

IEM intoxication type

Amino Acids Metabolism Disorders

H.U.B

HÔPITAL UNIVERSITAIRE
DE BRUXELLES
ACADEMISCH ZIEKENHUIS
BRUSSEL



Corinne De Laet

Nutrition and Metabolism Clinic

▶▶ Simplified Classification of EIM in 3 groups

« Impairment of specific enzymes or biochemical pathway is intrinsic to the pathomechanisms of the EIMs » E Morava et al, 2015

Group 1: Small molecule disorders

- Accumulation of small molecules
- Deficiency of small molecules

Group 2: Complex molecule disorders

Group 3: Disorders involving energy metabolism

Embryo-fetal development N

Free-interval period

Signs of intoxication

acute (coma, vomiting, liver failure, ...)
or chronic (developmental delay, failure to thrive,
ectopia lentis, cardiomyopathy, ...)

Diagnosis: AA, ur OA, acylcarnitines

Most are treatable:

specific diet, drugs , ...
extracorporeal procedures

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01

PHENYLKETONURIA

*Phenylalanine hydroxylase
deficiency*

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F. van Spronsen et al, 2017

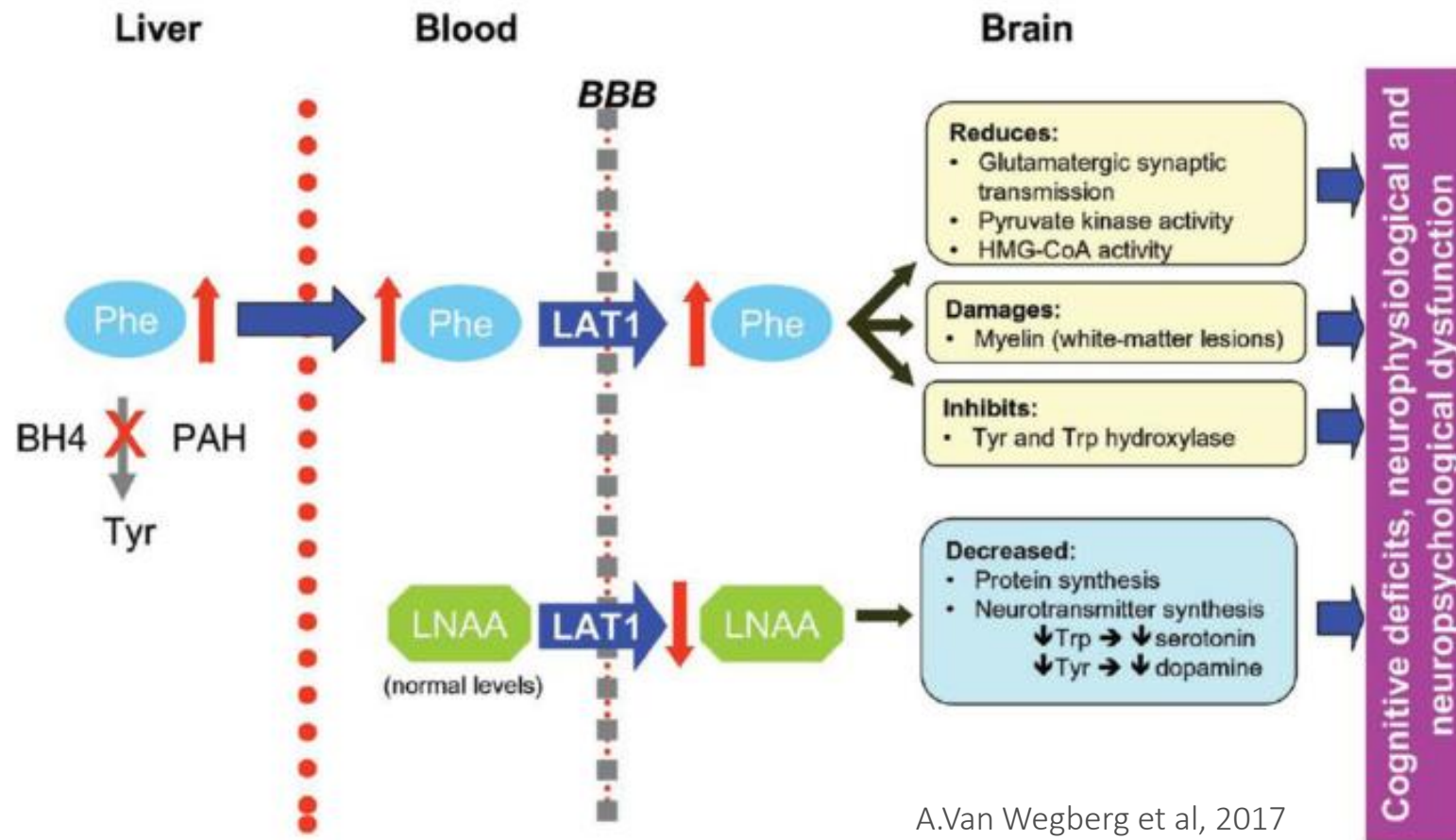
Phenylalanine hydroxylase deficiency

Natural history without treatment

- Progressive and irreversible neurological impairment beginning in infancy
 - Moderate to profound intellectual developmental disorder (IQ < 50)
 - Epilepsy, tremor, spasticity of the limbs and EEG abnormalities
 - Pyramidal signs, Parkinsonian signs and abnormalities of gait
- Mouse-like odour, eczema, hypopigmentation, reduced growth and microcephaly
- Behavioural problems:
 - Autistic spectrum disorders, hyperactivity, stereotypy, aggressiveness, anxiety

Phenylalanine hydroxylase deficiency

Pathophysiology



A. Van Wegberg et al, 2017

Phenylalanine hydroxylase deficiency

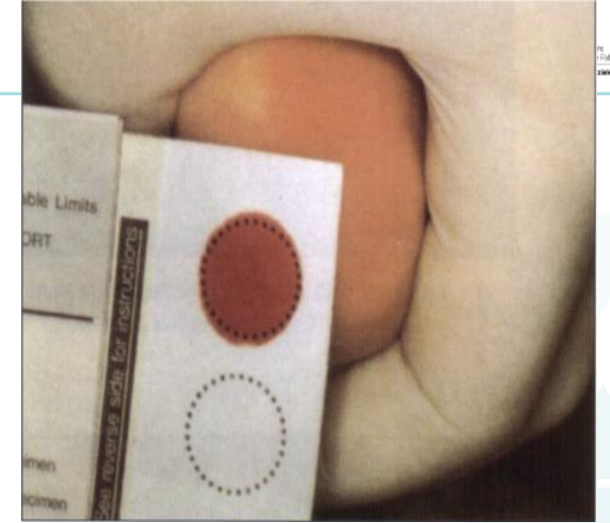
Newborn screening

Robert Guthrie

Microbiological inhibition test dried blood spot
Pilot study (Pediatrics 1963): 7 PKU in 26 955 NN

Screening started in Belgium in 1968

Neonatal screening combined with an adequate treatment, introduced early, has radically changed the prognosis of the disease



Phenylalanine hydroxylase deficiency

Diagnosis

Clinical suspicion or newborn screening (cut-off: p99,5th, > 150 $\mu\text{mol/l}$)

Diagnostic workup

- Amino acids in plasma
- Pterins in blood and urine
- Genetics: >1200 mutations, DatabasesBIOPKU (www.biopku.org/home/home.asp)
Genotypes correlate with biochemical phenotypes but correlation with clinical phenotype is weak
Genetic testing may help **predict BH4 responsiveness**.

S. Garbade et al , 2018

Phenylalanine hydroxylase deficiency

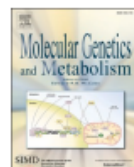
Treatment

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European guidelines on diagnosis and treatment of phenylketonuria: First revision[☆]

A.M.J. van Wegberg^a, A. MacDonald^b, K. Ahring^c, A. Bélanger-Quintana^d, S. Beblo^e, N. Blau^f,
A.M. Bosch^g, A. Burlina^h, J. Campistolⁱ, T. Coşkun^j, F. Feillet^k, M. Giżewska^l,
S.C. Huijbregts^m, V. Leuzziⁿ, F. Maillot^o, A.C. Muntau^p, J.C. Rocha^{q,r,s,t}, C. Romani^u, F. Trefz^v,
F.J. van Spronsen^{a,*}

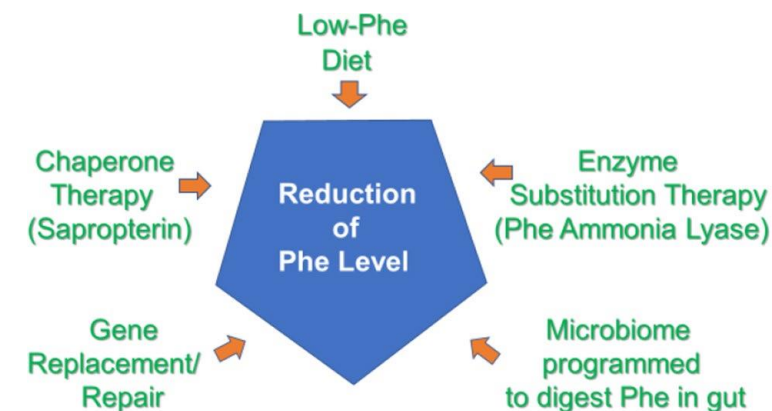
Target Phe

- Before the age 12 years: 120 - 360 µmol/l
- After the age of 12 years: 120 - 600 µmol/l

	Ger- many [7]	Nether- lands [26]	Switzer- land [100]	USA [10]	Australasia [7, 71]	Europe [11]	France [8]
Blood PHE concentration indicating treatment (µmol/l)	>600	Not specified	>400	>360	>360	>360	>360

Treatment ideally started before day 10

- Phe 360-600 µmol/l : age 12 years
with continued follow-up beyond, especially girls
- Phe > 600 µmol/l : throughout life



Lichter-Konecki and Vockley, 2019

Phenylalanine hydroxylase deficiency

Outcome

Intellectual outcome depends upon:

Age at start of treatment (<3 weeks)

Blood Phe concentrations across different age periods (particularly in infancy and childhood)

Duration of periods of blood Phe deficiency

Individual gradient for Phe transport across BBB

P Burgard et al, 2016

Normal school career if adhesion to the treatment during the first ten years

IQ of early and well-treated adults are similar to that of their unaffected family members

When examined closely, subtle neuropsychological deficits may still be detected

Pers et al, 2014

Quality of life

Despite the burden of strict dietary control, early treated patients can achieve a normal QoL

L. Aitkenhead et al, 2021

Phenylalanine hydroxylase deficiency

Complications in adulthood and maternal PKU

- Neurological abnormalities: cortical visual loss, complication of profound B12 deficiency
- Neuroimaging abnormalities: aN white matter (brain MRI) after long periods of high Phe (reversible)
- Neuropsychiatric abnormalities: emotional, behavioural symptoms, risks of depression
- Dietary deficiency: vitamin B12, other vitamins, minerals, osteopenia
- **Maternal PKU syndrome**
 - Teratogenic effects of Phe: developmental delay (92%), microcephaly (73%), cardiac defect (12%) and low birth weight (40%) and dysmorphic features Lenke and Levy, 1980
 - Prevention of maternal PKU syndrome: strict diet when pregnancy is planned (Phe: < 360µmol/l)

02

TYROSINAEMIA TYPE 1

Hepatorenal tyrosinaemia

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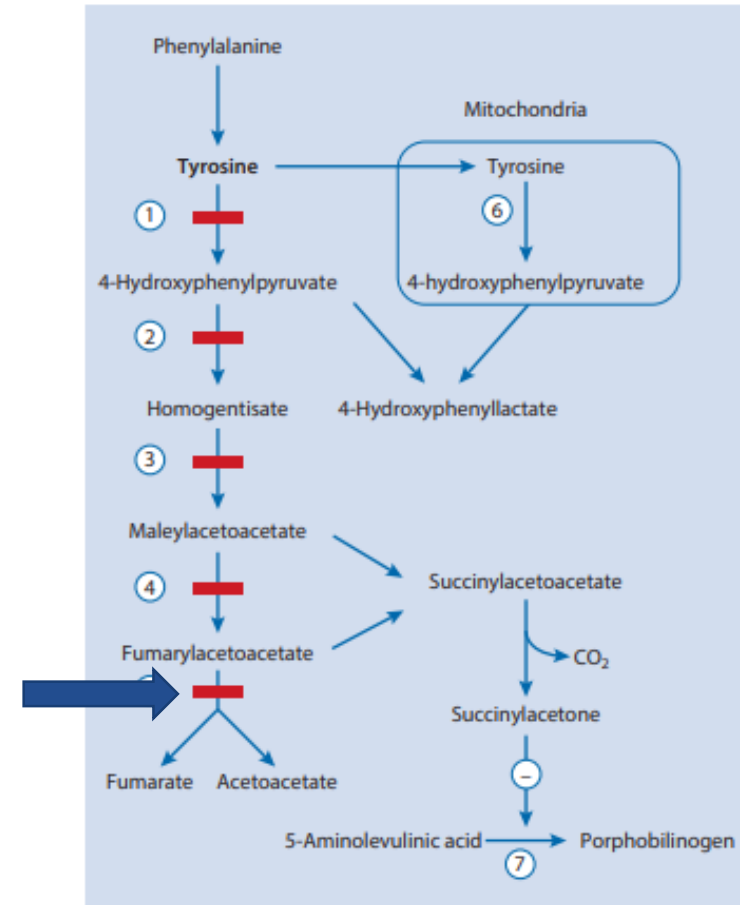
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Tyrosine metabolism

1. Oculocutaneous Tyrosinaemia (tyrosinaemia type II)
2. Hereditary Tyrosinaemia type III/Hawkinsinuria
3. Alkaptonuria
4. Maleylacetoacetate isomerase deficiency
(mild hypersuccinylacetonemia)
5. Hepatorenal Tyrosinaemia (tyrosinaemia type I)



Inborn Metabolic Diseases 7th Eds

Tyrosinaemia type 1

Clinical presentations

- Highly variable even between members of the same family,
- Can present at any age
- Classified according to age at onset (correlated with disease severity)

Acute form before 6 months, **subacute form** between 6m and 1year, **chronic form** after 1 year

Liver: acute hepatic failure (high mortality without treatment), cirrhosis

Kidney: proximal tubulopathy or glomerular dysfunction, hypophosphataemic rickets

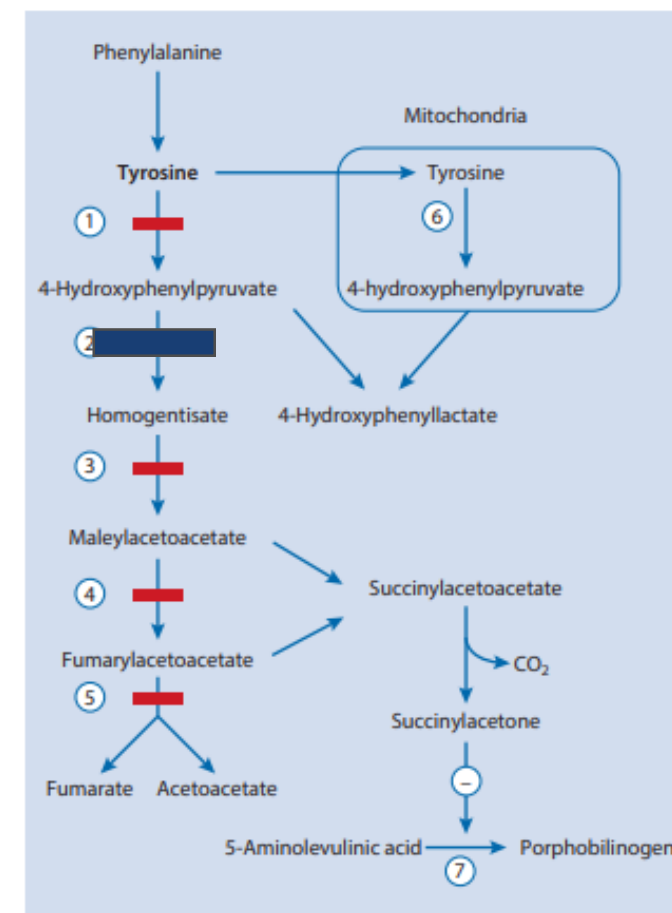
Neurological crises: porphyria like crises

Hepatocyte dysplasia is common with a high risk of malignant transformation

Tyrosinaemia type 1

Diagnosis and treatment

- Succinylacetone in blood or urine is pathognomonic
Newborn screening (both communities: SA)
Genetics: > 100 mutations (ex. c.1062+5G>A, c.554-1G>T)
No clear genotype - phenotype correlation
(spontaneous corrections of the mutation within regenerative nodules)
- Nitisinone (NTBC) has revolutionised the treatment (1992)
Rapid improvement, few adverse events
Liver transplantation: nitisinone non-responsive or HCC



Tyrosinaemia type 1

Outcome

Liver decompensations are not known to occur on nitisinone treatment.

Renal tubular dysfunction responds quickly (usually normalizes).

Neurological crises have never been reported in patients compliant with nitisinone

The risk of HCC appears to be related to the age at start of nitisinone (not been reported if in the first month of life)

J.Larochelle



Contents lists available at [SciVerse ScienceDirect](#)

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Québec

Jean Larochelle ^{a,1}, Fernando Alvarez ^{b,1}, Jean-François Bussi res ^{b,1}, Isabelle Chevalier ^{b,1}, Louis Dallaire ^{b,1,2}, Jos e Dubois ^{b,1}, Fr d ric Faucher ^{b,1}, Daphna Fenyves ^{c,1}, Paul Goodyer ^{d,1}, Andr  Grenier ^{e,1}, Elisabeth Holme ^{f,3}, Rachel Laframboise ^{e,1}, Marie Lambert ^{b,1,2}, Sven Lindstedt ^{f,3}, Bruno Maranda ^{g,1}, Serge Melan on ^{d,1}, Aicha Merouani ^{b,1}, John Mitchell ^{d,1}, Guy Parizeault ^{a,1}, Luc Pelletier ^{h,1}, V ronique Phan ^{b,1}, Piero Rinaldo ^{h,1}, C. Ronald Scott ^{i,1}, Charles Scriver ^{d,1}, Grant A. Mitchell ^{b,*,1}

Table 2

Effect of NTBC Treatment on liver transplantation and death in hepatorenal tyrosinemia in Qu bec.

Group	N (never-treated)	L + E (treated at any time)	L (late-treated)	E (early-treated)
Patients (n)	28	50	26	24
Transplantation	20	7***	7***	0***,†††
Death	10	2***	2**	0***,†
Death before transplantation	8	0	0	0
Death after transplantation	2	2	2	0

Comparisons with the following groups are as indicated: N, *; L, †. The number of repetitions indicates the level of significance. e.g., for asterisks: *, <0.05; **, <0.01; ***, <0.001.

Tyrosinaemia type 1

Questions remain

- Long-term vigilance is however required in all patients as the lifelong risk of hepatocarcinoma remains unknown
- Neurodevelopmental difficulties:
low IQ, school performance, impaired executive function.
The aetiology is uncertain: may be related to the nitisinone treatment, high tyrosine levels, low phenylalanine levels, intrinsic feature of tyrosinaemia type 1

van Ginkel et al, 2017

03

CLASSICAL HOMOCYSTINURIA

*Cystathionine β synthase
deficiency*



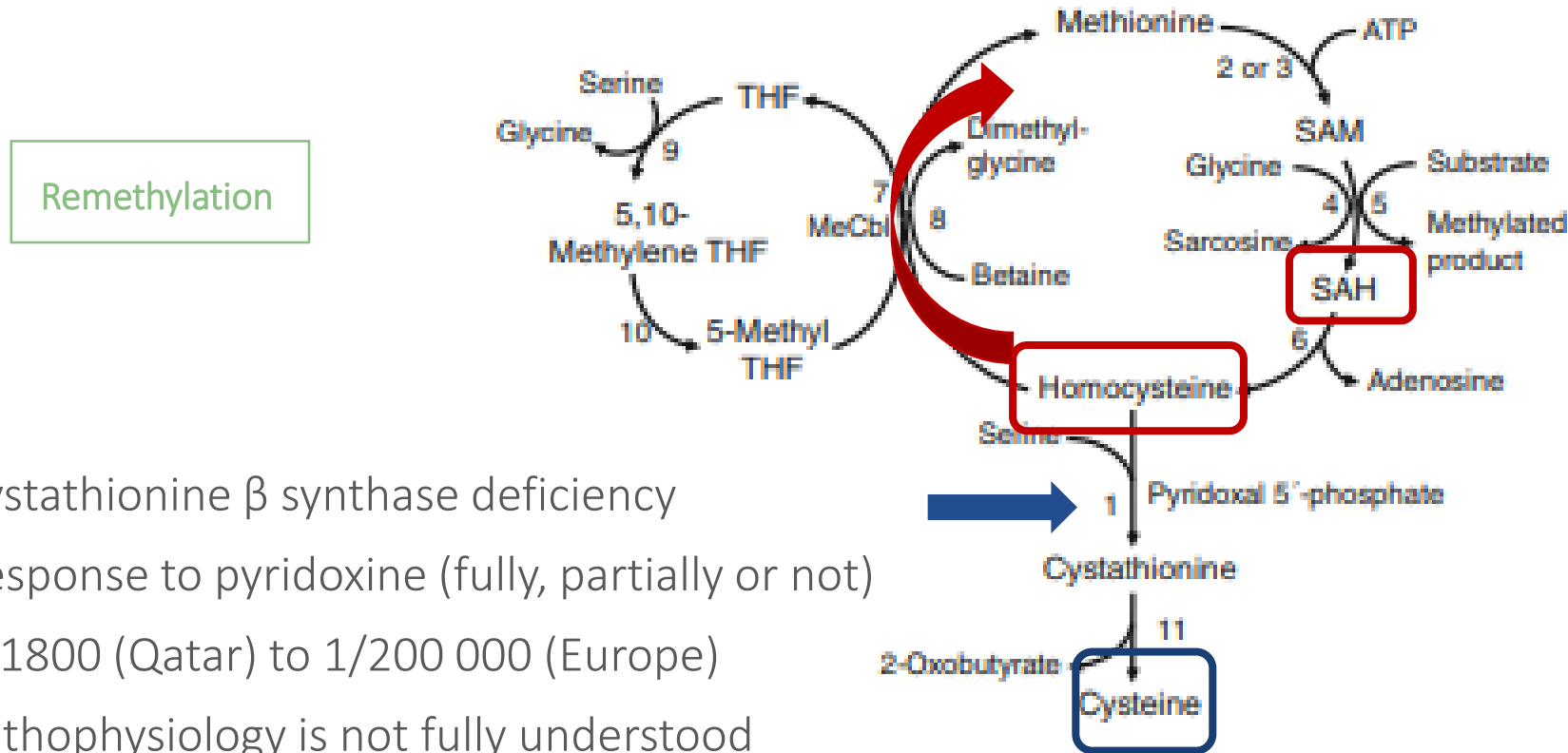
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Erasme

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Methionine metabolism



Cystathionine β synthase deficiency
Response to pyridoxine (fully, partially or not)
1/1800 (Qatar) to 1/200 000 (Europe)
Pathophysiology is not fully understood

A. Morris et al, 2017; V. Kozich et al, 2022



Classical homocystinuria

Clinical presentations

Severity and age at presentation vary widely and correlate with the patient's response to pyridoxine

- **Eye:** Ectopia lentis (2-12 y), severe myopia, risk of glaucoma
- **Skeleton:** Excessive growth, « marfanoid habitus » with stiff joints, genu valgum, pectus excavatum,...
Premature osteoporosis (scoliosis, fractures)
- **Brain:** Learning difficulties in 50% ; seizures or dystonia; psychiatric problems
- **Vascular system:**
Deep venous thrombosis (adults), cerebral venous sinus thrombosis (children)
Risk of artery thrombosis (renal and carotid)
B6^{R-} : 50% thrombosis before the age of 30y, 20% die

M.Almuqbil et al, 2019

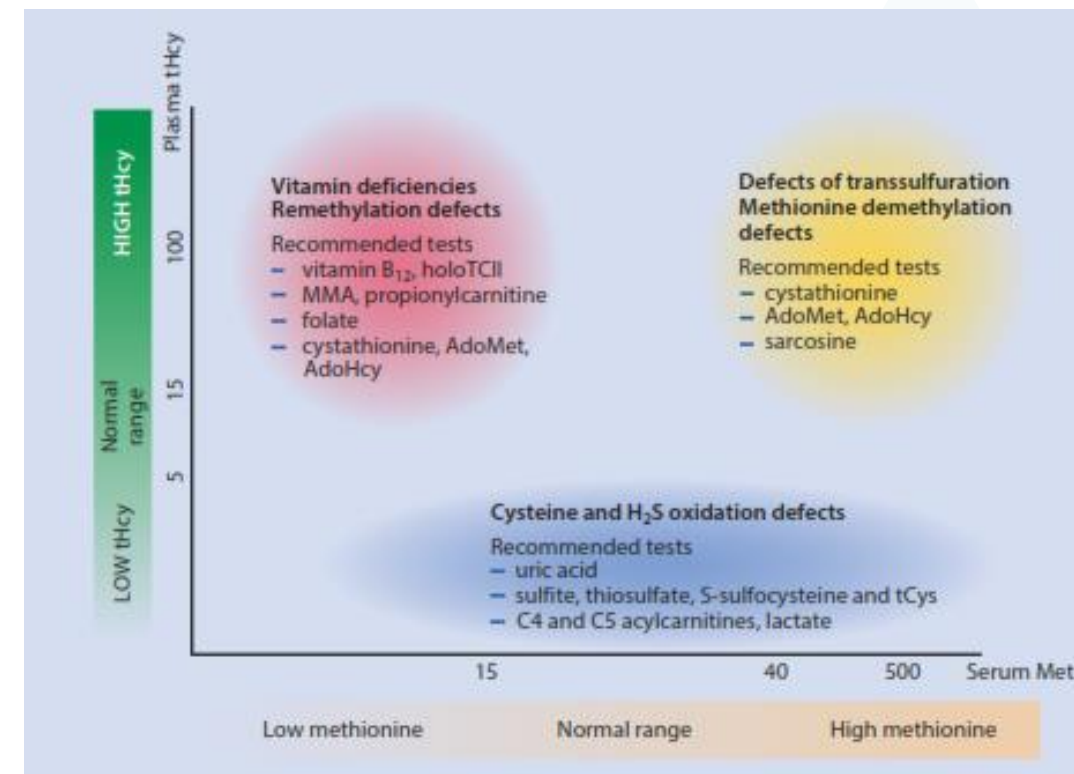
J Picker and H. Levy, 2017

Classical homocystinuria

Diagnosis

- Plasma: high tHcy and high methionine
low-N cystathionine
(avoid B6 supplements for at least 2w before)
- Newborn screening :
Met: mainly B6^{R-} V. Kozich et al, 2021
Hcy: first-line test (other homocystinurias)
- Genetics: > 160 mutations in CBS Mutation Database
Mutations with B6^{R-} phenotype (ex c. 919 G>A).
Mutations with B6^{R+/++} (ex. c.833 T>C)

J.Kraus et al, 1999



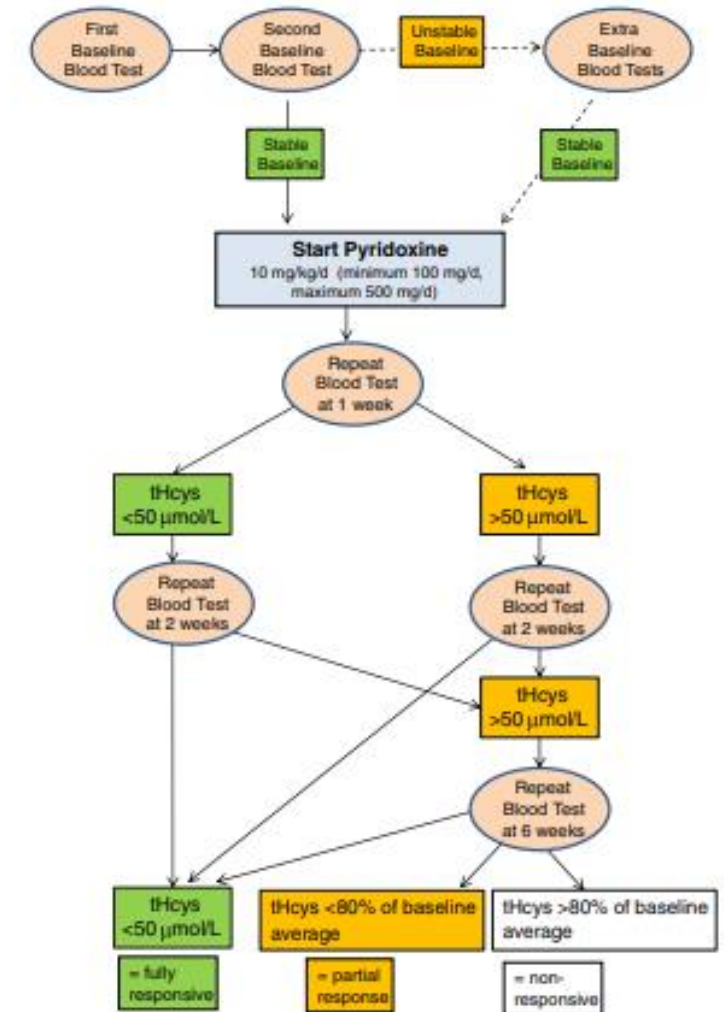
V. Kozich et al, Inborn Metabolic Diseases 7th Eds

Classical homocystinuria

Treatment and prognosis

- Vitamin B6 in responsive patient (50%)
Methionine-restricted diet
Folic acid, vitamin B12, cysteine, betaine
- Aspirin, low molecular weight heparin (perioperative, pregnancy)
- tHcy target under treatment:
Hcy <100 $\mu\text{mol/l}$ (in B6^{R-} ; < 50 $\mu\text{mol/l}$ if B6^{R+})
- **Prognosis improved with treatment**
All the major complications can be prevented if patients are diagnosed through NBS and adhere to treatment (even when metabolic control is imperfect, treatment reduces vascular risk)

Yap et al , 2001



A. Morris et al, 2017

04

ORGANIC ACIDURIAS

Methylmalonic Aciduria
Propionic Aciduria

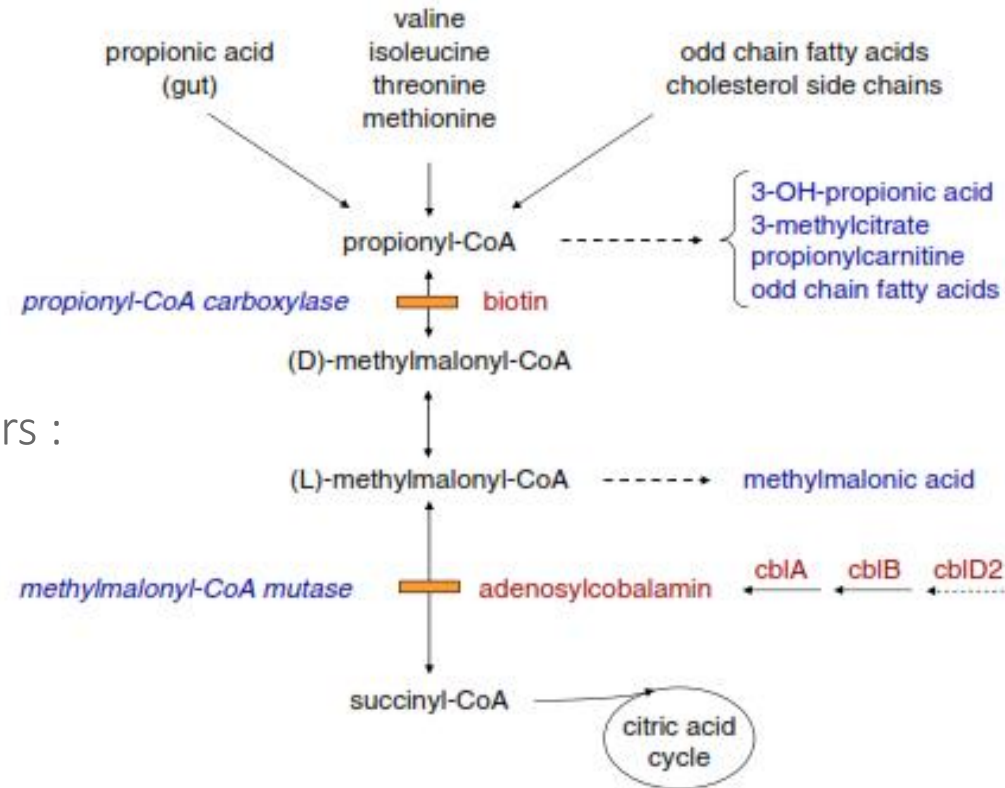


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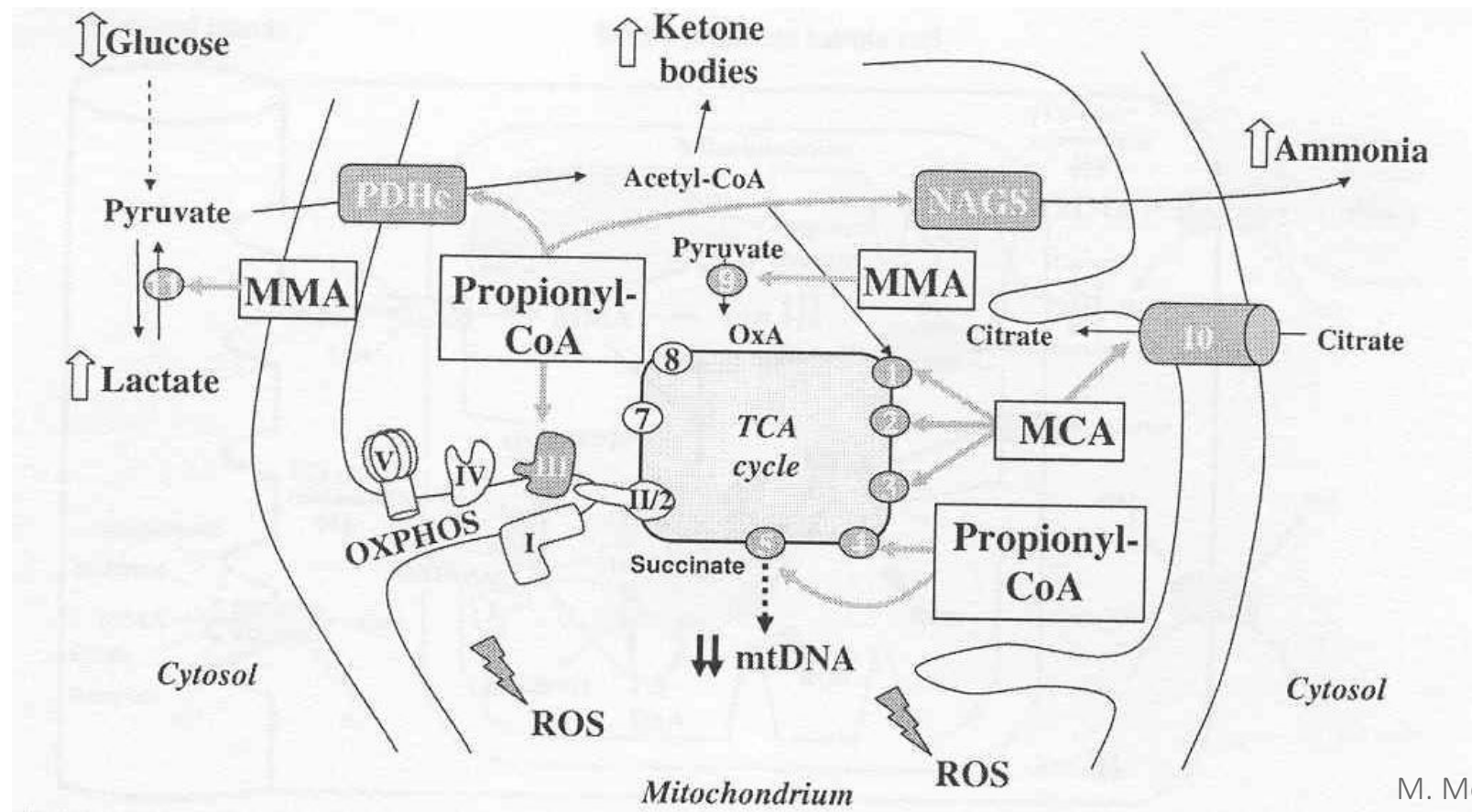
Propionic and Methylmalonic acidurias

Autosomal recessive disorders :
1 / 50 000 à 1/ 100 000



M. Baumgartner et al, 2014

Pathophysiology



M. Morath et al, 2008

Propionic and methylmalonic acidurias

Clinical presentations

- A severe neonatal-onset form with acute metabolic decompensation and neurological distress
- An acute intermittent, late-onset form with recurrent metabolic decompensations
- A chronic progressive form

Symptoms can often worsen or occur for the first time following a trigger event

P. Forny et al, 2021

Acute presentation	Chronic presentation
<i>Nervous system</i>	
Acute encephalopathy	Hypotonia
Seizures	Developmental delay
Movement disorders (more frequent in PA)	Seizures
Stroke-like episodes (more frequent in MMA)	Movement disorders/dystonia
<i>Gastrointestinal system</i>	
Vomiting	Recurrent vomiting with ketoacidosis
Feeding difficulties	Failure to thrive
	Pancreatitis
<i>Haematopoietic system</i>	
Neutropenia, pancytopenia	Neutropenia, pancytopenia
<i>Heart (mostly in PA)</i>	
Acute cardiac failure (mostly based on cardiomyopathy)	Cardiomyopathy
Arrhythmias	Prolonged QTc in ECG
<i>Kidney</i>	
	Chronic renal failure (almost exclusively in MMA)

Propionic and methylmalonic acidurias

Trigger events

Table 9 Triggers, clinical signs & symptoms and biochemical signs of acute decompensation in MMA/PA*

Triggers	Clinical signs and symptoms	Biochemical signs
Infection	Poor feeding	Metabolic acidosis (pH <7.3, anion gap >20 mmol/l, low pCO ₂ or base excess greater than -5 mmol/l)
Fever	Vomiting	
Prolonged fasting	Lethargy	Elevated blood lactate (>3 mmol/l)
Medication (e.g. chemotherapy, high dose glucocorticoids)	Hypotonia	Hyperammonemia
Prolonged or intense physical exercise, surgery and/or general anesthesia	Irritability	Ketonuria (greater than trace in infants or greater than + in children)
Acute trauma, significant hemorrhage	Respiratory distress	Uric acid and/or elevated urinary urea (urea/creatinine > 20) as signs of catabolism
Psychological stress	Hypothermia	Neutropenia
Excessive protein intake	Dehydration and weight loss	Thrombocytopenia

*Please note that columns are independent from each other. Thus a given line in a column does not refer to the line in the neighboring column.

Grade of recommendation: D.

M. Baumgartner et al, 2014

	Organic acids in urine			Acylcarnitines in dried blood or plasma	Plasma	Vitamin	Holotranscobalamin
	Methylmalonic acid	3-hydroxy-propionate	2-methylcitrate	Propionylcarnitine	Homocysteine	B12	
Diseases discussed in these guidelines							
MMA ^a	↑-↑↑↑	↑	↑	↑↑	n	n	n
PA	n	↑	↑(↑)	↑↑ (↑)	n	n	n
Other defects and deficiencies causing raised methylmalonic acid							
MCEE deficiency	↑	(↑)	(↑)	(↑)	n	n	n
ACSF3 deficiency ^b	↑	n	n	n	n	n	n
Adenosyl- and methylcobalamin synthesis defects ^c	↑ - ↑↑↑	↑	↑	↑-↑↑	↑ - ↑↑↑	n	n
Transcobalamin deficiency	↑	n-↑	n-↑	n-↑	↑	n-↓	↓
Transcobalamin receptor deficiency	↑	n/a	n/a	n/a	n-↑	n/a	n/a
IF deficiency and Imerslund-Najman-Gräsbeck syndrome	↑ - ↑↑	n-↑	n-↑	n-↑	↑ - ↑↑	↓↓	↓
Nutritional vitamin B12 deficiency	↑ - ↑↑	n-↑	n-↑	n-↑	↑ - ↑↑	↓-↓↓	↓-↓↓

- Biochemical
pH, lactate
Acylcarnitine
- Newborn screening (C3, C3/C2; Belgium)

P. Forny et al, 2021

- Diagnostic confirmation
 - Direct enzyme assay, rarely performed
 - Genetics
 - PCCA- PCCB: > 200 mutations
 - MUT, MMAA, MMAB: > 200 mutations

Propionic and methylmalonic acidurias

Treatment

- Acute metabolic decompensation (initial or intercurrent)

As soon as MMA/PA is suspected, specific therapies should be initiated,

Patient should be referred to a specialist centre

Dietetic treatment, medication, extracorporeal detoxification

- During metabolic stability

Specific diet, medication, avoidance of catabolism

- Transplantation (liver, liver-kidney, kidney):

No clear recommendations

Potential benefits as well as associated risks

Yap et al, 2020

- New therapeutic approaches

Guidelines for the diagnosis and management of methylmalonic acidemia and propionic acidemia: First revision

Patrick Forny¹  | Friederike Hörster² | Diana Ballhausen³ |
Anupam Chakrapani⁴ | Kimberly A. Chapman⁵ | Carlo Dionisi-Vici⁶ |
Marjorie Dixon⁷ | Sarah C. Grünert⁸ | Stephanie Grunewald⁴ |
Goknur Haliloglu⁹ | Michel Hochuli¹⁰ | Tomas Honzik¹¹ | Daniela Karall¹² |
Diego Martinelli⁶ | Femke Molema¹³ | Jörn Oliver Sass¹⁴ |
Sabine Scholl-Bürgi¹² | Galit Tal¹⁵ | Monique Williams¹³ |
Martina Huemer^{1,16} | Matthias R. Baumgartner¹

▶ Propionic and methylmalonic acidurias

Outcome

- Improved survival, mortality around 20%
H Ogier et al , 2005, H. Haijes et al , 2019
- Numerous complications
- Poorer prognosis :
neonatal-onset PA
B12 unresponsiveness MMA

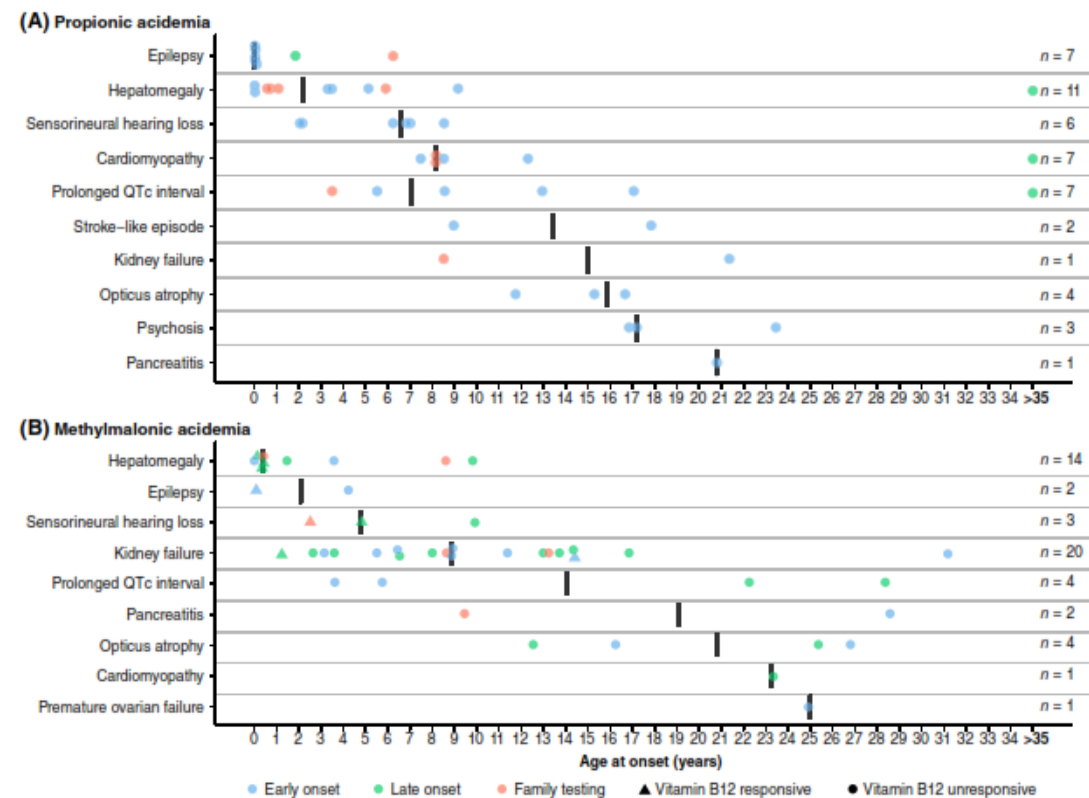
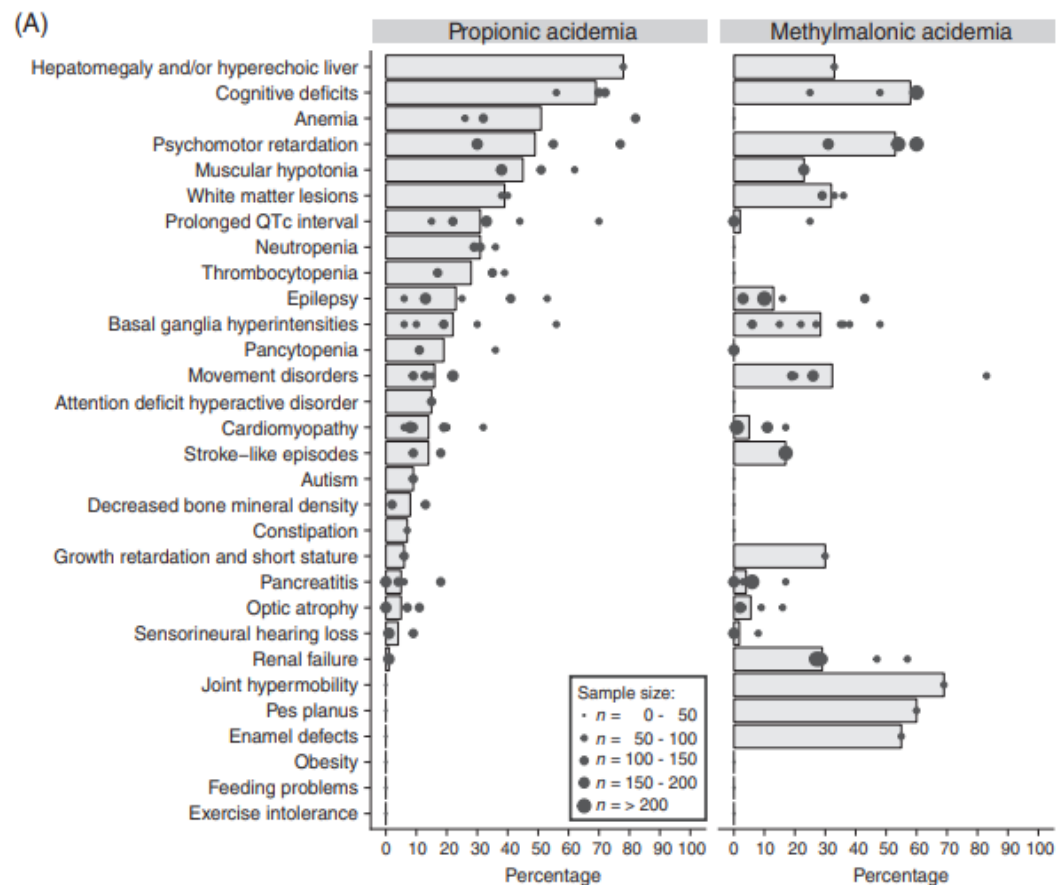
H. Haijes et al , 2019

Outcome parameter	Median rating of importance of outcome
Survival	9
Health-related quality of life	9
Metabolic stability	8
Cognitive development	8
Epilepsy	8
Metabolic stroke	7
Vision and hearing	7
Early diagnosis	7
Cardiomyopathy	7
Kidney dysfunction	7
Pancreatitis	6
Normal growth	6
Neutropenia	6
Anaemia	5.5
Bone health	5

P. Forny et al, 2021

Propionic and methylmalonic acidurias

Outcome



H. Haijes et al , 2019

Propionic and methylmalonic acidurias

Newborn screening and outcome

- Increase the chance of early diagnosis
- Early diagnosis of late-onset cases
- Trend towards lower mortality
- No difference in terms of decompensations and complications

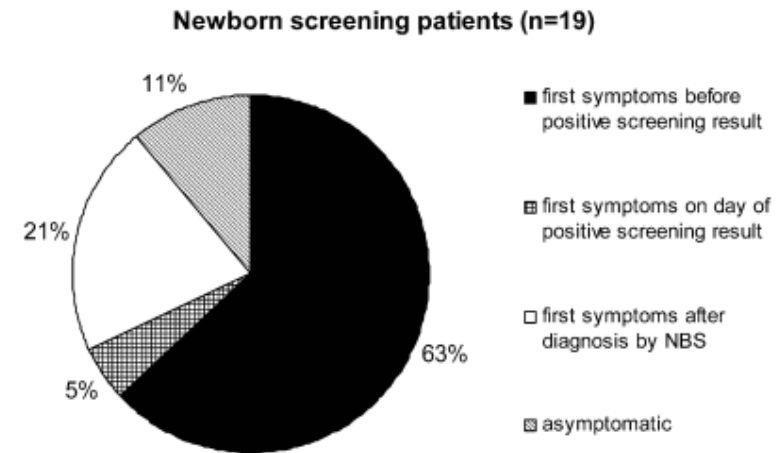


Fig. 1 Manifestation of propionic acidemia (PA) symptoms related to the time when newborn screening (NBS) results became available

C. Dionisi-Vici et al, 2006; S.Grunert et al, 2012; J.Heringer et al, 2015; H.Haijes et al, 2019

05

MARPLE SYRUP URINE DISEASE

Leucinosi



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Branched-Chain Amino acids metabolism

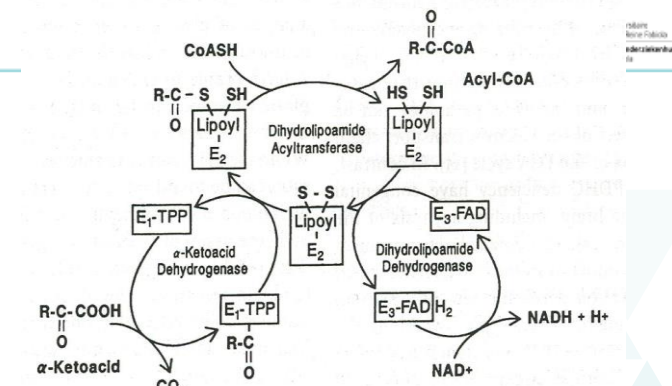
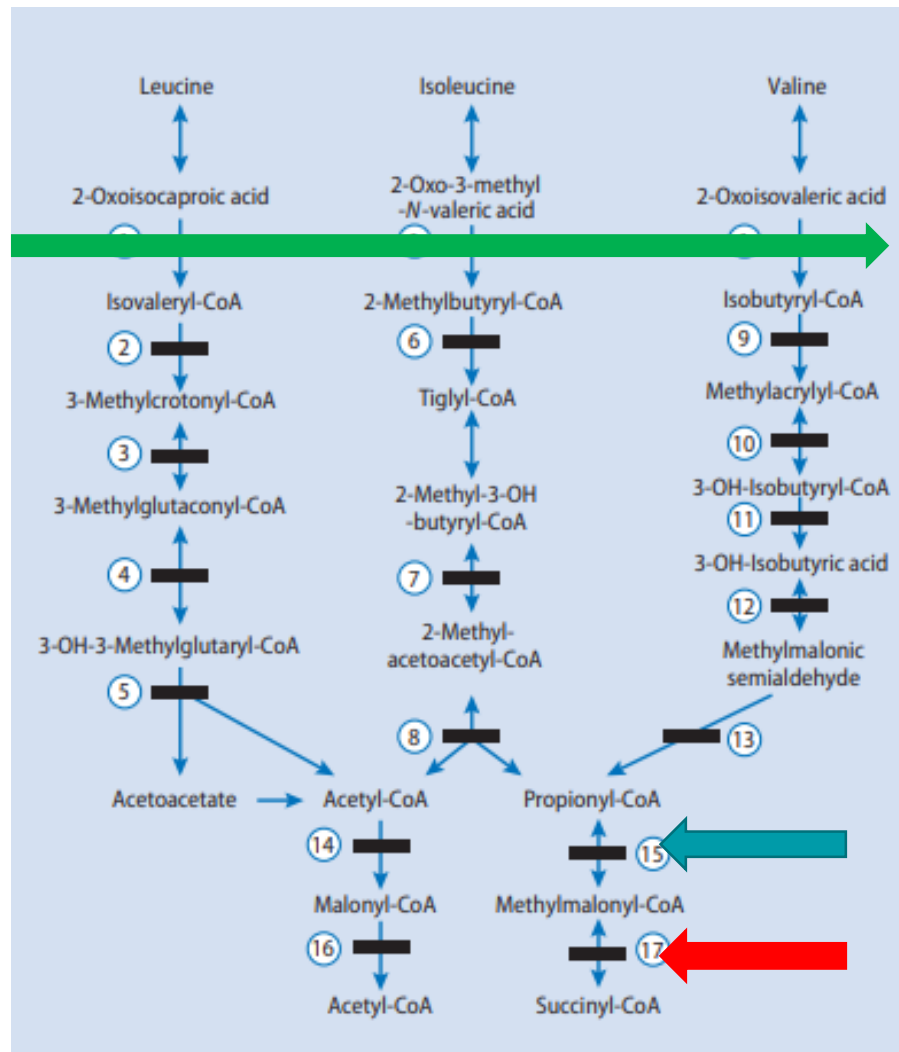
Leucine and 2-oxoisocaproic acid
the most neurotoxic

Acute cerebral oedema

White matter changes

- Interfere with Leu-Glu cycle
- Water homeostasis
- Oxidative stress
- Nitrogen homeostasis

K. Strauss et al, 2020;
P Blackburn et al, 2017



MSUD

Autosomal recessive

1/120 000 to 500 000

E1 α (45%), E1 β (35%), E2 (20%)

PA

MMA

Inborn Metabolic Diseases 7th Eds

Marple Syrup Urine Disease

Clinical presentations

- A severe neonatal-onset form with acute toxic encephalopathy
 - marple- syrup-like odour (caramel-like)
 - compared to PA/MMA: not severely dehydrated, no metabolic acidosis (no elevated lactate), no hyperammonaemia, normal blood cell count
 - hypertonic episodes with opisthotonus , pedalling movements
- An acute intermittent, late-onset form with recurrent metabolic decompensations
 - Recurrent attacks of ataxia (no signs between the attacks)
- A chronic progressive form
 - hypotonia, spastic diplegia, developmental delay and failure to thrive

MSUD can be diagnosed by using plasma amino acid alone (BCAA, allo-isoleucine)

Marple Syrup Urine Disease

Treatment and outcome

- Specific adjustments of the treatment in comparison with PA and MMA:
 - Principles of dietary treatment, mainly those applied to PKU (BCAA-free amino acids mixture)
 - Extracorporeal toxin removal in critically ill children
 - Liver transplantation
- Treated patients with classic neonatal MSUD generally survive
 - Average intellectual performance is below normal (Verbal > Performance)
 - Outcome depends on duration that Leu remains > 1000 $\mu\text{mol/l}$ and the quality of long-term metabolic control
 - Importance of neonatal screening for rapid management (in Belgium: xLeu+Val)
 - Some patients may experience mental health issues despite good metabolic control (hyperactivity, anxiety, depression)

J.Bouchereau et al , 2017

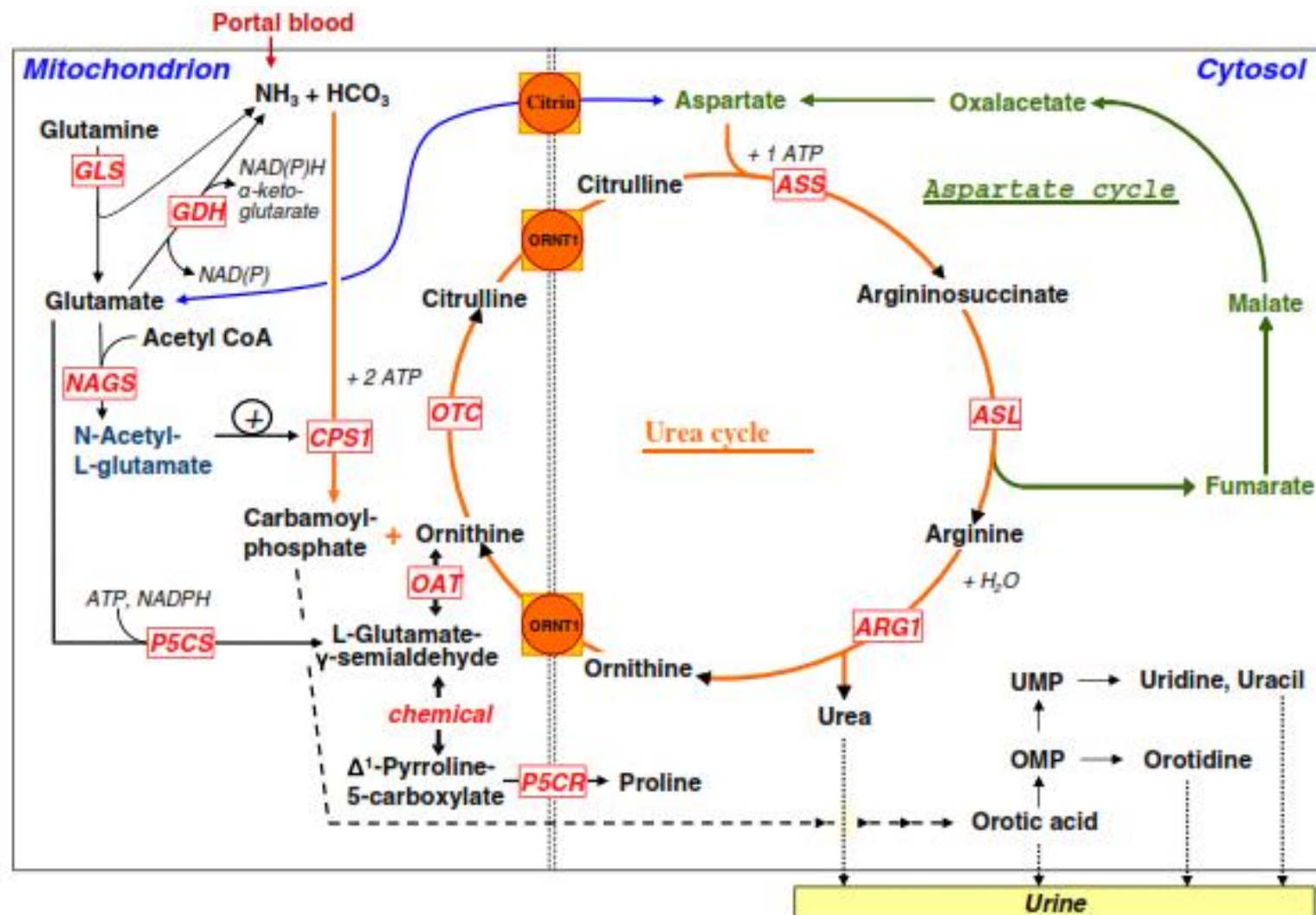
M.Abi-Wardé et al , 2017

06

UREA CYCLE DISORDERS



Urea Cycle



J. Häberle et al, 2012

Frequency 1 / 35 000
60% OTC deficiency
AR, except OTC (X-linked)
Hyperammonaemia
AA disturbances

Urea Cycle Disorders

Hyperammonaemia

- High ammonium/a levels are neurotoxic ($\text{NH}_3 + \text{H}^+ \leftrightarrow \text{NH}_4^+$)
- Acute severe hyperammonaemia:
 - Seizures, coma with cerebral oedema
 - If prolonged, permanent neurological sequelae
 - cortical atrophy, demyelination, neurocognitive delay, cerebral palsy
- Mechanisms of neurotoxicity
 - Excessive glial glutamine > astrocytes swelling (excess of Gln has also a neurotoxic effect)
 - Alters several AA pathways and neurotransmitter systems (glutamergic and GABA), cerebral energy metabolism, NO synthesis, oxydative stress
 - Alteration in neuronal differentiation and patterns of cell death
 - Chronic moderate hyperNH₃ induces neuroinflammation > cognitive and motor deficits

O.Braissant et al, 2014; V.Felipo et al, 2014

Urea Cycle disorders

Clinical manifestations

Potential triggers of hyperammonemic crises in UCD patients

- Birth of the patient: passage from intrauterine to extrauterine life
- Infections
- Fever
- Vomiting
- Gastrointestinal or internal bleeding
- Decreased energy or protein intake (eg, fasting pre surgery, major weight loss in neonates)
- Catabolism and involution of the uterus during the postpartum period (mostly OTC females)
- Chemotherapy, high-dose glucocorticoids
- Prolonged or intense physical exercise
- Surgery under general anesthesia
- Unusual protein load (eg, a barbecue, parenteral nutrition)
- Drugs: Mainly **valproate** and **L-asparaginase/pegaspargase**.
Topiramate, carbamazepine, phenobarbitone, phenytoine, primidone, furosemide, hydrochlorothiazide and salicylates have also been associated with hyperammonemic decompensation.

J.Häberle et al, 2019

Acute presentation

- Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication
- Acute encephalopathy (see below)
- Seizures (mostly under situation of altered level of consciousness)
- Ataxia: mostly under situation of altered level of consciousness
- Stroke-like episodes
- Transient visual loss
- Vomiting and progressive poor appetite
- Liver failure, coagulopathy (esp. in OTCD and HHH)
- Multiorgan failure
- Peripheral circulatory failure
- Psychiatric symptoms (hallucinations, paranoia, mania, emotional or personality changes)
- "Post-partum psychosis"
- In neonates: sepsis-like picture, temperature instability, respiratory distress, hyperventilation

Chronic presentation

- Confusion, lethargy, dizziness
- Headaches, migraine-like, tremor, ataxia, dysarthria flapping tremor (in adults)
- Learning disabilities, cognitive impairment
- Epilepsy
- Chorea, cerebral palsy
- Protracted cortical visual loss
- Progressive spastic diplegia or quadriplegia starting in childhood (described in ARG1D and HHH syndrome)
- Protein aversion, self-selected low-protein diet
- (Recurrent) abdominal pain, vomiting
- Failure to thrive
- Hepatomegaly, elevated liver enzymes
- Psychiatric symptoms: hyperactivity, mood alteration, behavioral changes, aggressiveness
- Self-injurious behaviour
- Autism-like symptoms
- Fragile hair (mainly in ASLD)
- Dermatitis
- Episodic character of signs and symptoms
- Specific neuropsychological phenotype in heterozygous OTC females

Urea Cycle Disorders

Diagnosis

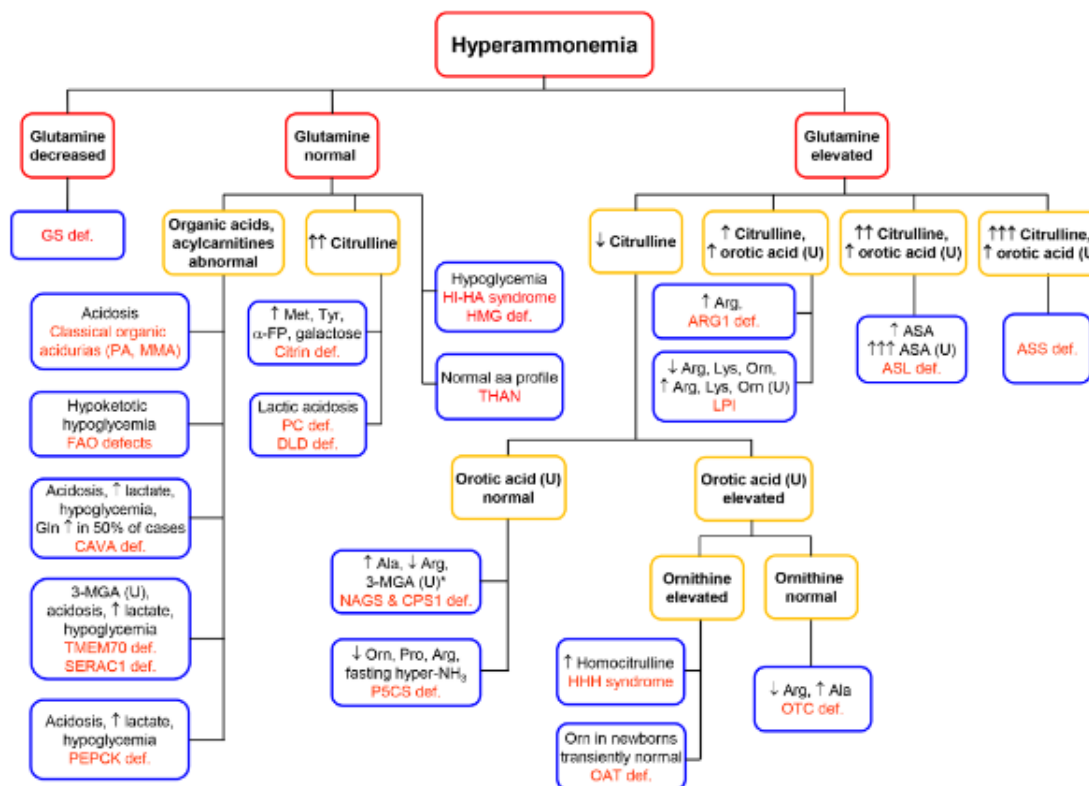
In any acute or intermittent **neurological deterioration** or **psychiatric illness**, **acute liver failure**, suspected **intoxication** or in the differential diagnosis of **neonatal sepsis**.

Catabolism or protein load may represent triggering factors

- NH3 (emergency!)

Parameter	Condition							
	UCDs	Organic acidurias	β-oxidation defects	Carbonic anhydrase Va def.	HMG-CoA lyase def.	HI HA syndrome	Pyruvate carboxylase def. ^a	PEPCK def.
Acidosis	+/-	+	+/-	+	+	-	+	+
Ketonuria ^a	-	+	absent	+	absent	-	++	+
Hypoglycemia ^b	-	+/-	+	+/-	+	+	+	+/-
↑ Lactic acid ^c	-	+	+/-	+	+/-	-	+	+/-
↑ AST and ALT	(+) ^d	-	+	-	+/-	-	+/-	++
↑ CPK	-	-	+	-	+/-	-	-	-
↑ Uric acid	-	+	+/-	-	+	-	-	-
↓ WBC/RBC/Plt	-	+	-	-	+/-	-	-	-
Weight loss	-	+	-	-	+/-	-	+	-

- Pl/ur amino acids, ur. orotic acid



J.Häberle et al, 2019

Urea Cycle Disorders

Genetic analysis

- Sensitivity of the molecular analysis < 100% (OTC +/- 80%)
- Intronic regions, regulatory domains,...
- > additionnal methods: RNA-based sequencing (blood cells, liver, fibroblasts) MLPA, CGH,....
- The Leiden Open (source) Variation Database is freely available and displays DNA variations for most UCD genes

J.Häberle et al, 2020; J.Häberle et al, 2022

Urea Cycle Disorders

Treatment

- Emergency management
 - Stop exogenous protein supply
 - Prevent endogenous protein catabolism (high energy supply)
 - Reduce ammonia: medication and extracorporeal toxin removal
- Maintenance treatment
 - NAGS deficiency > treatment with Carglumic acid is almost curative
 - Low protein diet, drugs (nitrogen scavenging, Arg/Cit to maximize the residual UC activity)
- Preventive treatment in situations that may trigger decompensation
- Liver transplantation
- Emerging therapies

J.Häberle et al, 2019

Urea Cycle Disorders

Outcome

- Risk of death and neurological sequelae depending on the duration and the extend of hyperammonaemia
- Survival: better for ASS, ASL than for OTC, CPS1
- Specific neurocognitive pattern, even in patients with normal IQ :
weakness in fine motor dexterity, in non verbal intelligence,
in visual-memory, attention and executive skills
- Frequent emotional and behavioral problems
- ASL: poor cognitive outcome despite good metabolic control, progressive liver disease
and hepatomegaly, hypertension (ASL required for NO production)
- ARG1 (toxicity of Arg and metabolites): important risk of progressive spastic paraplegia

Prognosis very poor if

1. Coma > 3 days
2. Significant elevated intracranial pressure
3. $\text{NH}_3 > 1000 \mu\text{mol/l}$
(clinical situation, duration)

L Krivitzky et al, 2009

D.Jamolkowski et al, 2016

J.Häberle et al, 2019

HUDERT



UKZKF

I Thank you for your attention

