Inborn Errors of metabolism

Katarzyna Kuśmierska

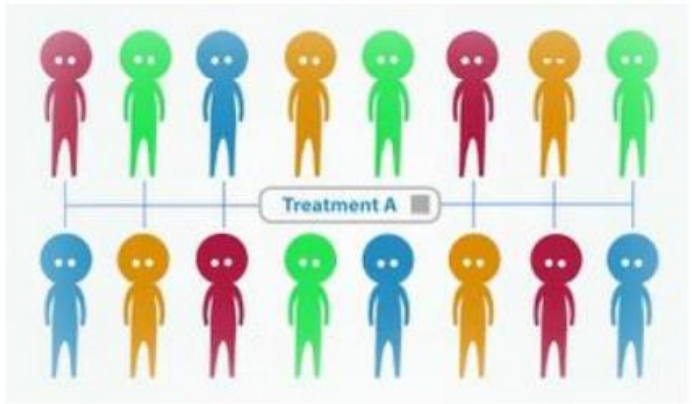
IEM

- Inborn errors of metabolism (IEMs) are particularly prevalent as diseases of the nervous system
- the whole group of neurometabolic disorders, many of them lacking biomarkers, is expected to experience substantial growth in the near future as a result of advanced genetic diagnostic techniques. In fact, as long as biochemistry is involved, any kind of monogenic disease can become an IEM.
- Metabolism involves thousands of proteins, mostly enzymes, receptors and transporters, the deficit of which causes IEM. Deficits can affect small or complex molecules. The number of IMD (inborn metabolic diseases) obviously depends on the definition of an IMD, and in the -omics era, this is changing quickly.

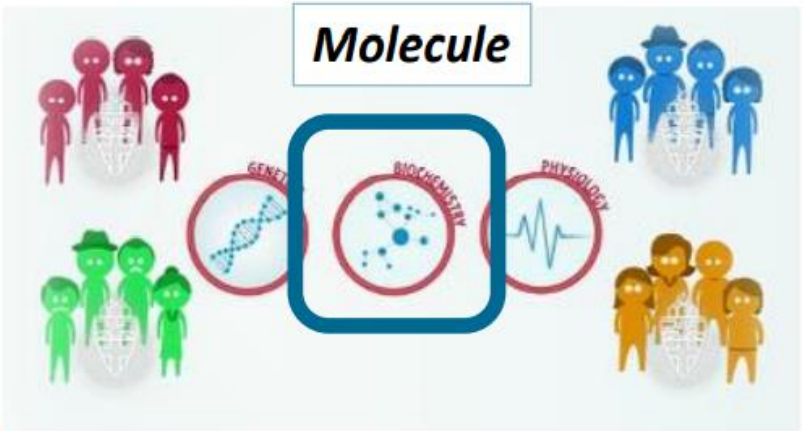
"According to Morava, the classification of a disorder as an IMD requires only that impairment of specific enzymes or biochemical pathways is intrinsic to the pathomechanism"

Garcia et al.

Personalized Healthcare @ Radboudumc



People are different

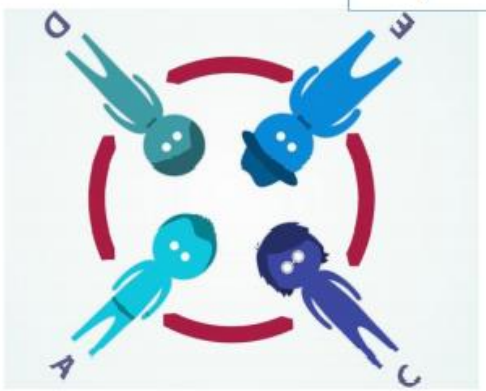


Stratification by multilevel diagnosis

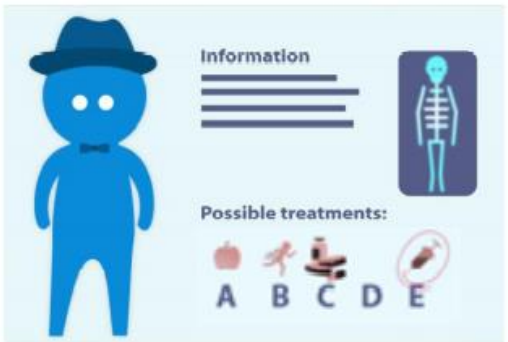
+

Patient's preference of treatment

Population



Exchange experiences in care communities



Select personalized therapy

Patient

Radboudumc

Patients Included

- A simplified and updated classification of IEM mixes elements from the practical diagnostic approach with pathophysiological considerations into three large categories based on the size of molecules:

- small and simple
- large and complex and their implication in energy metabolism.

- The role of molecules depends on their size, the metabolites involved in IEM may play in the brain function as signalling molecules, structural components and fuels, and many metabolites have more than one role:

- **Disorders of small and simple molecules:**

- metabolic marker(s) - Their diagnosis relies on plasma, urine, and CSF investigations. Many of them can be detected by neonatal metabolic screening.

There are two subcategories in small molecule disorders:

1. Diseases linked to an accumulation: Intoxication disorders

2. Diseases linked to the deficiency

Diseases linked to an accumulation: Intoxication disorders

The disorders in this group are the most typical for IEM and are characterised by signs and symptoms resulting primarily from the abnormal accumulation of the compound(s) proximal to the block and potentially reverse as soon as the accumulation is removed. They share some characteristics:

1. *They do not interfere with embryo and foetal development and present after a symptom free interval with clinical signs of intoxication (acute, intermittent, chronic and even progressive) provoked by intercurrent events and food intake.*

2. Most of these disorders are treatable.

3. This group from IEM of amino acid (AA) catabolism (PKU or MSUD), urea cycle defects, organic acidurias (MMA, GA1 etc.), carbohydrate intoxications metals accumulation and porphyrias

Some purines/pyrimidines and metabolite repair defects (D/L-2-OH-glutaric, NADPH etc.) could be also included in this group.

In the brain, molecules that accumulate in intoxication disorders can behave as neurotransmitters in the case of amino acids or stimulate biological pathways related to impaired autophagy and nerve growth factors.

Synaptic plasticity and excitability are almost constantly impaired and executive functions are especially vulnerable. Therefore, and in spite of proper metabolic control, most of these patients display behavioural, emotional and learning difficulties.

„BIOCHEMISTRY (METABOLISM) AND **CELL NEUROBIOLOGY** NEED TO MEET.

ADDITIONALLY, THE BRAIN SHOULD BE STUDIED AS A SYSTEM

(CONNECTING DIFFERENT LEVELS OF COMPLEXITY).”

Àngels García-Cazorla 2018

BIOCHEMIA (METABOLIZM) I NEUROBIOLOGIA KOMÓRKI MUSZĄ SIĘ SPOTKAĆ.

MÓZG POWINIEN BYĆ BADANY JAKO SYSTEM ŁĄCZĄCY RÓŻNE POZIOMY ZŁOŻONOŚCI.

Diseases linked to the deficiency

- Symptoms result primarily from the defective synthesis of compounds or from the defective transport of an essential molecule through intestinal epithelium, blood- brain barrier and cytoplasmic or organelle membranes.

- most of these defects interfere with embryofetal development causing a neurodevelopmental disruption, have a congenital presentation and share many characteristics with disorders in the complex molecules group.

Diseases of transport across the blood-brain-barrier. Mechanisms and symptoms

	Transport mechanism	Disorders	Symptoms
Glucose	Facilitated diffusion	GLUT-1 defect GLUT-10 (not glucose transport but a similar substance)	Epilepsy, ID, abnormal movements Arterial tortuosity syndrome, strokes
Lactate, keton bodies	Diffusional, saturable cotransport with protons	MCT-1 defect	Episodes of severe ketoacidosis in early childhood
Amino acids	Large neutral aa transporter (L-system) Na+ dependent aa transport	BCAA defect (gene SLC7a5) Serine transport defect (gene SLC6a14) DHA (docohexanoic acid) transporter defect	Microcephaly, brain malformation, early death

- Major neurodevelopmental disruptions lead to severe global encephalopathies where almost all neurological functions are chronically altered.

- In early onset presentations, patients display severe psychomotor delays affecting both motor and cognitive milestones.

- **Microcephaly** and **hypomyelination** are very common as epilepsy and movement disorders. These defects mimic early non-metabolic genetic encephalopathies that affect crucial neurodevelopmental functions such as neuronal precursor proliferation, migration, pruning and dendrite development - because these small molecules contribute to antenatal brain construction in terms of signalling, cytoskeleton guidance, synapse formation and later on in experience dependent synapse remodelling.

Energy-related defects

"IEM with symptoms due, at least in part, to a deficiency in energy production or utilisation within the liver, myocardium, muscle, brain and other tissues"

1. Membrane carriers of energetic molecules (glucose: GLUT, FA, ketone bodies, monocarboxylic acids: MCT) display many tissue specific isozymes as GLUT-1 and MCT-1

2. Mitochondrial defects encompass aerobic glucose oxidation defects presenting with congenital lactic acidemias (pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase system and Krebs cycle defects), mitochondrial respiratory chain disorders, mitochondrial transporters of energetic and other indispensable molecules, coenzyme Q biosynthesis, FA oxidation and ketone body defects.

3. Cytoplasmic energy defects include glycolysis, glycogen metabolism, gluconeogenesis, hyperinsulinism, creatine metabolism disorders and finally inborn errors of the pentose phosphate pathways.

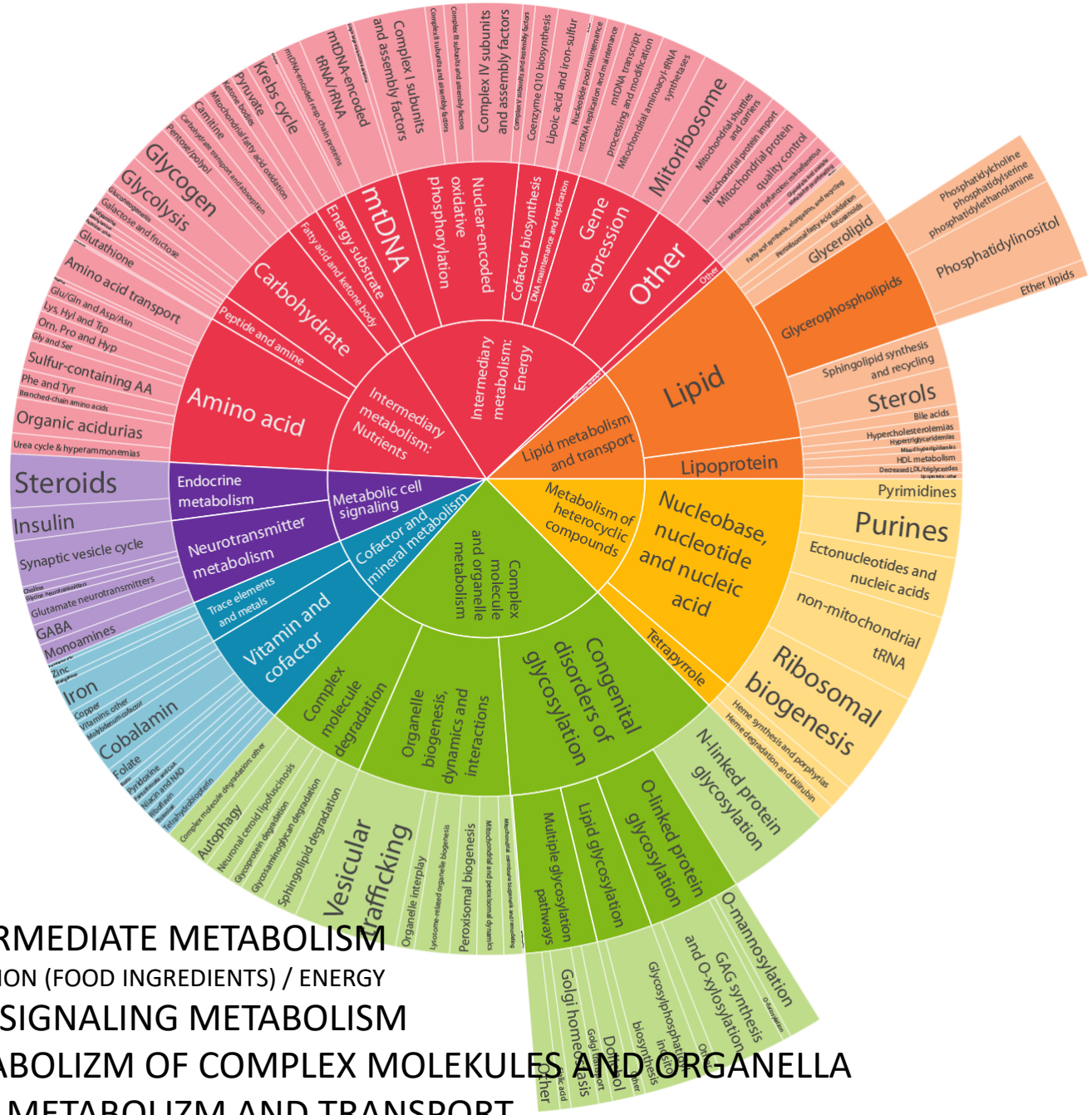
- The brain accounts for 20% of an adult's energy expenditure at rest and more than 50% in a child
- Neurons expend 70–80% of total energy (the remaining portion used by glia) and the great majority (80%) is utilised to fuel neuronal channels.
- Fuel molecules such as ATP and lactate also have signalling roles promoting synaptic plasticity.
- Glucose is the obligatory fuel for adult brain, but lactate produced from glucose by astrocytes within brain during activation has been proposed to serve as neuronal fuel

Given the vulnerability of energy homeostasis in the brain, most neurological disorders, and in particular, neurodegenerative diseases are necessarily linked to disturbances in energy metabolism.

(García-Cazorla, 2018)

From symptoms to diagnosis of IEM

- Recognizing individuals with inherited diseases can be difficult as signs and symptoms often overlap those of common medical conditions.
- Existing resources aim to provide an overview of many individual disorders, and are not always designed to guide clinicians in the diagnostic process.
- Therefore, digital translation and standardization of the IEM community knowledgebase are urgently needed to bridge the knowledge gap



INTERMEDIATE METABOLISM

NUTRITION (FOOD INGREDIENTS) / ENERGY

CELL SIGNALING METABOLISM

METABOLIZM OF COMPLEX MOLEKULES AND ORGANELLA

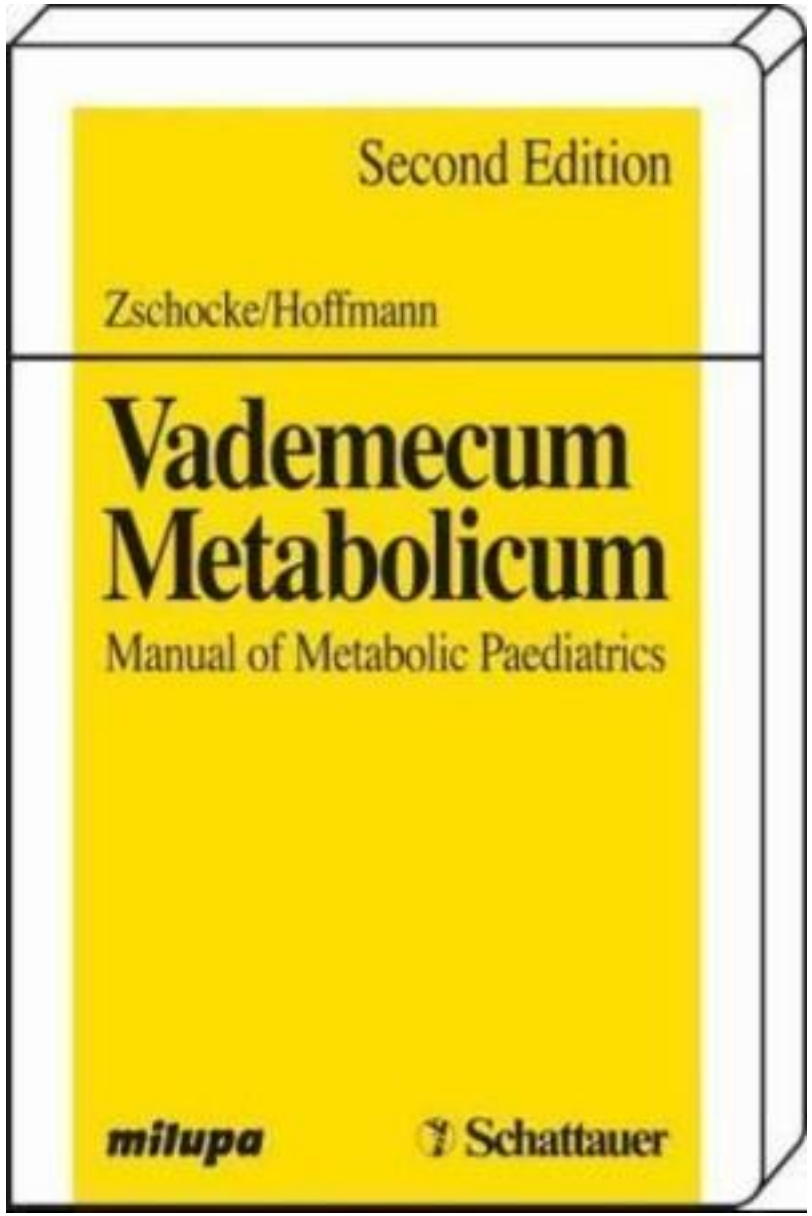
LIPID METABOLIZM AND TRANSPORT

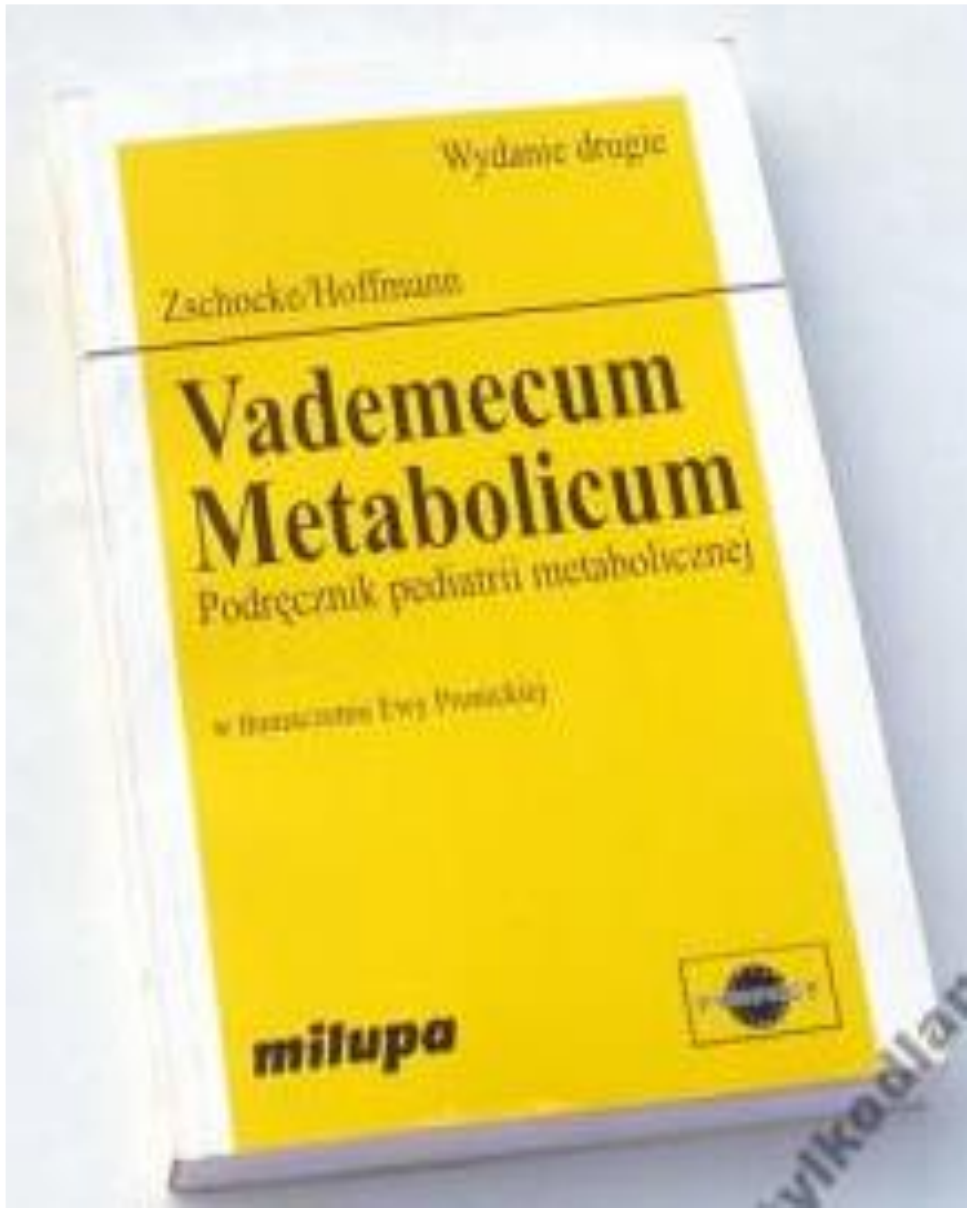
International Classification of Inherited Metabolic Disorders(ICIMD)
– involves 1450 disorders , DIVIDED INTO 24 CATEGORIES with 124 groups www.icimd.org

ICIMD is intended to cover any primary genetic disorder in which an alteration of a biochemical pathway is inherently associated with specific biochemical, clinical and/or pathophysiological features.

can serve as a basis for teaching purposes (including textbooks and seminars), electronic resources, other existing disease databases, patient registries, rare disease initiatives, and many other purposes.

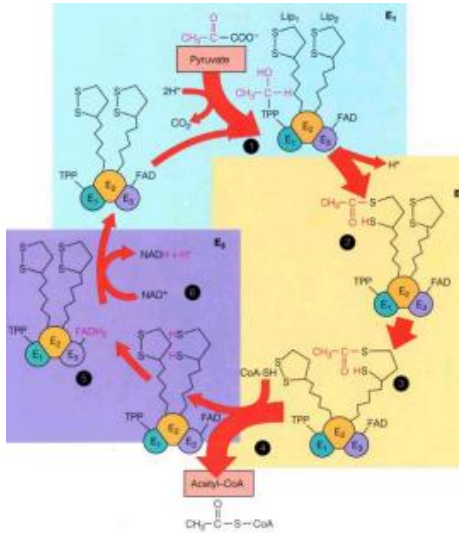
J Inherit Metab Dis . 2021 January ; 44(1): 164–177. doi:10.1002/jimd.12348.





Vademecum Metabolicum Pediatria metaboliczna - Zschocke, Hoffman

Biochemical division due to incorrect metabolic pathway through enzyme blocks:



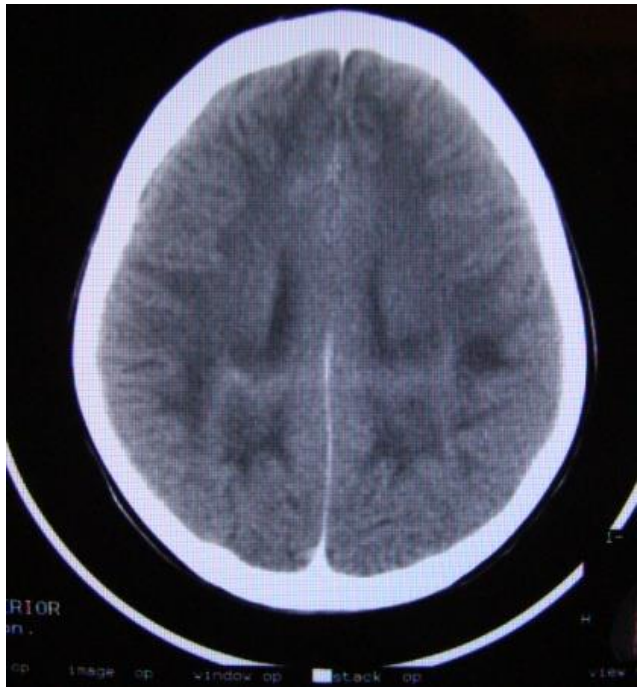
LIPIDOSIS

MUCOPOLISACHARYDOSIS

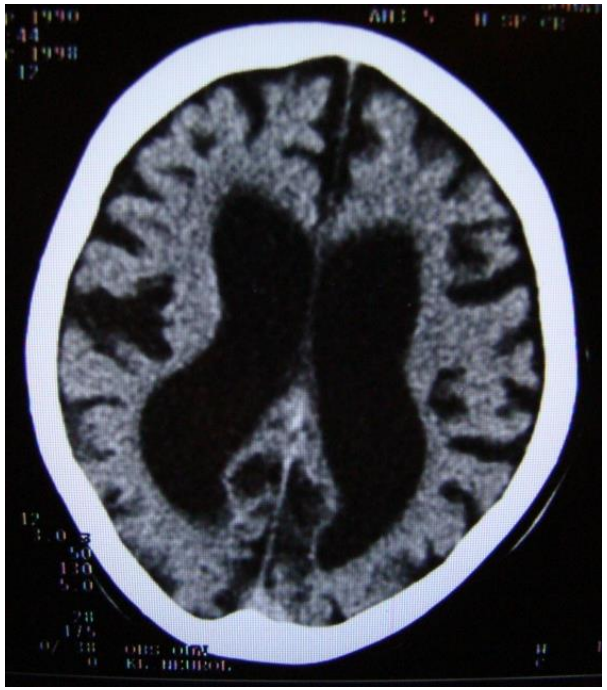
AMINOACIDOPATIE

VERY LONG-CHAIN FATTY ACID β-OXYDATION DISORDERS

DIVISION DUE TO PRIMARY STRUCTURE DAMAGE
LOCATION OF CHANGES
DAMAGE TO GRAY MATTER OR WHITE MATTER



DAMAGE OF WHITE MATTER



DAMAGE OF GRAY MATTER

FACTORS RESPONSIBLE FOR DISORDERS IN THE FUNCTIONING OF THE NERVOUS SYSTEM

GEN → **PROTEINS**

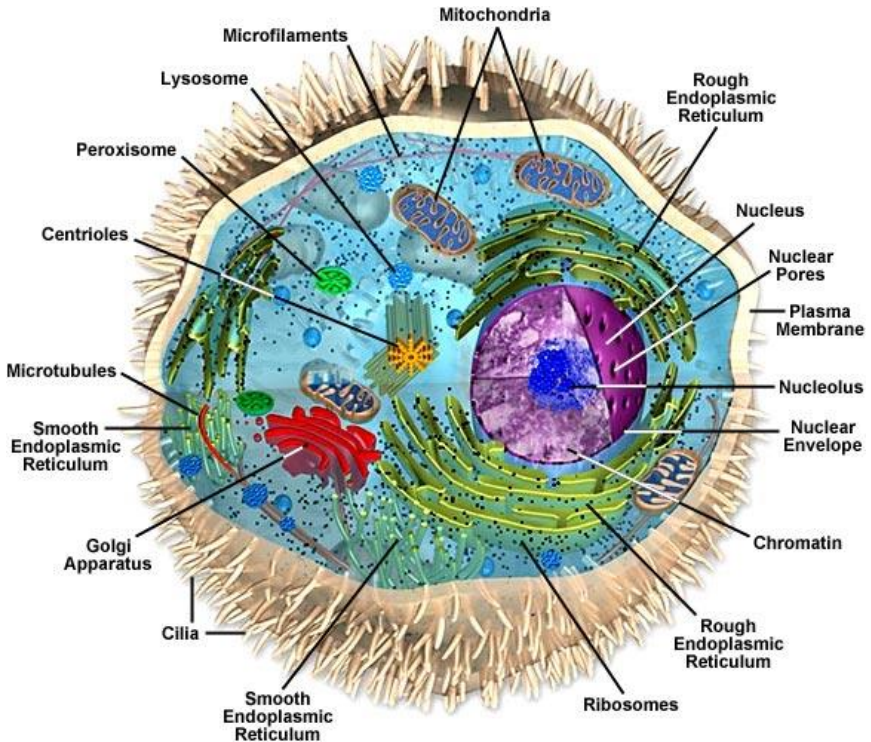
FORMATION OF STRUCTURAL PROTEINS

SYNTHESIS OF ENZYMES

FORMATION OF TRANSPORTERS

FORMATION OF RECEPTORS

FORMATION OF FUNCTIONAL PROTEINS
(m.in.. CHAPERERONES**,** INITIATING TRANSLATION**)**



INTERMEDIATE METABOLISM PATHWAYS

SYNTHESIS OF BASIC MOLECULES

SYGNALING

BUILDINGS

DECOMPOSITION OF MACRO AND MICRO PARTICLES

PROTEIN AND LIPID MODIFICATION PATHWAYS

PATHWAYS OF ENERGY GENERATION IN A FORM AVAILABLE TO THE ORGANISM!!!

DEFICIT OF ENZYMES:

AMINO ACIDS,

CARBOHYDRATES

FATTY ACIDS

PURINE BASES (ADENINA, GUANINA) PIRYMIDINES (CYTOZYNA TYMINA URACYL)

ENERGY METABOLISM (MITOCHONDRIALNEGO)

Newborn screening

- Inborn disorders–after asymptomatic period severe illness, developmental impairment or death

- Early detection in presymptomatic period allows for preventive treatment

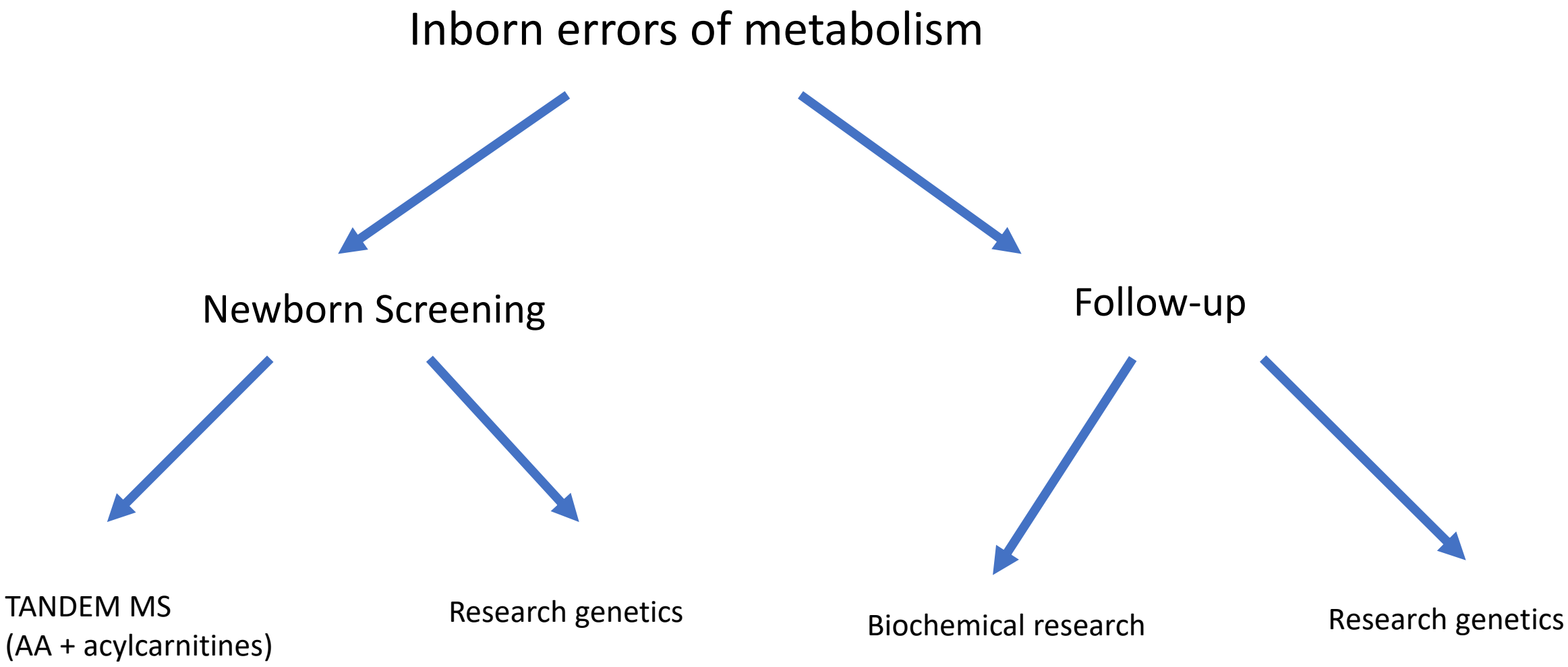
CURRENT METABOLIC NBS PANEL

- Biotinidase deficiency
- Phenylketonuria (PKU)
- Maple sirup urine disease (MSUD)
- Glutaric aciduria type I (GA I)
- Isovaleric aciduria (IVA)
- MCAD deficiency
- VLCAD deficiency
- LCHAD deficiency
- Carnitine palmitoyltransferase I deficiency (CPT I)
- Carnitine palmitoyltransferase II deficiency (CPT II)
- Carnitine acylcarnitine translocase deficiency (CACTD)

CURRENT METABOLIC NBS PANEL - 2

- Propionic aciduria (PA)
- Methylmalonic aciduria / Cobalamin C/D defects (MMA / Cbl C/D)
- Citrullinaemia (CIT)
- Argininosuccinate lyase deficiency (ASLD)
- Tyrosinaemia I / III
- Non-ketotic hyperglycinaemia (NKH)
- Carnitine transporter deficiency (CTD)
- Multiple acyl-CoA dehydrogenase deficiency (MADD)
- 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (3-HMG-CoA LD)
- Short-chain acyl-CoA dehydrogenase deficiency (SCADD)
- 3-Methylcrotonyl-CoA carboxylase deficiency (3-MCCD)

Diagnostics

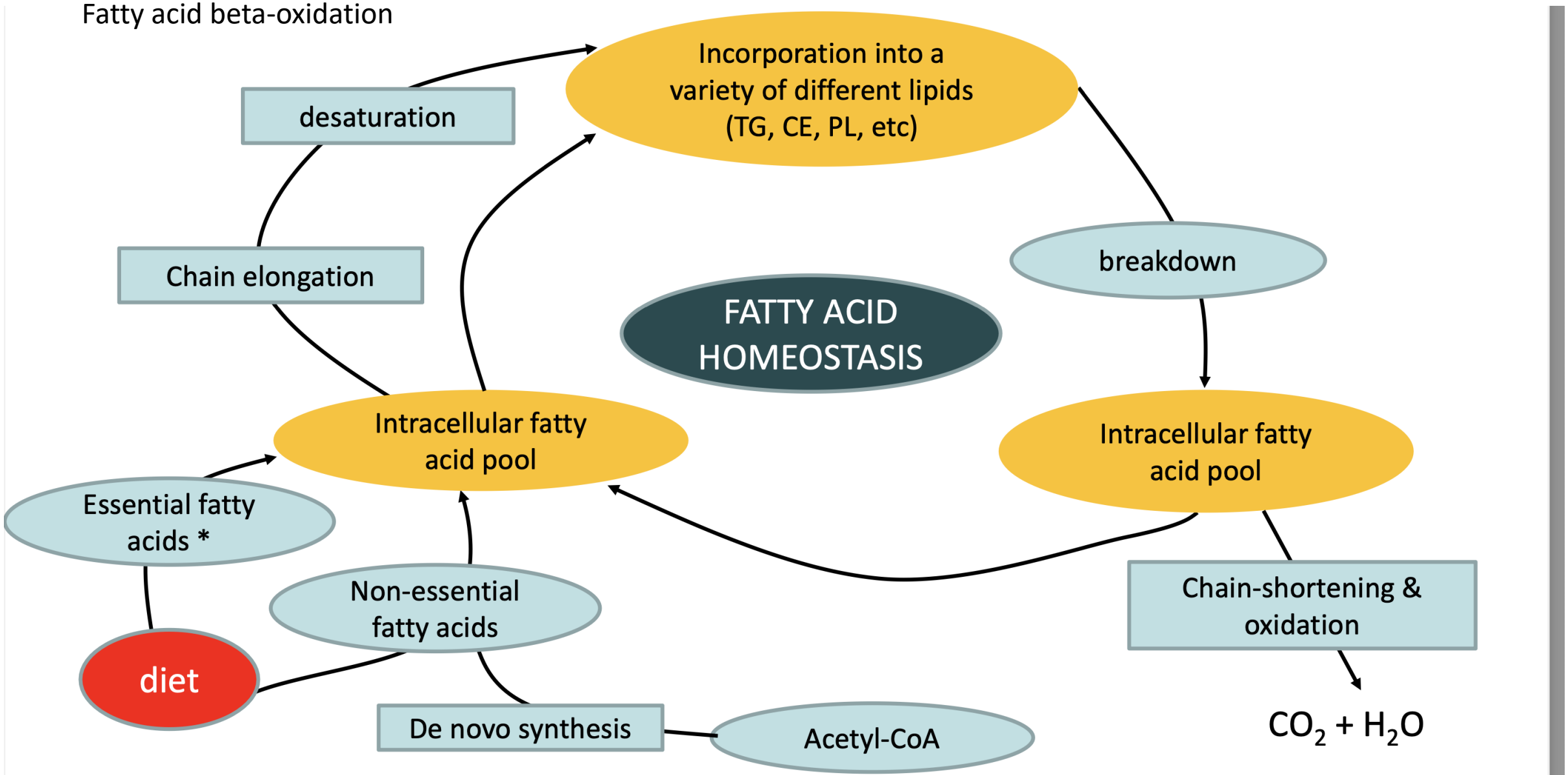


Newborn screening

➢ Fatty acids beta oxidation disorders

Defekt	Profil MS/MS
Deficyt CAT	↓C0
SCAD	↑C4
MCAD	↑C6; ↑C8; ↑C10
VLCAD	↑C14:1; ↑C14:2; ↑C14; ↑C16
LCHAD/TFP	↑C16:OH; ↑C18:OH; ↑C14:1; ↑C18:1; ↑C16
CPTII	↑C16; ↑C18; ↑C18:1; ↑FC
CPTI	↓C16;↓C18↓C18:1; ↑/N FC
MAD	↑C4; ↑C5; ↑C8; ↑C10; ↑C12; ↑C14; ↑C16;

Fatty acid beta-oxidation

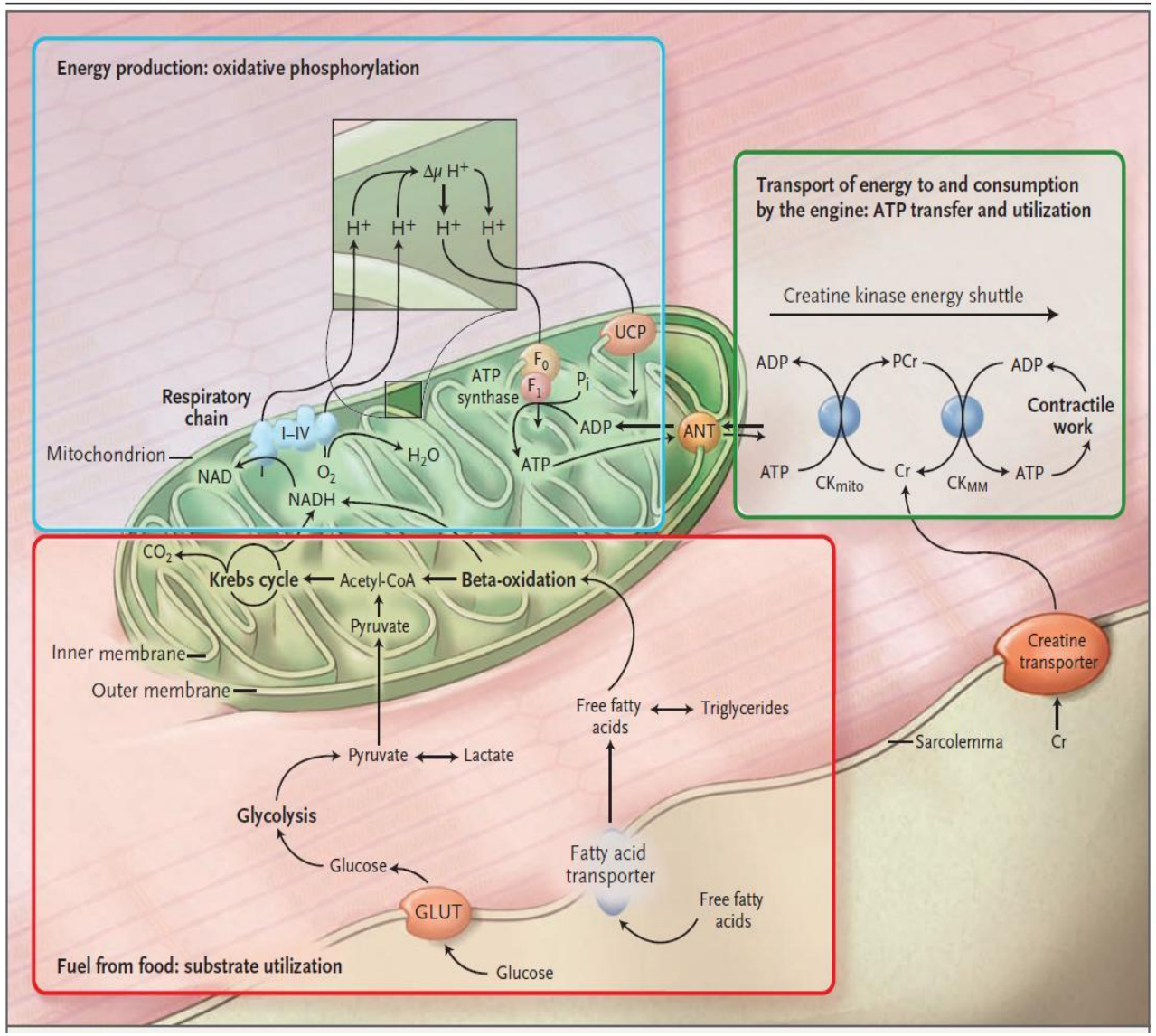


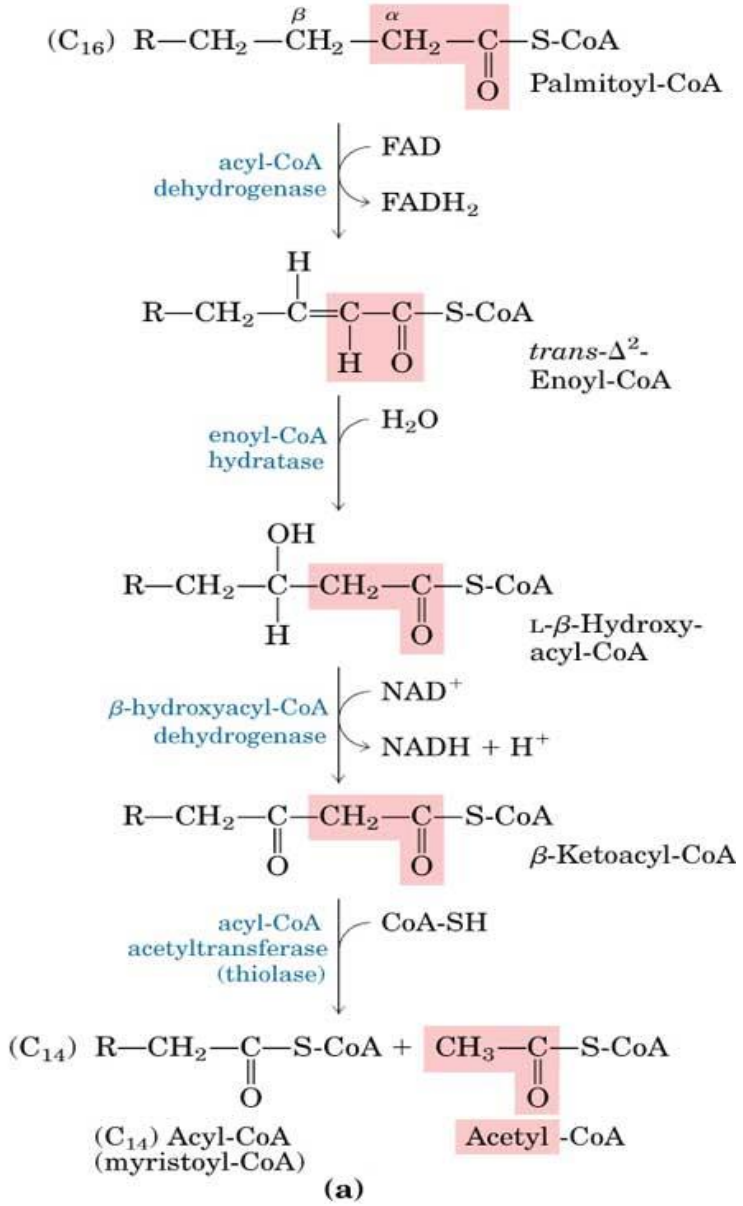
* Linoleic acid (C18:2ω6) & linolenic acid (C18:3ω3)

Abbreviations : TG = triglycerides ; CE = Cholesterol esters ; PL = Phospholipids

2 stages of oxidation:

- Cutting fatty acids into –two carbon fragments - **acetyl-CoA**
- acetyl-CoA oxidation in the Krebs cycle





1. *Dehydrogenene reaction of acyl-CoA by dehydrogenase*
2. *Hydration of 2-enoyl-CoA to 3-hydroxyacyl-CoA by hydratase*
3. *Oxidation 3-hydroxyacyl-CoA to 3-keto-acyl-CoA by dehydrogenase*
4. *As a results of thiolysis, acetyl-CoA and acyl-CoA shorter by 2carbon atoms is formed*

Medium-chain Acyl-CoA Dehydrogenase (MCAD) deficiency

Most frequent disorder of fatty acid oxidation

- Prevalence 1:10.800

Without newborn screening:

- Metabolic crises e.g. during infections with severe hypoglycemia
- 25% fatal outcome in first crisis
- High percentage of survivers severe neurological sequelae

With newborn screening Treatment

- Avoidance of fasting
- High carbohydrate intake in episodes of infections

Outcome

Almost complete prevention of morbidity and mortality by prophylactic treatment

Glutaric aciduria type I

- Prevalance about 1:120.000
- No specific clinical signs
- Macrocephaly
- **Without presymptomatic diagnosis**
- Encephalopathic crisis
- Severe dystonia
- Insidious onset

Glutaric aciduria type I

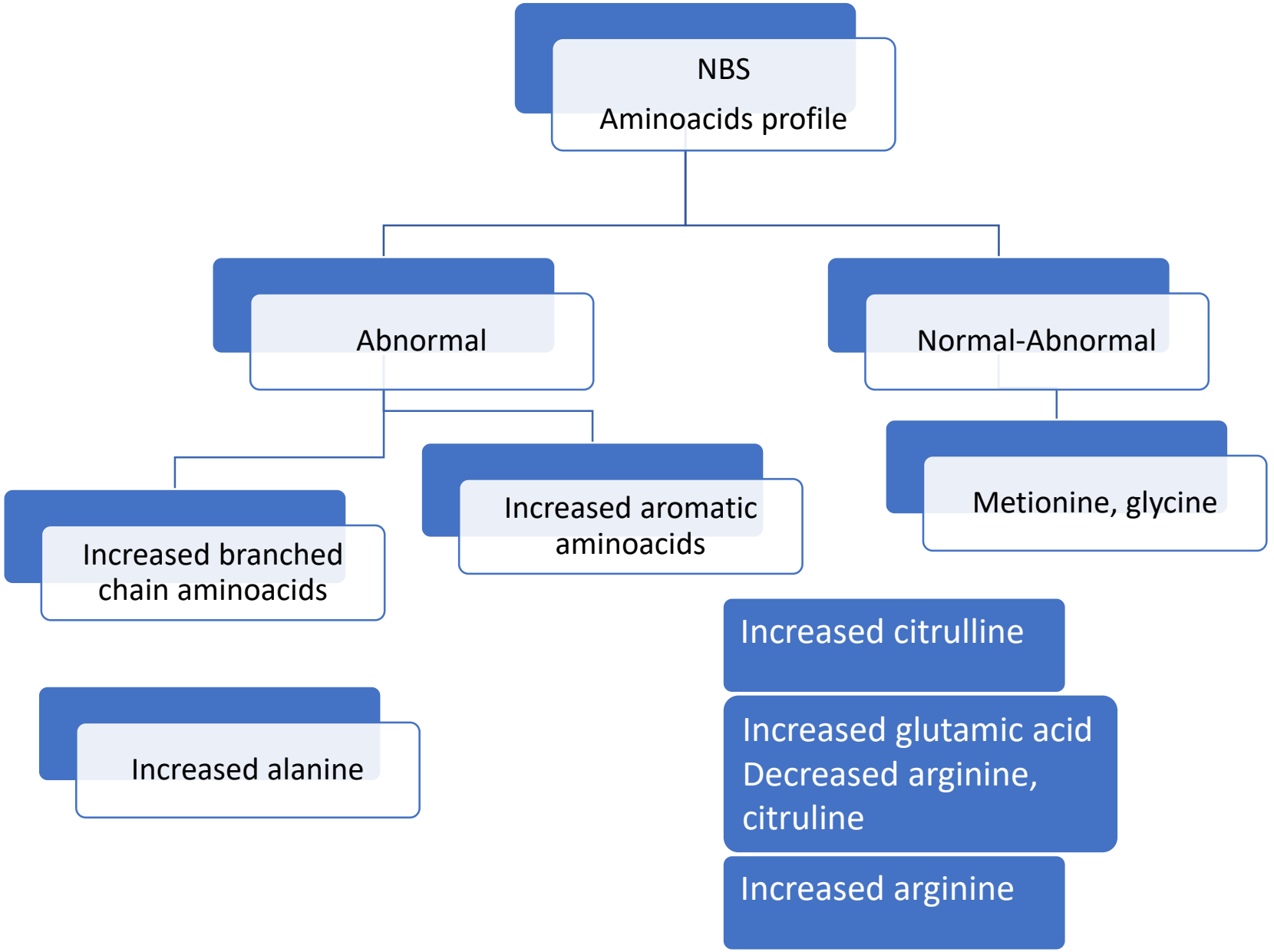
Treatment

- Dietary treatment, carnitine supplementation
- Emergency treatment in episodes of infection

With presymptomatic treatment

- Prevention of encephalopathic crises in 89% of patients
- Adherence to guidelines for basic and emergency
- treatment + supervision by metabolic center improves outcome

Heringer et al. 2010, Ann Neurol


NBS
Aminoacids profile
Abnormal
Normal-Abnormal
Increased branched chain aminoacids
Increased aromatic aminoacids
Metionine, glycine
Increased alanine
Increased citrulline
Increased glutamic acid
Decreased arginine, citruline
Increased arginine

Aromatic amino acids metabolism disorders

Phenylketonuria (PKU)

Microcephaly

- is considered a clinical sign in which the brain doesn’t have normal growth

Definition:

„ occipital frontal head circumference (OFC) is 2 SD less than expected avarage for age, gender and population. The term severe microcephaly is used when the OFC is less than 3 SD from the average”

Pediatric and Neonatology 62 (2021) 354 - 360

AROMATIC AMINO ACIDS metabolism DISORDERS

Disorders of Phenylalanine and Tetrahydrobiopterin (BH4) Metabolism:

- **Hiperphenylalaninemia – disorders of phenylalanine catabolism is caused by:**
  - **PAH deficiency – Phenylketonuria (PKU)**

one of the enzymes involved in cofactor BH4 biosynthesis:

- **GTPCH deficiency**
- **PTPS deficiency**
- **DHPR defciency**
- **PCD deficiency**

Diagnostic work-up

Newborn screening

- part of screening programs in many countries – pathological findings: hyperphenylalaninaemia – exclusion of BH4-deficiency
- pterins (blood/urine)
- DHPR-activity (DBS)

BH4-loading Test

- confirmation/exclusion of BH4-responsive PKU

Hiperphenylalaninemia (HPA)
(aromatic aminoacids metabolism disorders)

- **Disorders of phenylalanine catabolism causing by a deficiency of the hepatic phenylalanine hydroxlase (PAH) or one of the enzymes involved in its cofactor tetrahydrobiopterin (BH4) biosynthesis (GTPCH I – GTP cyclohydrolase, 6-pyruvoyl-tetrahydropterin synthase - PTPS) or regenaration (dihydropteridine reductase – DHPR and pterin -4-a-carbinolamine dehydratase – PCD).**

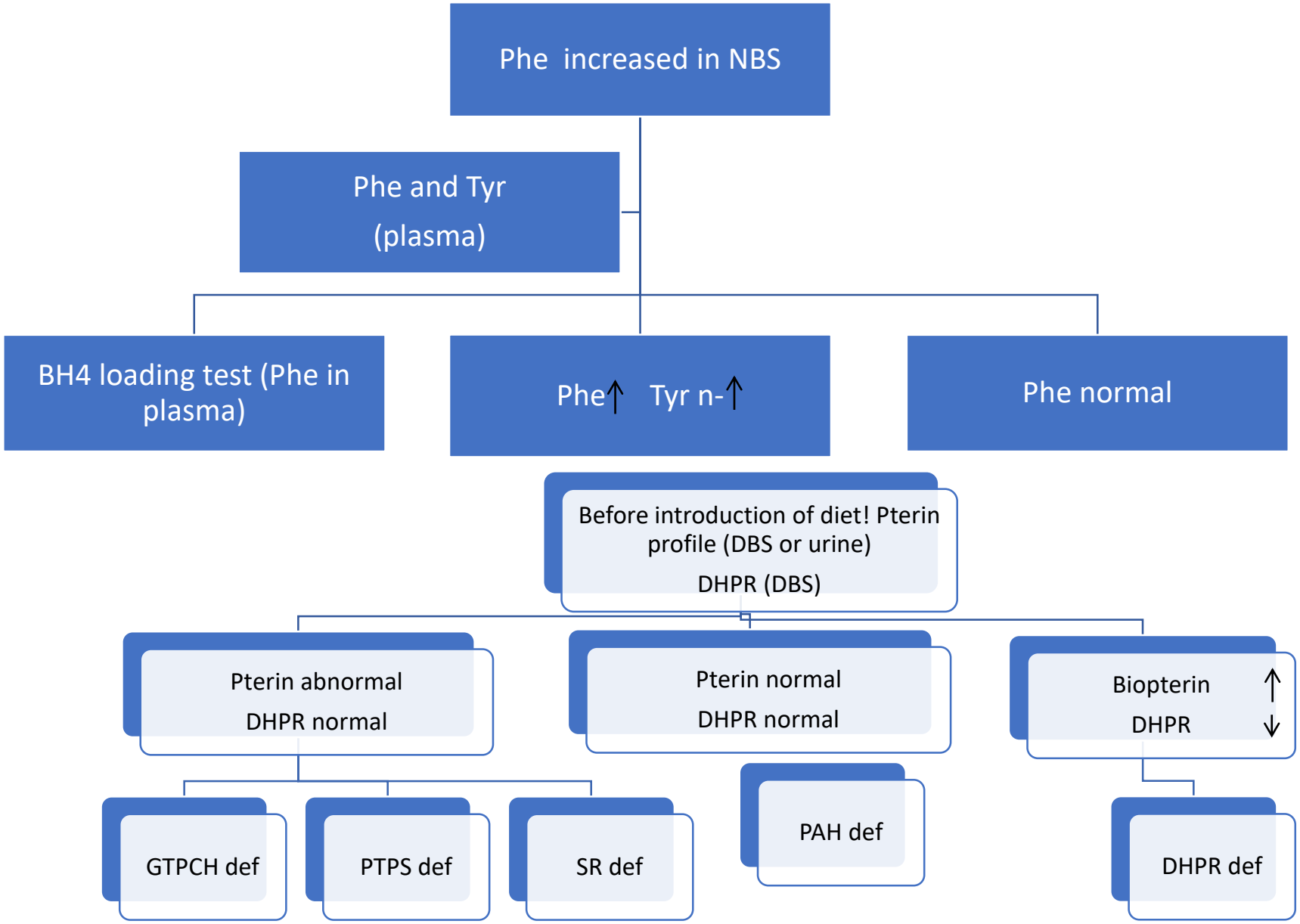
- **Two groups of HPA (PAH and BH4 deficiency) are heterogeneous disorders varying from severe (classical PKU) , to mild and benign forms.**

- **For the BH4 defects clinical symptoms may manifest during the first weeks of life but usually are noted within the first half year of life.**

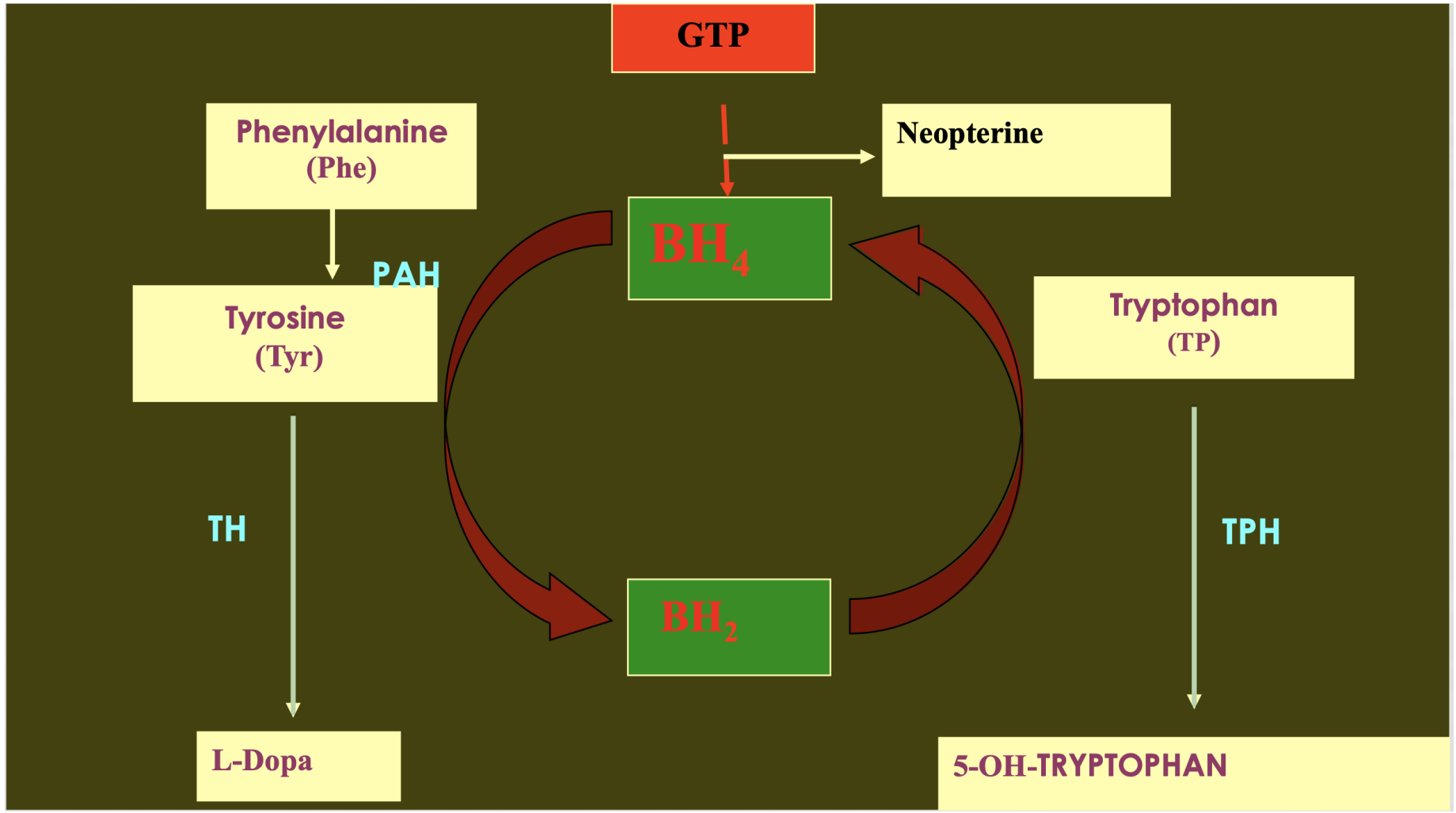
- **Two disorders of BH4 metabolism may present without HPA (dopa-responsive dystonia – GTPCH autosomal dominant manner, and SR – sepiapterin reductase).**

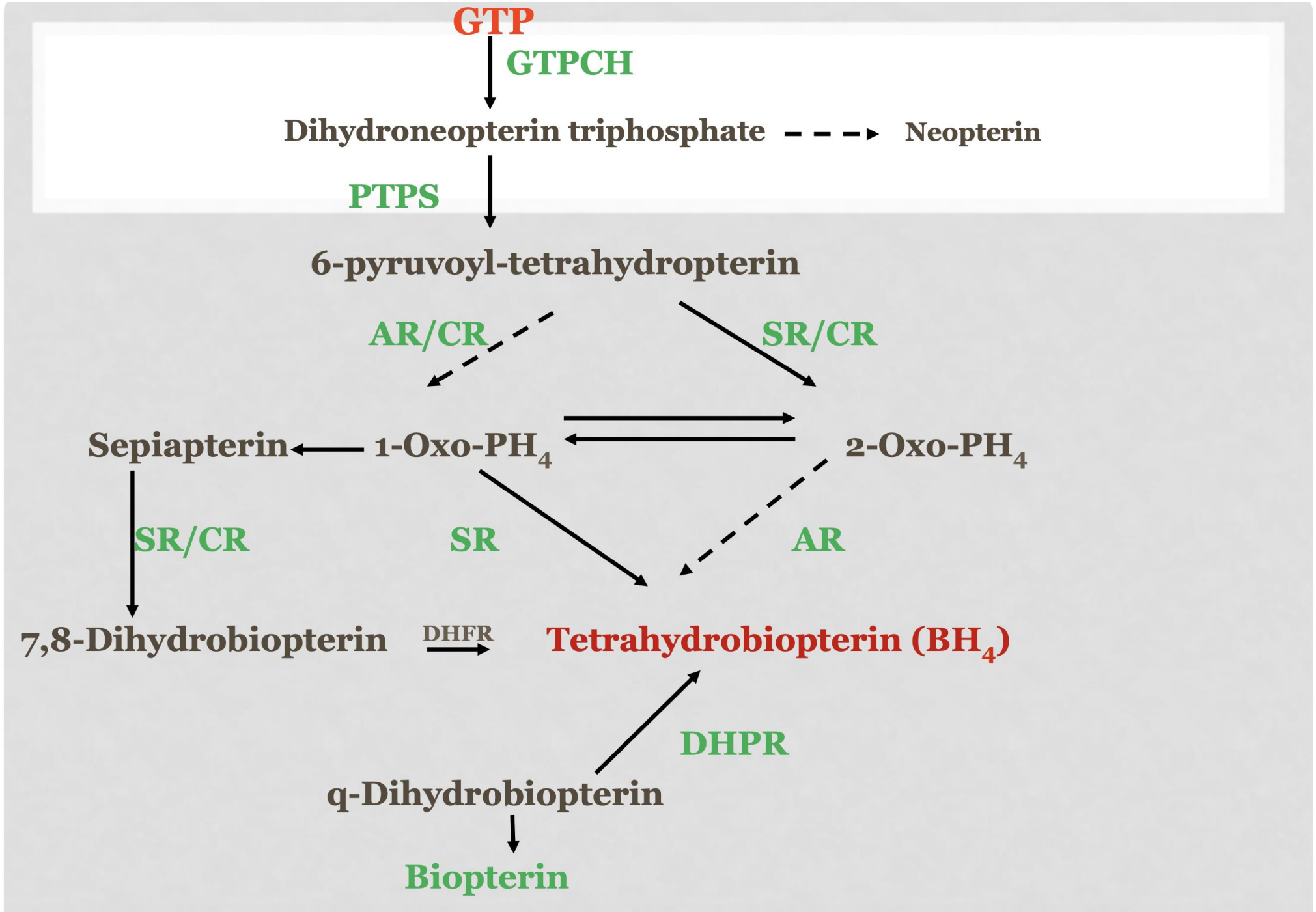
Diagnosis of HPA

- Confirmation of an elevated blood Phe level obtained on a normal diet, following a positive NBS test.
- Using quantitative test enable the differentiation between BH4 – responsive PKU and BH4 deficiency.
- BH4 deficiency – analysis pterin (biopterin and neopterin) profile in urine or blood spot
- Amino acids profile in plasma
- Late detection of PAH or BH4 deficiencies and late introduction of treatment lead to irreversible brain damage.


Phe increased in NBS
Phe and Tyr (plasma)
BH4 loading test (Phe in plasma)
Phe↑ Tyr n-↑
Phe normal
Before introduction of diet! Pterin profile (DBS or urine)
DHPR (DBS)
Pterin abnormal
DHPR normal
Pterin normal
DHPR normal
Biopterin ↑
DHPR ↓
GTPCH def
PTPS def
SR def
PAH def
DHPR def

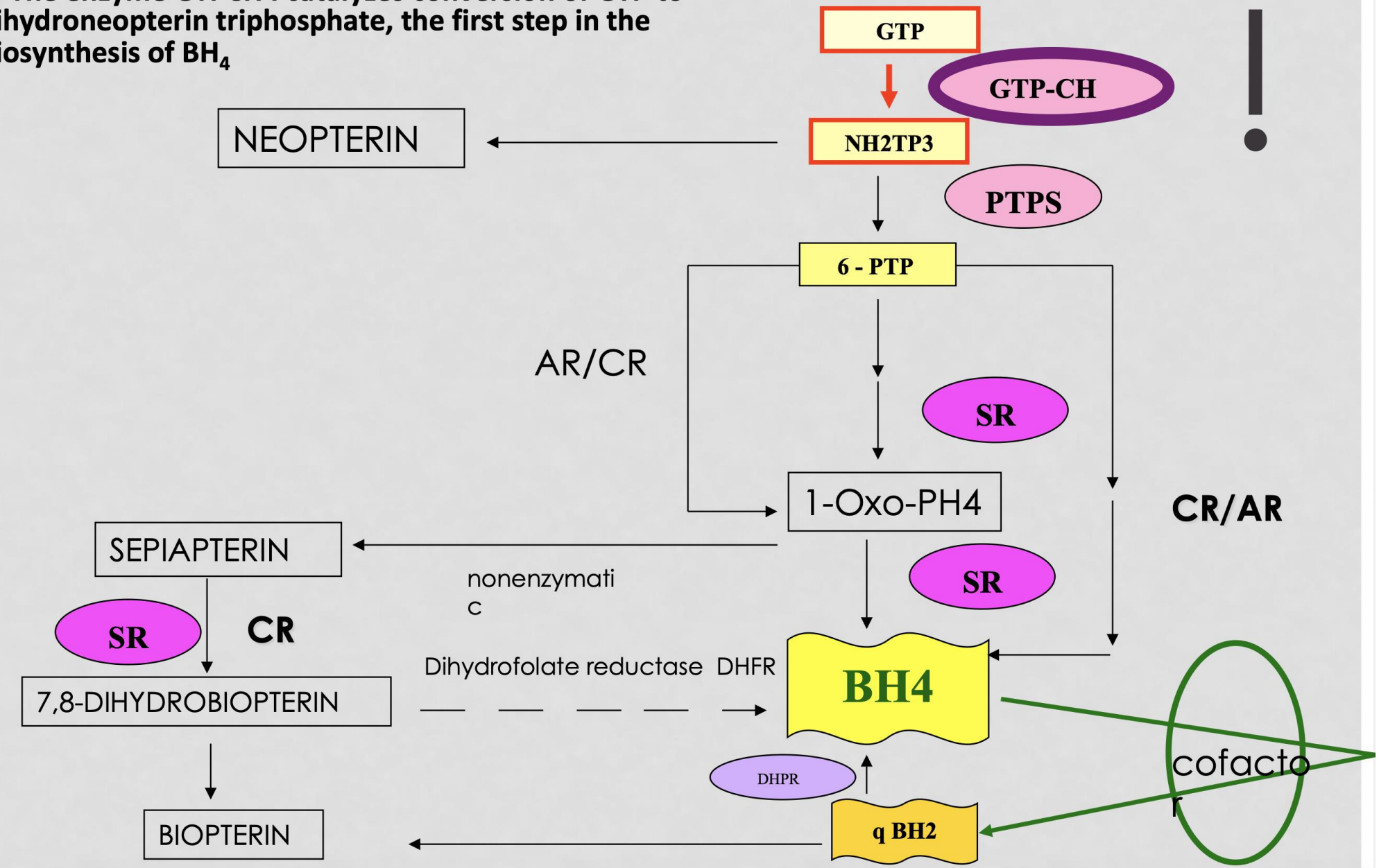
PHENYLALANINE METABOLISM




GTP
GTPCH
Dihydroneopterin triphosphate
Neopterin
PTPS
6-pyruvoyl-tetrahydropterin
AR/CR
SR/CR
Sepiapterin
1-Oxo-PH4
2-Oxo-PH4
SR/CR
SR
AR
7,8-Dihydrobiopterin
DHFR
Tetrahydrobiopterin (BH4)
DHPR
q-Dihydrobiopterin
Biopterin

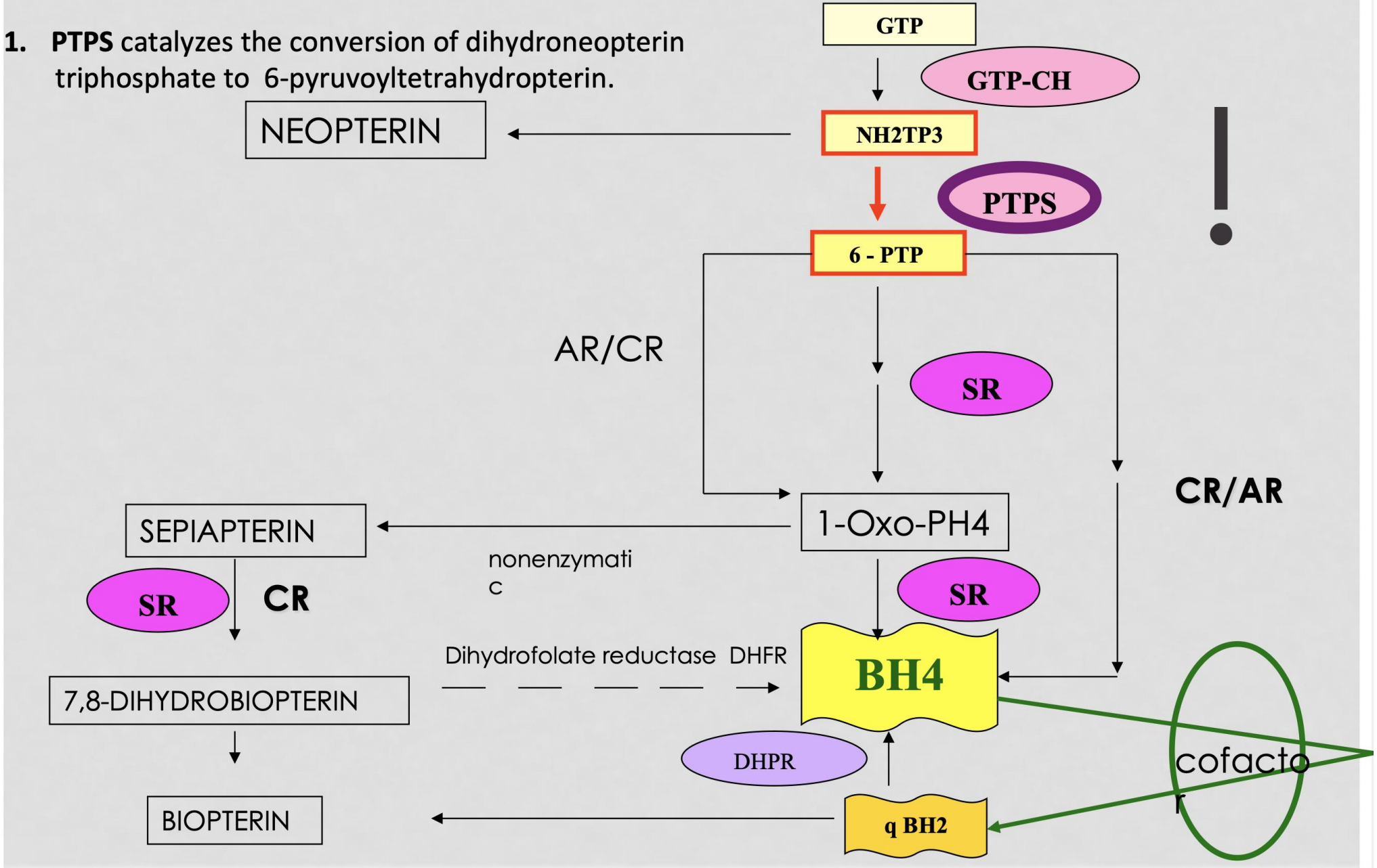
GUANOSINE TRIPHOSPHATE (GTP) CYCLOHYDROLASE I DEFICIENCY (GTPCH I)

1. The enzyme GTPCH I catalyzes conversion of GTP to dihydroneopterin triphosphate, the first step in the biosynthesis of BH_4

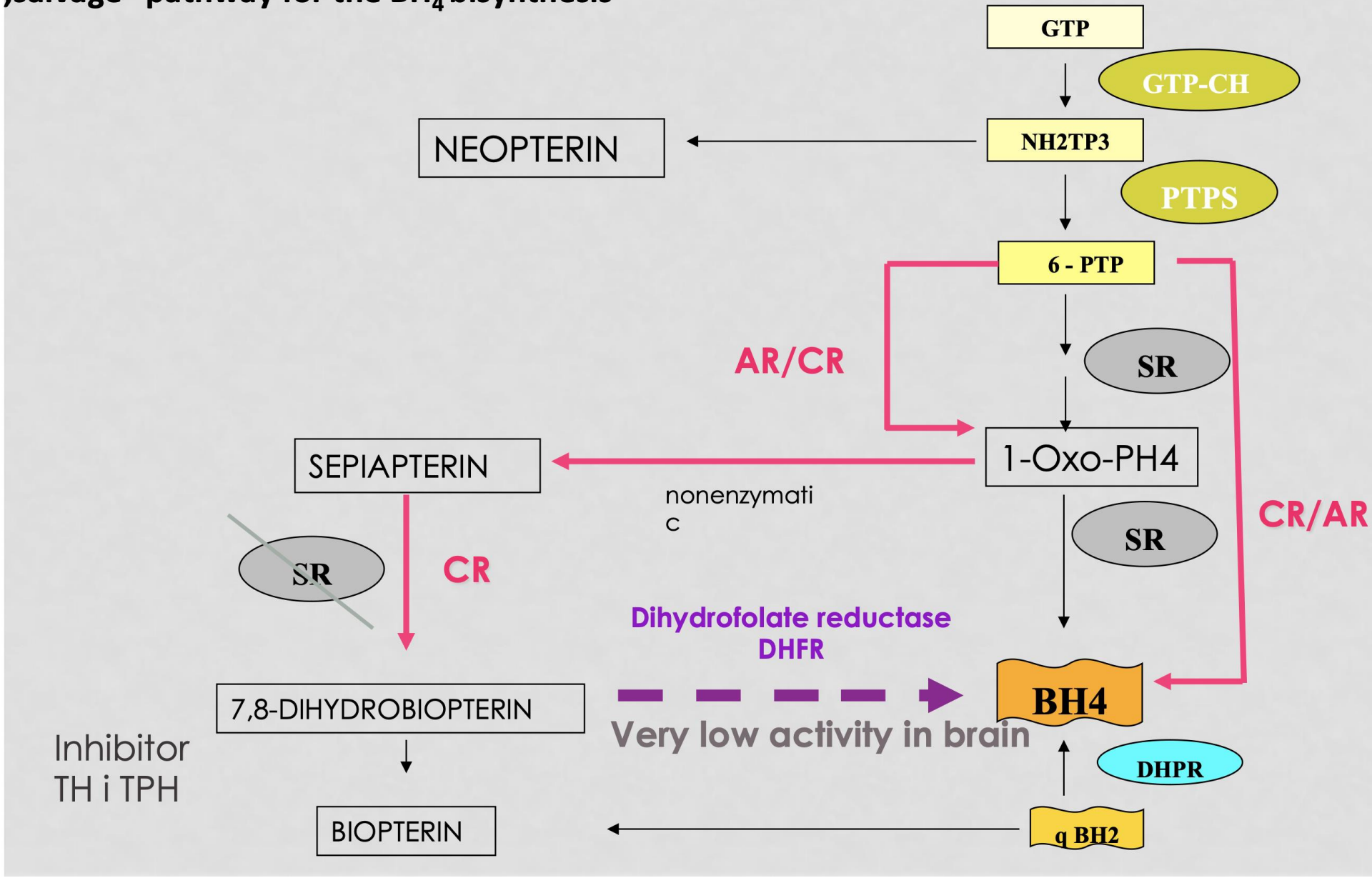


6-PYRUVOYL-TETRAHYDROPTERIN SYNTHASE DEFICIENCY (PTPS)

1. **PTPS** catalyzes the conversion of dihydroneopterin triphosphate to 6-pyruvoyltetrahydropterin.

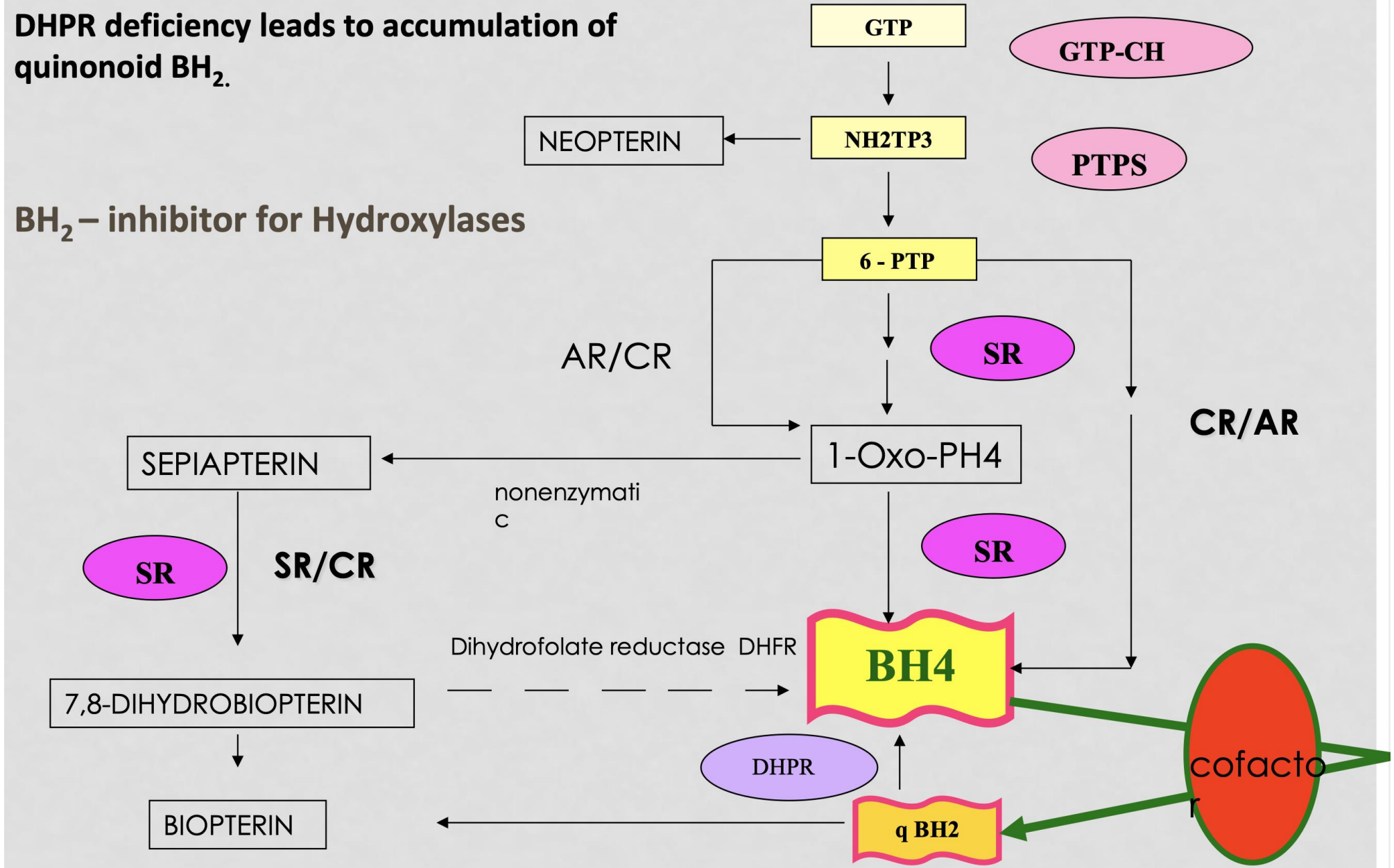


Carbonyl reductase (CR)
Aldose reductase (AR)
‚salvage" pathway for the BH_4 bisynthesis



DIHYDROPTERIDIN REDUCTASE (DHPR)

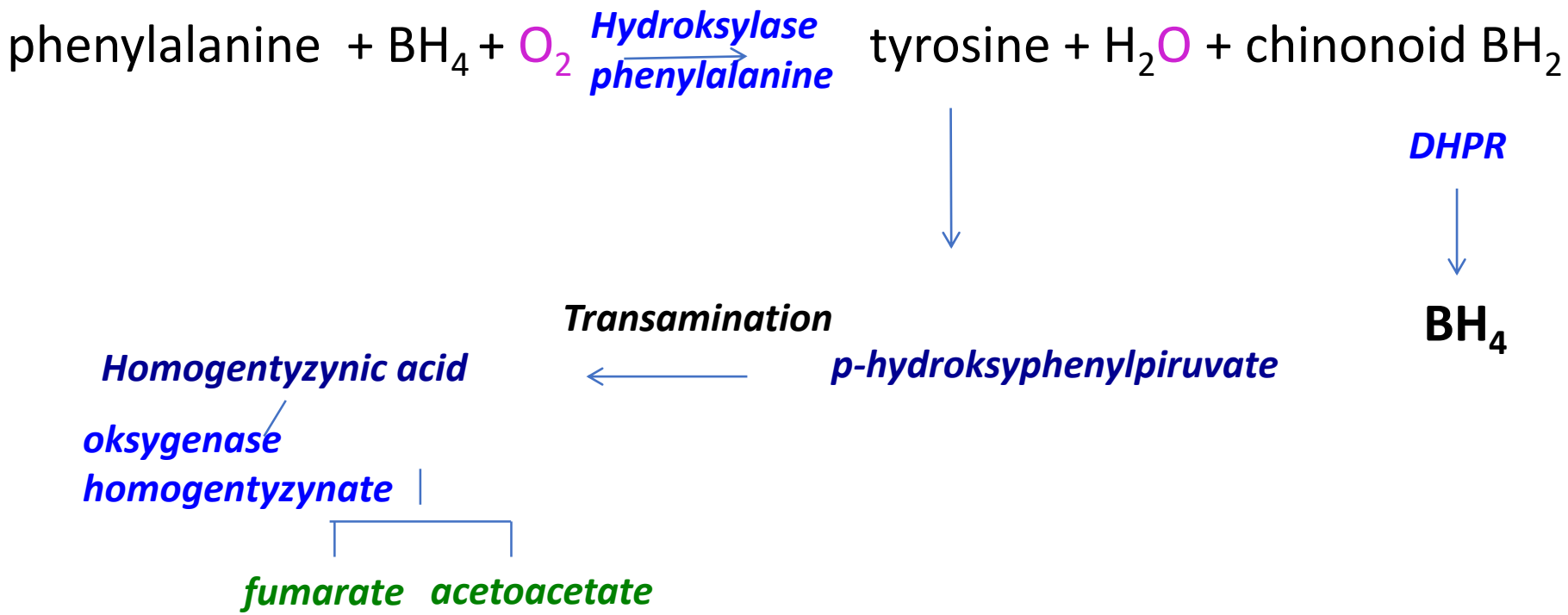
DHPR deficiency leads to accumulation of quinonoid BH_2.



Aromatic amino acids

phenylalanine and tyrosine share an interesting degradation path

molecular oxygen is used to break the aromatic ring



Tyrosinaemia type I

deficiency of the enzyme fumarylacetoacetate hydrolase (FAH)

toxic metabolites: succinylacetone, maleylacetoacetate, fumarylacetoacetate

Clinical presentation

high variability of clinical manifestation

severity correlates with the age at onset of symptoms

Acute form: before 6 months
acute liver failure, sepsis

Subacute form: between 6 months and 1 year
liver disease, coagulopathy, hepatosplenomegaly, rickets, failure to thrive

Chronic form: after first year of life: cirrhosis, hepatocellular carcinoma, renal tubulopathy resulting in hypophosphatasemia rickets, generalized aminoaciduria, tubular acidosis, glycosuria, nephrocalcinosis, porphyria-like neurological crisis, neuropathy, pancreatic cell hypertrophy, cardiomyopathy

Tyrosine metabolism

- The tyrosine degradation pathway includes five enzymatic steps. Inherited disorders have been identified at four of these steps.

- Under normal conditions the concentration of tyrosine is regulated by the first enzyme (tyrosine aminotransferase)

- In tyrosinaemia type I, the primary defect in the last enzyme of the pathway (fumarylacetoacetase deficiency)

- In NBS tyrosine concentration can be elevated or normal, only present of succinylacetone in blood or urine is the specific for tyrosinemia type I.

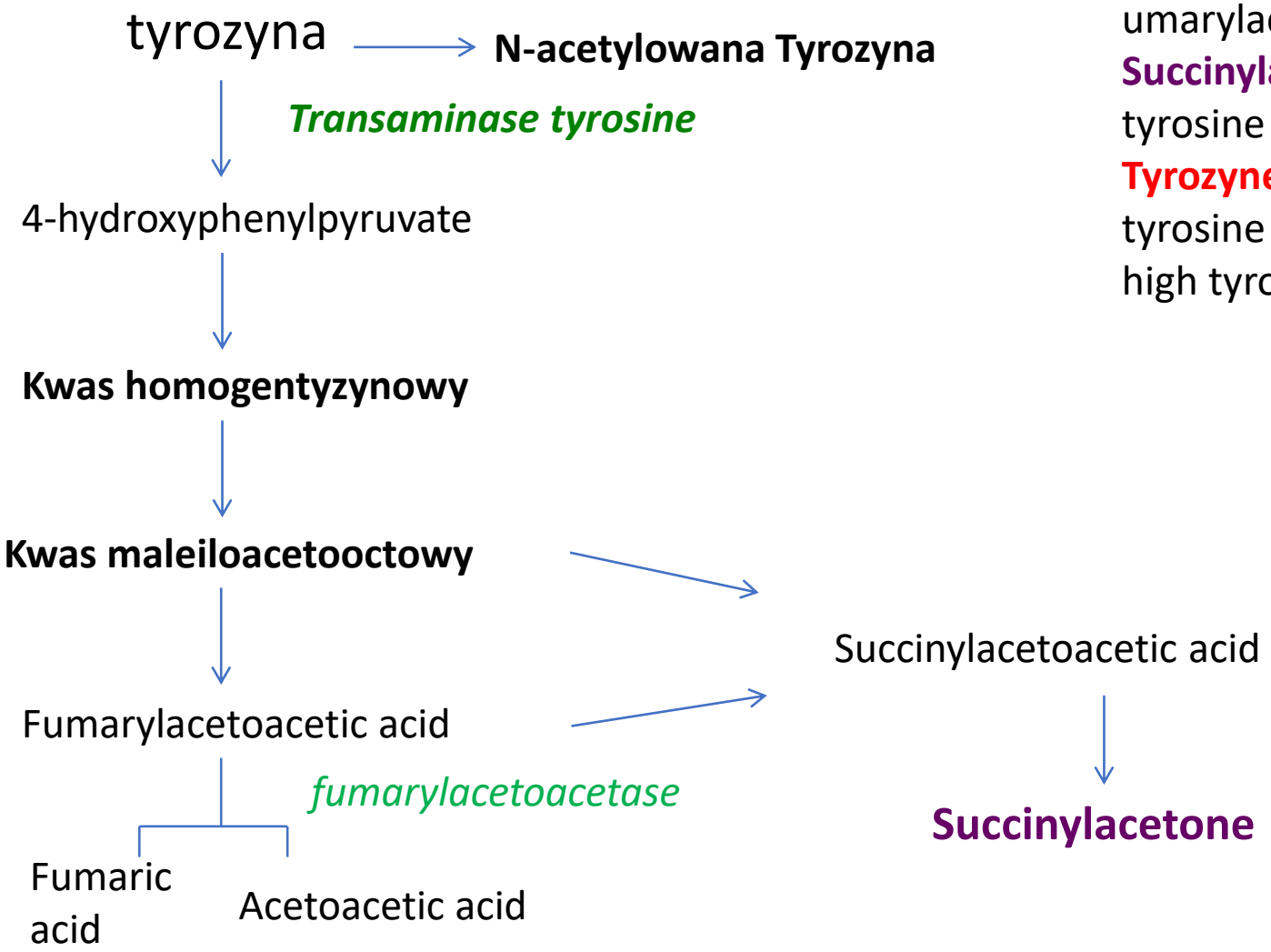
- In tyrosinaemia type II, secand defect in the first enzyme of the pathway (tyrosine aminotransferase deficiency)

- In tyrosninaemia type III, defect of 4-hydroxyphenylpyruvate dioxygenase deficiency

- Hawkinsinuria – rare and incompletely understood disorder, that is characterised by failur e to thrive and acidisis in some affected infants; tyrosine is not good diagnostic marker. The diagnosis is based on identification of hawkinsin (2-cystenyl-1,4-dihydroxycyclohexenylacetate) formed from a reactive tyrosine metabolites that has been detoxified by reaction with glutathion

- Alkaptonuria (homogentisate 1,2-dioxygenase deficiency) – abnormal darkening of urine on standing; homogentisate in urine is main diagnostic marker

Tyrosinemia type I and II



Tyrozynemia typ I –
umarylacetoacetase deficiency, excretion **Succinylacetone,**
tyrosine concentration may be normal.
Tyrozynemia typ II –
tyrosine transaminase deficiency,
high tyrosine concentration

Diagnostic work-up

- **Organic acids (urine)**

  succinylacetone

  elevated concentrations of 4-OH-phenolic acids

- **Amino acid profile (plasma)**

  elevated concentrations of tyrosine, methionine, phenylalanine

- **Newborn screening**

  not part of screening programs in many countries pathological findings: succinylacetone

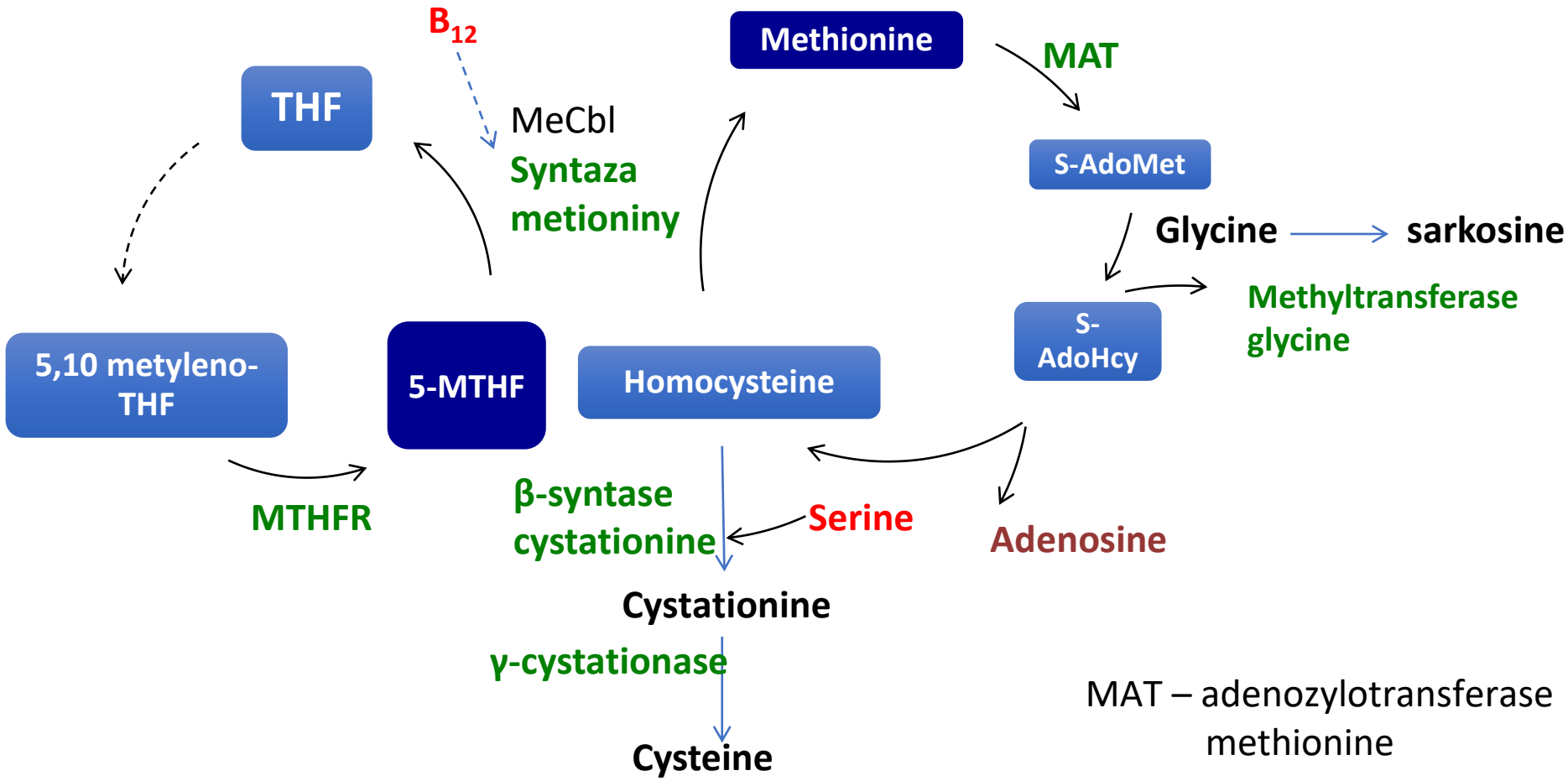
  highly sensitive and specific early detection and early initiation of treatment

Sulphur aminoacids

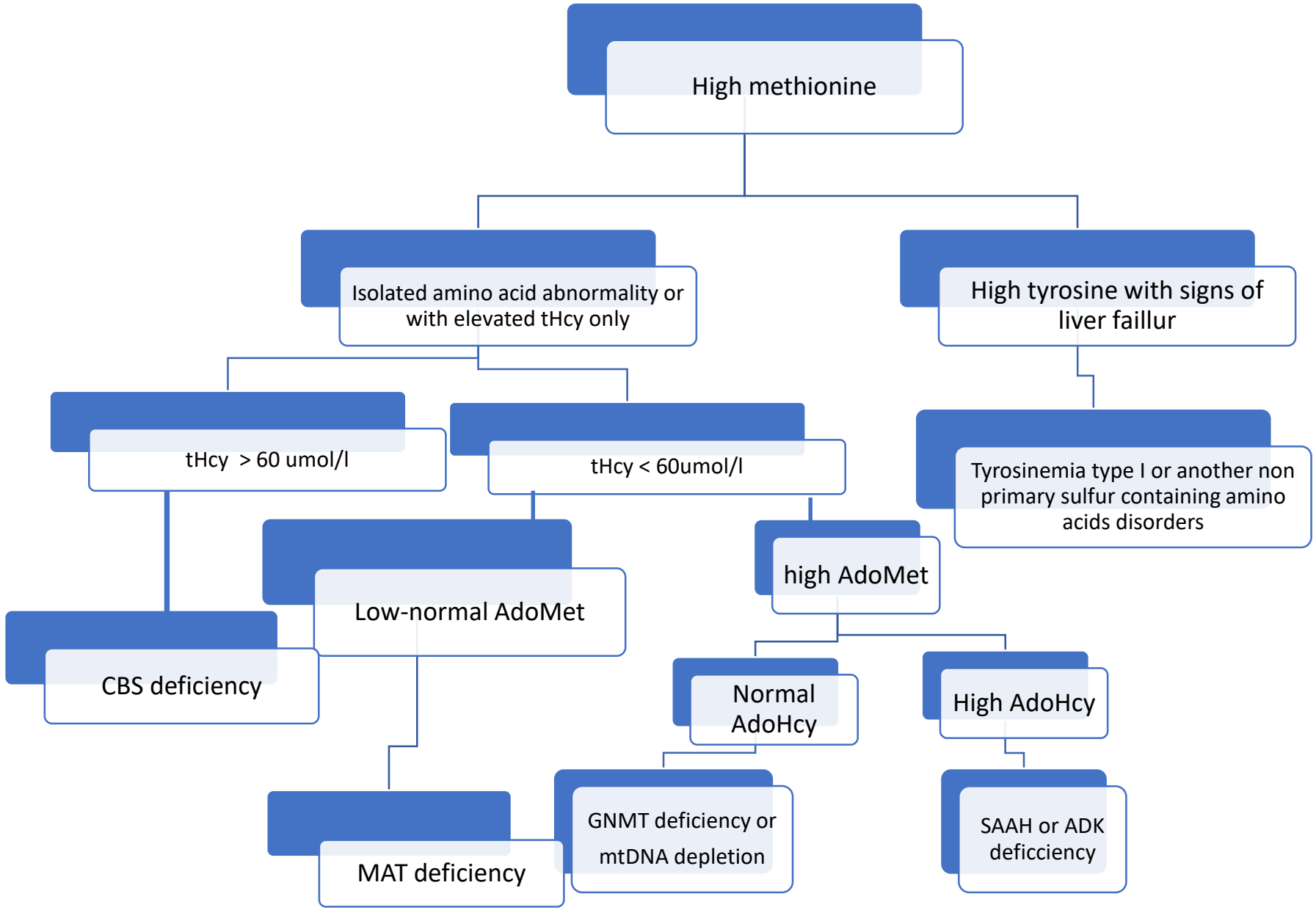
- Sulphur-containing amino acids include methionine, homocysteine, cystathionine, cysteine and taurine.

- Related inherited disorders include deficiencies of enzymes in the transsulphuration pathway that converts sulphur from methionine via homocysteine and cysteine to sulphate and in the remetylation of homocysteine to methionine

Cobalamin (B12) in biochemical reactions



MAT – adenozylotransferase methionine


High methionine
Isolated amino acid abnormality or with elevated tHcy only
High tyrosine with signs of liver faillur
tHcy > 60 umol/l
tHcy < 60umol/l
Tyrosinemia type I or another non primary sulfur containing amino acids disorders
Low-normal AdoMet
high AdoMet
CBS deficiency
Normal AdoHcy
High AdoHcy
GNMT deficiency or mtDNA depletion
SAAH or ADK deficciency
MAT deficiency

Inherited metabolic disorders dependent on vitamin B12

- **Homocystynuria:** very high level of Hcy i Met in plasma

  Deficit of β-syntazy cystathionin

  (concentration of Hcy: 100 – 500 umol/L)

  remetylation disorders connected with MTHF reductase deficiency

  (concentration of Hcy: 100 – 250 umol/l)

  Methionine synthase deficiency

  (concentration of Hcy: 100 – 250 umol/l)

  Cobalamin metabolism disorders: CblF, CblC, CblD

  (concentration of Hcy: 100 – 250 umol/l)

- **Folic acid deficiency:** elevated Hcy concentration and normal Met concentration

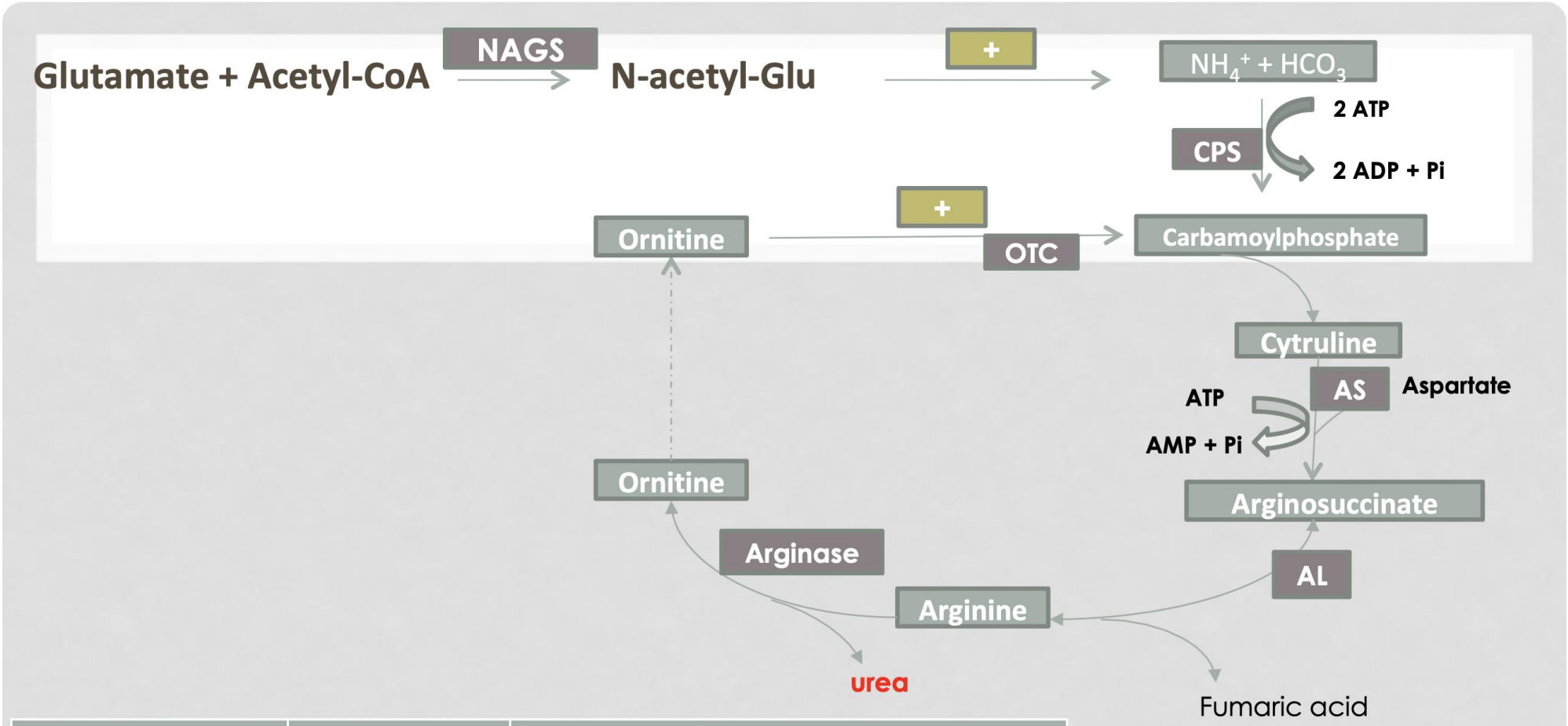
  (concentration of Hcy: 25 – 65 umol/l)

- **Deficyt B_{12}:** increased Hcy concentration

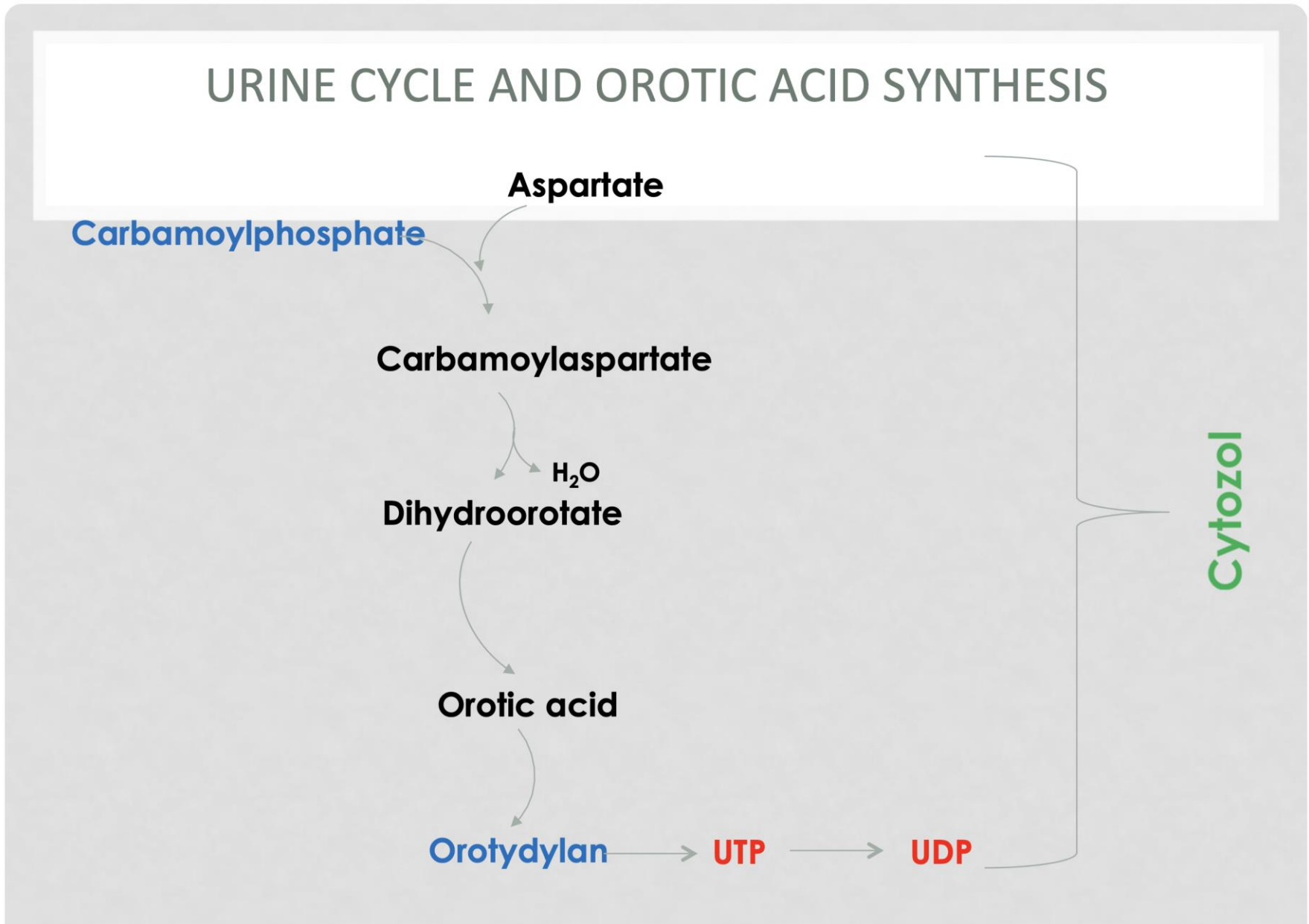
  (concentration of Hcy: 40 – 100 umol/l)

HYPERAMMONEMIAS

- The term hyperammonaemia describes a clinical situation marked by increased plasma ammonia concentration.
- Plasma ammonia exceeds upper normal limits – 100 umol/L in newborns and 50 umol/l in adults children/older individuals.
- Ammonia disposal proceeds mainly by its conversion to urea in the periportal hepatocytes of the liver, followed by urinary urea excretion.
- The periportal hepatocytes are the only cells having all the enzymes of the urea cycle.



ENZYMY	Komórka	Występowanie
NAGS	Mitochondrium	Liver, intestine, spleen, kidneys (trace)
CPS1	Mitochondrium	Liver, intestine, erythrocytes, , kidneys (trace)
OTC	Mitochondrium	Liver, intestine, kidneys (trace)
ASS1	Cytozol	Liver, kidneys fibroblasts, brain (trace)
ASL	Cytozol	Liver, kidneys, brain fibroblasts
Arginaza	Cytozol	Liver, erythrocytes, kidneys, brain (trace), lens


URINE CYCLE AND OROTIC ACID SYNTHESIS
Aspartate
Carbamoylphosphate
Carbamoylaspartate
H_2O
Dihydroorotate
Orotic acid
Orotydylan
UTP
UDP
Cytozol

INHERITED UREA SYNTHESIS DISORDERS

- prevalence 1 : 8000 Frequency of individual enzyme defects in the urea cycle:

- Def.OTC - 1:14000
- Def.CPS - 1:62000
- Def.AS - 1:57000
- Def.AL - 1:70000
- Def. Arginase - 1:363000

Practical points for analysis of plasma ammonia

Consider plasma ammonia determination in every:

- unexplained encephalopathy
- suspected intoxication
- neonatal sepsis

Initial diagnostics

- Basic tests: Glucose, blood gases, electrolytes, crea, AST, ALT, ketones

- Specific „metabolic“ tests

glutamine in blood

citrulline in blood

arginine in blood

argininosuccinic acid in urine

homocitrulline in urine

orotic acid

organic acids

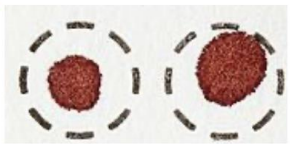
propionylcarnitine

methylmalonylcarnitine

amino acids

organic acids

acylcarnitines



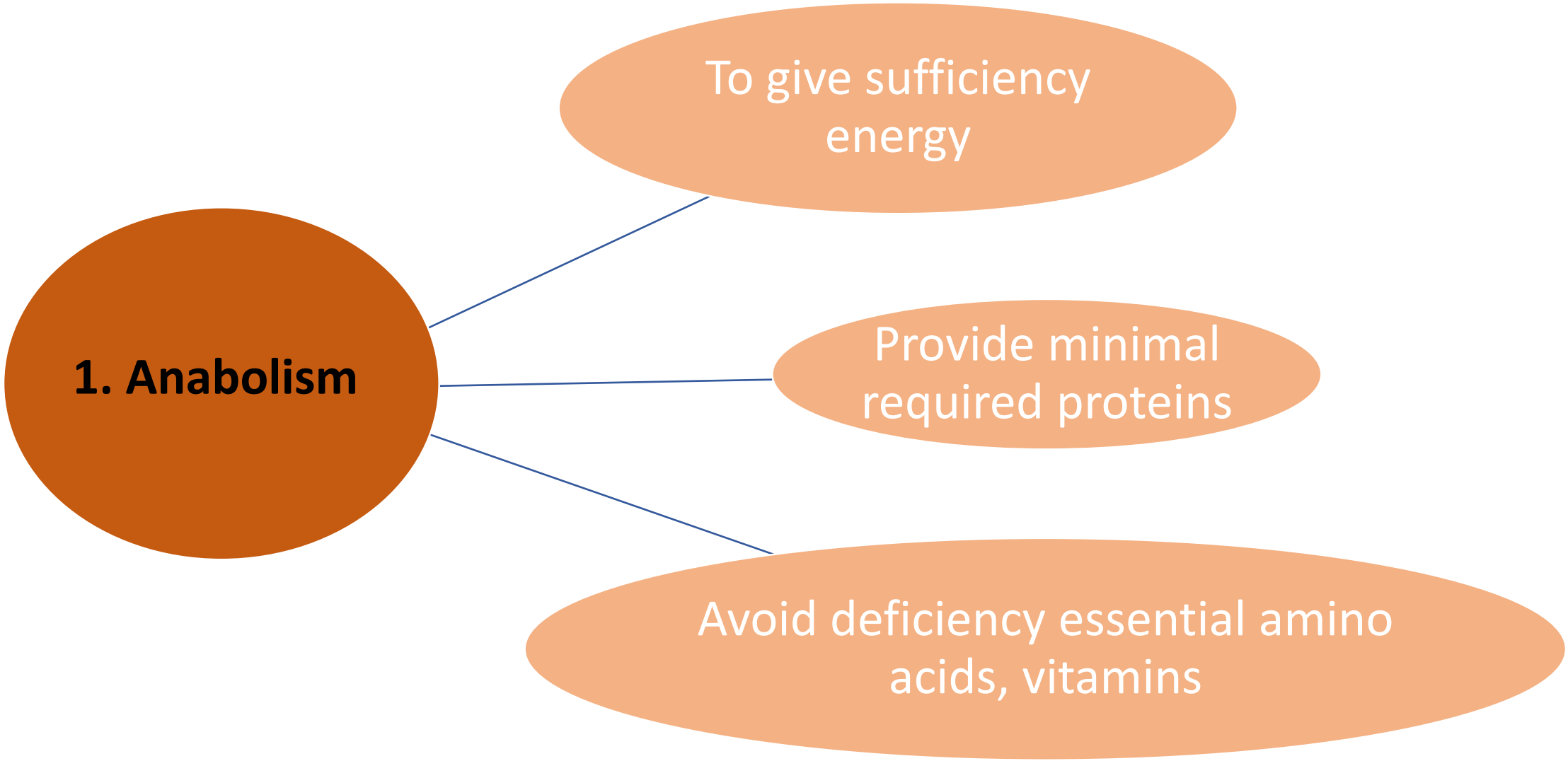
Confirmation of diagnosis

1. Metabolites - ASA for ASL deficiency high citrulline for ASS deficiency

2. Enzyme analysis - ARG deficiency

- 3. Molecular diagnosis - method of choice
  genetic counselling
  prenatal diagnostics

Principles of therapy– 2 main aims



Häberle et al, OJRD, 201
Al-Fadhel et al, Ther Clin Risk Manag, 2016

Principles of therapy– 2 main aims, cd..

2. Ammonia removal

- **Nitrogen scavengers**
- haemodialysis

Häberle et al, OJRD, 201
Al-Fadhel et al, Ther Clin Risk Manag, 2016

Rationale of drug therapy

Nitrogen scavengers:

- sodium benzoate
- sodium phenylbutyrate

Amino acids - to support residual urea cycle function

- Arginine
- Citrulline

Activator - to stimulate first urea cycle enzyme (CPS1)

- carbamylglutamate

detoxification

- When to start???

Immediately if ammonia is 300-500 µmol/L

If no response to drug treatment within 4 hours

- Methods
- First choice: hemo(dia)filtration or hemodialysis
- Peritoneal dialysis: if no first choice method available
- Continue scavenger therapy during dialysis

Häberle et al, OJRD, 2012
Al-Fadhel et al, Ther Clin Risk Manag, 2016

Liver transplantation

- Currently only cure
- Treatment of choice for neonatal onset CPS1 & OTC deficiencies
- Maybe treatment of choice for neonatal onset ASS deficiency
- To be done early = before severe brain damage
- Recommended time point: > 3 months & > 5 kg bw

Häberle et al, OJRD, 201
Al-Fadhel et al, Ther Clin Risk Manag, 2016

Practical key points

- Act immediately to avoid brain damage
- Achieve an anabolic state by providing sufficient energy
- Avoid protein deficiency
- Detoxify ammonia by drugs and/or dialysis
- Some conditions respond to carbamylglutamate
- Consider transfer of patient to metabolic center

Häberle et al, OJRD, 201
Al-Fadhel et al, Ther Clin Risk Manag, 2016