IEM intoxication type

Amino Acids Metabolism disorders

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Simplified Classification of EIM in 3 groups

« Impairment of specific enzymes or biochemical pathway is intrinsic to the pathomecanisms 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, cleansing drugs , …
extracorporeal procedures

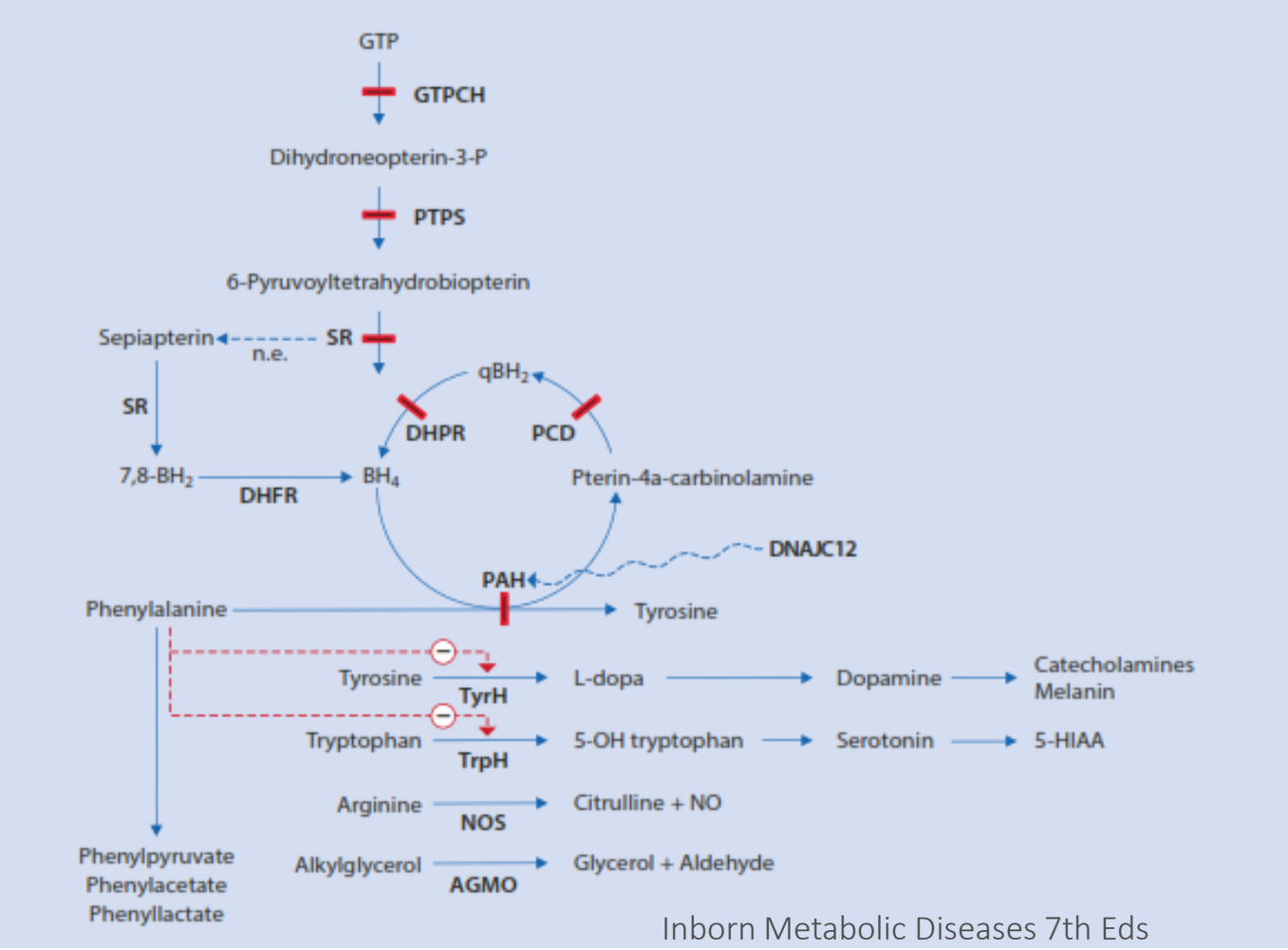
Contents

01

PHENYLKETONURIA

Phenylalanine hydroxylase deficiency

Phenylalanine metabolism



Inborn Metabolic Diseases 7th Eds

Phenylalanine hydroxylase deficiency

Autosomal recessive

1/10 000 (Europe)

Continuum in spectrum of severities

F van Spronsen et al, 2017

Phenylalanine hydroxylase deficiency

Natural history without treatment

Progressive and irreversible neurological impairment during infancy

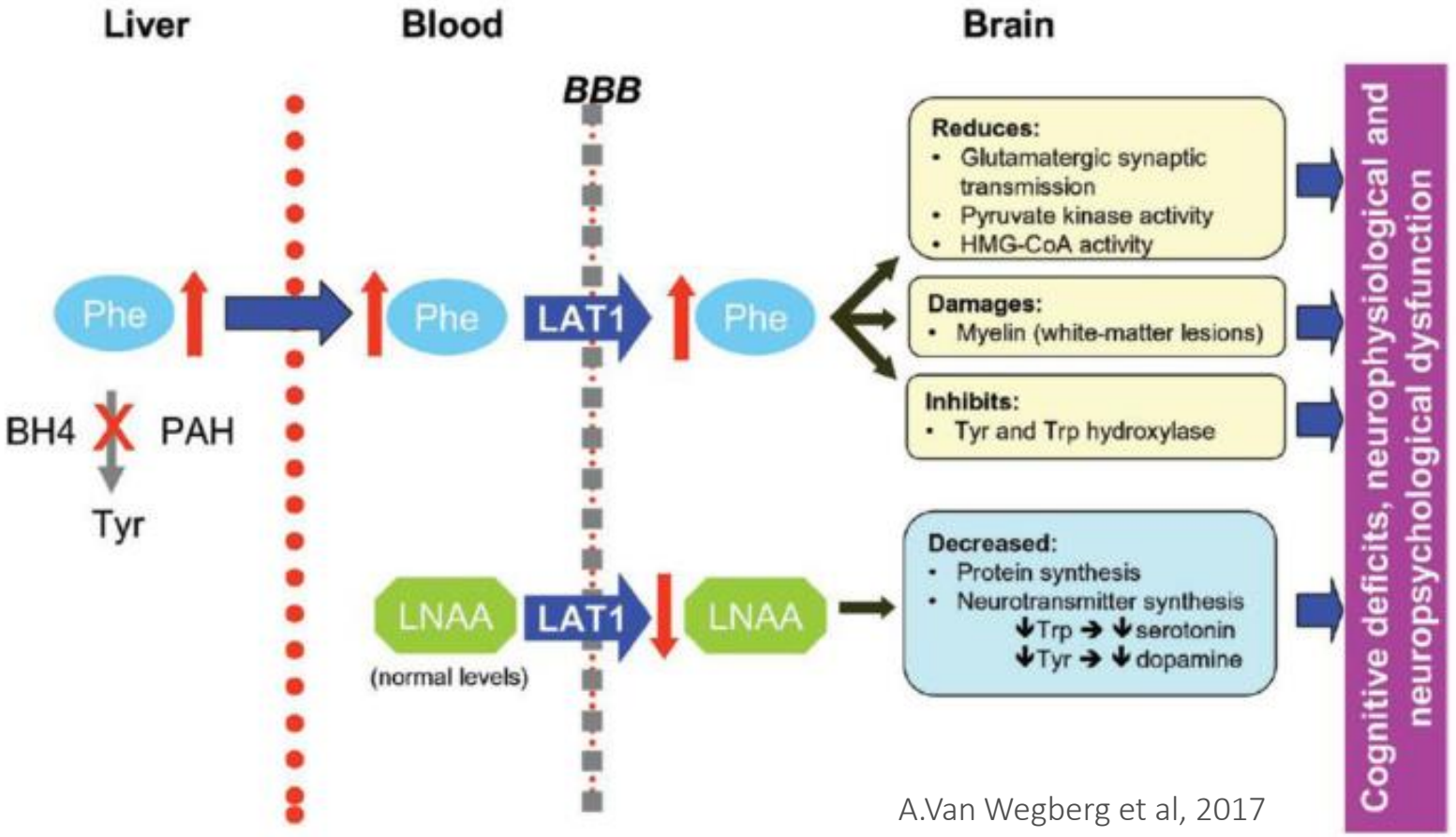
- Moderate to profound intellectual developmental disorder (IQ < 50)
- Epilepsy, tremor, spasticity of the limbs and EEG abnormalities
- Pyramidal signs, Parkinsonian signs and abnormalities of gait

Mousey odour, eczema, reduced pigmentation, reduced growth and microcephaly

Behavioural problems: autistic spectrum disorders, hyperactivity, stereotypy, aggressiveness, anxiety

Phenylalanine hydroxylase deficiency

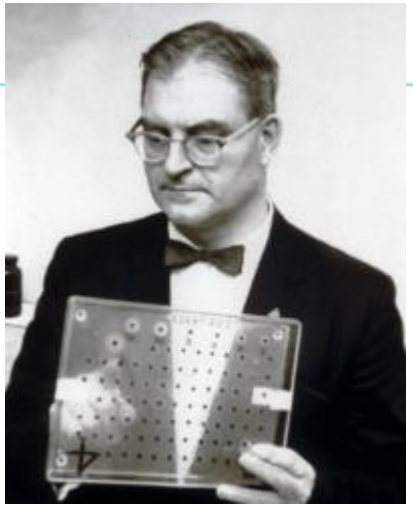
Pathophysiology

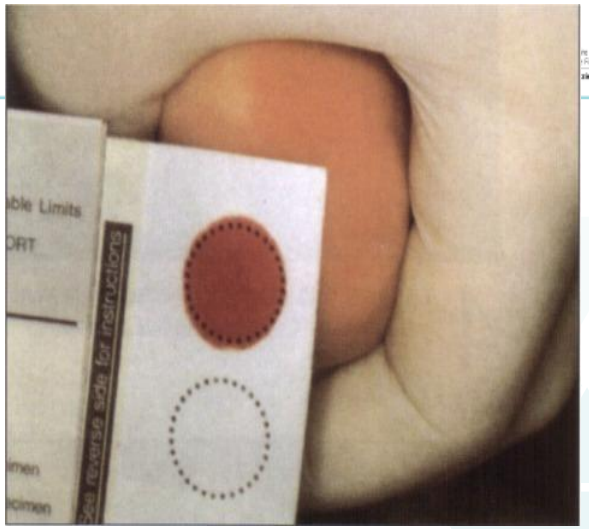


A.Van Wegberg et al, 2017

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 µmol/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
  May be of value in determining genotypes associated with BH4 responsiveness

S. Garbade et al , 2018

Phenylalanine hydroxylase deficiency

Treatment

	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

van Wegberg *et al. Orphanet Journal of Rare Diseases* (2017) 12:162
DOI 10.1186/s13023-017-0685-2

Orphanet Journal of Rare Diseases

REVIEW Open Access

The complete European guidelines on phenylketonuria: diagnosis and treatment

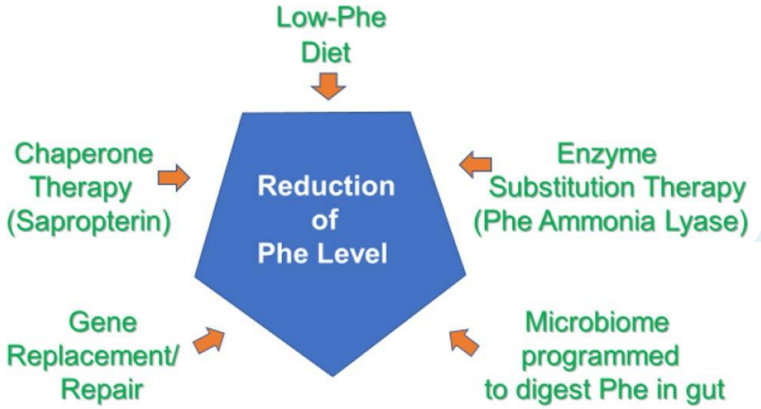
A. M. J. van Wegberg[1], A. MacDonald[2], K. Ahring[3], A. Bélanger-Quintana[4], N. Blau[5,6], A. M. Bosch[7], A. Burlina[8], J. Campistol[9], F. Feillet[10], M. Giżewska[11], S. C. Huijbregts[12], S. Kearney[13], V. Leuzzi[14], F. Maillot[15], A. C. Muntau[16], M. van Rijn[1], F. Trefz[17], J. H. Walter[18] and F. J. van Spronsen[1*]

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

Target Phe

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



Lichter-Konecki and Vockley, 2019

Phenylalanine hydroxylase deficiency

Outcome

Intellectual outcome depends upon:

- The age at start of treatment (<3 weeks)
- Blood Phe concentrations in different age periods (mainly 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 compliance to the treatment during the first ten years

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

When studied in detail, subtle neuropsychological deficits have been found Pers et al, 2014

Quality of life

Despite the burden of strict dietary control, early treated patients can have 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

  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)

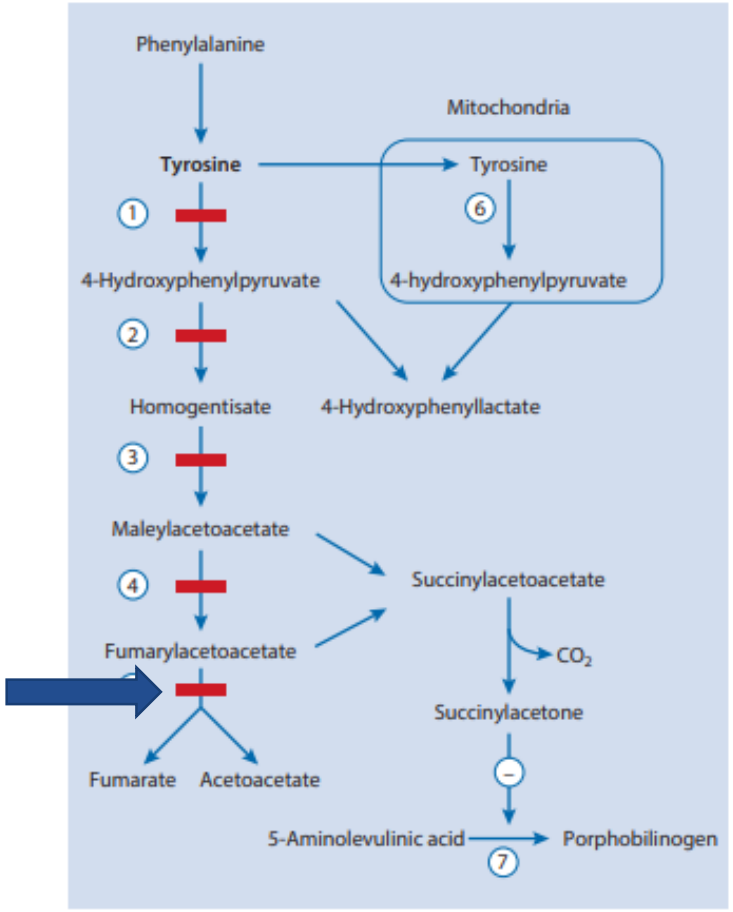
02

TYROSINAEMIA TYPE 1

Hepatorenal tyrosinaemia

Tyrosine metabolism

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



Inborn Metabolic Diseases 7th Eds

Tyrosinaemia type 1

Clinical presentations

- Very variable even between members of the same family,
- At any age
- Classified based on the age at onset (correlated with disease severity)

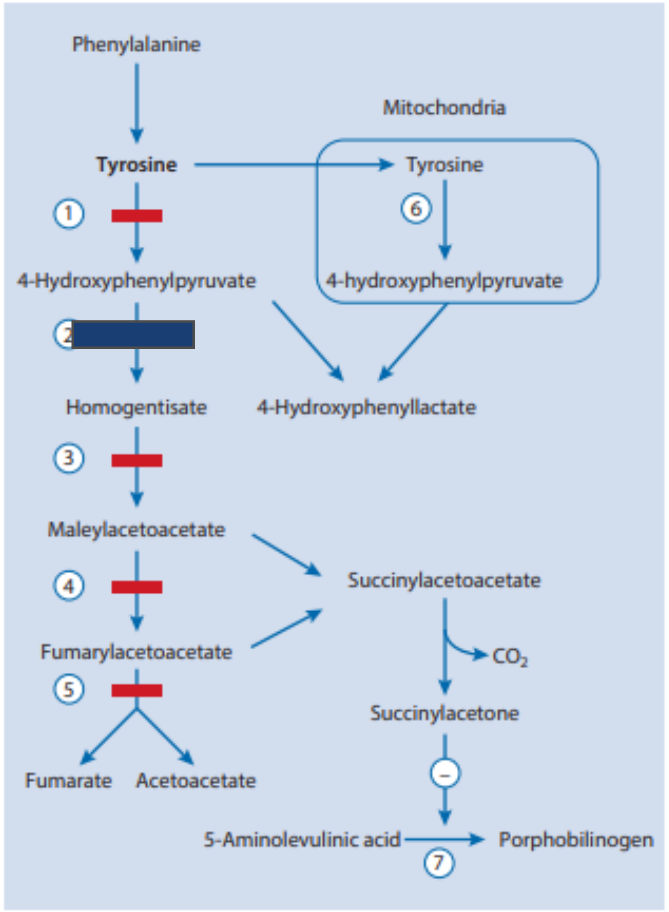
  Acute form before 6 months, **subacute form** between 6m and 1y, **chronic form** after 1 year

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; Tyr/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

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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 Bussières [b,1], Isabelle Chevalier [b,1], Louis Dallaire [b,1,2], Josée Dubois [b,1], Frédéric Faucher [b,1], Daphna Fenyves [c,1], Paul Goodyer [d,1], André 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 Melançon [d,1], Aicha Merouani [b,1], John Mitchell [d,1], Guy Parizeault [a,1], Luc Pelletier [h,1], Véronique 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 Québec.

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 necessary in all patients as the lifelong risk of hepatocarcinoma is still unknown
- Neurodevelomental difficulties:

  low IQ, school performance, impaired executive function.
  The aetiology is uncertain: related to the nitisinone treatment, high tyrosine levels, low phenylalanine levels, intrinsic feature of tyrosinaemia type 1

van Ginkel et al, 2017

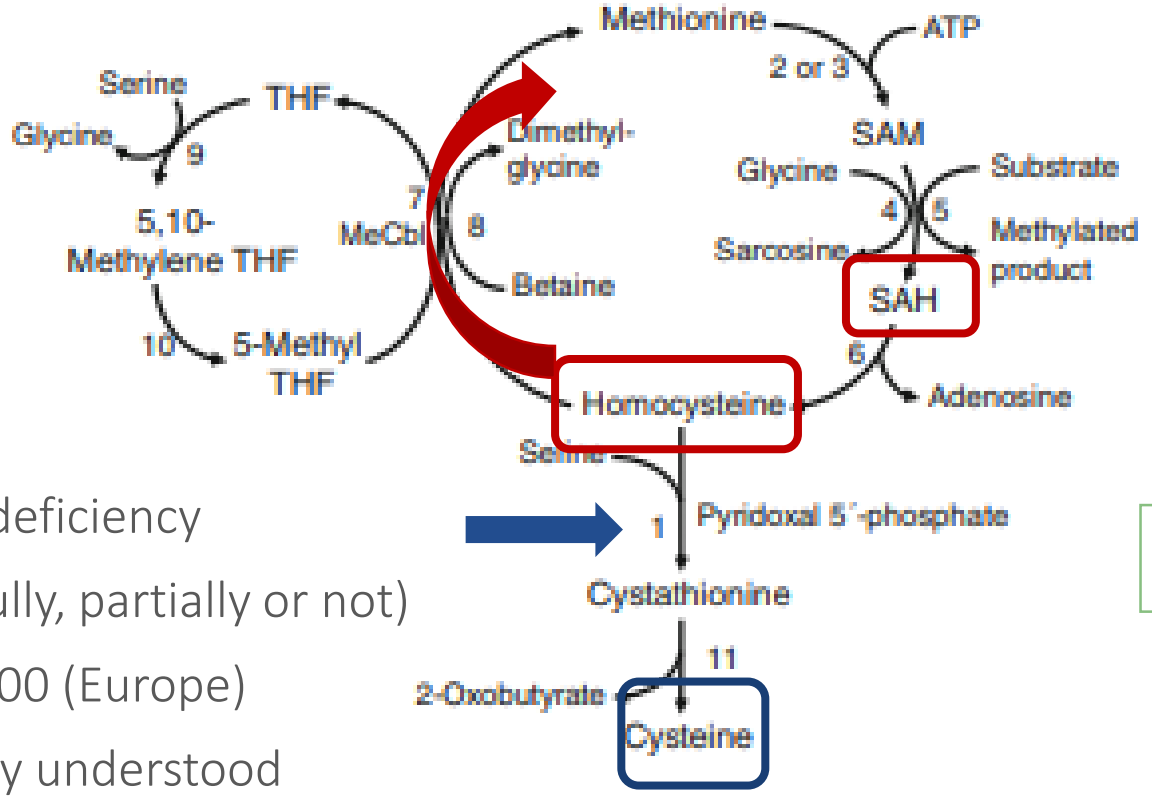
03

CLASSICAL HOMOCYSTINURIA

Cystathionine β synthase deficiency

Methionine metabolism

Remethylation



Demethylation

Transsulfuration

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 presentation

Severity and age at presentation vary markedly 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:** 50% learning difficulties ; seizures or dystonia; psychiatric problems M.Almuqbil et al, 2019
- **Vascular system:** Deep venous thrombosis (adult), cerebral venous sinus thrombosis (children)
  Risk of artery thrombosis (renal and carotid)
  $B6^{R-}$: 50% thrombosis before the age of 30y, 20% die Picker et Levy, 2014

Classical homocystinuria

Diagnosis

- Plasma: high tHcy and high methionine
  low-N cystathionine

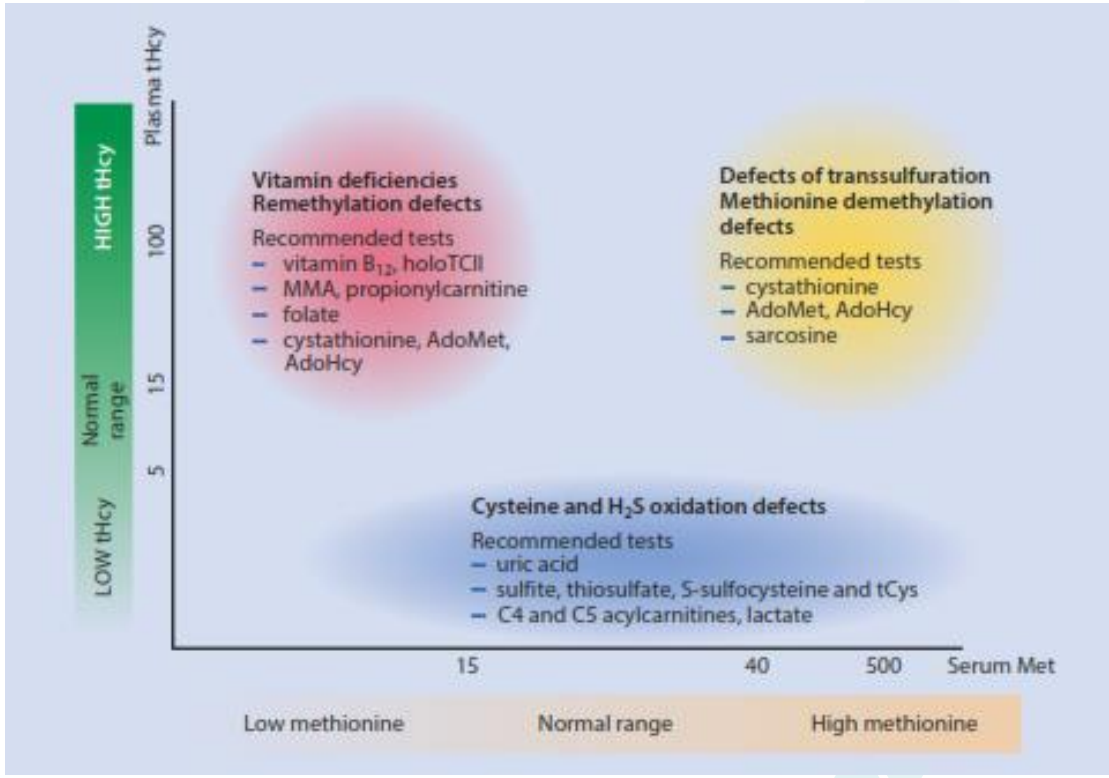
  avoid B6 supplements for at least 2w before
- Newborn screening (Met/Hcy-RWB): mainly B6 $^{R-}$

  V. Kozich et al, 2021
- 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

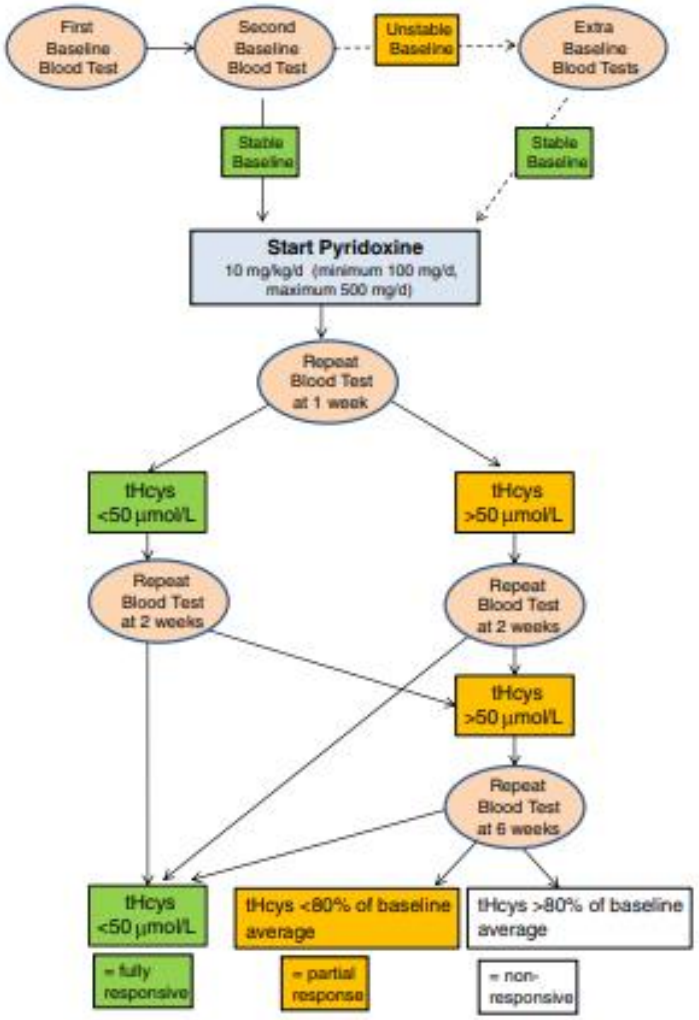
Treatment and prognosis

- Vitamin B6 if the patient is responsive (50%)
  Methionine restricted diet
  Folic acid, vitamin B12, Cysteine, Betaine

  Aspirin, low molecular weight heparin (perioperative, pregnancy)
- tHcy target under treatment:
  Hcy <100 µmol/l (in $B6^{R-}$; < 50 µmol/l if $B6^{R+}$)
- **Prognosis improved under treatment**

All the major complications can be prevented if patients are diagnosed by newborn screening and comply with treatment (even when control is imperfect, treatment reduces the vascular risk)

Yap et al , 2001



A. Morris et al, 2017

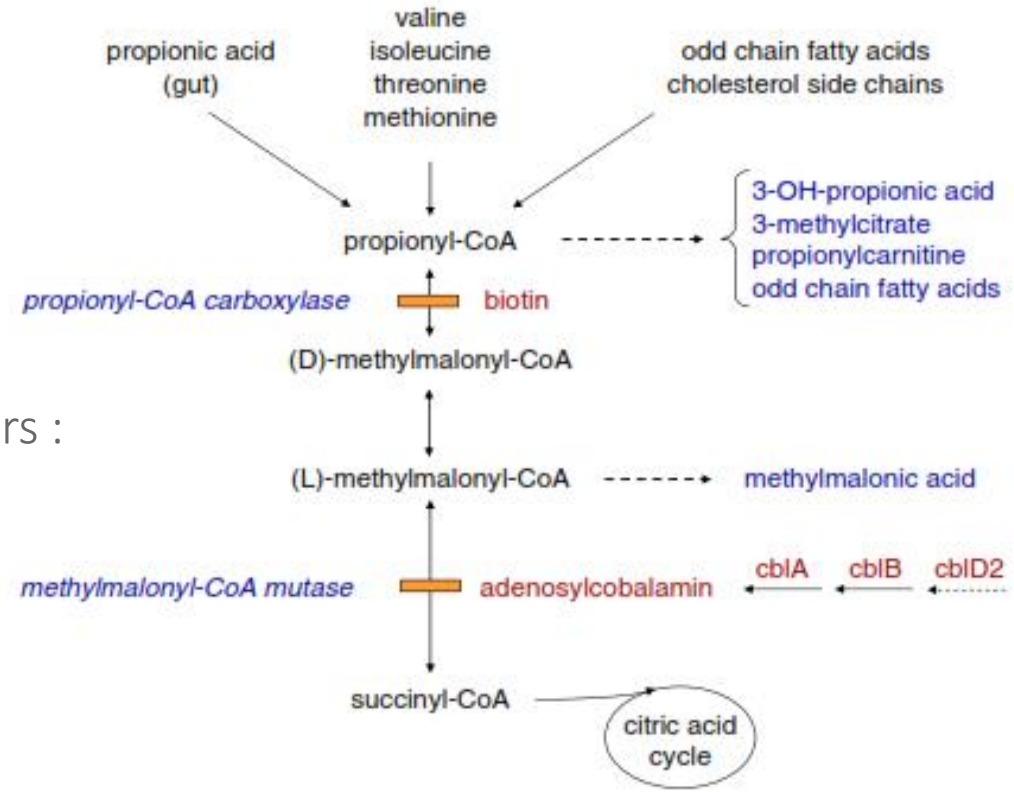
04

ORGANIC ACIDURIA

Methylmalonic Aciduria
Propionic Aciduria

Propionic and Methylmalonic aciduria

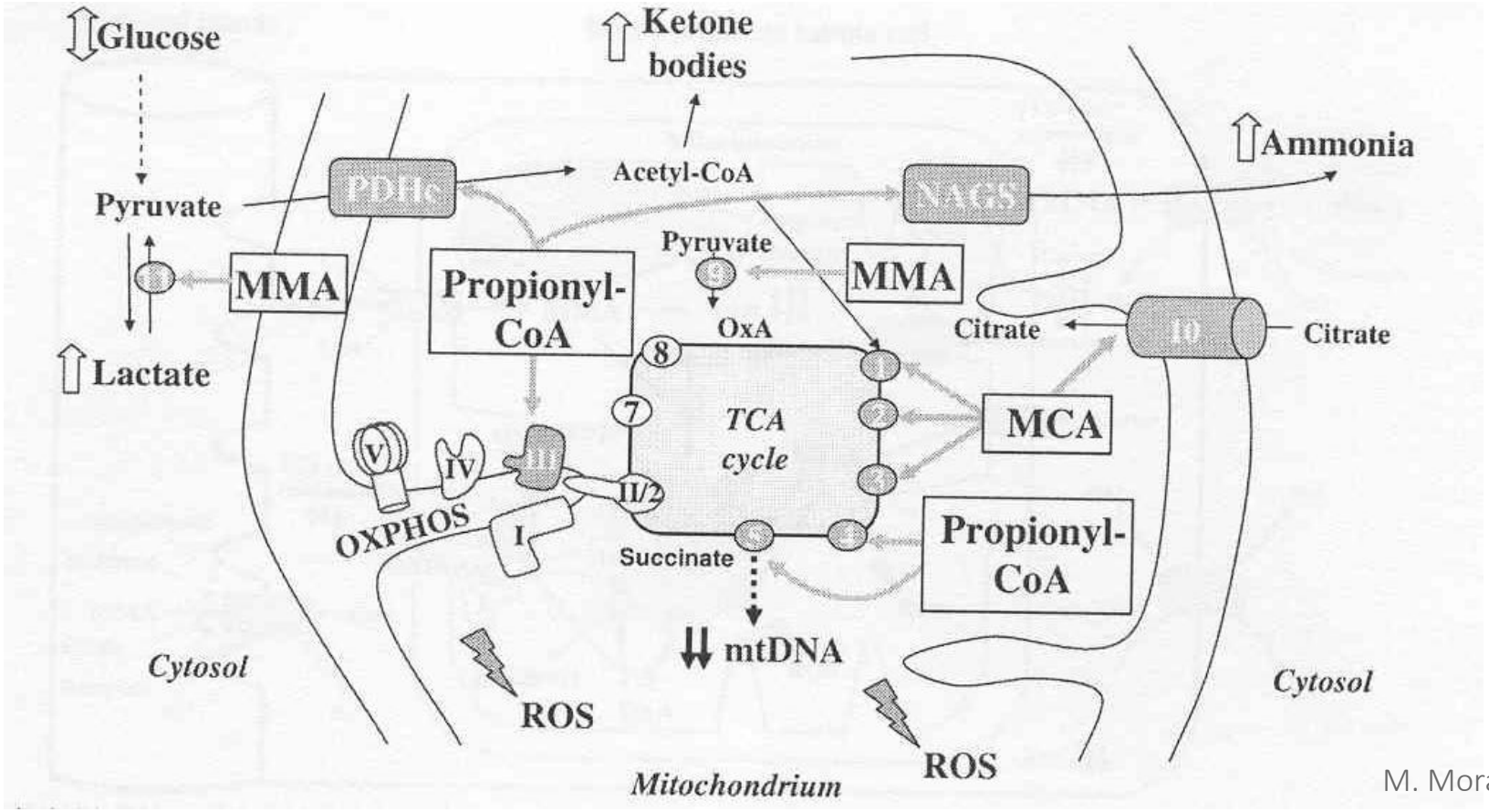
Autosomal recessive disorders :
1 / 50 000 à 1/ 100 000



M. Baumgartner et al, 2014

Propionic and methylmalonic acidurias

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 aggravate or occur for the first time following a trigger event

P. Forny et al, 2021

Acute presentation	Chronic presentation
Nervous system	
Acute encephalopathy	Hypotonia
Seizures	Developmental delay
Movement disorders (more frequent in PA)	Seizures
Stroke-like episodes (more frequent in MMA)	Movement disorders/ dystonia
Gastrointestinal system	
Vomiting	Recurrent vomiting with ketoacidosis
Feeding difficulties	Failure to thrive
	Pancreatitis
Haematopoietic system	
Neutropenia, pancytopenia	Neutropenia, pancytopenia
Heart (mostly in PA)	
Acute cardiac failure (mostly based on cardiomyopathy)	Cardiomyopathy
Arrhythmias	Prolonged QTc in ECG
Kidney	
	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 pCO2 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

Propionic a

Diagnosis

- Biochemica
  pH, lactate,
  Acylcarnitin

	Organic acids in urine			Acylcarnitines in dried blood or plasma	Plasma		
	Methylmalonic acid	3-hydroxy-propionate	2-methylcitrate	Propionylcarnitine	Homocysteine	Vitamin B12	Holotranscobalamin
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-↑	↑ - ↑↑	↓-↓↓	↓-↓↓

P. Forny et al, 2021

- Newborn screening (C3, C3/C2; Belgium)

- 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 the diagnosis of MMA/PA is suspected, specific therapies should be initiated,
  - Patient should be referred to a specialist centre
  - Dietetic treatment, drugs, extracorporeal detoxification
- During metabolic stability
  - Specific diet, medication, avoiding catabolism
- Transplantation (liver, liver-kidney, kidney): no clear recommendations
  - Potential benefits as well as associated risks
- New therapeutic approachs

Yap et al, 2020

Received: 10 October 2020 | Revised: 3 February 2021 | Accepted: 15 February 2021
DOI: 10.1002/jimd.12370

ORIGINAL ARTICLE

JIMD SSIEM WILEY

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

Patrick Forny[1] | Friederike Hörster[2] | Diana Ballhausen[3] | Anupam Chakrapani[4] | Kimberly A. Chapman[5] | Carlo Dionisi-Vici[6] | Marjorie Dixon[7] | Sarah C. Grünert[8] | Stephanie Grunewald[4] | Goknur Haliloglu[9] | Michel Hochuli[10] | Tomas Honzik[11] | Daniela Karall[12] | Diego Martinelli[6] | Femke Molema[13] | Jörn Oliver Sass[14] | Sabine Scholl-Bürgi[12] | Galit Tal[15] | Monique Williams[13] | Martina Huemer[1,16] | Matthias R. Baumgartner[1]

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

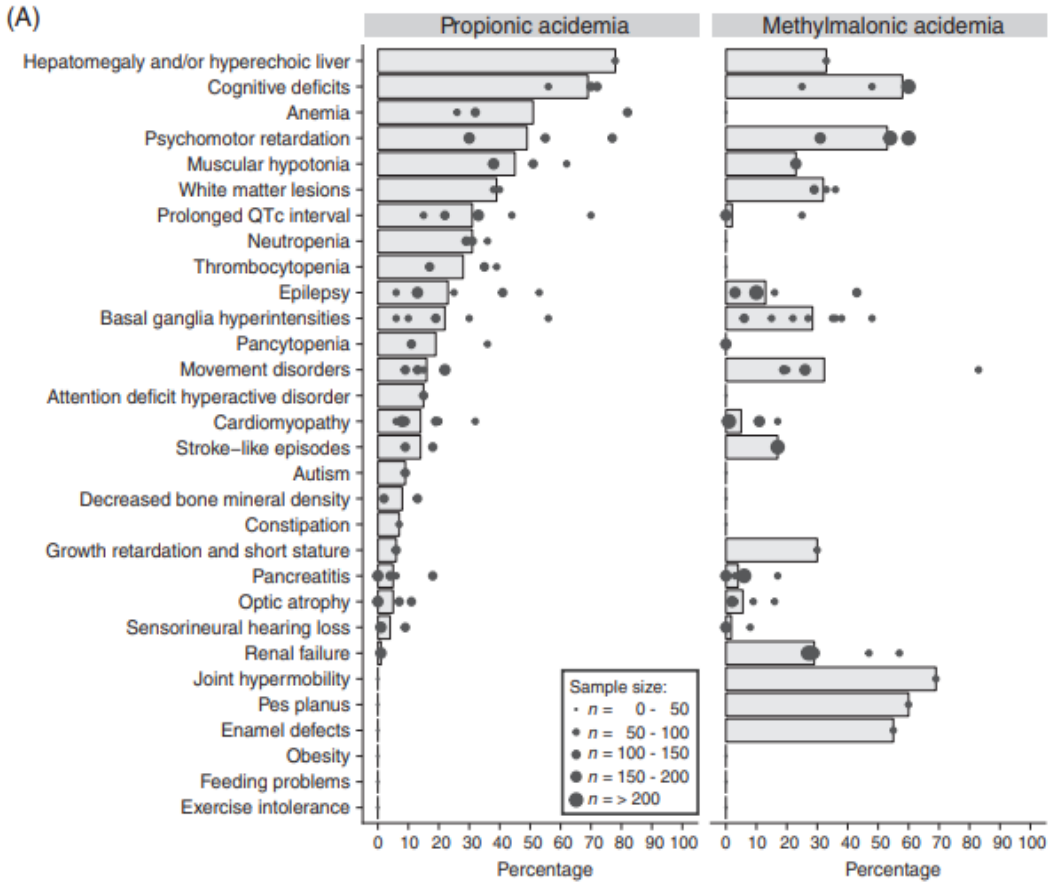
  H. Haijes et al , 2019

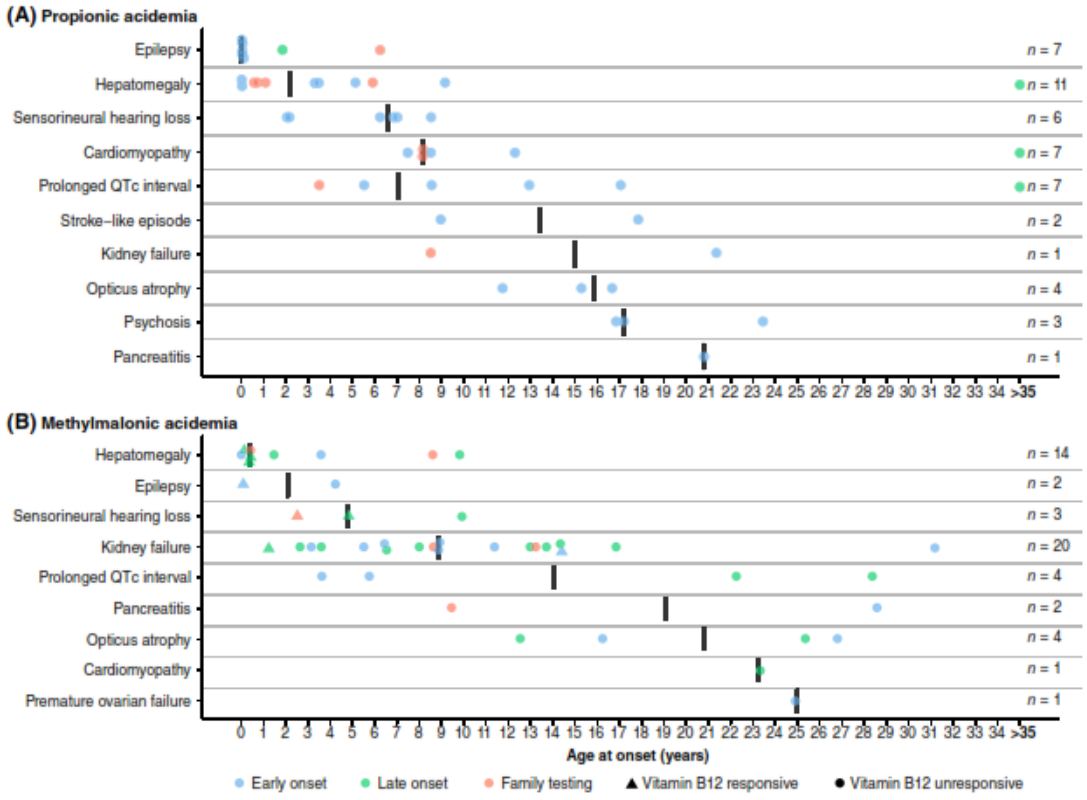
Outcome parameter	Median rating of importance of outcome
Survival	9
Health-related quality of life	9
Metabolic stability	8
Cognitive development	8
Epilepsy	8
Metabolic stroke	7
Vision and hearing	7
Early diagnosis	7
Cardiomyopathy	7
Kidney dysfunction	7
Pancreatitis	6
Normal growth	6
Neutropenia	6
Anaemia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

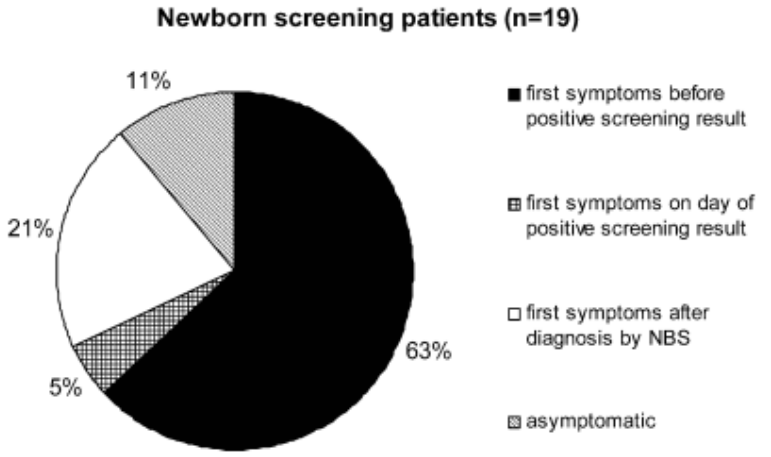


Fig. 1 Manifestation of propionic acidemia (PA) symptoms related to the time when newborn screening (NBS) results became available

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

Leucinosis

Branched-Chain Amino acids metabolism

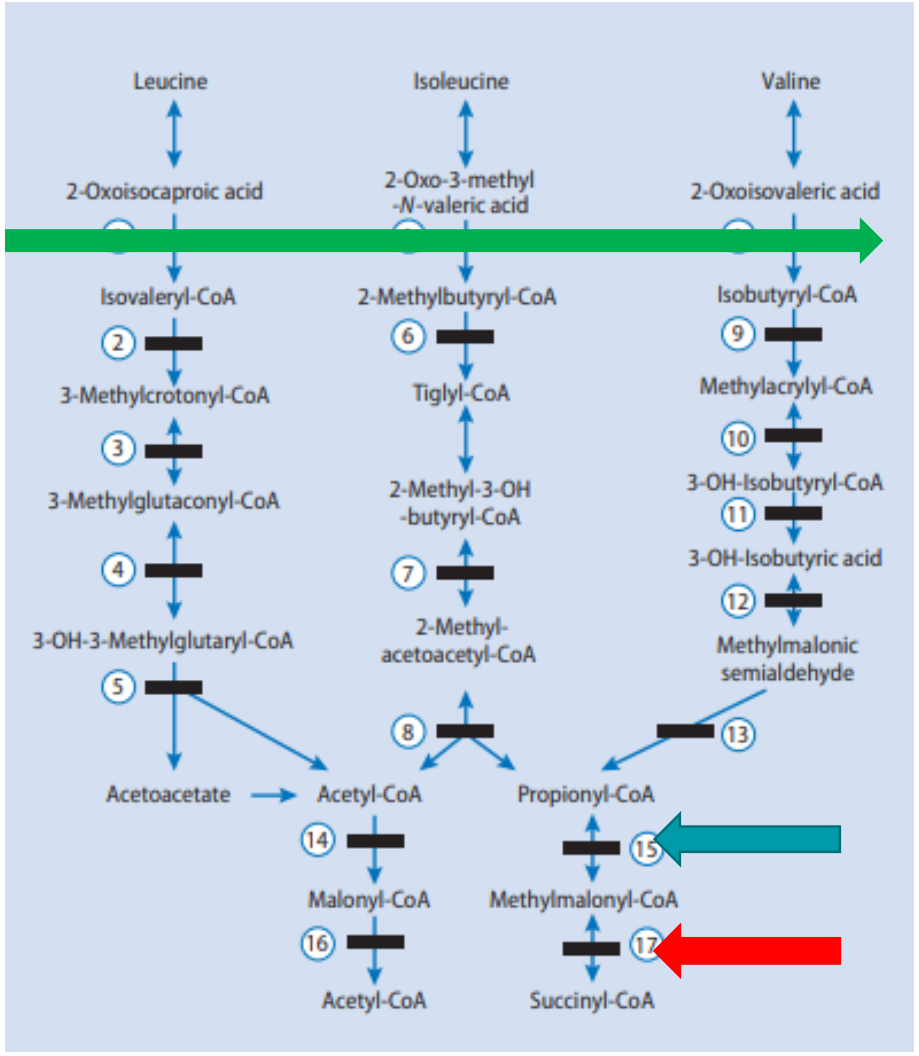
Leucine and 2-oxoisocaproic ac the most neurotoxic

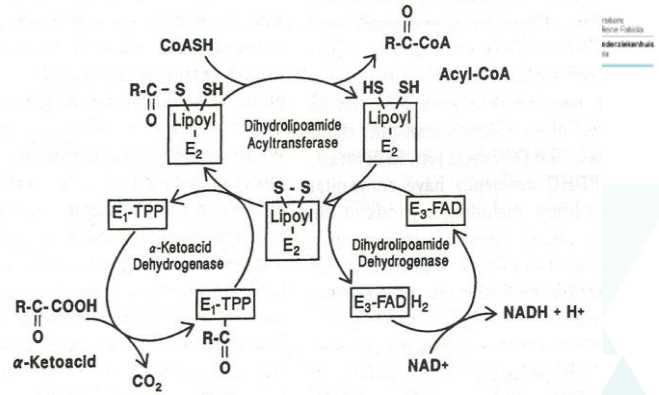
Acute cerebral oedema

White matter changes

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

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





MSUD

Autosomal recessive

1/120 000 to 500 000

E1α (45%), E1β (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 severly dehydrated, no metabolic acidosis (no 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 sign 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, essentially those that apply 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 the normal (Verbal> Performance) J.Bouchereau et al , 2017

  Depends on how long Leu remains > 1000 µmol/l and the quality of long term metabolic control

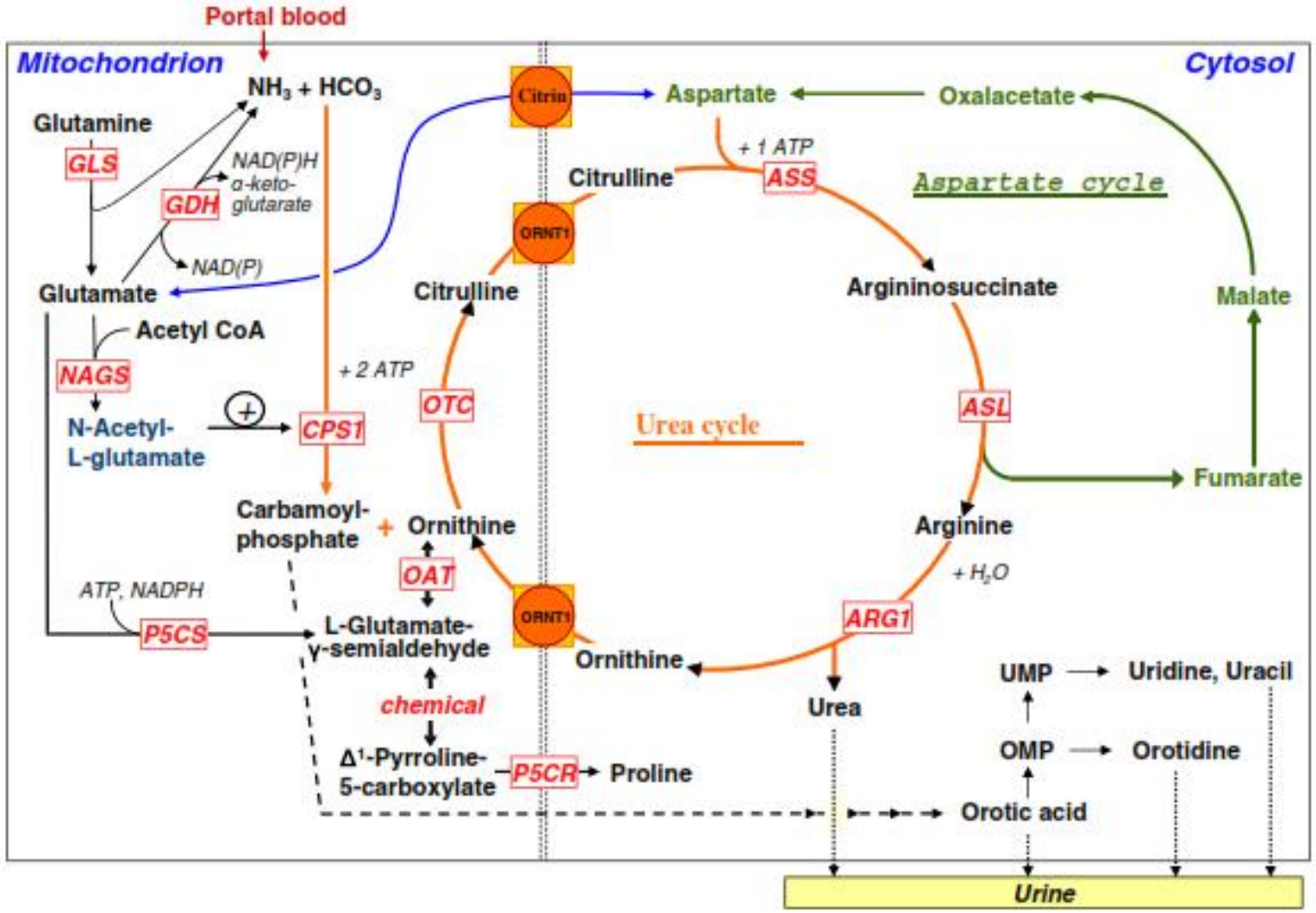
  Interest of neonatal screening for rapid management (in Belgium: xLeu+Val)

  Some patients may present mental health problems despite good metabolic control (hyperactivity, anxiety, depression) 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 ($NH3 + H^+ \leftrightarrow NH4^+$)
- Acute severe hyperammonaemia:
  Seizures, coma with cerebral oedema
  If prolonged, permanent neurological sequelae
  cortical atrophy, demyelination, neurocognitive delay, cerebral palsy
- 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 metabolisme, NO synthesis, oxydative stress
- Alteration in neuronal differentiation and patterns of cell death
- Chronic moderate hyperNH3 induces neuroinflammation > cognitive and motor alterations

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

Urea Cycle disorders

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.

Acute presentation	Chronic presentation
• **Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication**	• **Confusion, lethargy, dizziness**
• **Acute encephalopathy (see below)**	• **Headaches, migraine-like, tremor, ataxia, dysarthria flapping tremor (in adults)**
• **Seizures (mostly under situation of altered level of consciousness)**	• **Learning disabilities, cognitive impairment**
• Ataxia: mostly under situation of altered level of consciousness	• Epilepsy
• Stroke-like episodes	• Chorea, cerebral palsy
• Transient visual loss	• Protracted cortical visual loss
• **Vomiting and progressive poor appetite**	• Progressive spastic diplegia or quadriplegia starting in childhood (described in ARG1D and HHH syndrome)
• Liver failure, coagulopathy (esp. in OTCD and HHH)	• **Protein aversion, self-selected low-protein diet**
• **Multiorgan failure**	• **(Recurrent) abdominal pain, vomiting**
• **Peripheral circulatory failure**	• **Failure to thrive**
• **Psychiatric symptoms (hallucinations, paranoia, mania, emotional or personality changes)**	• **Hepatomegaly, elevated liver enzymes**
• "Post-partum psychosis"	• **Psychiatric symptoms: hyperactivity, mood alteration, behavioral changes, aggressiveness**
• **In neonates: sepsis-like picture, temperature instability, respiratory distress, hyperventilation**	• 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

J.Häberle et al, 2019

Urea Cycle Disorders

Diagnosis

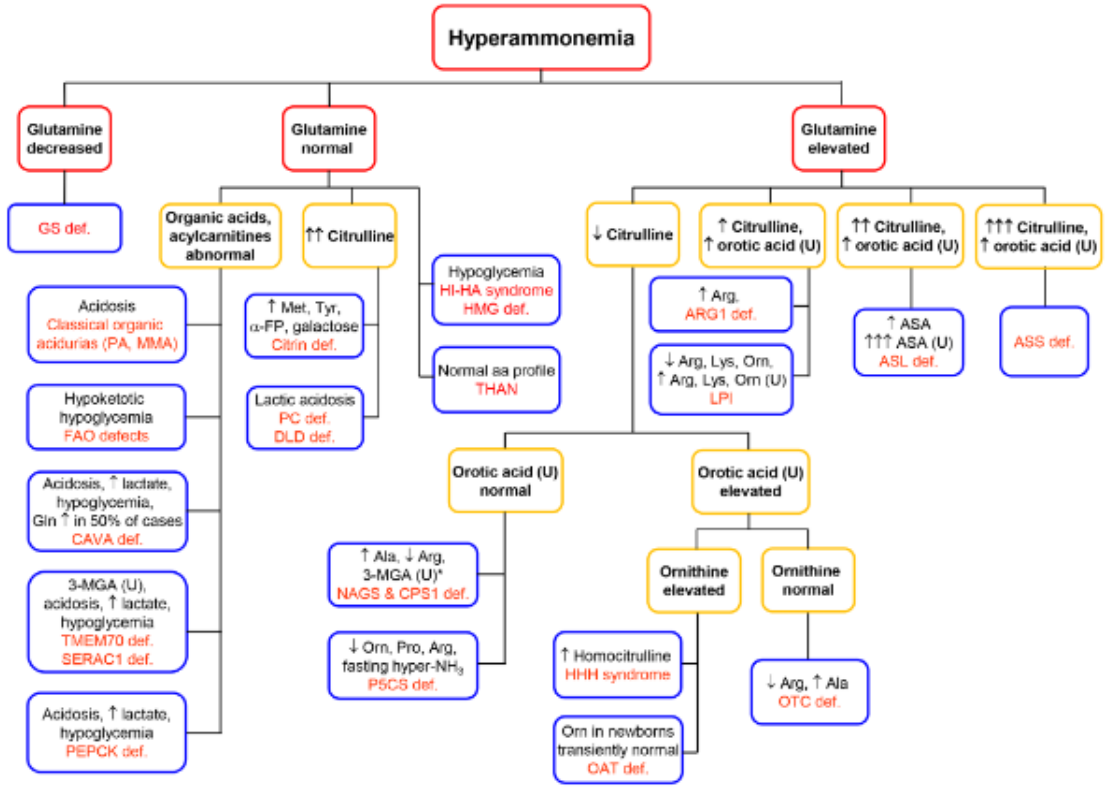
In any acute or intermittent **neurological deterioration** or **psychiatric illness**, **acute liver failure**, suspected **intoxication** or in the differential diagnosis of **neonatal sepsis**.

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.[g]	PEPCK def.
Acidosis	+/–	+[e]	+/–	+	+	–	+	+
Ketonuria[a]	–	+	absent	+	absent	–	++	+
Hypoglycemia[b]	–	+/–	+	+/–	+	+	+	+/–
↑ Lactic acid[c]	–	+	+/–	+	+/–	–	+	+/–
↑ AST and ALT	(+)[d]	–	+	–	+/–	–	+/–	++
↑ CPK	–	–	+	–	+/–	–	–	–
↑ Uric acid	–	+	+/–	–	+	–	–	
↓ WBC/RBC/Plt	–	+	–	–	+/–	–	–	–
Weight loss	–	+[f]	–	–	+/–	–	+	

- 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, tissue- liver, fibroblast) 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: drugs 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

Prognosis very poor if

- 1. Coma > 3 days
- 2. Significant elevated intracranial pressure
- 3. NH3 > 1000 µmol/l (clinical situation, duration)

- 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 L Krivitzky et al, 2009
- Frequent emotional and behavioral problems D.Jamiolkowski et al, 2016
- 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 J.Häberle et al, 2019

I Thank you for your attention