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EPNS

Infantile encephalopathies

Acute presentations of inborn errors of metabolism

Barbara Plecko

Division of Child Neurology

University Childrens' Hospital Zurich

Das Spital der
Eleonorenstiftung

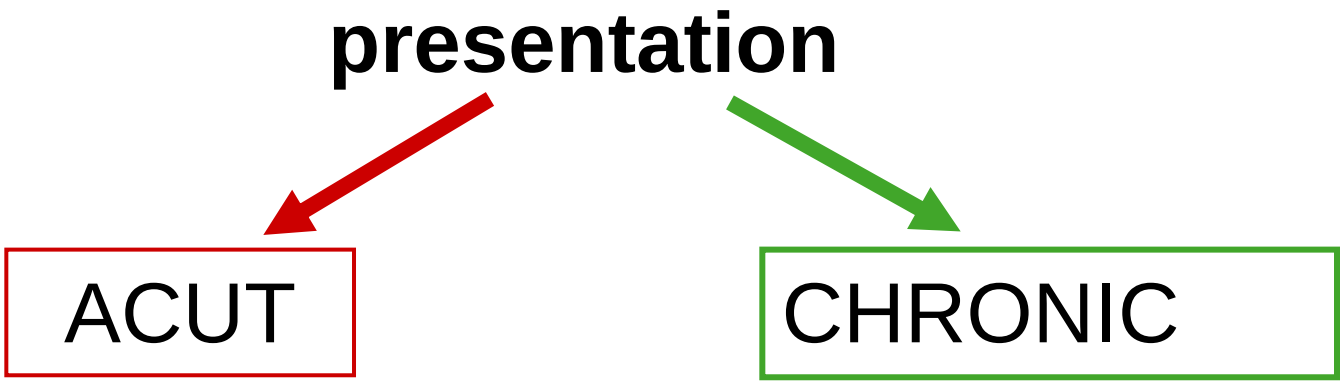
CHILDREN'S
RESEARCH CENTER (CRC)

Contents

- Acute presentation of IEM
- Intoxication type disorders
- Substrate deficiency

- Somnolence and coma
- Movement disorders
- Seizures and epilepsy

Metabolic Encephalopathies



Intoxikation type

urea cycle defects,
amino-organoacidopathies

Energy deficiency

fatty acid oxidation defects
primary lactic acidosis defects of gluconeogenesis

Cofactor defects

Mitochondriopathies

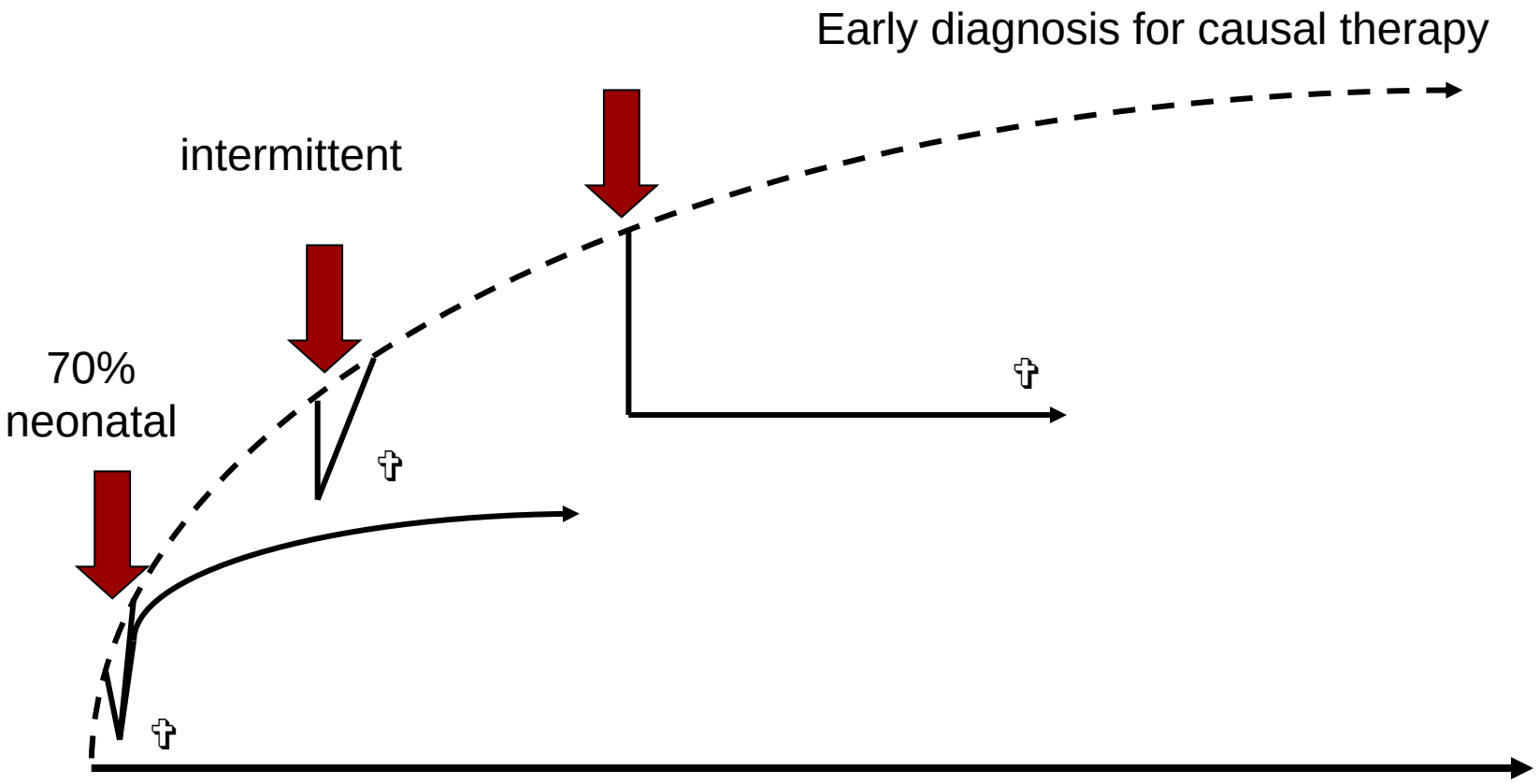
LSD (hydrops)

Peroxisomal disorders

CDG syndromes

Neurotransmitter defects

Acute metabolic crises can occur at any age and are potentially fatal

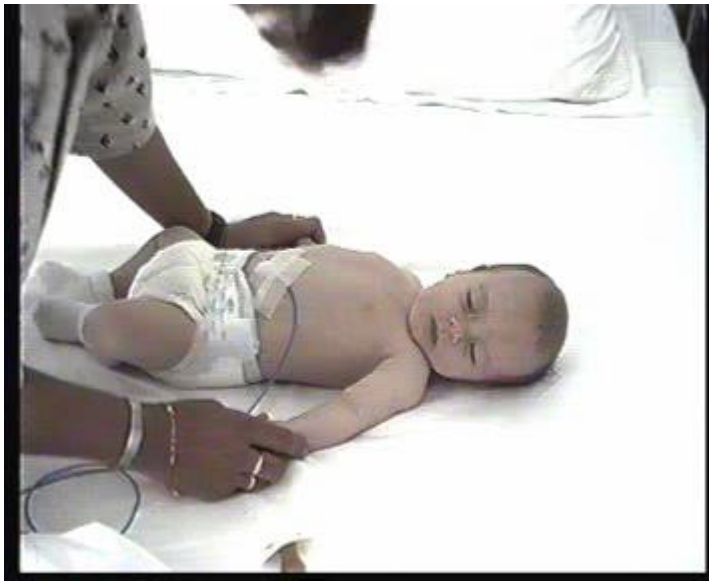


examples: urea cycle defects, organoacidopathies, Cobalamin defects, mitochondriopathies (eg. MELAS)

Acute Encephalopathy
Neonatal manifestation

- Ca. 70% of IEM manifest in the neonatal period
- Symptom free period of hours or days
- Poor feeding, recurrent vomiting
- Drowsiness– somnolence -coma
- Abnormal breathing (tachypnea)
- Progression over hours /days

- Misdiagnosis:
- Sepsis of unknown origin
- Intestinal obstruction
- Encephalitis



Biotinidase deficiency

4 week old girl

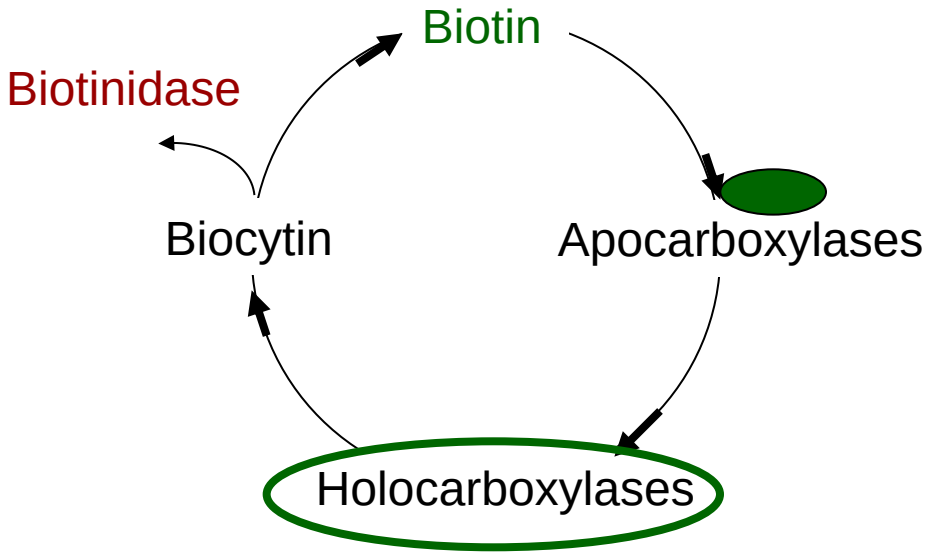
Pregnancy and delivery uneventful

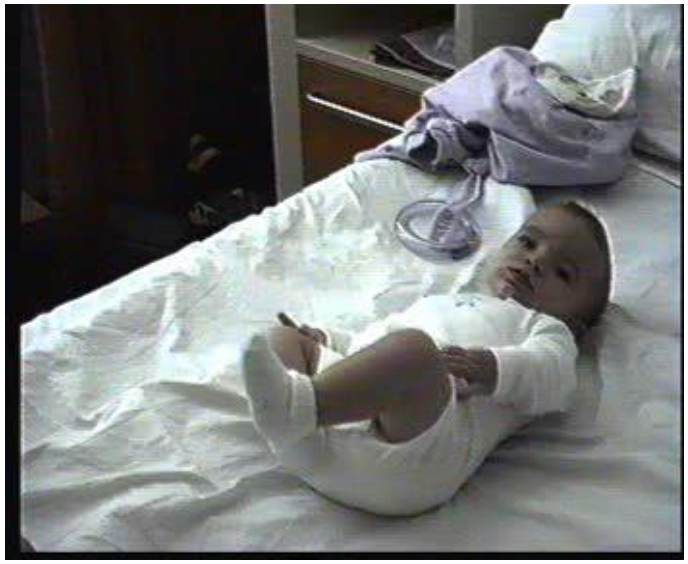
Presented with poor feeding

Progressive sleepyness

pH: 7.15, BE -16, anion gap 25, lactate 4.8 mmol/l

Org. acids:↑3OHIVA, ↑lactate, ↑ methylcrotonylglycine, ↑ methylcitrate





Propionyl CoA Carboxylase, 3-MethylcrotonylCoA Carboxylase, Pyruvat Carboxylase……

Newborn Screening Programm

Disease	Method	Incidence
PKU	TMS	1:10.000
Galactosemia	Enzymatic	1:80.000
Biotinidase deficiency	Colorimetric	1:60.000
Hypothyroidism	FIA / DELFIA	1: 3.500
AGS	FIA / DELFIA	1:10.000
Fatty acid oxidation defects: MCAD,LCHAD,VLCAD, CPT1/2,CT,MADD	TMS	ca. 1:10.000
Organoacidopathies: IVA, GA I	TMS	
Maple sirup urine disease	TMS	ca.1:100.000

Limitations of Newborn Screening Programms

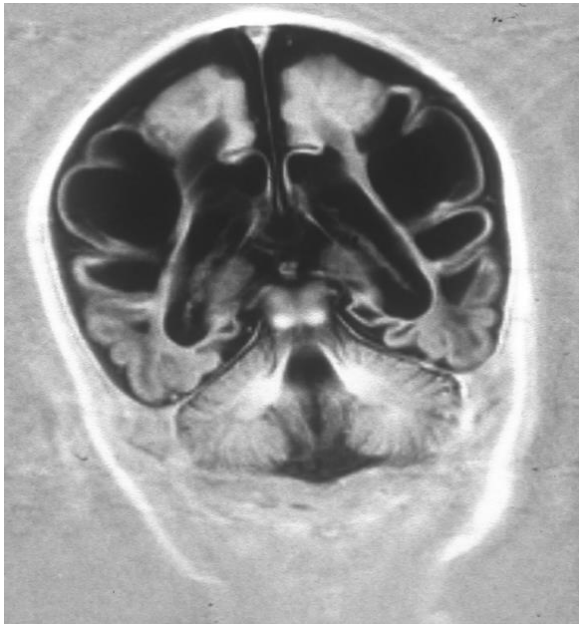
- Sampling in 36th-72nd hour of life
- Receipt of results 6th-9th day of life
- At this time many affected newborns will be symptomatic
- eg. MMA, PA, MSUD, class. galactosemia
- Prognosis may be poor depsite early detection (eg. PA, MMA removed from German programm)

- Urea cycle disorders (UCD) are not detected (except Citr.)

- Perform extended routine lab and selective screening in the presence of unclear / progressive encephalopathy, inform metabolic lab about emergency analysis

Christoph

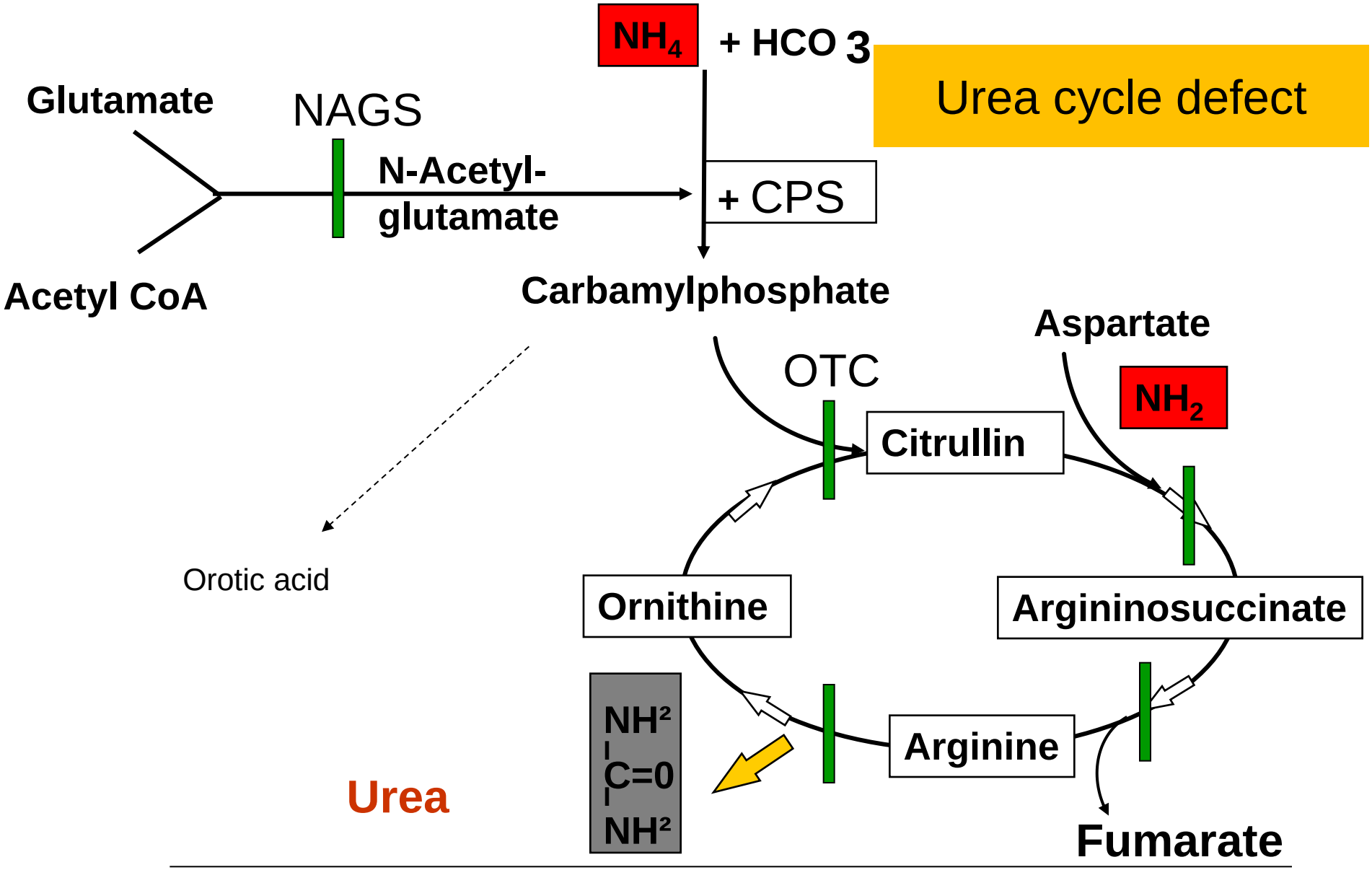
- 1st child of healthy unrelated parents
- Pregnancy and delivery uneventful
- Poor sucking from day 3
- From day 4 apathy, rec. vomiting, tachypnea, ↓pCO_2 , respiratory alkalosis
- Cranial US and CSF normal. From day 4 recurrent seizures



Leukomalacia after protracted hyperammonemia

- On day 5 first determination of NH3:
  1800 µmol/l (<100µmol/l)
- orotic acid positiv, citrullin markedly decreased

Urea cycle defect



Urea cycle defects
symptoms at first episode n=260

Summar et al 2008

Symptoms	Numbers	%
Neurologic	208	80
↓conciousness	164	63
Altered mental status	83	32
Abnormal motor function	78	30
Seizures	25	10
Gastrointestinal	85	33
Vomiting	50	19
Poor feeding	24	9
Infection	75	30
Fever	17	3.5

Information from the Routine lab

- **Hypoglycemia** (NB<35 mg/dl; >1 Mo <50 mg/dl) glycogenosis, defects of gluconeogenesis, fatty acid oxidation defects, sec. with organoacidpathies, endocrine: hyperinsulinism, cortisol-, deficiency
- Blood glucose „decreases“ with time -preanalytical error
- „physiologic hypoglycemia“ < 4y with fasting >4-6h

(Na+K)-(Cl+NaHCO3)

- **Metab. acidosis** (pH↓, PCO2↓, anion gap >20) organoacidopathies, prim. und sec. lactic acidosis

- **Respiratory alkalosis** (pH↑, PCO_2 ↓) urea cycle defects

Information from the routine lab

- **Hyperammonemia** (NB >100 µmol/l; >1 Mo > 50 µmol/l)- Urea cycle defects, sec. in organoacidopathies, liver failure
- NH_3 increases with time- preanalytical error

- **Lactate** ↑ in mitochondriopathies (primary),
  ↑ (sekundary) in organoacidopathies, defects of glycolysis- and gluconeogenesis, evt. in urea cycle defects

- unspec. in impaired circulation (shock), cyanot. heart defects

  caveat: lactate increases with tourniqué

Miriam

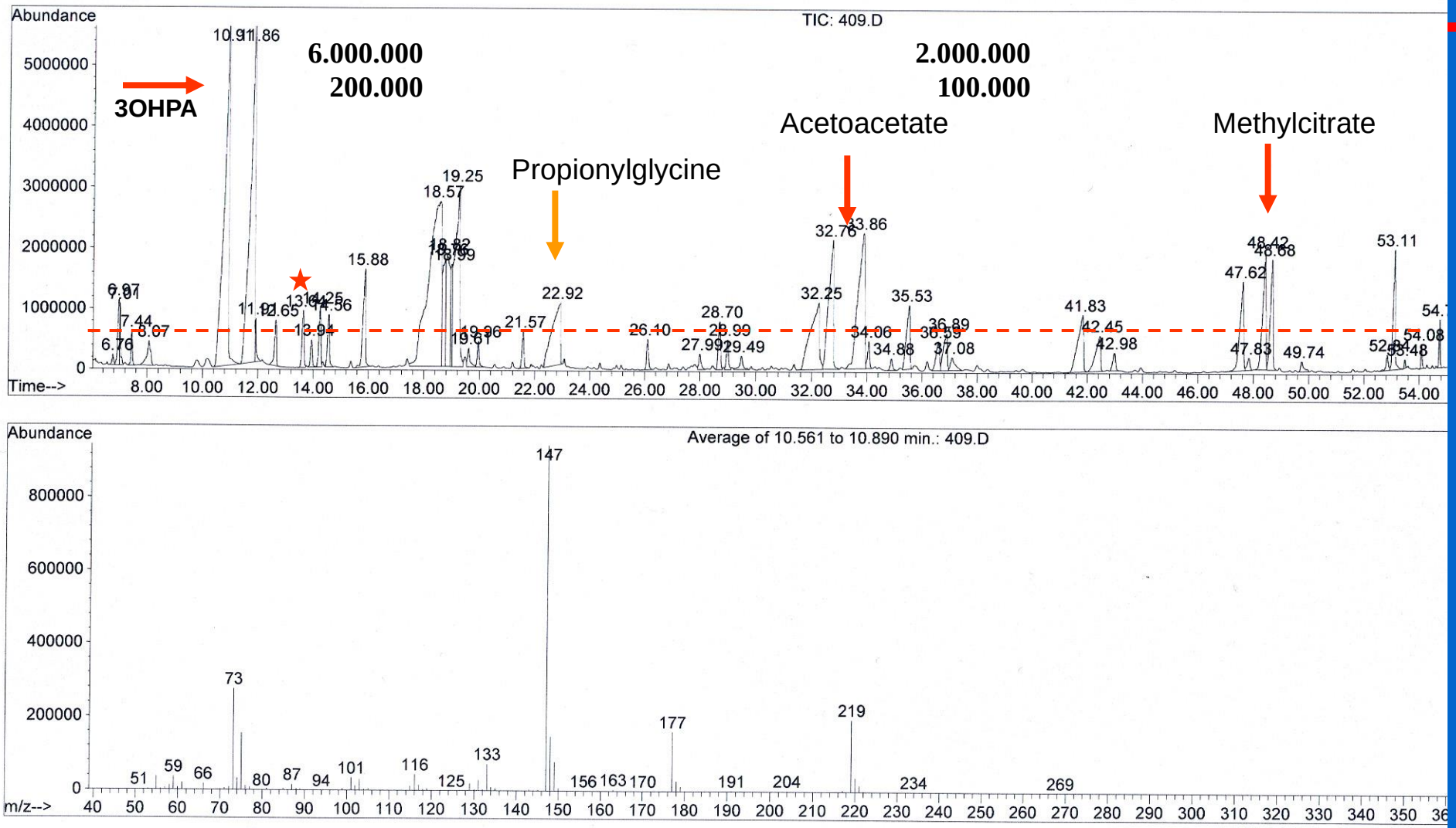
- 2nd child of healthy unrelated parents
- Premature labour 32nd week
- BW 1500g, BL 42 cm
- Early onset sepsis
- Prolonged metabolic acidosis
- Recurrent hypoglycemia

- Moderate hyperammonemia (357 µmol/l)

- Selective screening for amino and organoacidopathies

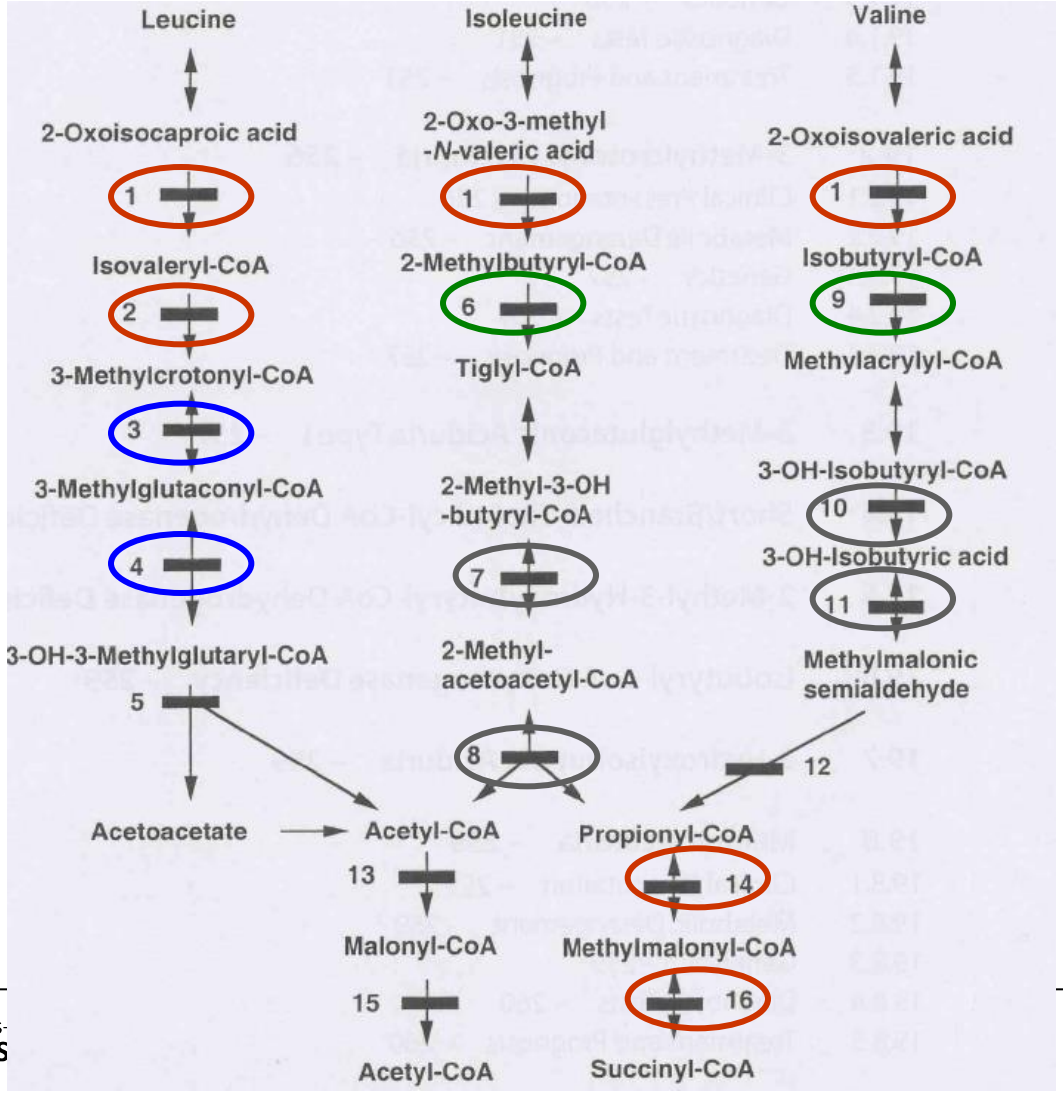
Acquired : 12 Mar 2004 1:39 pm using AcqMethod ORGSCAN
Instrument : GC/MS Ins
Sample Name: 409
Misc Info :
Vial Number: 1

Propionic acidemia GCMS of urine



ORGANOACIDURIAS OF BRANCHED CHAIN AMINOACIDS

classic OA‘s rare OA‘s variable phenotypes non-disease



1	MSUD
2	ISOVALERIC A
3	MCC
4	MGA
5	HMG Lyase
6	MBD
7	MHBD
8	MAT β-ketothiolase
9	IBD
10	HIBDeacylase
11	HIBA
12	MMA SAD
13	ACC
14	PROPIONIC A
15	Malonyl-CoA
16	METHYLMAL A

(Sub) Acute movement disorders and metabolic decompensation

- Different vulnerability of systems
- Dystonia-chorea: organacidurias (GA I, late onset PA) mitochondriopathies, biotin responsive BG Disease, late onset ISOD or MOCOD
- Ataxia: hyperammonemia, intermittierent MSUD, organoacidurias
- Hemiparesis: metabolic stroke eg. UCD, organoacidurias, mitochondriopathies

Glutaric aciduria Type I

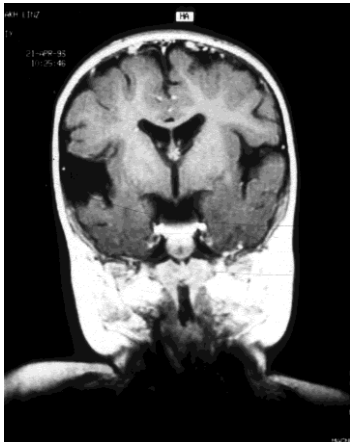
90% of patients manifest from 3mo-36mo

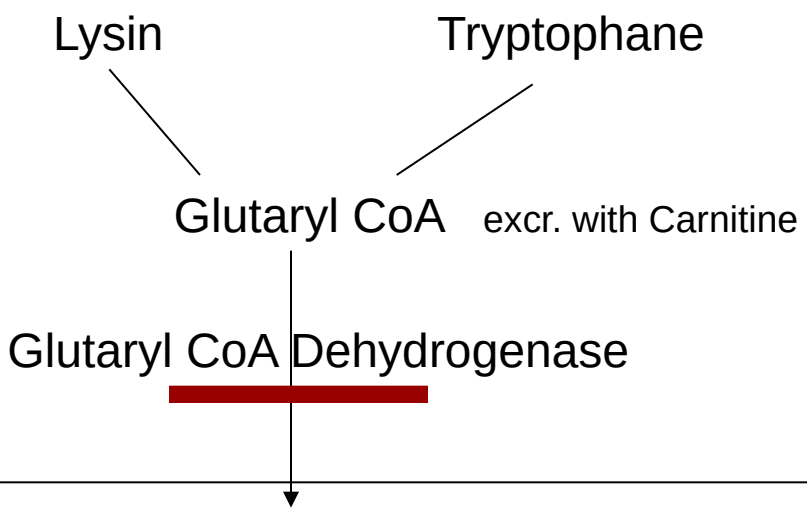
encephalopathic crisis triggered / catabolism

10-20% insidious onset

About 70% of patients have macrocephaly

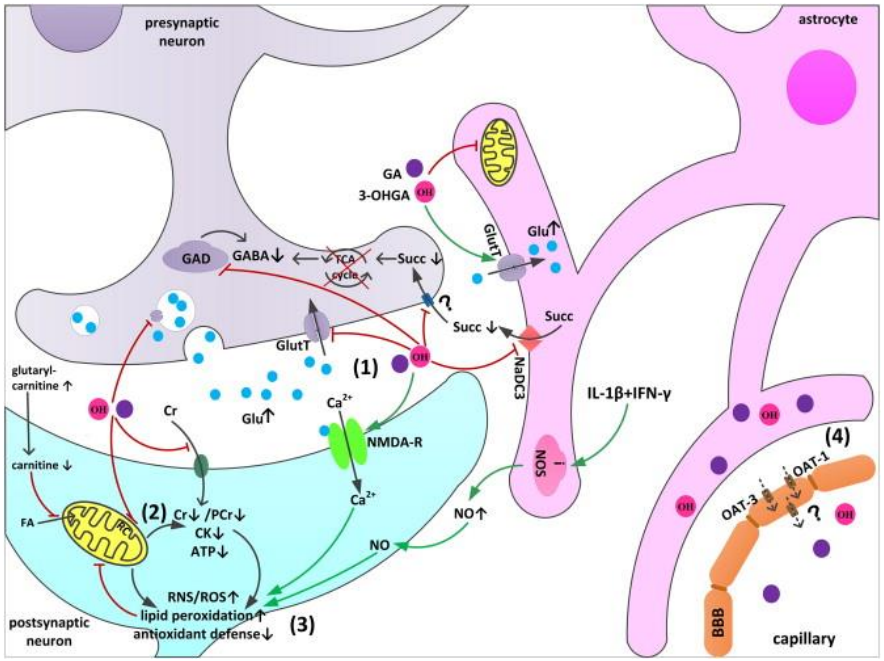
- Extrapyramidal movement disorder, aphasia





Hypothesis on neuropathogenesis in GA I

Kölker et al. JIMD 2008, Sauer et al. Bioch. Biophys 2010, Jafari et al. MGM 2011



Jafari et al.

GA

3-OHGA

1) **Direct excitotoxicity**
2) **Energy breakdown**
3) **Oxidative stress**
4) **Limited efflux / BBB**

Age dependent vulnerability of basal ganglia

Pathogenic mechanisms in metabolic encephalopathies

- Toxicity (eg. urea cycle defects, organoacidurias)
- Secondary inhibition of pathways (organoacidurias)
- Substrate deficiency (eg. creatin, GLUT1)
- Combination of substrate deficiency and toxicity (eg. GA I)

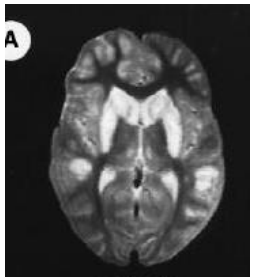
- Imbalance (eg. PKU, neurotransmitter defects)
- Storage (eg. lysosomal disease)

- Secondary phenomena (eg. ganglioside storage in MPS, inflammation in c-ALD)
- Mechanisms often not fully understood

Thiamine transporter deficiency SLC19A3

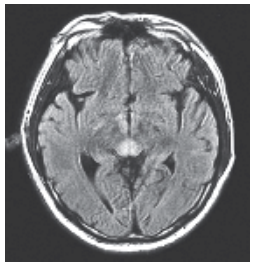
Zeng et al., Am J Hum. Genet. 2005

3 phenotypes of SLC19A3 mutations



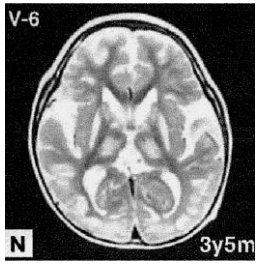
BBGD: subacute encephalopathy with confusion, dystonia, dysarthria and epilepsy, onset during childhood
response to biotin only (5-10 mg/kg)

N=10 (Ozand et al., Brain 1998) N=2 (Serrano et al. abstract)



Wernicke-like encephalopathy with ophthalmoplegia, nystagmus, ataxia and status epilepticus
onset during 2nd decade
response to thiamin (100-600mg/day)

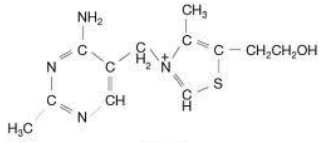
N=2 (1pedigree) (Kono et al, NEJM 2009)



Infantile spasms with severe psychomotor retardation
onset in 1st year of life
unresponsive to biotin

N=4 (1 pedigree) (Yamada et al., BMC Medical Genetics 2010)

Thiamine metabolism



DGE recommendation: 4.0 mg / infants, 1.0f / 1.2m / adults /day

meat, fish, eggs, beans, peas, nuts

Free thiamin + thiaminP

SLC19A2 SLC19A3

Rogers Syndrome

Acquired thiamine deficiency
Wernicke encephalopathy

BBGD, Wernicke-likeS, IS

No biomarker !

Thiamine kinase

Thiamine-pyrophosphate

PDHC, BCKDH
α KGDH

TPP

TPP

Transketolase

SLC25A19

Human cell

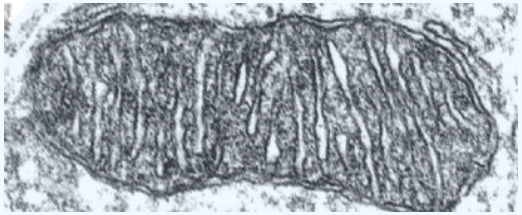
mitochondria

Amish lethal microcephaly
Bilateral striatal necrosis*

Mitochondriopathies

- Relatively frequent, ~1:3.000-1:10.000
- Autosomal recessive-, X-linked, maternal inheritance and sporadic forms (eg. PDHC)
-
- Congenital primary lactic acidosis
- Single well known syndromes (eg. Leigh disease)
- Others unspecific, hypotonia, epilepsy, evt. leukodystrophy
- Multisystem involvement (brain, heart, liver..)

Mitochondria: energy metabolism



Protein

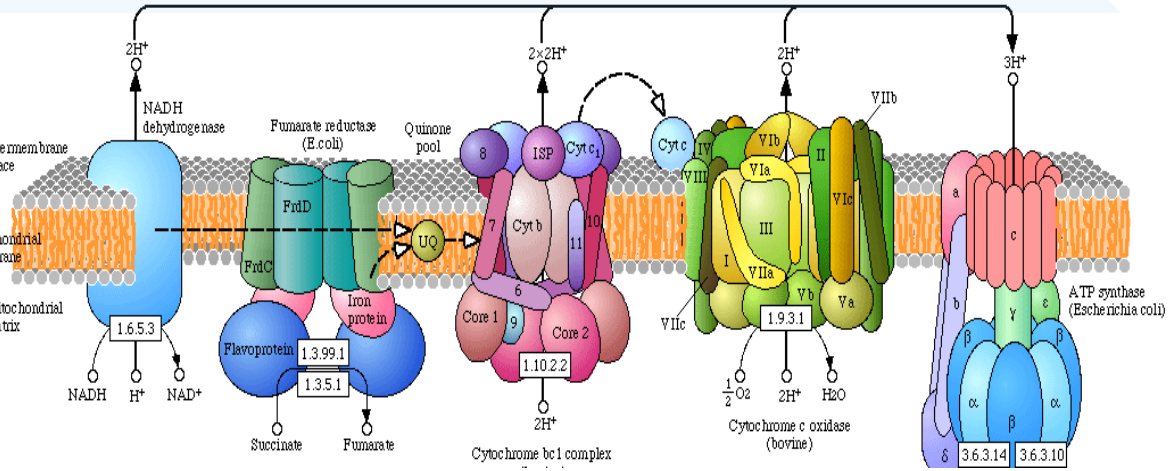
Fat

CH

Acetyl CoA

Krebs cycle

PDH



ATP

PDHC

3 catalytic enzymes E_1, E_2, E_3,
3 regulatory enzymes

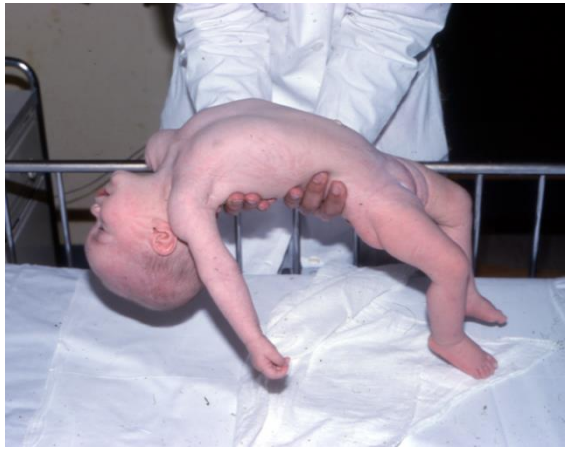
$E_1\alpha$-X-linked (dominant)

Respiratory chain enzymes encoded by nuclear and mtDNA

CI 45 proteins / **7 mit DNA**
CII 4 proteins **all nuclear**
CIII 11 proteins / **1 mit DNA**
CIV 13 proteins / **3 mit DNA**
CV 12 proteins / **2 mit DNA**

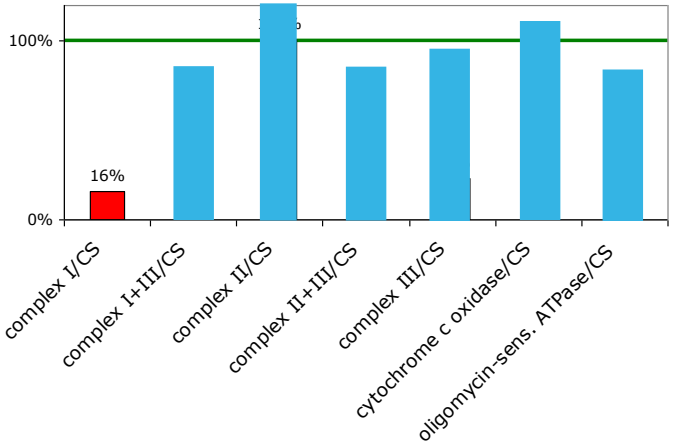
DiMauro, NEJM 2003, 348:2656-68

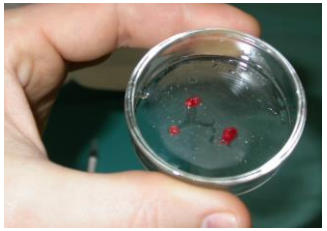
Case vignette lactic acidosis and Complex I deficiency



Floppy baby, poor sucking

3 months, hypotonia, West syndrome

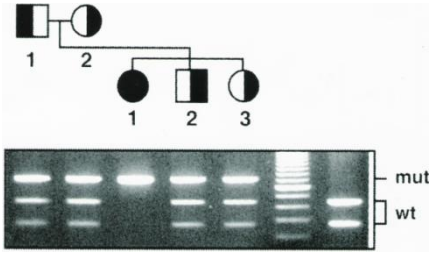




Muscle biopsy

plasma lactate 7 mmol/l,
aminoacid in plasma ↑ alanine
organic acids normal

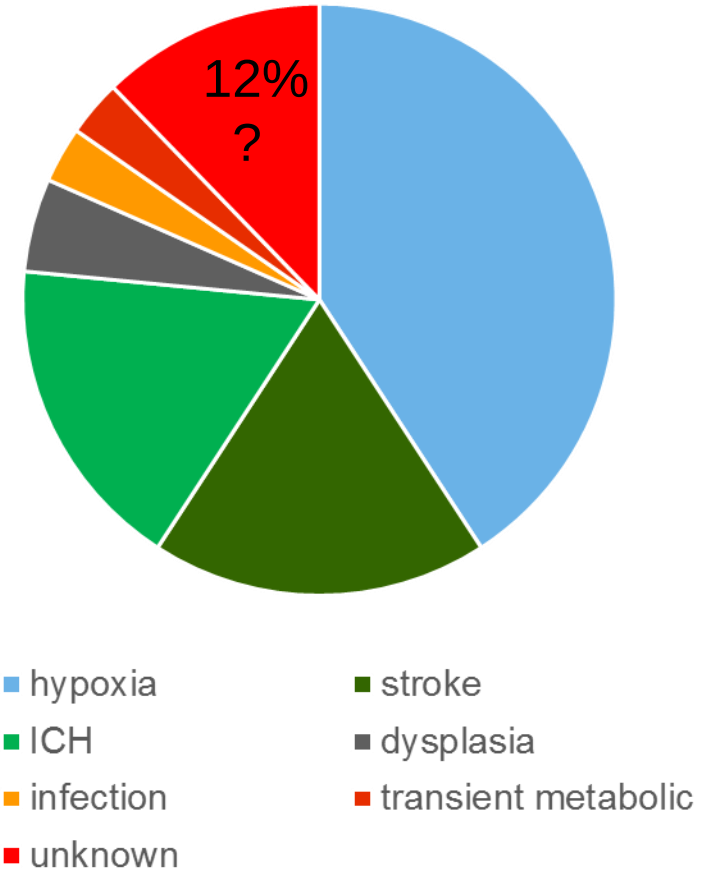
NDUFV1 Gen



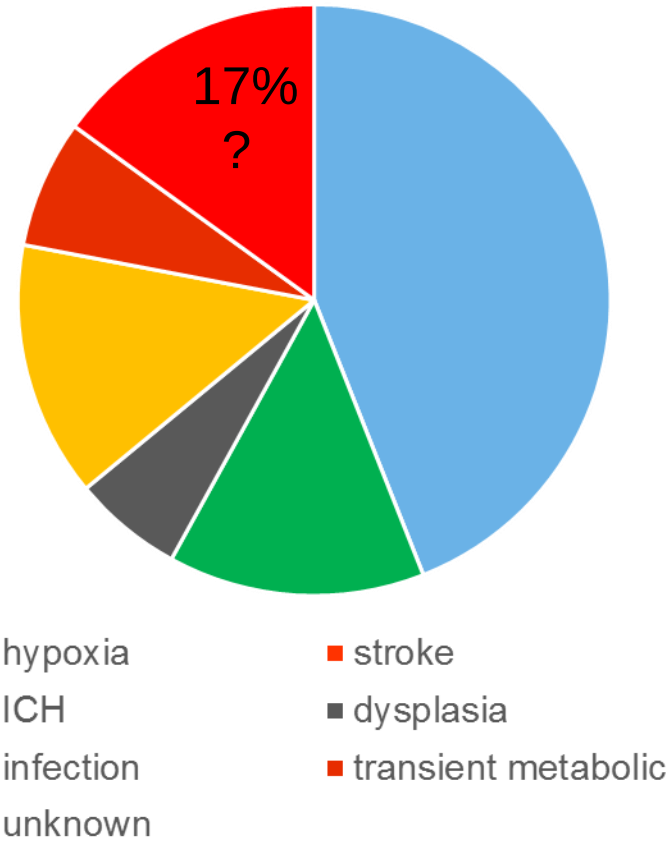
Prenatal diagnosis !

Etiology of neonatal seizures

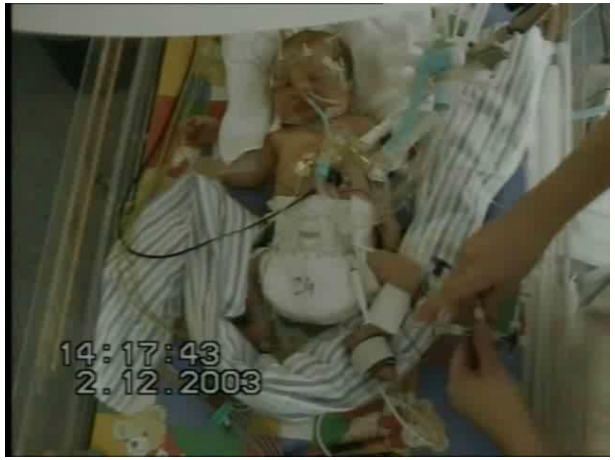
89 mature NB, Tegkul et al.2006



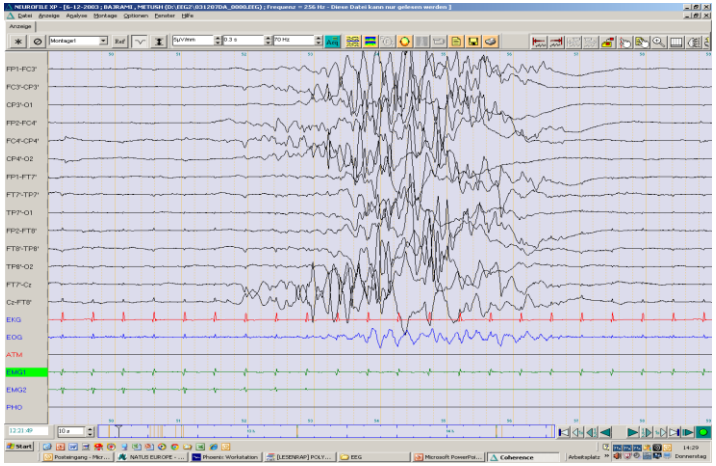
106 NB and pNB, Pisani et al. 2007



EEG patterns do not tell etiology



Courtesy G. Wohlrab



- 2nd child of healthy parents
- Pregnancy and delivery uneventful
- Myoclonic seizures 1st day of life
- One sibling died from neonatal seizures of unclear etiology
- Partial response to Phb

Burst suppression pattern seen in EME, Ohtahara syndrome

HIE

Brain malformation

Metabolic etiologies

Genetic disorders

First think of treatable conditions

TREATABLE	Plecko FoN 2004 adapted 2016	UNTREATABLE
Amino-and Organoacidopathies		
Typical phenylketonuria*		**Nonketotic hyperglycinemia (NKH)**
Serine biosynthesis defects		**D-2 Hydroxyglutaric aciduria**
Cofactor disturbances		
Biotinidase deficiency*		
Atypical phenylketonuria*		
Pyridoxine dependent epilepsies (PDE)		
Pyridoxalphosphate dependent epilepsy (PNPO)		**Isolated sulfite oxidase deficiency**
Molybdenum cofactor deficiency type A (MOCOD A)		**Molybdenum cofactor deficiency type B (MOCOD B)**
Folate receptor deficiency (FOLR1)		
Inborn errors of energy metabolism		
Glucose transporter type 1 deficiency (GLUT1)		Creatine transporter defect
Creatine synthesis defects (GAMT, AGAT)		**Mitochondriopathies**
Peroxisomal disorders		
		Zellweger syndrome
		Neonatal ALD
Lysosomal disorders		
		Neuronal ceroid lipofuscinosis (CLN10)
		Gangliosidoses
		Sialidosis
Disorders of neurotransmitters		
		GABA transaminase deficiency
Congenital disorders of glycosylation		
		CDG Ic, Ik, II
Disorders of purin metabolism		
		Adenylosuccinate lyase deficiency

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Neonatal onset

* Covered by newborn screening

Classification according to age of onset

- Newborn period: cofactor disturbancies, amino-organoacidopathies, Zellweger syndrome
- Infancy: GLUT1 deficiency, Creatin deficiency syndromes, (PDE), serine deficiency, amino-organoacidopathies, CDG syndromes, NCL1
- Toddlers: FOLR1, (GLUT1, PDE), Alpers syndrome, *NCL2*
- School age: NCL 3, Alpers syndrome, mitochondriopathies, LSD‘s

IEM and seizure type

Myoclonic seizures: PDE, PNPO, NKH, GAMT deficiency, FOLR1, GLUT1 deficiency, mitochondriopathies, NCL2,

Focal, tonic-clonic: MOCOD, GLUT1 deficiency (infancy)

Generalized tonic-clonic: NCL 2 und 3, GLUT1 (toddlers)

Atypical absences: GLUT1 deficiency (toddlers)

West syndrome: mitochondriopathies, NKH (late), *Menkes disease*, biotinidase deficiency, PNPO deficiency

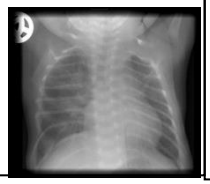
Status epilepticus: PDE, Alpers

Inborn errors and vitamin B_6 dependent epilepsy

B6 response in KCNQ2 deficiency

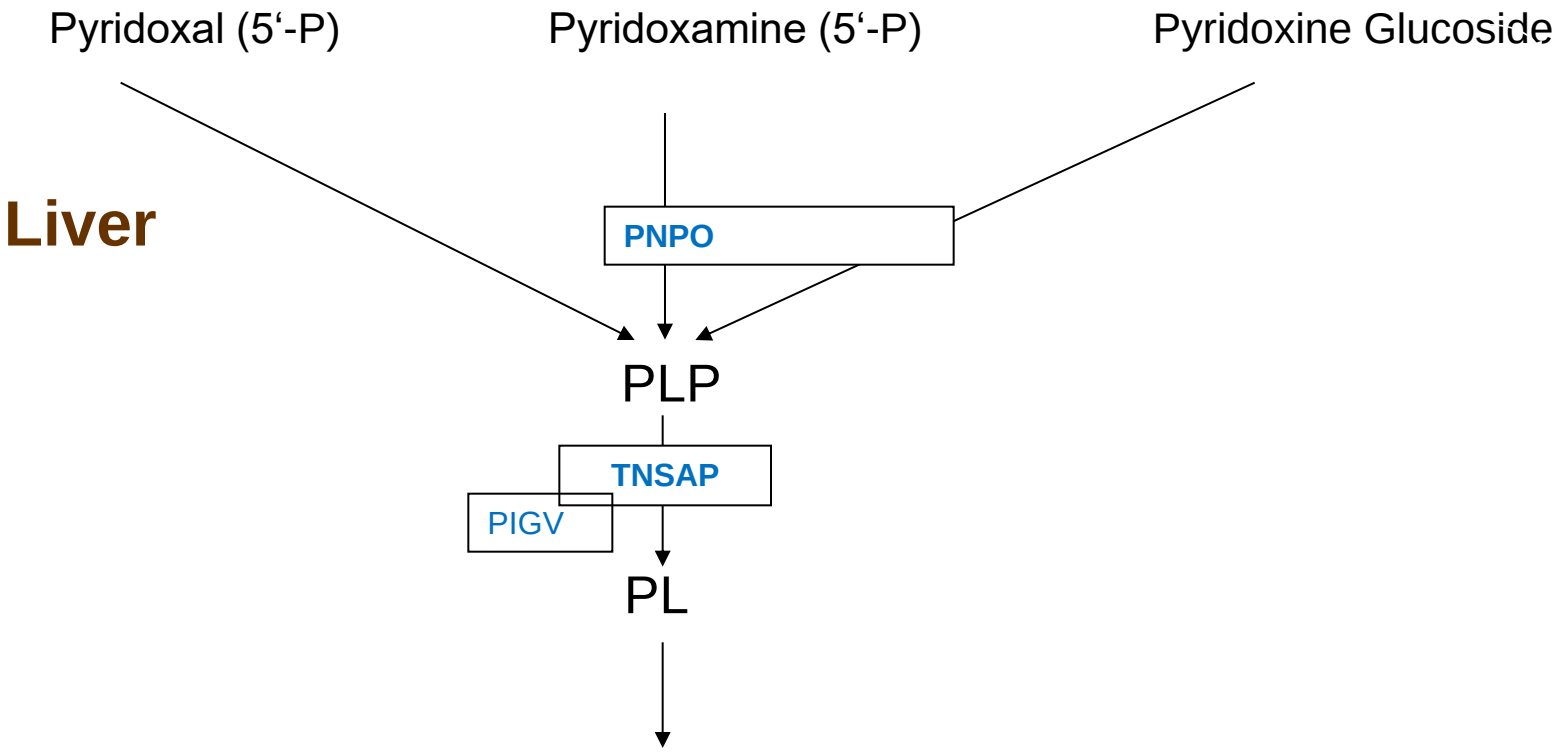
increased utilization of PLP

reduced synthesis/uptake of PLP

TYPE II HYPER-PROLINEMIA	ANTIQUITIN DEFICIENCY	PNPO DEFICIENCY	CONGENITAL HYPOPHOSPHATASIA	MABRY SYNDROME
Seizure onset infancy to childhood +/- response to common antiepileptic drugs +/- mental retardation	Neonatal onset of myoclonic seizures Resistance to common anticonvulsants 30% poor adaptation / HIE 30% signs of encephalopathy prematurity Systemic manifestations (abd. distension, vomiting..)	Neonatal seizures – in lethal neonatal or infantile forms Resistance to common anticonvulsants May occur before skeletal manifestations Death due to resp. insufficiency 	Floppy infants Dysmorphy Brachytele-phalangy Mental retardation Seizures (1-3y)

Vitamin B_6 metabolism

Diet



PLP is a cofactor of > 140 enzyme reactions in aminoacid- and neurotransmitter metabolism

Vitamin B_6 (PLP) cofactor of >140 reactions (AA and NT)

Threonine —(PLP, Threonine-dehydratase)→ **2 Oxobutyrate + NH_4^+**

Serine —(PLP, Serine-dehydratase)→ **Pyruvate + NH_4^+**

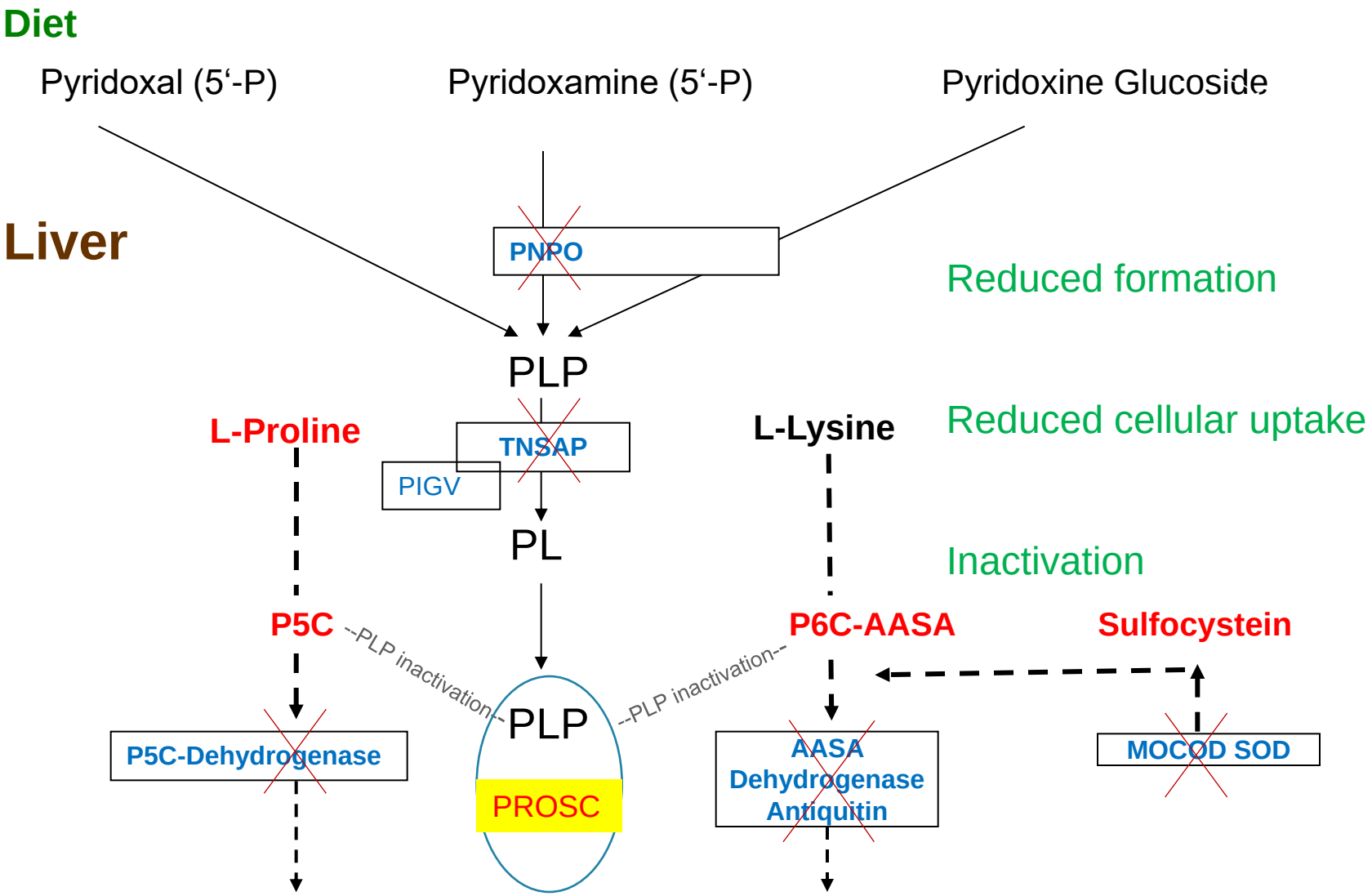
Glycine —(PLP, Glycine-cleavage system)→ **CO2 + NH_4^+**

Glutamate —(PLP, Glutamate decarboxylase)→ **GABA + CO_2**

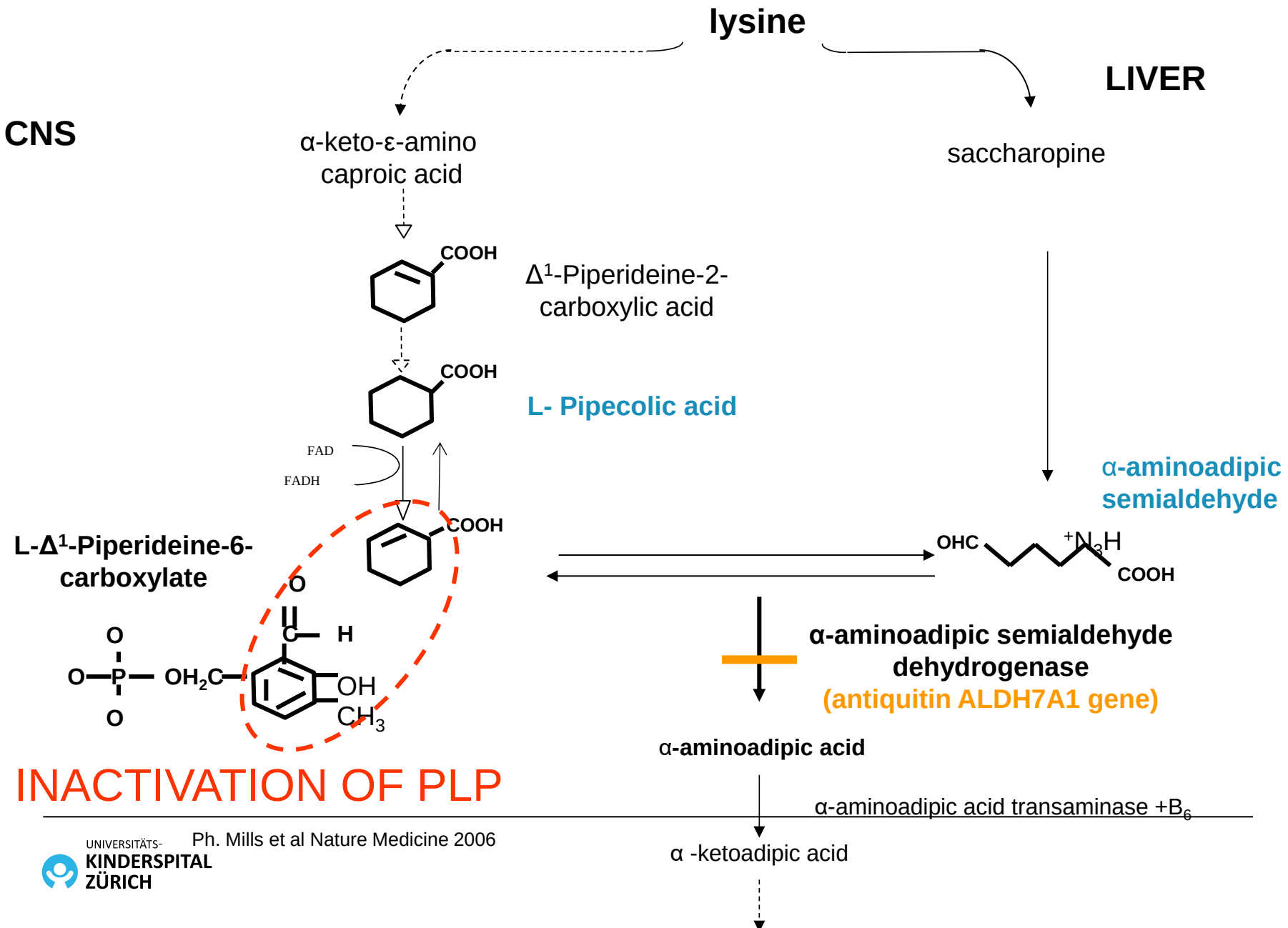
GABA +2 Oxoglutarate —(PLP, GABA transaminase)→ **succinic semialdehyde + glutamate**

2 Oxoglutarate + Leucine —(PLP, BCAA transferase)→ **Glutamate + 2 Oxoisocaproate**

Vitamin B_6 metabolism and inborn errors with epilepsy



PDE and Antiquitin deficiency



INACTIVATION OF PLP

Ph. Mills et al Nature Medicine 2006

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Diagnostic biomarkers of vitamin B_6 dependent neonatal epilepsies

unspecific specific

	Urin	Plasma	CSF	B6 Response
Antiquitin	↑ AASA, ↑ P6C, ↑ PA*	↑ PA	↑ AASA, P6C, ↓PLP, ↑ PA, sec NT abn.	Pyridoxine or PLP
PNPO deficiency	(Vanillactate)	↑pyridox-amine	↓ PLP, sec NT abn.	PLP or pyridoxine Mills et al. Brain 2014 Plecko et al. Neurology 2014
Congenital Hypophosph		↓ AP, ↓ Ph, ↑ Ca	(↓ PLP ?)	Pyridoxine or PLP
MOCOD, ISOD	Sulfocysteine ↑ AASA, ↑ P6C	↓ uric acid	↑ AASA, P6C ↓PLP, ↑ PA	Pyridoxine or PLP Type A cPMP iv.

AASA alpha aminoadipic semialdehyde; P6C piperideine-6-carboxylate; NT neurotransmitters, PA pipecolic acid, PLP pyridoxal 5´-phosphate

Suggested diagnostic algorithm for neonatal seizures

neonatal seizures of unknown etiology

↓

„resistance“ to first line drugs (eg. phb, pht, benzodiazepins)

↓

save plasma, urine , evt. CSF (freeze at -80°) Biomarkers

↓

pyridoxine, 100 mg iv. followed by 30 mg/kg/day in 2-3 SD over 1-3 days
ambigous response in ca. 15%. EEG not helpful

↓

BEWARE OF APNEA IN RESPONSIVE PATIENTS

e consider add on of folinic acid 3-5 mg/kg/day in 1-2 SD

Switch to PLP 30 to 60 mg/kg/day in 4-6 SD over 3 days
(may need adjustment for break through seizures)

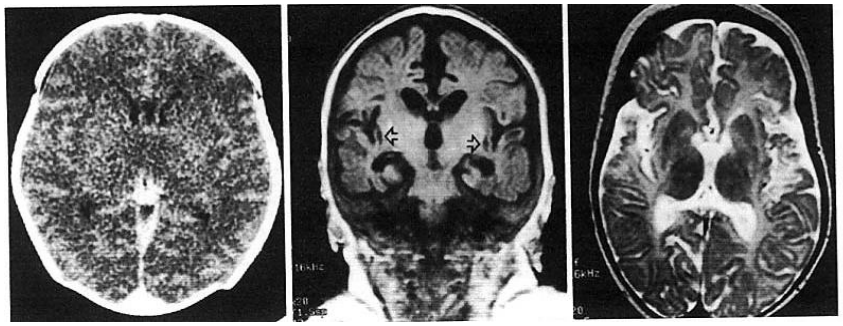
↓

no withdrawal

if seizures stop, continue pyridoxine or PLP until results are available

Molybdenum cofactor deficiency (MOCOD)

- Neonatal onset of bilateral tonic and clonic seizures
- Failure to thrive, evt. facial dysmorphism
- EEG – multifocal discharges or BSP
- Therapyresistance

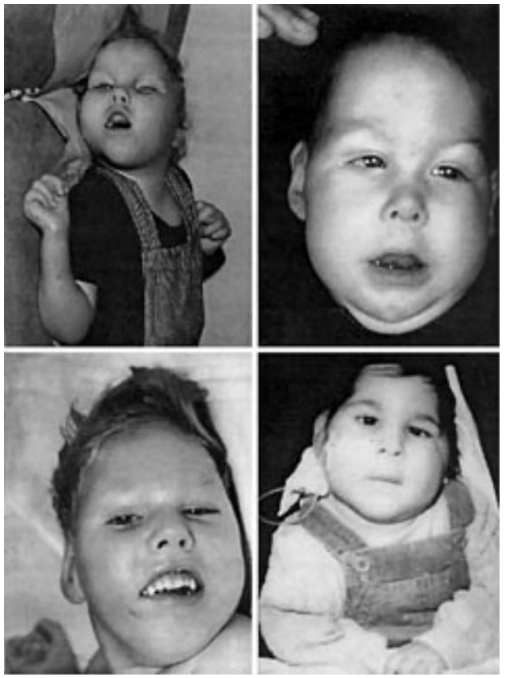


CT newborn MRI 6 weeks MRI 4 months

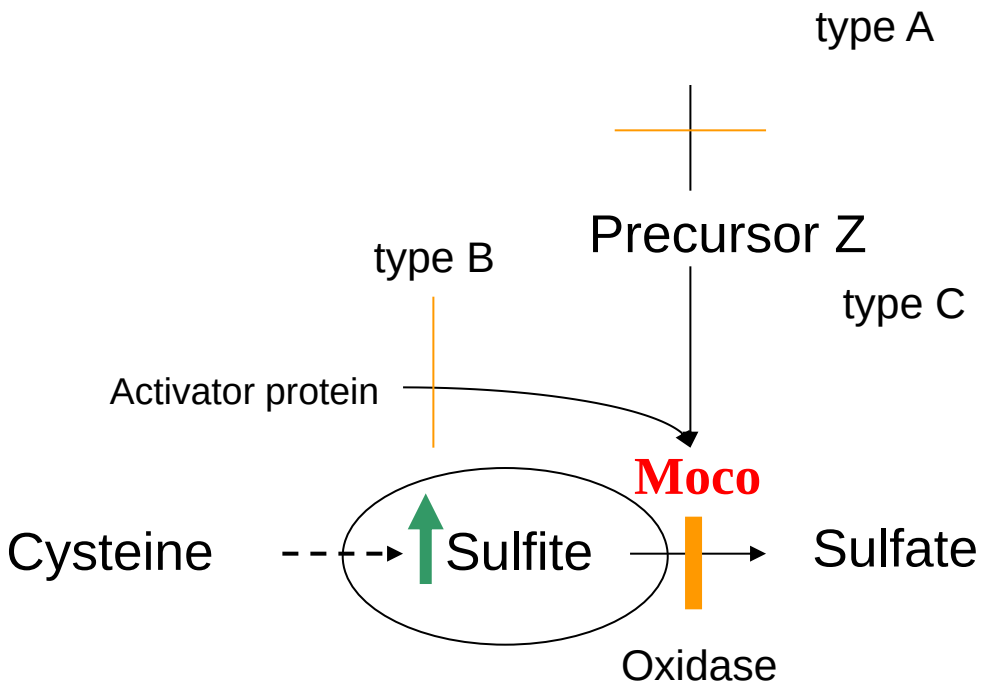
Appignani et al 1996

- Truncal hypotonia, later spasticity
- Lens subluxation beyond the neonatal period

OMMBiD



Pathogenesis of MOCOD and isolated sulfate oxidase deficiency ISOD



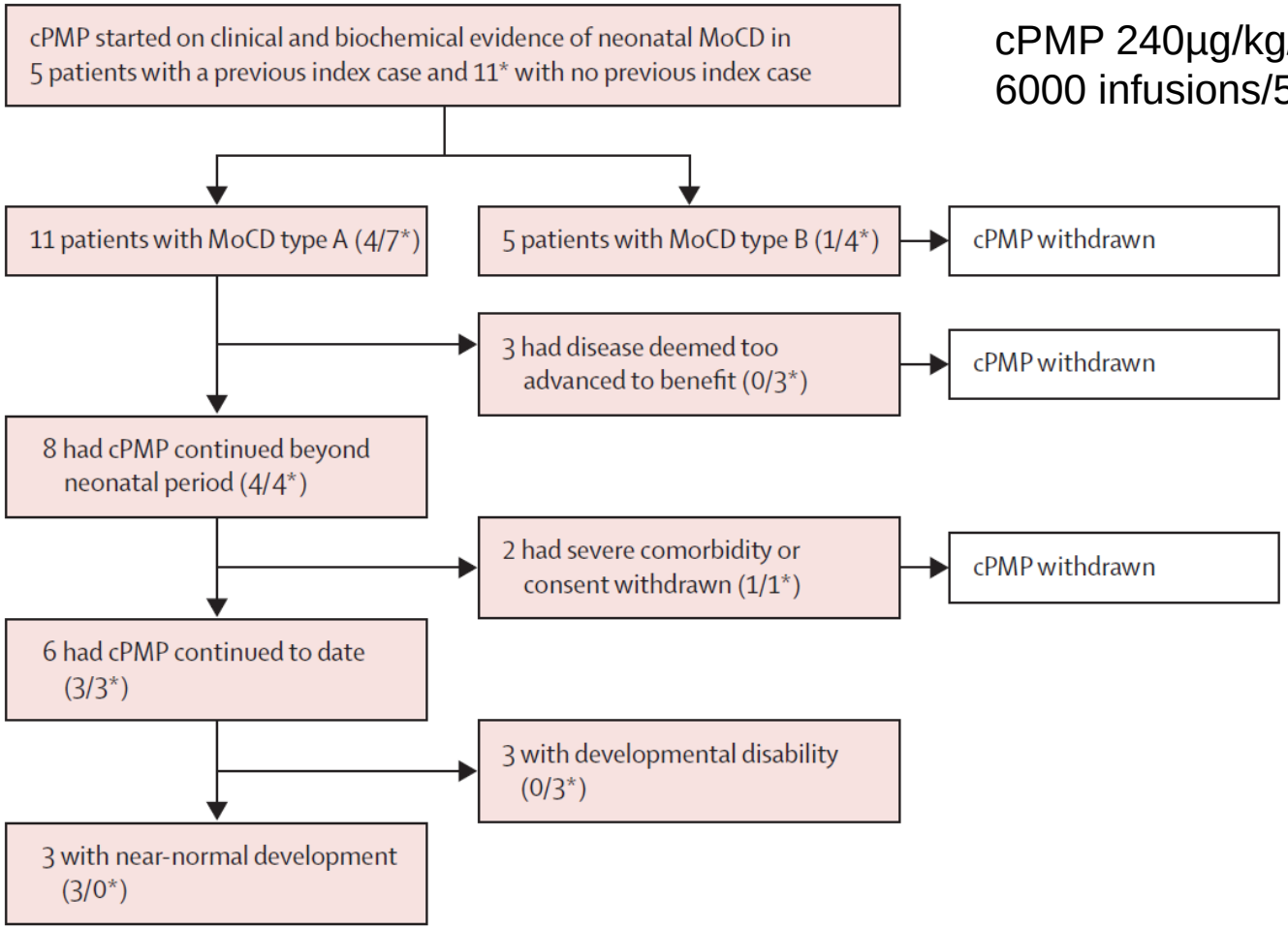
îv cPMP for Type A

cyclic pyranopterin monophosphate

Biomarkers

↓ uric acid/P, ↑ sulfite/U* (dipstick/false negative results), ↑ sulfocysteine/U, ↑ xanthin

cPMP Trial for MOCOD deficiency



cPMP 240µg/kg/day in 30-60 min inf.
6000 infusions/5y no SEA

All 3 had index siblings and early diagnosis and treatment

Schwahn et al. Lancet 2015

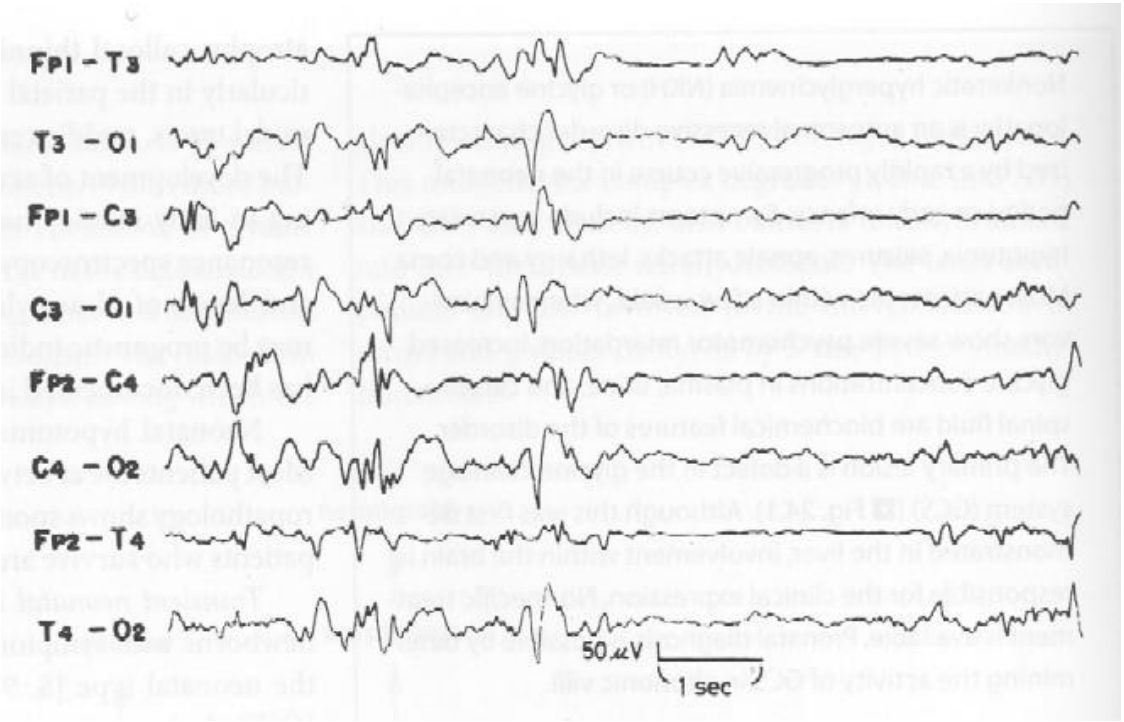
Veldman et al. Pediatrics 2012, Hitzert et al Pediatrics 2012

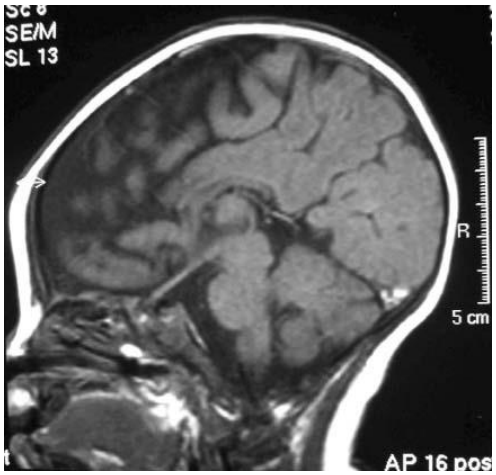
Non ketotic hyperglycinemia

- Estimated incidence 1:250.000
- neonatal, infantile, late-onset form
- neonatal onset from day 1 to day 7
- sever hypotonia, apnea, myoclonic seizures, coma

- Diagnosis: ratio CSF/P > 0.04 (>0.08)
- Glycine ratio correlates with phenotype / age of onset
- Pitfall - secondary ↑ of glycine with valproate therapy
- Aut. rec. defect in the glycine cleavage system
  (4 enzyme steps, 4 coding genes)

Burst Suppression pattern in NKH



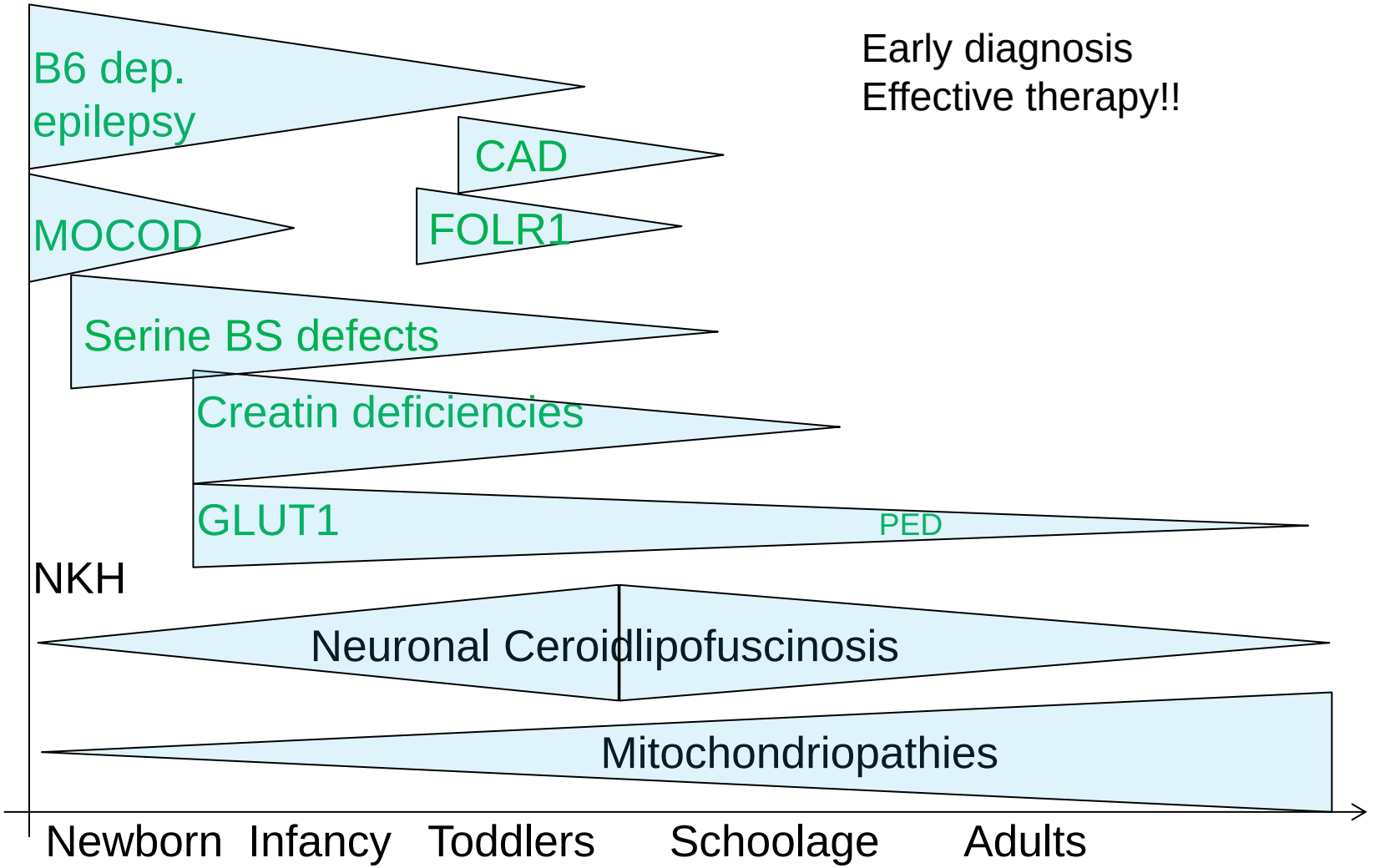


CC anomalies
Inconsistent finding

- Most neonatal forms are caused by P or T protein defects / GCSH or AMT gene (Kure et al, 2006; Kanno et al 2007, van Hove et al. 2007)
- Transient NKH – better prognosis (Schiffmann et al 1989)
- A802V mutation better prognosis - therapeutic dilemma

Typical age of onset of metabolic epilepsies

O. Dulac, B. Plecko, S. Gattaulina, N. Wolf. Lancet Neurol 2014; 13: 727–39



GAMT deficiency

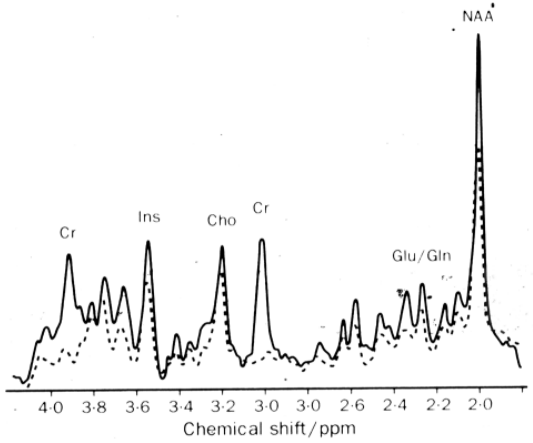
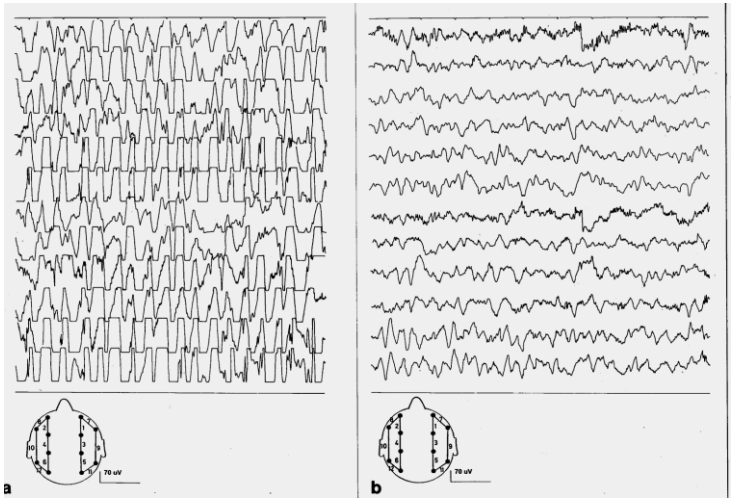


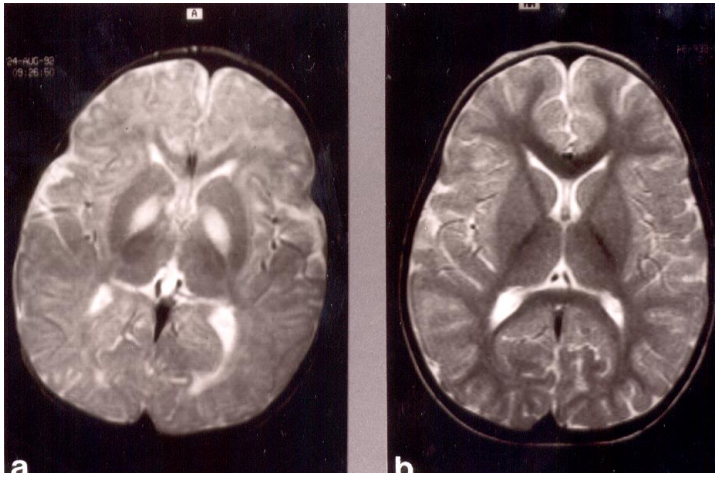
Figure 1: **In-vivo proton magnetic resonance (^{1}H-NMR) spectra of parietal grey matter in patient with GAMT deficiency (stimulated echo acquisition mode [STEAM]: repetition time/echo time/middle interval=6000/20/30 ms, 64 accumulations, 8 mL volume-of-interest)**
Dotted tracing: at age 22 mo, before treatment; solid tracing: at 48 mo, after 25 mo of oral creatine replacement. Cr, creatine and creatine-phosphate; Ins, *myo*-inositol; Cho, choline-containing compounds; Glu, glutamate; Gln, glutamine; NAA, N-acetyl aspartate.

Age 14 Mo, before therapy

On therapie for 2 ½ years



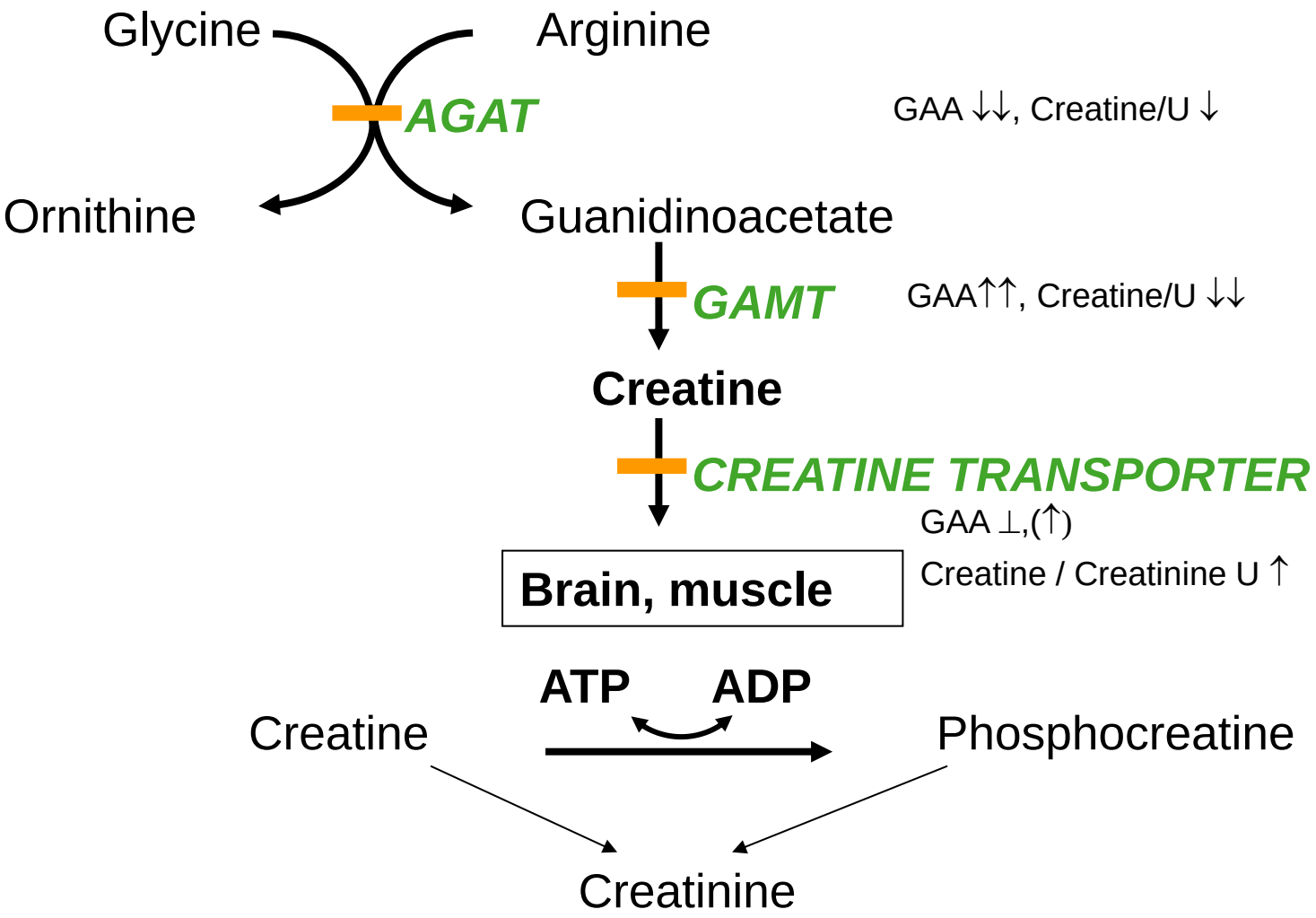
EEG, 18 mo, before and under Creatine



Bilat signal ↑ glob pall. Int. edema?

Courtesy Sylvia Stöckler-Ipsiroglu (AJHG 1996)

Creatine metabolism



Symptoms in Creatine deficiency syndromes

Mercimek & Salomons Gene Reviews Dec2015

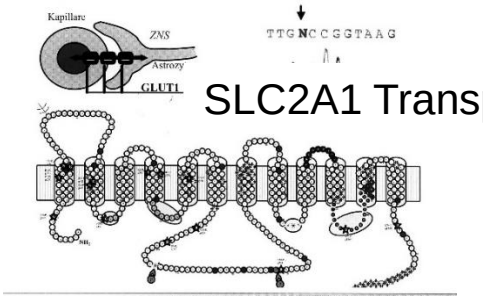
	MR	Epilepsy	EPMS		Patients
AGAT (2001)	++	14%	-	aut. rec.	14
GAMT (1994)	+/+++	3-6 mo 86% 46% TR	38%	aut. rec.	Ca.110
CRTR (2001)	+/++ Absent speech	60%♂ 5%TR	40%	X-rec.	>200

TR therapy resistence, EPMS extrapyramidal motor symptoms

Glucose Transporter Defect (DeVivo Disease 1991)

Wilhelmina G. Leen et al. Brain 2010:133;655-670.n=54

90% mutations
10% deletions
De novo or AD



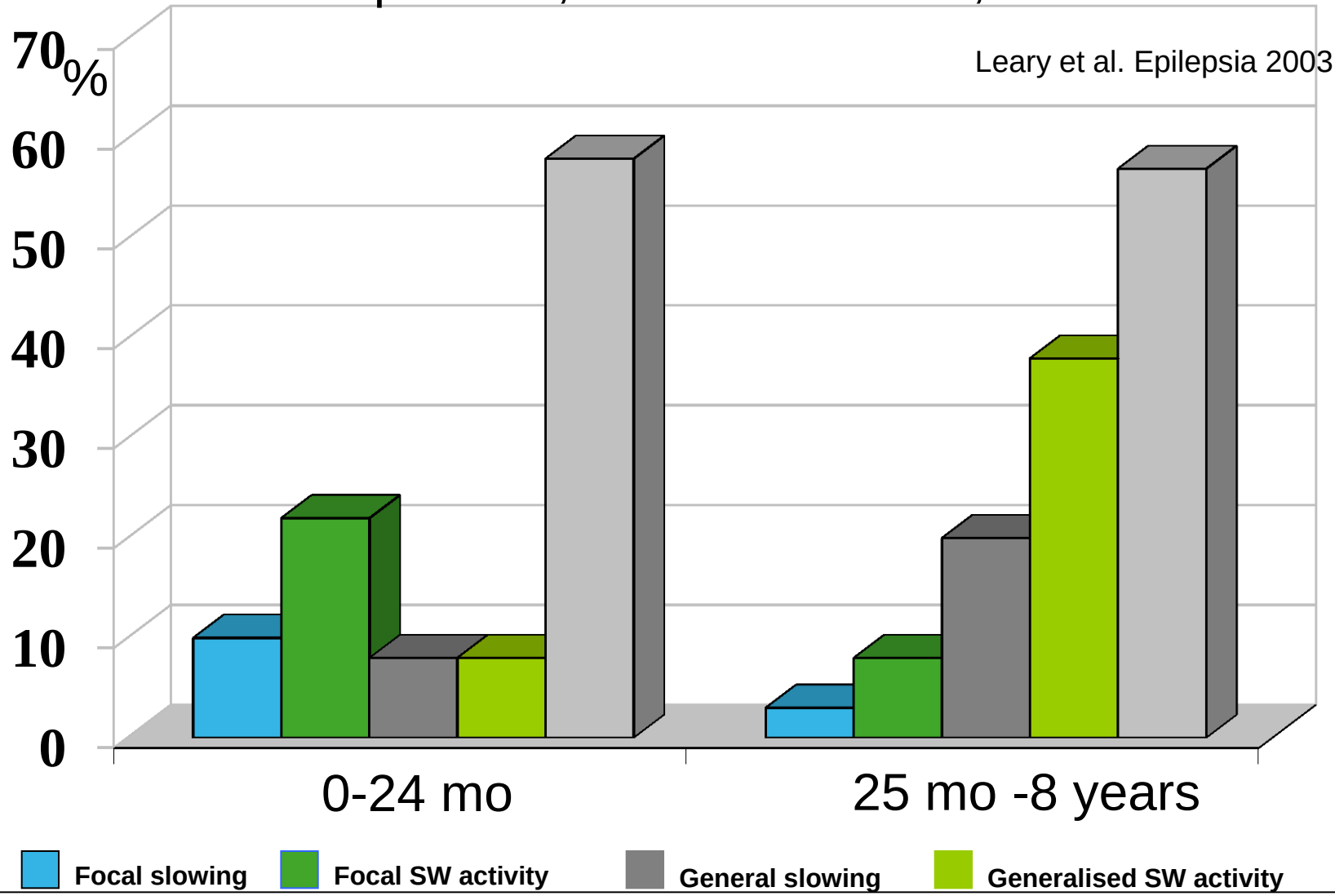
SLC2A1 Transporter

CSF/Plasma Glc Ratio
<0.45 (class Ph.)
Normal ≥ 0.6

- Focal seizure onset 1st-2nd year – later generalized
- Therapyresistense
- Secondary microcephaly (ca.50%)
- Mental retardation (90%)
- Ataxia, spasticity
- Paroxysmal exersice induced dyskinesia (PED)
- Aggravation before meals (take a good history)

- Atypical absences (onset 2-3rd year)
- 15% have no seizures- pure MR

EEG changes in GLUT 1 deficiency
20 GLUT1 patients, 40 routine –EEG, 24 x 24h EEG



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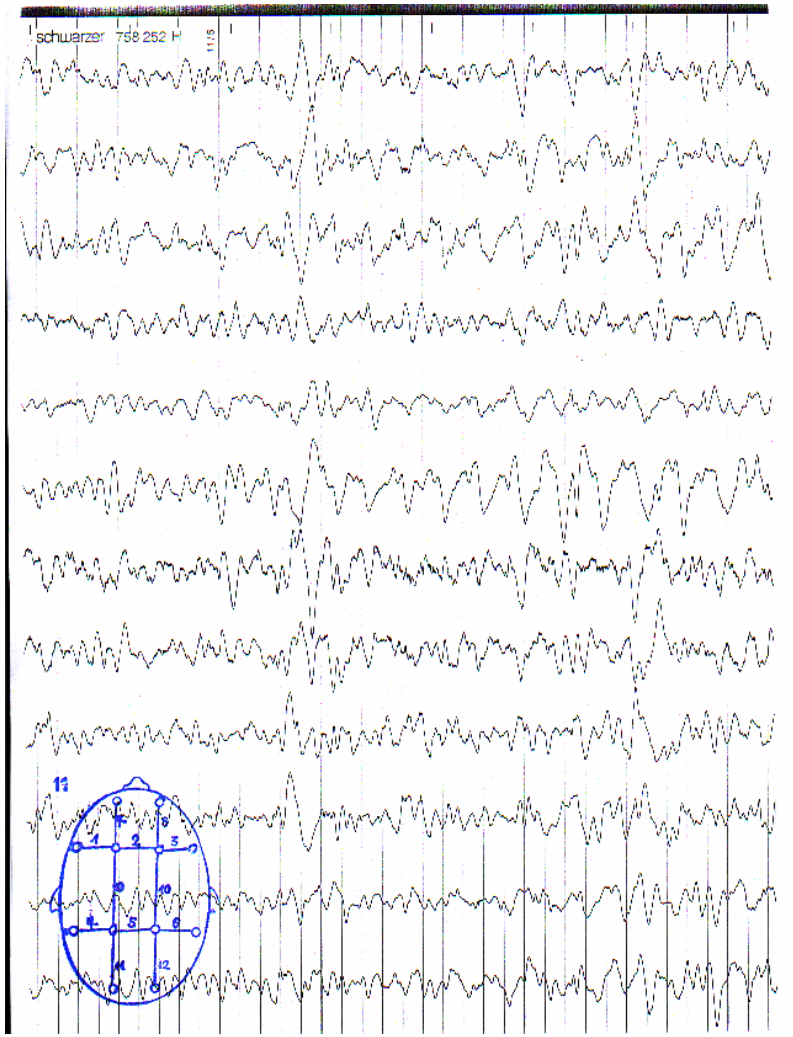
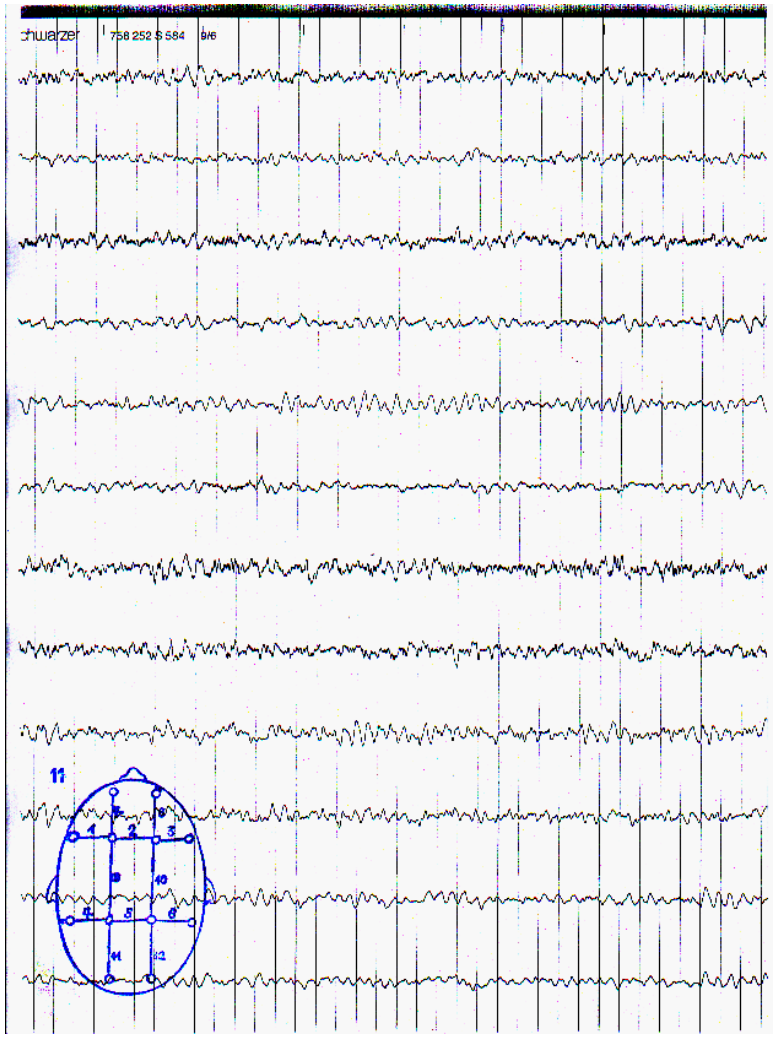
EEG changes in GLUT 1 deficiency



unfed



postprandial

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Courtesy Jörg Klepper

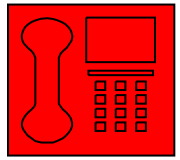
Metabolic work- up of infantile therapyresistant seizures

Disease	Urin	Plasma	CSF	Treatment	Gene
Antiquitin deficiency	↑ AASA, ↑ PA*	↑ PA	↑ AASA, P6C, ↓PLP, ↑ PA, sec NT abn.	Pyridoxine	ALDH7A1
PNPO deficiency	(Vanillactate)	B_6 profile ↑ pyridoxamine	↓ PLP, sec NT abnorm.	PLP (or Pyridoxine)	PNPO
Congital Hypophosphatasia		↓ AP, ↓ Ph, ↑ Ca B_6 profile ↑ PLP	(↓ PLP ?)	Pyridoxine (or PLP)	TNSALP
MOCOD, ISOD	sulfocysteine ↑ AASA, ↑ P6C	↓ uric acid	↑ AASA, P6C ↓PLP, ↑ PA	Pyridoxine or PLP Type A cPMP iv.	MOCS1, MOCS2, GPNH
NKH (non ketotic hyperglycinemia)		aminoacids (glycine)	aminoacids (glycine) CSF/plasma >0.004	-	4 enzymes cleavage system
Organoacidurias (eg. D2HGA)	organic acid profile	aminoacids		-	…
CDG syndromes		Transferrin isoelectric focussing		-	Common in CDG type II (ALG1,3,8..)
Zellweger Syndrome		VLCFA, PA, phytanic acid, pristanic acid		-	PEX gene 1-13
Adenylosuccinate lyase deficiency	purines			-	ADSL gene

Dulac, Plecko, Gataullina, Wolf Lancet Neurology 2014; Campistol & Plecko Epileptic Disorders 2015,

Investigations in unclear acute encephalopathy

- Blood glucose, gases, AST, ALT, Crea, Urea, LDH NH3, lactate, ketostix / urin or cap. blood
- Selective screening (even if routine lab is normal): aminoacids + acylcarnitines /pl, org. acids / U, homocysteine /pl
- Suggestive pattern on cMRI?



- EEG – exclusion of non-convulsive status epilepticus, (most frequent finding is that of diffuse slowing)