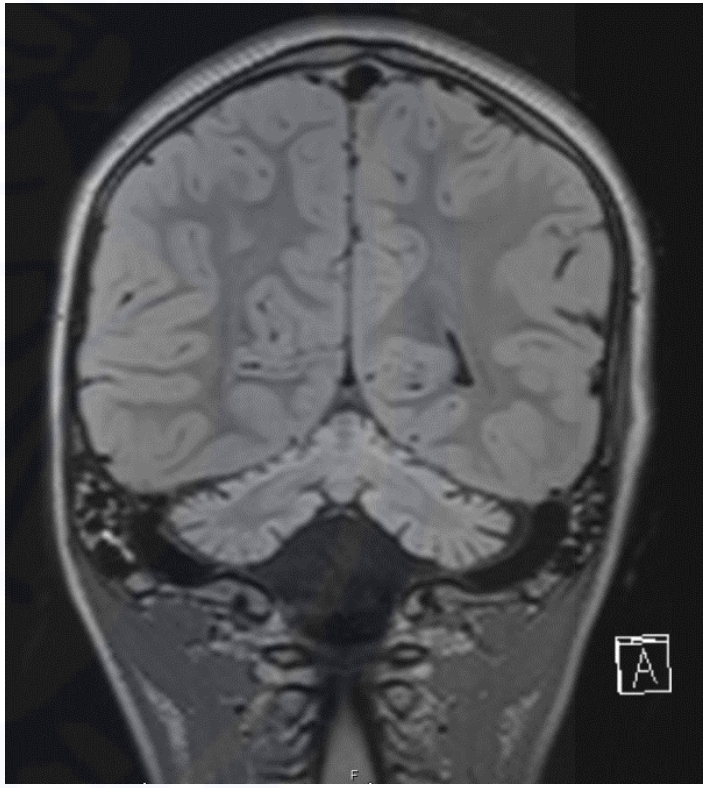
CDG Type 1a

- Most common CDG

- Clinical presentation
  - Static developmental delay
  - Hypotonia
  - Dysmorphic features, inverted nipples
  - Fat pads/lipodystrophy
  - Coagulopathy
  - Secretory diarrhea
  - Pericardial effusion
  - Stroke/stroke-like episodes
  - Hyperinsulinism

The “small bright cerebellum”





4 year old with CDG1a

Summary (1): Small Molecule Disorders

Category	Presentation	Diagnosis
Urea cycle disorders	Hyperammonemic encephalopathy	Ammonia, plasma amino acids, urine organic acids
Fatty acid oxidation & carnitine disorders	Hypoketotic hypoglycemia, encephalopathy, episodic rhabdomyolysis, cardiomyopathy, hepatopathy	Plasma acylcarnitines, free/total carnitine
Organic acidemias	Ketoacidosis, hyperammonemia, metabolic stroke, developmental delay	Urine organic acids, plasma acylcarnitines
Amino acidopathies	Variable, but common features include epilepsy, developmental delay, cerebral white matter injury	Plasma amino acids, additional metabolic studies based on suspected diagnosis

Summary (2): Large Molecule Disorders

Category	Presentation	Diagnosis
Peroxisomal disorders	Variable, but common features include retinopathy, sensorineural hearing loss, brain malformation, dysmorphisms, cholestasis, leukoencephalopathy, skeletal dysplasia	Plasma VLCFAs, phytanic acid, pipecolic acid, plasmalogens, bile acid intermediates
Lysosomal disorders	Variable, but common features include Hurler phenotype, leukoencephalopathy, PME, cherry red spot, organomegaly, supranuclear gaze palsy	Enzymology, urine MPS screen, urine oligosaccharides
Smith-Lemli-Opitz syndrome	Dysmorphic features, multiple congenital anomalies, microcephaly, growth restriction, 2-3 toe syndactyly, static global developmental delay, behavioral abnormalities	Increased 7-dehydrocholesterol, reduced total cholesterol
Congenital Disorders of Glycosylation	Highly variable based on disorder. Common features include static neurodevelopmental abnormalities, epilepsy, dysmorphic features, blood clotting abnormalities, and immunological abnormalities. Liver disease and hyperinsulinism also reported in multiple subtypes. MR brain may demonstrate “small bright cerebellum”.	Transferrin analysis, N-glycan and O-glycan analysis, urine oligosaccharides and free glycans, gene panels

Useful Resources

- GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/)
- Online Metabolic and Molecular Basis of Inherited Disease (OMMBID)
- Fernandes et al. Inborn Metabolic disease 4th edition
- Zschocke et al. Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism, 3rd edition
- New England Consortium of Metabolic Programs: Acute Illness Protocols (http://newenglandconsortium.org/for-professionals/acute-illness-protocols/)