Inborn Errors of Metabolism and Epilepsy

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NNPS møde pre-course
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Speaker honoraria from Novo Nordisk and Actelion
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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)

- 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 10^15!)

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

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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)

• 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

- 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 vitamins and co-factors
- Metabolism of metals

Epilepsy can manifest in all groups

Metabolism of purines/pyrimidines, lysosomal and peroxisomal diseases, isoprenoids/sterols, ...

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

Sabine Grønborg
NNPS pre-course, 2018.09.05
IEM – neurological symptoms

- 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)
IEM – neurological symptoms

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• IEM as cause probably underdiagnosed (e.g. found in 5-15% of patients with ID)
IEM and CNS manifestations - Challenges

- 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
• > 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?

Contemporary scope of inborn errors of metabolism involving epilepsy or seizures

Birutė Tumienė ¹,² • Borut Peterlin ³ • Aleš Maver ³ • Algirdas Utkus ¹
<table>
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<td>• Pyridoxine-dependent epilepsy</td>
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<td>• PLP-dependent epilepsy</td>
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<tr>
<td>• Biotinidase deficiency</td>
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<td><strong>Transportopathies</strong></td>
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<td>• Glucose transporter 1 deficiency</td>
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<td>• Cerebral folate deficiency</td>
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<td>• Biotine thiamine responsive basal ganglia disease</td>
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<td><strong>Selected amino and organic acid disorders</strong></td>
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<td>• Serine synthesis defects</td>
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<td>• Molybdenum co-factor deficiency</td>
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<td>• Creatine synthesis defects</td>
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<td>• Disorders of cobalamin metabolism</td>
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<td>• Glycine encephalopathy</td>
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<td><strong>Mitochondriopathies</strong></td>
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<td><strong>Neurotransmitter disorders</strong></td>
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<td>• Disorders of biopterin synthesis</td>
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<td><strong>Lysosomal diseases</strong></td>
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<tr>
<td>• Neuronal ceroid lipofuscinosis (CLN2)</td>
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<td><strong>Metabolic crisis of different IEM</strong></td>
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<tr>
<td>• e.g. urea cycle defects, MSUD</td>
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</table>
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**
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 cofactor 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
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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 glycinergetic NMDA receptor
Treatable “epileptic” IEMs – CLN2

Lysosomal diseases
• **Neuronal ceroid lipofuscinosis (CLN2)**

  • 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)

CLN2 disease – classic late infantile NCL (Jansky Bielschowsky disease):
• Tripeptidyl-peptidase deficiency (**TPP1**)


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A Change in Motor-Language Score

<table>
<thead>
<tr>
<th>Week</th>
<th>No. at Risk</th>
<th>Cerliponase alfa</th>
<th>Historical controls</th>
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**Age distribution**

<table>
<thead>
<tr>
<th>Neonatal period to early infancy</th>
<th>Late infancy to early childhood</th>
<th>Late childhood to adolescence</th>
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<tbody>
<tr>
<td>PDE</td>
<td>Creatine synthesis defects</td>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt; deficiency</td>
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<td>PNPO deficiency</td>
<td>Infantile and late infantile NCL</td>
<td>Lafora body and Unverricht–Lundborg disease</td>
</tr>
<tr>
<td>Folinic acid responsive seizures</td>
<td>Mitochondrial disorders (Alpers syndrome and others)</td>
<td>MERRF</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>Sialidosis</td>
<td>MELAS</td>
</tr>
<tr>
<td>GLUT1 deficiency</td>
<td>Gangliosidosis</td>
<td>POLG-related disease: MIRAS, SCAE, MEMSA</td>
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<td>Non-ketotic hyperglycinaemia</td>
<td>Milder variants of PDE and PNPO deficiency</td>
<td>Juvenile NCL</td>
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<tr>
<td>Serine biosynthesis defects</td>
<td>Congenital disorders of glycosylation</td>
<td>Late onset GM2 gangliosidosis (Sandhoff, Tay–Sachs)</td>
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<tr>
<td>Molybdenum cofactor and sulphite oxidase deficiencies</td>
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<td>Gaucher type III</td>
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<td>Menkes disease</td>
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<td>Niemann–Pick type C</td>
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<td>Disorders of peroxisome biogenesis and β-oxidation</td>
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<td>Cathepsin D deficiency (congenital NCL)</td>
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**Table I: Classification of metabolic epilepsies according to age at presentation**

Typical presentation and “red flags”

- 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

Epilepsy with ...

- secondary microcephaly
- facial dysmorphism
- movement disorder

Rule out ...

- GLUT1 deficiency
- Inborn errors of serine deficiency
- Cerebral folate deficiency
- PDH, and others
- Molybdenum co-factor deficiency
- Dystonia – PDE and GLUT1
- Choreoathetosis/ballismus – creatine metabolism disorders
- Ataxia – GLUT1D; biotinidase, serine, folate deficiency

CASE 1

- **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:

  \[ PDHA1 \ \text{gene} \ c.1176\_1238\text{dup} \ (p.\text{Pro}412\_\text{Phe}413\text{ins}21fs). \]

- Confirmed by enzymatic testing of *pyruvate dehydrogenase activity* in skin fibroblasts

**X-linked PDH deficiency**
CASE 1 – Pyruvate dehydrogenase deficiency

- 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 deficiency:**
- 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

- 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: seizing 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
Mutations in PROSC Disrupt
Cellular Pyridoxal Phosphate Homeostasis
and Cause Vitamin-B<sub>6</sub>-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. Clayton2,16,*

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

Vitamin-B<sub>6</sub>-dependent epilepsy due to PLPBP/PROSC mutation

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

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<td>• Benefits of early therapeutic intervention</td>
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Adapted from Platt FM 2017
Diagnostic considerations

Traditional approach:
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- Inform choices for future pregnancies
- Elimination of the diagnostic odyssey

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!