Inborn Errors of Metabolism and Epilepsy

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Disclosures

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PI - Arimoclomol prospective study in patients diagnosed with Niemann Pick disease type C, Orphazyme

SI - Phase 2/3 study on Glut1 deficiency, Ultragenyx

SI - Phase 1/2 study on MLD, Shire

SI – Phase 2 study alpha-mannosidosis, Zymenex/Chiesi

Inborn Errors of Metabolism (IEM)

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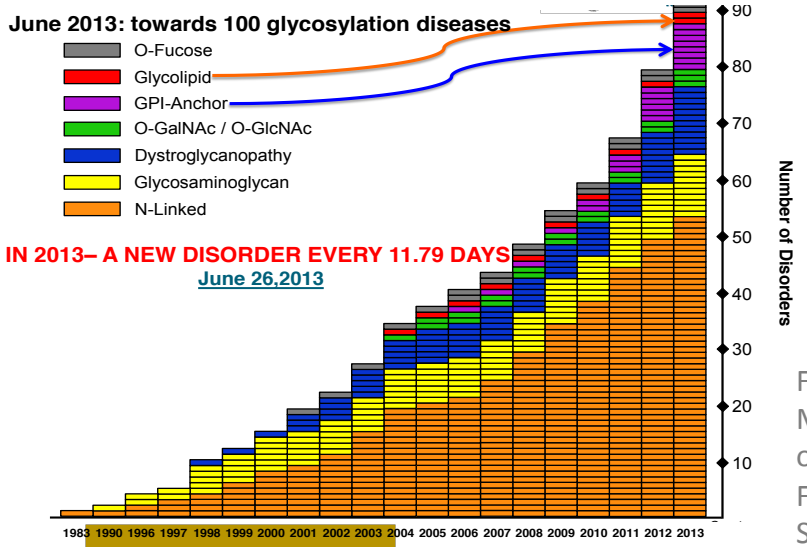
- Genetic defects in the biosynthesis or breakdown of substances in specific pathways
- Historically identified by specific biochemical test
- **Total number** of identified IEM **increasing** exponentially (currently **1015!**)

- **CDG syndromes:**
  (1983-2013)



Ferreira CR et al. Genetics in Medicine 2018. A proposed nosology of IEM.

Freeze HH et al. AJHG 2014. Solving glycosylation disorders: …

Inborn Errors of Metabolism (IEM)

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- Genetic defects in the biosynthesis or breakdown of substances in specific pathways
- Historically identified by specific biochemical test
- **Total number** of identified IEM **increasing** exponentially (currently **1015!**)
- **Increasing number** of IEM can be **treated** by metabolic interventions

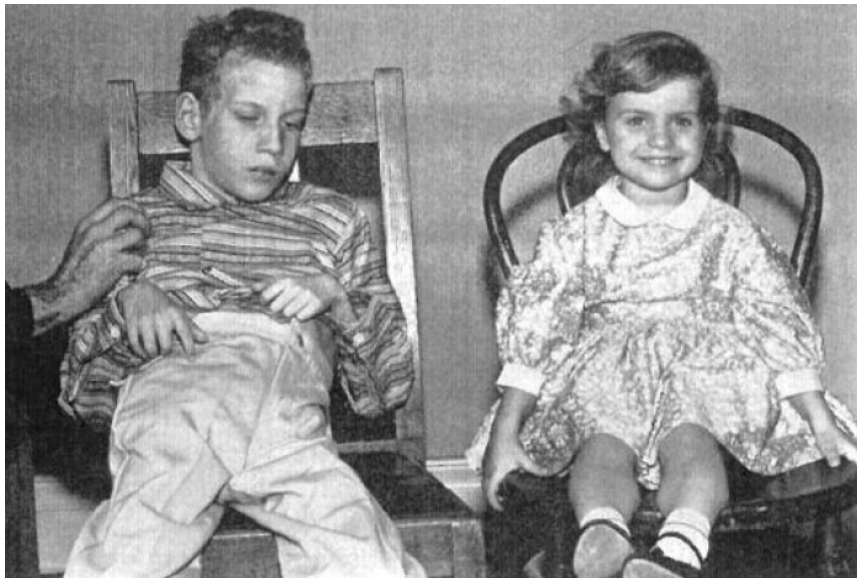
- **Phenylketonuria (PKU):**

  Treatment with protein reduced diet
  amino acid substitution
  phe monitoring

  ➔ **excellent outcome**

- **Biotinidase deficiency**

  Treatment with biotin supplementation



Inborn Errors of Metabolism - Categories

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- Intermediary metabolism
  - standard metabolic tests
  - fluctuating symptoms, acute presentations
  - therapeutic interventions often possible
- Biosynthesis/breakdown of complex molecules
  - slowly progressive
  - specific analyses necessary for diagnostics
- Neurotransmitter diseases
- Metabolism of vitamines og co-factors
- Metabolism of metals

amino acids, carbohydrates, fatty acids, mitochondrial energy metabolism, urea cycle, …

Epilepsy can manifest in all groups

Metabolism of purins/ pyrimidines, lysomomal and peroxisomal diseases, isoprenoids/sterols, …

IEM – neurological symptoms

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- Onset at all ages – acute or chronic/chronic-progressive
  - **+/-** developmental delay (DD) and ID
  - **+/-** seizures
  - **+/-** encephalopathy
  - **+/-** syndromic/multiple congenital anomalies
  - **+/-** autism
  - **+/-** muscular
  - **+/-** movement disorder, CP mimic
  - **+/-** psychiatric
  - **+/-** neurodegenerative (WM, GM, BG, cerebellum)

- IEM as cause probably underdiagnosed (e.g. found in **5-15%** of patients with ID)

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… with common neurological co-morbidity

- IEM as cause probably underdiagnosed (e.g. found in **5-15%** of patients with ID)

IEM and CNS manifestations - Challenges

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- Increasing number of IEM
- Overlapping and unspecific symptoms
- Possible lack of biochemical markers (or unavailable)

➔ Making a diagnosis is challenging

! Consider IEM early on

! Define at risk-patient population

! Optimize diagnostic strategy

… because timely diagnosis has the potential to improve outcome

IEM and Epilepsy

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- **> 370 IEM** disease genes have been associated with epilepsy and seizures

- **25%** of these IEM have a specific treatment option
- Defects in energy metabolism, metabolism of amino acids, CDGs, lysosomal disorders, …

- **How often does IEM underlie pediatric epilepsies?**

?

Metabolic Brain Disease
https://doi.org/10.1007/s11011-018-0288-1

REVIEW ARTICLE

Contemporary scope of inborn errors of metabolism involving epilepsy or seizures

Birutė Tumienė[1,2] · Borut Peterlin[3] · Aleš Maver[3] · Algirdas Utkus[1]

Treatable "epileptic" IEMs

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Vitamin responsive metabolic epilepsies

- **Pyridoxine-dependent epilepsy**
- **PLP-dependent epilepsy**
- Biotinidase deficiency

Selected amino and organic acid disorders

- Serine synthesis defects
- Molybdenum co-factor deficiency
- **Creatine synthesis defects**
- Disorders of cobalamin metabolism
- **Glycine encephalopathy**

Lysosomal diseases

- **Neuronal ceroid lipofuscinosis (CLN2)**

Transportopathies

- Glucose transporter 1 deficiency
- Cerebral folate deficiency
- Biotine thiamine responsive basal ganglia disease

Mitochondriopathies

- Pyruvate dehydrogenase deficiency

Neurotransmitter disorders

- Disorders of biopterin synthesis

Metabolic crisis of different IEM

- e.g. urea cycle defects, MSUD

Treatable "epileptic" IEMs - PDE

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Vitamin responsive metabolic epilepsies

- **Pyridoxine-dependent epilepsy (PDE)**
- **PLP-dependent epilepsy (PNPO)**
- Biotinidase deficiency

Pyridoxine-dependent epilepsy (PDE):

ALDH7A1 gene - Antiquitin (α-aminoadipic semialdehyde dehydrogenase) deficiency – AR

Defect in **lysine catabolism** leading to **pyridoxal-5'-phosphate (PLP) depletion**

Early onset epileptic encephalopathy (milder forms reported)

Biochemical **biomarkers**

Therapeutic trial with **pyridoxine** 100 mg i.v. OR 30 mg/kg/d p.os., continue in responders

+ lysine-restricted diet

+ L-arginine supplementation – together **improving cognitive outcome**

Treatable "epileptic" IEMs - PNPO

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Vitamin responsive metabolic epilepsies

- **Pyridoxine-dependent epilepsy (PDE)**
- **PLP-dependent epilepsy (PNPO)**
- Biotinidase deficiency

Pyridoxal-5'-phosphate (PLP) dependent epilepsy:

- ***PNPO*** - Pyridoxine-5'-phosphate oxidase – **rate limiting step** in **synthesis of PLP**
- AR – rare
- Severe early-onset epileptic encephalopathy
- Dystonia, metabolic derangement, gastrointestinal symptoms
- Can lead to **premature birth** and **mimic HIE**

- **Treatment** with **PLP** 30-60 (-100) mg/kg/d p.os.

- Reported normal neurodevelopmental outcome with **early treatment**

Treatable "epileptic" IEMs – Creatine synthesis defect

Selected amino and organic acid disorders

- Serine synthesis defects
- Sulfite oxidase deficiency/Molybdenum co-factor deficiency
- **Creatine synthesis defects**
- Cobalamin deficiencies
- **Glycine encephalopathy**

Creatine synthesis defects:

- **Guanidinoacetate methyltransferase (GAMT)**
- Arginine:glycine amidinotransferase (AGAT)

- **Decrease** in **cerebral creatine** and accumulation of **toxic metabolites** (in GAMT)

- **ID** and **behavioural** problems (hyperacitivity, self injury, autism), movement disorder (40%)
- Severe and early seizures in GAMT, onset 3 months to 3 years

- Biomarkers: lack of creatine peak on **MRS**, creatine metabolites in urine/plasma

- **GAMT deficiency treatment**: creatine and ornithine supplementation, arginine restriction

Treatable "epileptic" IEMs – Glycine encephalopathy

Selected amino and organic acid disorders

- Serine synthesis defects
- Sulfite oxidase deficiency/Molybdenum co-factor deficiency
- **Creatine synthesis defects**
- Cobalamin deficiencies
- **Glycine encephalopathy**

Glycine encephalopathy:

- **Non-ketotic hyperglycinemia** – **accumulation of glycine** due to deficiency of glycine cleavage enzyme complex
- *GLDC*/*AMT*/*GCSH* genes (75/20/<1%)
- **Biomarker**: ↑glycine in blood and csf; ↑ csf-to-plasma glycine ratio

- Neonatal and infantile forms, 20% with attenuated outcome; rare later-onset/mild forms
- **Classic neonatal** presentation: **progressive lethargy** from birth, **myoclonic** jerks, **apnea** and **burst-suppression** on EEG; **minimal** psychomotor development

- Prevalence 1:50,000-60,000 in some populations

- **Treatment:** Sodium benzoate to lower glycine
  Dextromethorphan to block glycinergic NMDA receptor

Treatable "epileptic" IEMs – CLN2

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Lysosomal diseases

- **Neuronal ceroid lipofuscinosis (CLN2)**

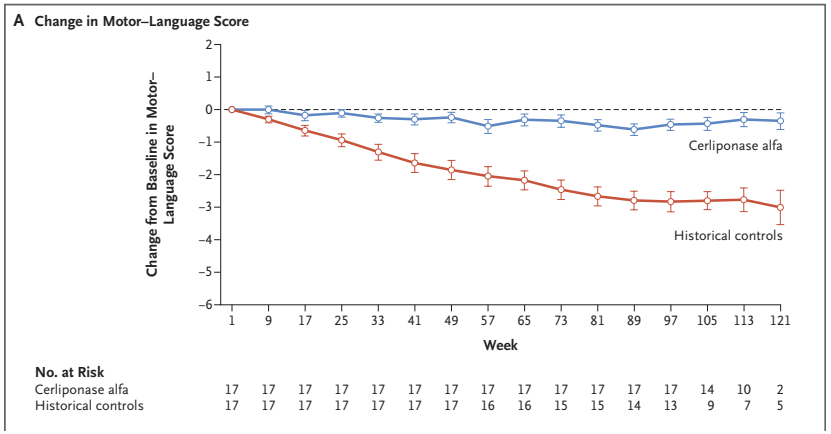
CLN2 disease – classic late infantile NCL (Jansky Bielschowsky disease):

- Tripeptidyl-peptidase deficiency (*TPP1*)

- UK prevalence estimated 1:1,300,000
- Onset **age 2-4 years**: **seizures, language delay or loss of language**, myoclonia, ataxia, spasticity, dementia; **vision loss starts age 4-6** years and progresses rapidly
- Diagnosis – enzyme activity; molecular genetics analysis (average 2 yr delay after 1st seizure)

- **Treatment:**

  i.c.v. ERT (cerliponase alpha)



Schulz A et al 2018. Study of intraventricular Cerliponase alfa for CLN2 disease. NEJM 378:1898

Age distribution

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Table I: Classification of metabolic epilepsies according to age at presentation

Neonatal period to early infancy	Late infancy to early childhood	Late childhood to adolescence
PDE	Creatine synthesis defects	CoQ_{10} deficiency
PNPO deficiency	Infantile and late infantile NCL	Lafora body and Unverricht–Lundborg disease
Folinic acid responsive seizures	Mitochondrial disorders (Alpers syndrome and others)	MERRF
Biotinidase deficiency	Sialidosis	MELAS
GLUT1 deficiency	Gangliosidosis	*POLG*-related disease: MIRAS, SCAE, MEMSA
Non-ketotic hyperglycinaemia	Milder variants of PDE and PNPO deficiency	Juvenile NCL
Serine biosynthesis defects	Congenital disorders of glycosylation	Late onset GM2 gangliosidosis (Sandhoff, Tay–Sachs)
Molybdenum cofactor and sulphite oxidase deficiencies		Gaucher type III
Menkes disease		Niemann–Pick type C
Disorders of peroxisome biogenesis and β-oxidation		Peroxisomal disorders
Congenital disorders of glycosylation		
Cathepsin D deficiency (congenital NCL)		

Rahman S et al 2013. Inborn errors of metabolism causing epilepsy. Dev Med Child Neurol 55: 23-36

Typical presentation and "red flags"

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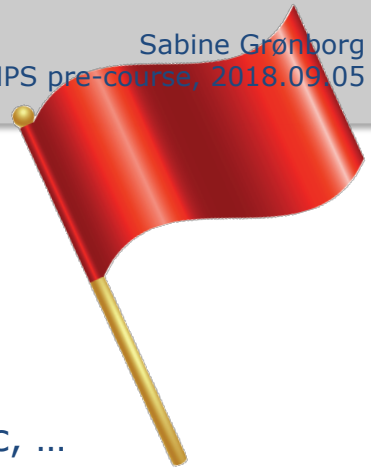
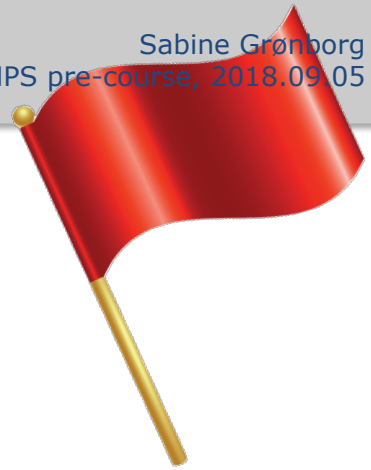


- Early onset (neonatal, infantile)
- Impaired feeding – encephalopathic
- Myoclonic seizures, but also apnea, oculofacial movements, spasms, tonic, …
- EEG: burst-suppression, generalized, multifocal, hypsarrythmia
- Poor response to AED
- Suspicion of HIE or presence of structural abnormalities does not rule out IEM
- Developmental delay
- Failure to thrive, vomiting
- Familiy history of consanguinity, metabolic disorder

Pearl PL 2016. Amenable treatable severe pediatric epilepsies. Semin Pediatr Neurol 23: 158

More "red flags"



Epilepsy with …	Rule out …
• secondary microcephaly	GLUT1 deficiency Inborn errors of serine deficiency Cerebral folate deficiency PDH, and others
• facial dysmorphism	Molybdenum co-factor deficiency
• movement disorder	Dystonia – PDE and GLUT1 Choreoathetosis/ballismus – creatine metabolism disorders Ataxia – GLUT1D; biotinidase, serine, folate deficiency

Mastrangelo M et al 2018. Actual insights into treatable inborn errors of metabolism causing epilepsy. J Pediatr Neurosci 13: 13

CASE 1

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- **Muscular hypotonia** (1 month), reduced eye contact, generalized **seizures** (3 months)
- **Lactic acidosis** (6-9 mmol/l) and increased alanine in plasma amino acids
- Cerebral MRI (4 months): normal

- Targeted WGS analysis -
  2031+ genes associated with IEM/epileptic encephalopathy/mitochondrial disease:
  PDHA1 gene c.1176_1238dup (p.Pro412_Phe413ins21fs).
- Confirmed by enzymatic testing of **pyruvate dehydrogenase activity** in skin fibroblasts

X-linked PDH deficiency

CASE 1 – Pyruvate dehydrogenase deficiency

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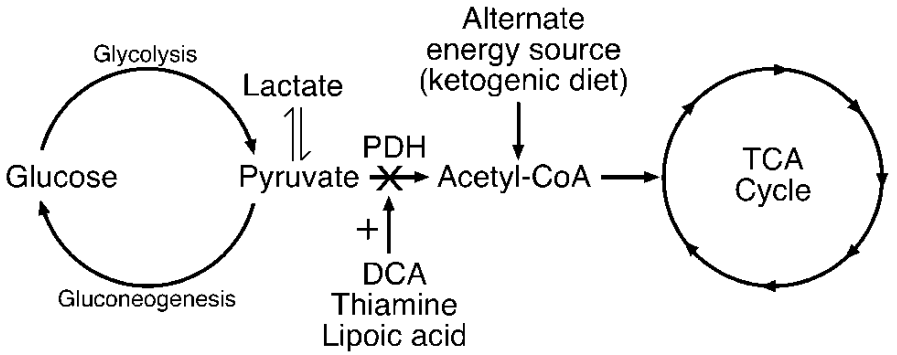
- Uncomplicated start with **classical ketogenic diet**
- Trial with **thiamine** (20 mg/kg/d)

- **Seizure free** after reaching **ketosis**
- Normalization of lactic acidosis
- Slight developmental progress



PDH defiency:

- X-linked (PDHA1) and five AR forms
- Broad phenotype; classical with onset 1st year, seizures, psychomotor delay and progression, structural changes on cerebral MRI
- **Ketogenic diet** can effectively treat seizures and motor symptoms if started early

CASE 2

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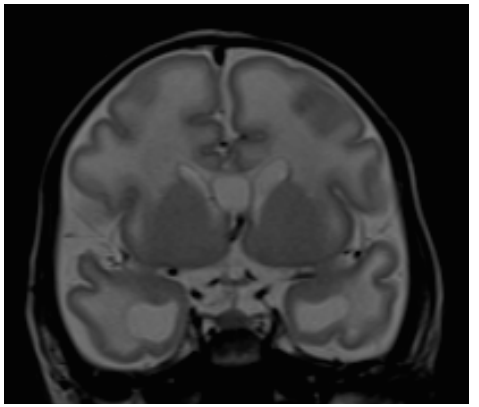
- At term baby boy – **seizures on 1st day** with myoclonia, tonic extension
- **Seizures refractory** to p.os. and i.v. escalation therapy
- Day 4: **pyridoxin 100 mg i.v.** – no further seizures
- Continues levetiracetam and pyridoxine p.os. to two months of age

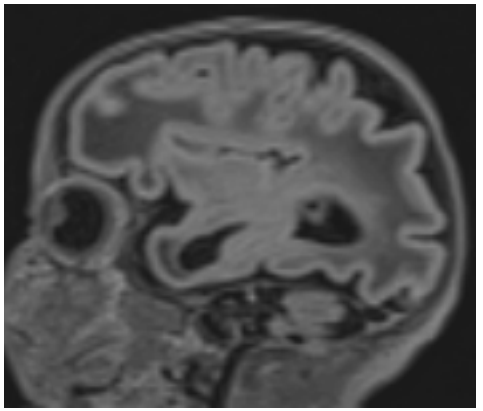
- Metabolic workup with **normal pipecolic** acid in plasma and csf
  ➔ Pyridoxine withdrawal at age 2 months: seizuring after 3 days

- Starts pyridoxal 5’ phosphate 30 mg/kg/d and achieves seizure control

- Gene panel for epileptic encephalopathy: **normal results** including ***ALDH7A1*** and ***PNPO*** genes

MR of cerebrum day 3:





CASE 2

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Mutations in *PROSC* Disrupt Cellular Pyridoxal Phosphate Homeostasis and Cause Vitamin-B_6-Dependent Epilepsy

Niklas Darin,[1] Emma Reid,[2] Laurence Prunetti,[3] Lena Samuelsson,[4] Ralf A. Husain,[5] Matthew Wilson,[2] Basma El Yacoubi,[3,17] Emma Footitt,[6] W.K. Chong,[7] Louise C. Wilson,[8] Helen Prunty,[9] Simon Pope,[10] Simon Heales,[2,9,10] Karine Lascelles,[11] Mike Champion,[12] Evangeline Wassmer,[13] Pierangelo Veggiotti,[14,15] Valérie de Crécy-Lagard,[3] Philippa B. Mills,[2,16,*] and Peter T. Clayton[2,16,*]

Darin N et al 2016. Am J Hum Genet 99: 1325

- Clinical WES: PLPBP/PROSC with homozygous splice site variant c.207+1G>A

  Vitamin-B6-dependent epilepsy due to PLPBP/PROSC mutation

- Seizures well-controlled on PLP and LEV
- Delayed development

Diagnostic considerations

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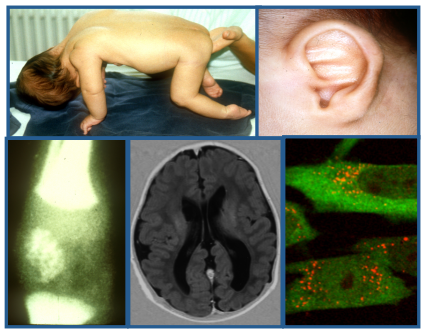
Traditional approach:



Selective screening

Genetic confirmation

Current development:

"Genetics first"

(NGS panels/clinical WES/ subacute metabolic panel)

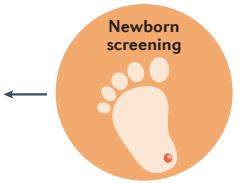
Biochemical tests for facilitation and confirmation of diagnosis and for disease monitoring

Multi-omics in the future

Newborn screening:

Practical issues

- Requires sensitive and specific high-throughput screening platforms
- Need for confirmatory tests and bioinformatics infrastructure
- Availability of treatments
- Benefits of early therapeutic intervention
- Economic considerations
- Inform choices for future pregnancies
- Elimination of the diagnostic odyssey



adapted from Platt FM 2017

Diagnostic considerations

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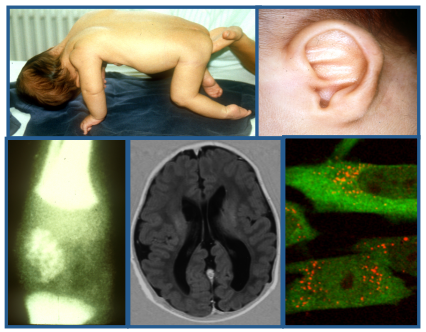

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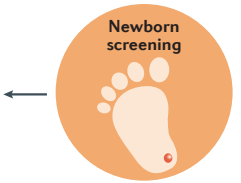

adapted from Platt FM 2017

IEM are a **rare but important** differential diagnosis for epilepsy and especially **early epileptic encephalopathy** – Consider this when choosing the diagnostic tools!

Thanks to the patients and families,

my colleagues, and

THANK YOU FOR YOUR ATTENTION!