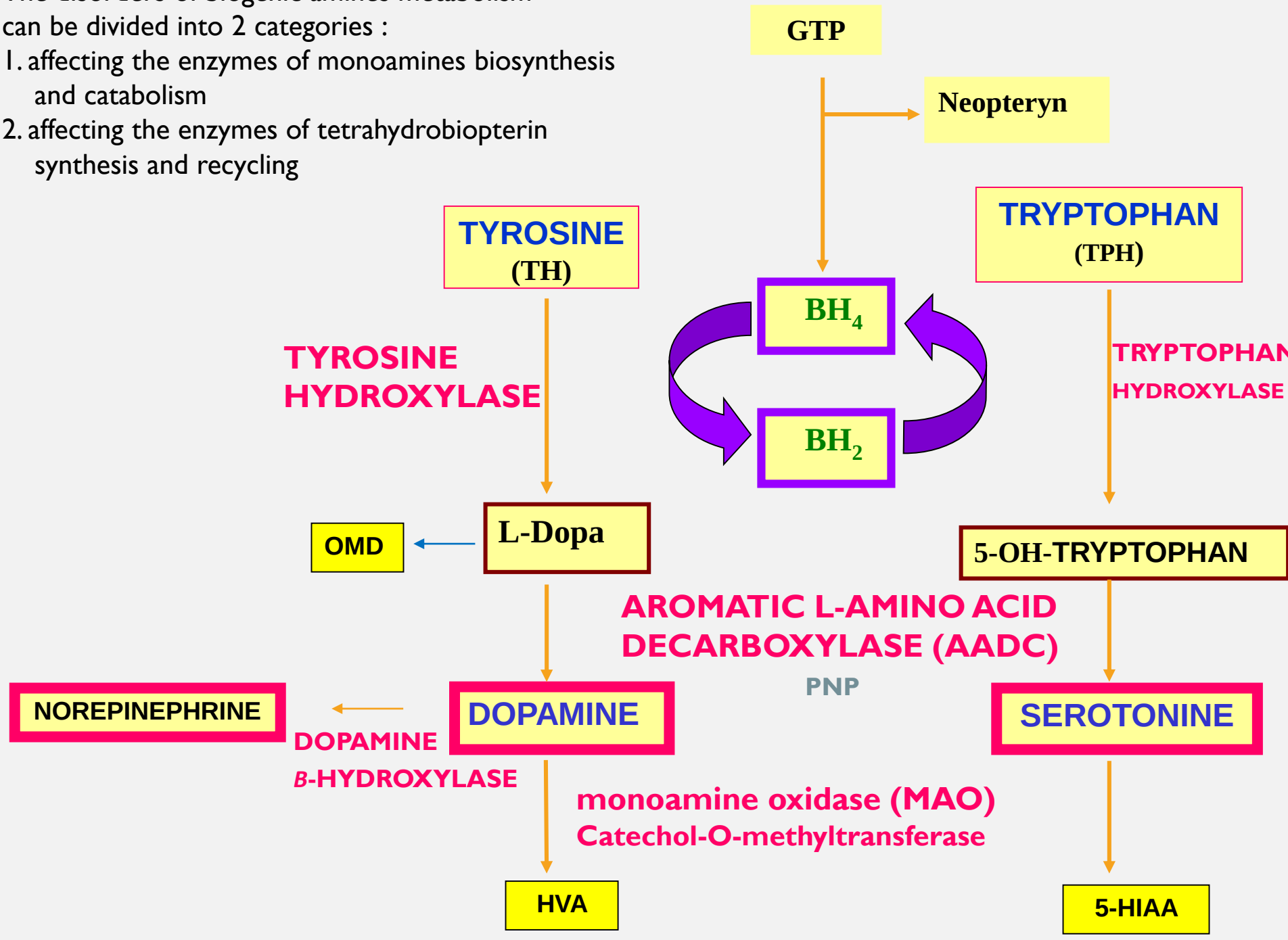
NEUROTRANSMITTERS - BIOGENIC AMINES

Katarzyna Kuśmierska,

The disorders of biogenic amines metabolism can be divided into 2 categories :

1. affecting the enzymes of monoamines biosynthesis and catabolism
2. affecting the enzymes of tetrahydrobiopterin synthesis and recycling



CATECHOLAMINES AND SEROTONIN ARE RELATED TO CENTRAL AND AUTONOMOUS VEGETATIVE NERVOUS SYSTEM FUNCTION HAVING A DIVERSE RANGE OF ACTION.

CATECHOLAMINES (dopamine, norepinephrine and epinephrine):

In the central nervous system they provide control of psychomotor function, being involved in the regulation of motor coordination and processing of sensory input.

Peripherally - involve the regulation of vascular tone and blood flow.

SEROTONIN:

Centrally, serotonin provides control of emotional stability, memory, appetite, mood, sleep.

Peripherally, the controle of thermoregulation.

CLINICAL SYMTOMS:

EARLY SIGNS

movement disorder with early onset truncal hypotonia; peripheral hypotonia/hypertonia, eye movement abnormalities

EXTRAPYRAMIDAL SYMPTOMS

parkinsonian signs (rigidity, tremor, bradykinesia, masked facies),

dystonia (Segawa dopa-responsive dystonia – diurnal fluctuation);

PERIODIC EPISODES

oculogyric crises, paroxysmal movements, paroxysmal general hypertonia

PSYCHIATRIC/BEHAVIORAL SYMPTOMS
irritability, depression, mental retardation

SLEEP DISTURBANCE
hypersomnolence, difficulty maintaining sleep

AUTONOMIC SYMPTOMS
temperature instability, gastrointestinal symptoms , excessive drooling,

DIURNAL FLUCTUATIONS

THE CLINICAL DIAGNOSIS OF INHERITED NEUROTRANSMITTERS DISORDERS IS VERY DIFFICULT
AND NEEDS BIOCHEMICAL FINDINGS LIKE A BIOGENIC AMINE METABOLITES

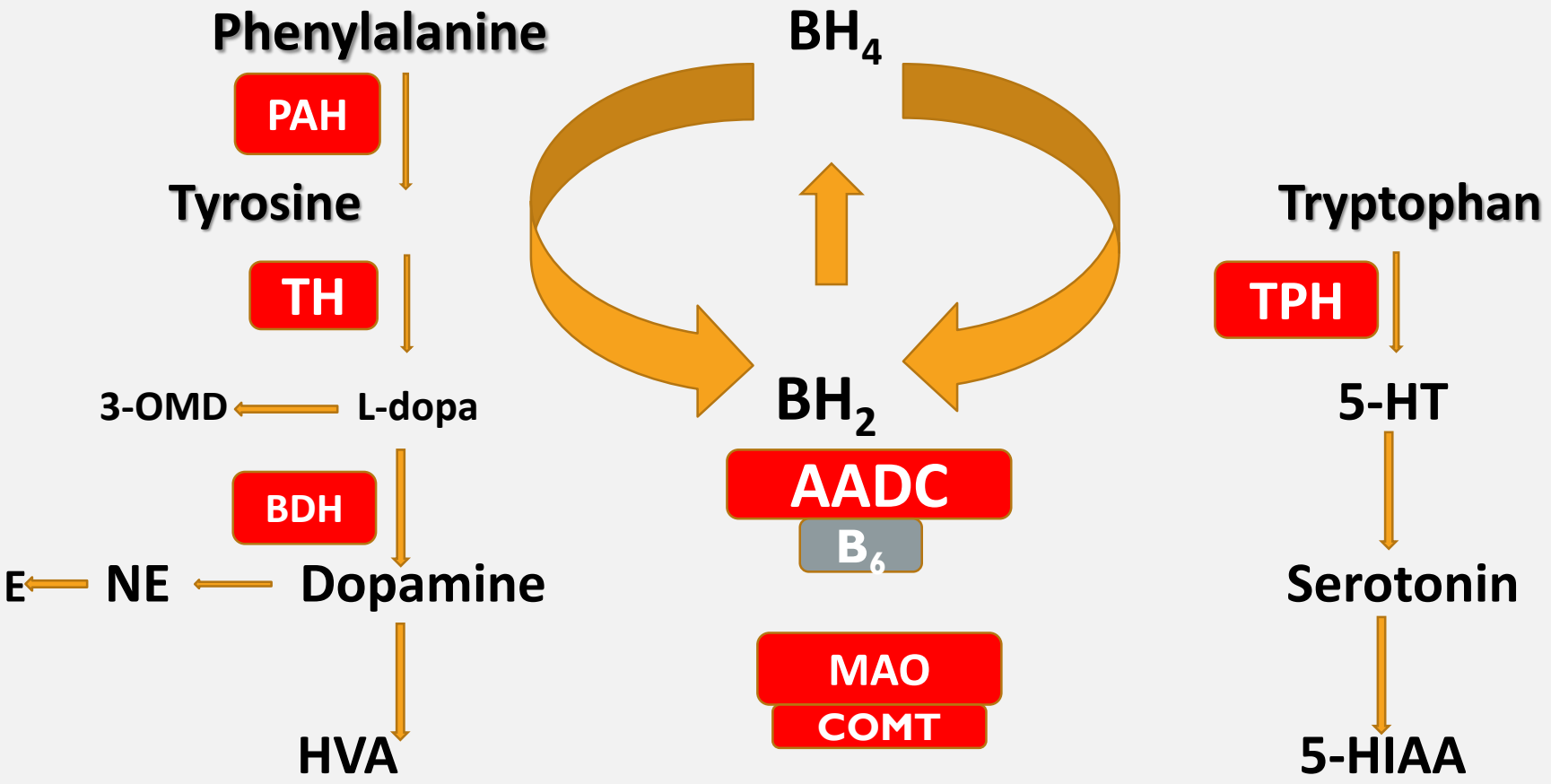
The investigation of biogenic amines metabolism is complicated
because
biochemical findings in peripheral fluids are generally uninformative

Analysis of biogenic amines metabolism requires

LUMBAR PUNCTURE

THE MAJOR METABOLITES OF BIOGENIC AMINES THAT APPEAR IN CSF:

- **homovanillic acid** (HVA) for dopamine metabolism,
- **5-hydroxyindoloacetic acid** (5-HIAA) for serotonin metabolism,
- **3-O-methyldopa** (3-OMD) as diagnostic metabolite of l-dopa.
- **Methyl-OH-phenylglicol** (MHPG) for norepinephrine metabolism



Disorders of biogenic amines metabolism include the deficiencies of

1. Tyrosine hydroxylase (TH)
2. Aromatic L-amino acid decarboxylase (AADC)
3. Dopamine β-hydroxylase (DBH)
4. Monoamine oxidase (MAO)
5. Catechol – O – methyltransferase (COMPT)

Tetrahydrobiopterin (BH_4) metabolism disorders

BH_4 IS ESSENTIAL COFACTOR FOR

BOTH TYROSINE AND TRYPTOPHAN HYDROXYLASES,

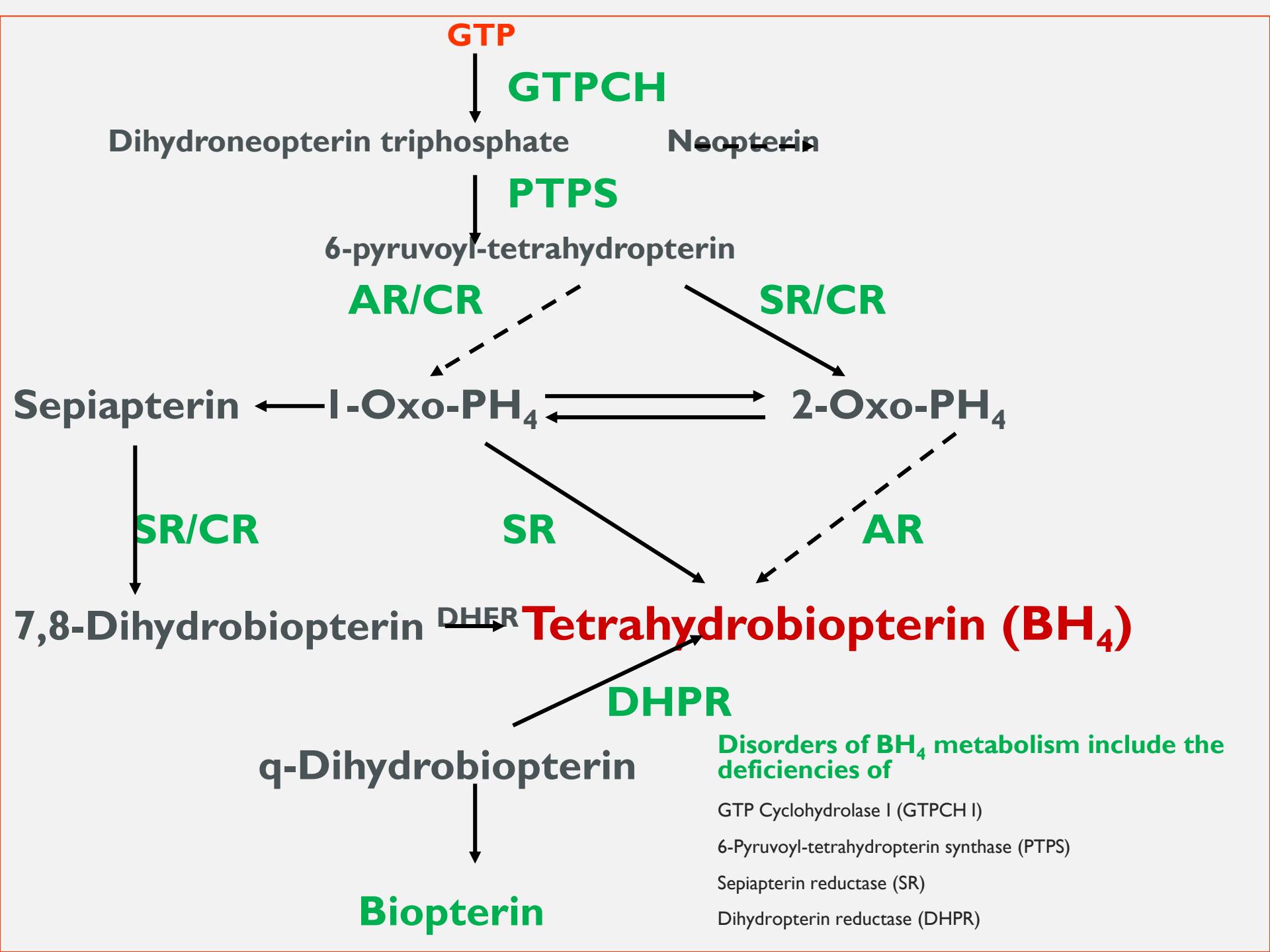
THE RATE – LIMITING ENZYMES IN THE BIOSYNTHESIS OF

DOPAMINE and **SEROTONIN**

TETRAHYDROBIOPTERIN (BH4) DEFICIENCIE CONTAINS A HETEROGENOUS GROUP OF DISORDERS CAUSED BY MUTATION IN ONE OF THE GENES ENCODING ENZYMES INVOLVED IN THE BIOSYNTHESIS OR REGENERATION OF BH4

THESE DISORDERS CAUSE

MONOAMINE NEUROTRANSMITTER DEFICIENCY



Disorders of BH_4 metabolism include the deficiencies of

GTP Cyclohydrolase I (GTPCH I)

6-Pyruvoyl-tetrahydropterin synthase (PTPS)

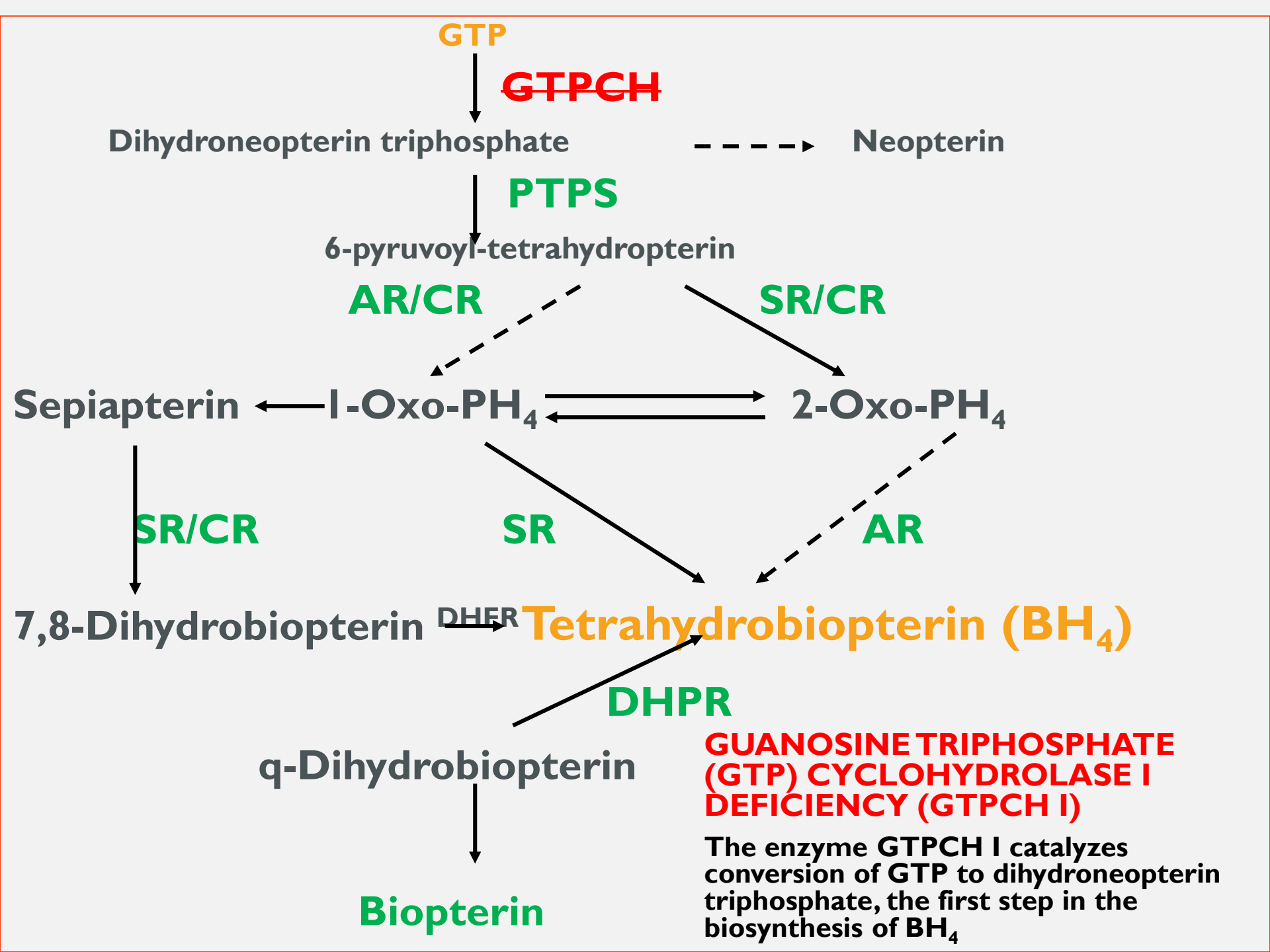
Sepiapterin reductase (SR)

Dihydropterin reductase (DHPR)

The enzymes deficiency lead to abnormal pattern of metabolites of monoamines and pterins

Metabolities / Enzymes	BH_4	BH_2	Neop	HVA	5HIAA	3OMD	MHPG
GTP -CH	↓↓	↓	↓	↓↓	↓↓	↓	↓↓
PTPS	↓↓	↓	↑	↓↓	↓↓	↓	↓
SR	↓	N-↑	N	↓↓↓	↓↓↓	↓	↓
DHPR	↓↓	↑↑	N-↑	↓↓	↓↓↓	↓	↓
TH	N	N	N	↓↓↓	N-↓	↓↓↓	↓↓
AADC	N	N	N	↓↓↓	↓↓↓	↑↑↑	↓

Biogenic amine enzymes, metabolites of catecholamine and serotonin and pterin profile.



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

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

GTPCH deficiency occurs in autosomal recessive (AR)

and

autosomal dominant (AD) forms

AR form presents with complex neurological disfunction, icluding global developmental delay, spasticity and seizures

AD form presents as Dopa-responsive dystonia (DRD)

Patients with AR form are usually recognized because of HPA

(elevated Phe cocentration in blood is typically evident on routine newborn screening)

HPA has never been reported in any patient with dominantly inherited GTPCH deficiency

BH4 DEFICIENCY WITHOUT HPA

CYKLOHYDROLASE GTP - GTP-CH I (AD!!!)

REDUCTASE SEPIAPTERIN– SR

- DYSTONIA (LOWER LIMBS, torso, UPPERS LIMBS, NECK)
- PARKINSONISM (tremor, muscle stiffness, bradykinesia, limitation of movements, hypommia)
- Oculogyric crisis(ONLY SR)
- COGNITIVE DELAY (ONLY SR)

GTP CH I (AD)

SEGAWA DYSTONIA
L-DOPA RESPONSIVE DYSTONIA

GTP CH I DEFICIENCY

AD – MUTATION IN ONE ALLELE

- SYMPTOMS MOST COMMON 4-10 years of age
- THEY MAY APPEAR FROM I TO 80 YEARS OF AGE.
- USUALLY LOWER LIMB DYSTONIA
- GOOD RESPONSE TO L-DOPA

AR – COMPOUND HETEROZYGOTE/HOMOZYGOTE

- HYPERPHENYLALANINEMIA + SYMPTOMS FROM I MONTHS
- REQUIRES COMPLEX TREATMENT BH4, L-DOPA, 5-HTP,

E.M. UR. 1983 (23 LATA)

- SEAT 6/12
- standing by the furniture 10/12
- walking near furniture 14/12 and begins to walk independently (walks unsteadily)
- rehabilitation from 2 y – without good results
- At the age 3rd she started walking on tiptoe

E.M. UR. 1983 (23 LATA)

- 4 yrs – Achilles tendon lengthening surgery
- 4-5 yrs . she doesn't walk, she starts sitting unsteadily;

- in a psychological examination at the age of 5 - normal

E.M. UR. 1983 (23 LATA)

- 9 – 10 yrs poor head stabilization, cannot sit independently
- problems with fine motor skills
- micturition disorders (urinary incontinence)

E.M. UR. 1983 (23 LATA)

- 11 – 12 years the best student in the class, she writes on the computer, she cannot stabilize her head
- 18 years – very painful periodic tension, muscle stiffness
- 19 years – speech disorders, swallowing disorders, excessive salivation

E.M. UR. 1983 (23 LATA)

- 20 years – intestinal peristalsis disorders, constipation, difficulties in eating, increasing cachexia

- **DIURNAL FLUCTUATION**

E.M. UR. 1983 (23 LATA)

- MRI BRAIN – normal
- AMINO ACIDS, ORGANIC ACIDS, LACTATE - normal
- EMG - normal

E.M. UR. 1983 (23 LATA)

21 yrs – First visit

- cachexia, permanent contractures in the feet,

- swallowing disorders, salivation
- dysarthric speech, temporary breathing difficulties

E.M. UR. 1983 (23 LATA)

- muscle stiffness, cogwheel, tremors, muscle jerks
- lack of deep reflexes

EXTRAPYRAMIDAL SYNDROM

Biochemical findings for the patient with GTPCH deficiency (AD)

	Before treatment (17 y)	Reference range
BA metabolites		
HVA [nmol/L] (CSF)	32	100 – 600
5-HIAA [nmol/L](CSF)	12	50 – 400
3-OMD [nmol/L] (CSF)	nd	< 50
Pterins (*)		
Bio [nmol/L] (CSF)	3,2	11 – 41
Neo [nmol/L] (CSF)	0,5	4,1 – 35
BH_2 [nmol/L] (CSF)	not analysis	
Sepiapterin	not analysis	
Prolactine	14	2,7 – 19,7
Phenylalanine loading test	**ABNORMAL**	
Response to l-dopa treatment	**Excellent**	

Summary

GTPCH deficiency presents with:

- abnormal concentration of biogenic amine metabolites in CSF
- abnormal profil of pterin in CSF

(very low concentration of neopterin and biopterin)

- abnormal phenylalanine loading test

GTPCH deficiency occurs in two forms: autosomal recessive and autosomal dominate

GTPCH deficiency presents with HPA (AR) and without HPA (AD)

Inherited PTPS deficiency is a heterogeneous disease with different phenotypes leading to BH4 depletion.

The severe form of PTPS deficiency causes HPA and monoamine neurotransmitter deficiency, whereas the mild form gives rise to HPA only.

Biochemical findings for the patient with PTPS deficiency

	Before treatment (1 m)	Reference range
BA metabolites		
HVA [nmol/L] (CSF)	21	100 – 600
5-HIAA [nmol/L](CSF)	4	50 – 400
3-OMD [nmol/L] (CSF)	nd	< 50
Pterins (*)		
Bio [nmol/L] (CSF)	14,7	11 – 41
Neo [nmol/L] (CSF)	**87**	4,1 – 35
BH_2 [nmol/L] (CSF)	not analysis	
Sepiapterin	not analysis	
Prolactine	n.a.	2,7 – 19,7
Phenylalanine loading test	**n.a.**	
Response to l-dopa treatment	**good**	

n.a. – not analysed

Girl was born 2010

Families history –

PARENTS, YOUNG, HEALTHY, UNRELATED

CIII PIII SN. 9/10 p.Apgar

INCREASED CONCENTRATION OF PHENYLALANINE IN THE NBS

SUMMARY

PTPS deficiency presents with:

- elevated phenylalanine concentration in plasma,
- abnormal biogenic amine metabolites in CSF
- abnormal pterin profile in CSF and urine

SIGNIFICANT INCREASE OF NEOPTERIN IN CSF

- reducing the activity of this enzyme

DIHYDROPTERINE REDUCTASE - KEY ROLE IN BH4 SYNTHESIS

DHPR DEFICIENCY IS, IN GENERAL, A SEVERE DISORDER LEADING TO HPA
AND LOW LEVELS OF HVA AND 5-HIAA IN CSF.

ELEVATED LEVELS OF TOTAL BIOPTERIN IN CSF AND URINE IS OBSERVED

A SECONDARY DEFICIT OF 5-METHYLTETRAHYDROFOLATE (MTHF)
CAN OCCUR IN DHPR DEFICIENCY

Biochemical findings for the patient with DHPR deficiency

	Before treatment (20 y)	Reference range
BA metabolites		
HVA [nmol/L] (CSF)	**nd**	200 – 800
5-HIAA [nmol/L](CSF)	**nd**	100 – 600
3-OMD [nmol/L] (CSF)	nd	< 50
Pterins (*)		
Bio [nmol/L] (CSF)	45	10 – 42
Neo [nmol/L] (CSF)	18	4,1 – 35
BH_2 [nmol/L] (CSF)	**90**	0,4 – 14
Sepiapterin	**n.a.**	nd
Phenylalanine [umol/L]	120	42 - 89
Phenylalanine loading test	**n.a.**	
5-MTHF	20	48 - 180

nd – not detected

n.a. – not analyzed

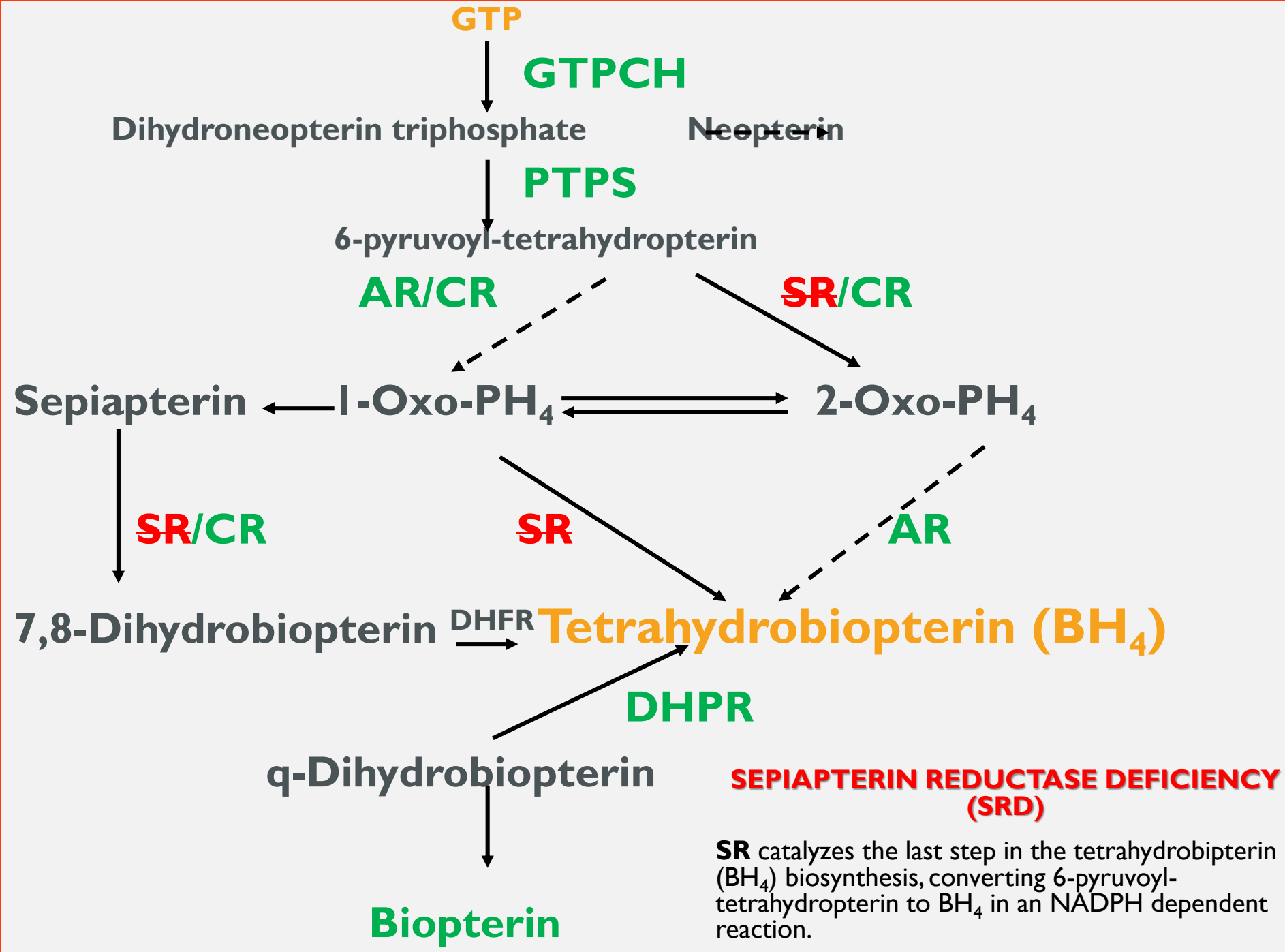
SUMMARY

DHPR deficiency presents with:

- elevated phenylalanine concentration in plasma and CSF
- abnormal concentration of biogenic amine metabolites in CSF
- abnormal pterin profile in CSF and urine

(hight concentration of BH_2 in CSF)

- decreased 5-MTHF in CSF
- decreased enzyme activity in whole blood



SEPIAPTERIN REDUCTASE DEFICIENCY (SRD)

SR catalyzes the last step in the tetrahydrobipterin (BH_4) biosynthesis, converting 6-pyruvoyl-tetrahydropterin to BH_4 in an NADPH dependent reaction.

Dopa-responsive dystonia

Diurnal fluctuation

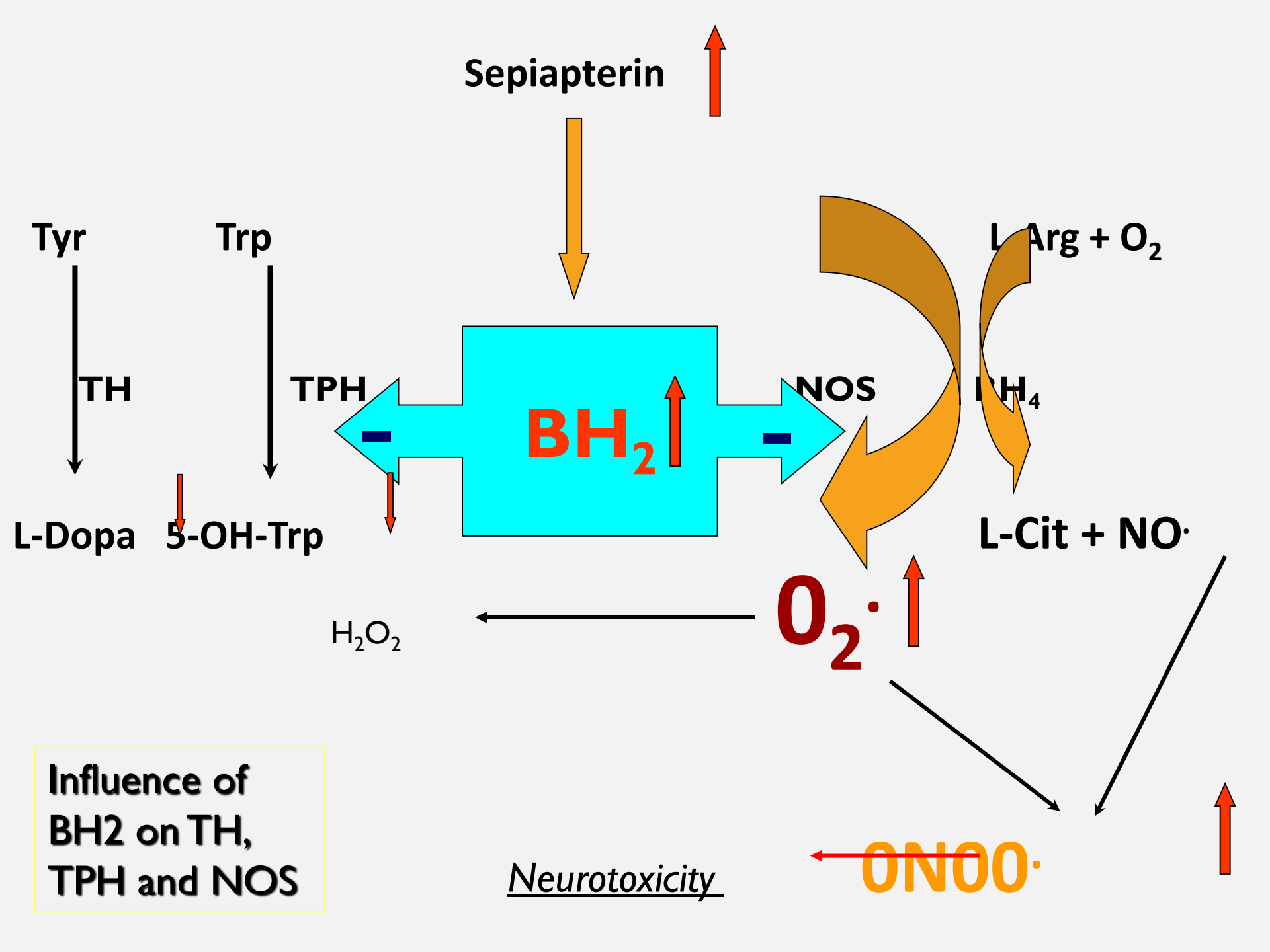
Oculogyric crisis (NAPADY WEJRZENIOWE)

BEHAVIORAL DISORDERS **:**
LACK OF SELF-REGULATION (sudden CRYING)
SLEEP DISORDERS (EXCESSIVE Drowsiness, DIFFICULTY IN SLEEPING)
IMPROVEMENT AFTER SLEEP

Sepiapterin reductase deficiency (SRD) is an autosomal recessive disorder

with normal phenylalanine (Phe) concentration

in blood.


Sepiapterin
Tyr
Trp
L-Arg + O_2
TH
TPH
NOS
BH_4
BH_2
L-Dopa
5-OH-Trp
L-Cit + NO·
O_2·
H_2O_2
ONOO·
Influence of BH2 on TH, TPH and NOS
Neurotoxicity

Girl was born 2005

PREGNANCY AND BIRTH AND THE NEWBORN PERIOD - normal

AT THE AGE OF 3 MONTHS PROLONGED EPISODES IMPROPER EYEBALL SETTINGS HORIZONTAL OR UP WITH A CRYING, OCCURRING MANY TIMES A DAY and THEY DISAPPEARED AFTER SLEEP

SYMPTOMS EXHIBITED DAILY CHANGES, INCREASING AT THE END OF THE DAY.

CASE REPORT

At 7 and 10 months of age intensive etiologic investigations were normal.

- plasma acylcarnitines, free carnitine,
- lactate and pyruvate,
- urinary organic acids,
- muscle biopsy,
- electroencephalograms,
- cerebral magnetic resonance imaging

Biochemical findings for the patient with SRD

	Before treatment (7 months)	11 months treated with l-dopa	15 months treated with L-dopa and 5-HT	Reference range
BA metabolites				
HVA [nmol/L] (CSF)	**79,7**	**119**	**82**	200 – 800
5-HIAA [nmol/L](CSF)	**12,3**	**12,5**	**< 5**	100 – 600
3-OMD [nmol/L] (CSF)	nd	46	54	< 50
Pterins (*)				
Bio [nmol/L] (CSF)	24	-	-	10 – 42
Neo [nmol/L] (CSF)	18	-	-	4,1 – 35
BH_2 [nmol/L] (CSF)	**69**	-	-	0,4 – 14
Sepiapterin	**14,7**			nd
Prolactine	15,3		-	2,7 – 19,7
Phenylalanine loading test	**Abnormal**			
Molecular study of *SPR* gen (**)	**g.1330C>G (p.N127K)**			

**Metabolic Unit, Dept. Clinical Chemistry, prof. C. Jakobs*

***Division of Clinical Chemistry and Biochemistry, prof. N.Blau*

Girl was born 2005

PSYCHOMOTORY DEVELOPMENT IS NORMAL UNTIL 4 MONTH,

AXIAL HYPOTONIA, LACK OF HEAD STABILIZATION

At the age 1:

SHE DIDN'T SIT DOWN, no HEAD STABILIZATION
Axial hypotonia, stiff limbs was observed
live tendom reflexe

girl ur. 30.03.2005

MRI brain - normal

EEG normal

gradual introduction of treatment, in small doses!!!!!

LEVODOPA + BENSERAZYD 7 mg/kg/day

NEXT L-DOPA + CARBIDOPA

NEXT 5-HYDROXYTRYPTOPHANU 1,5 mg/kg/day

SIT AFTER 2 MONTHS of treatment

SUMMARY

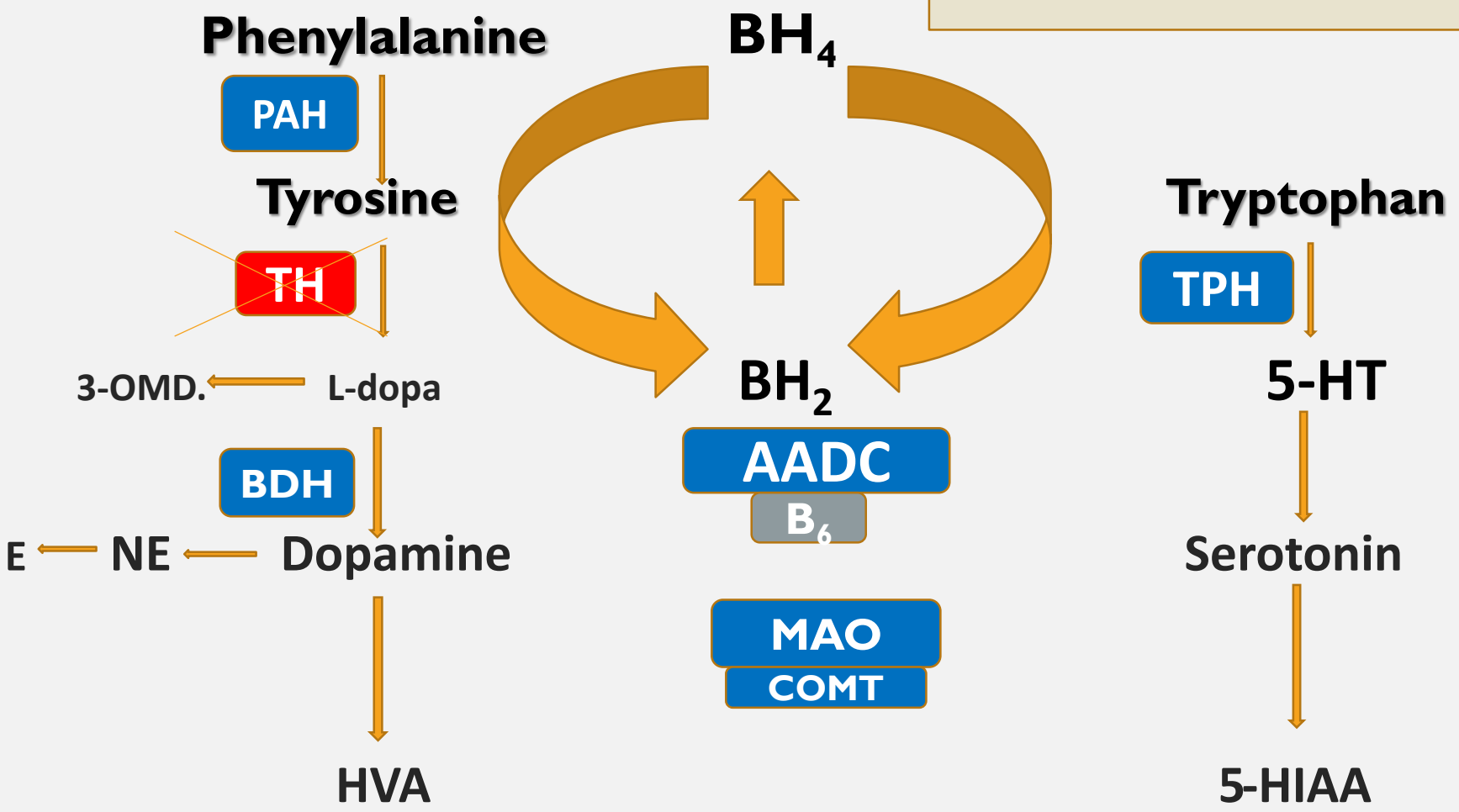
Sepiapterin reductase deficiency presents with:

- normal phenylalanine concentration in plasma
- abnormal concentration of biogenic amine metabolites in CSF
- abnormal pterin profile in CSF

(very hight concentration of sepiapterin in CSF)

- abnormal phenylalanine loading test
- normal/abnormal prolactine concentration in serum

TYROSINE HYDROXYLASE DEFICIENCY (THD)



- Tyrosine hydroxylase (TH, EC 1.14.16.2) catalyzes the hydroxylation of L-tyrosine to L-dopa, the rate limiting step in the biosynthesis of the dopamine, norepinephrine, and epinephrine.
- Reaction requires molecular oxygen, ferrous iron and the cofactor BH_4 for activity.

TYROSINE HYDROXYLASE DEFICIENCY (THD)

This disorder is known under different names in the literature, namely **'Segawa syndrome'**, **'infantile parkinsonism'** and **'L-dopa-responsive dystonia' (DRD)**.

'Segawa syndrome', however, is also used to indicate another defect in neurotransmitter biosynthesis, caused by GTP cyclohydrolase I mutations.

'Infantile parkinsonism' and DRD are not found in all patients with THD.

The phenotype of THD can be so different that it is not simply associated only with an extrapyramidal movement disorder.

BIOCHEMICAL FINDINGS IN TH DEFICIENCY:

- biogenic amine metabolites in CSF
- pterin profile in CSF
- phenylalanine loading test
- molecular study

TH deficiency

WIDE PHENOTYPE SPECTRUM

Based on the severity of symptoms and response to levodopa treatment,

(1) DOPA-RESPONSIVE DYSTONIA (MILD TH DEFICIENCY)

(2) INFANTILE PARKINSONISM WITH MOTOR DELAY (SEVERE FORM)

(3) PROGRESSIVE PEDIATRIC ENCEPHALOPATHY (VERY SEVERE FORM)

(1)DOPA-RESPONSIVE DYSTONIA (MILD TH DEFICIENCY)

(DYT5B, DYT-TH)
onset of symptoms 12 months and 12 years;

THE INITIAL SYMPTOMS ARE USUALLY LOWER LIMB DYSTONIA
AND/OR DIFFICULTY IN WALKING
DIURNAL FLUCTUATION
(SYMPTOMS WORSE IN THE EVENING AND IMPROVEMENT AFTER SLEEP).

INFANTILE PARKINSONISM WITH MOTOR DELAY

(SEVERE FORM)

THE BEGINNING OF THE DISEASE IT OCCURS FROM 3 TO 12 MONTHS

INFANT SHOW AXIAL HYPOTONIA
AND PARKINSON'S SYMPTOMS
(HYPOKINESIA, STIFFNESS OF LIMBS AND/OR TREMOR)

PROGRESSIVE PEDIATRIC ENCEPHALOPATHY (VERY SEVERE FORM)

THE ONENSE OF THE DISEASE OCCURS AT THE AGE OF THREE TO SIX MONTHS
IN MOST CASES, ABNORMALITIES DURING THE FETAL PERIOD

SIGNIFICANT DELAY IN MOTOR DEVELOPMENT,
AXIAL HYPOTONIA, SEVERE HYPOKINESIS,
LIMB HYPERTONIA (STIGNESS AND/OR SPASTICITY), EYELID DROPPING (PTOSIS)

INTELLECTUAL DISABILITY
PERIODS OF EXCESSIVE SLEEPY (WITH INCREASED SWEATING AND DIVILING)

EEG normal.

MRI - normal.

Age-appropriate myelination.
The ventricular system is of normal width, symmetrical.
Paracerebral fluid spaces not dilated.

Tandem MS-MS(MS/MS) - NORMAL

ORGANIC ACIDS PROFILE GC-MS - NORMAL

?

LUMBAR PUNCTION– NEUROTRANSMITTER ANALYSIS

BIOCHEMICAL RESULTS FOR THE PATIENT WITH THD

	Before treatment (7m)	Reference range
BA metabolites HVA [nmol/L] (CSF) 5-HIAA [nmol/L](CSF) 3-OMD [nmol/L] (CSF)	 **50** 199 nd	 300 – 1000 200 – 800 < 100
Pterins (*) Bio [nmol/L] (CSF) Neo [nmol/L] (CSF)	 41 15,5	 10 – 42 4,1 – 35
Prolactine	12,6	2,7 – 19,7
Phenylalanine loading test	Normal	
Molecular study of *TH* gen	During the study	
Excellent respons to low dose of L-dopa		

Summary

THD DEFICIENCY PRESENTS WITH:

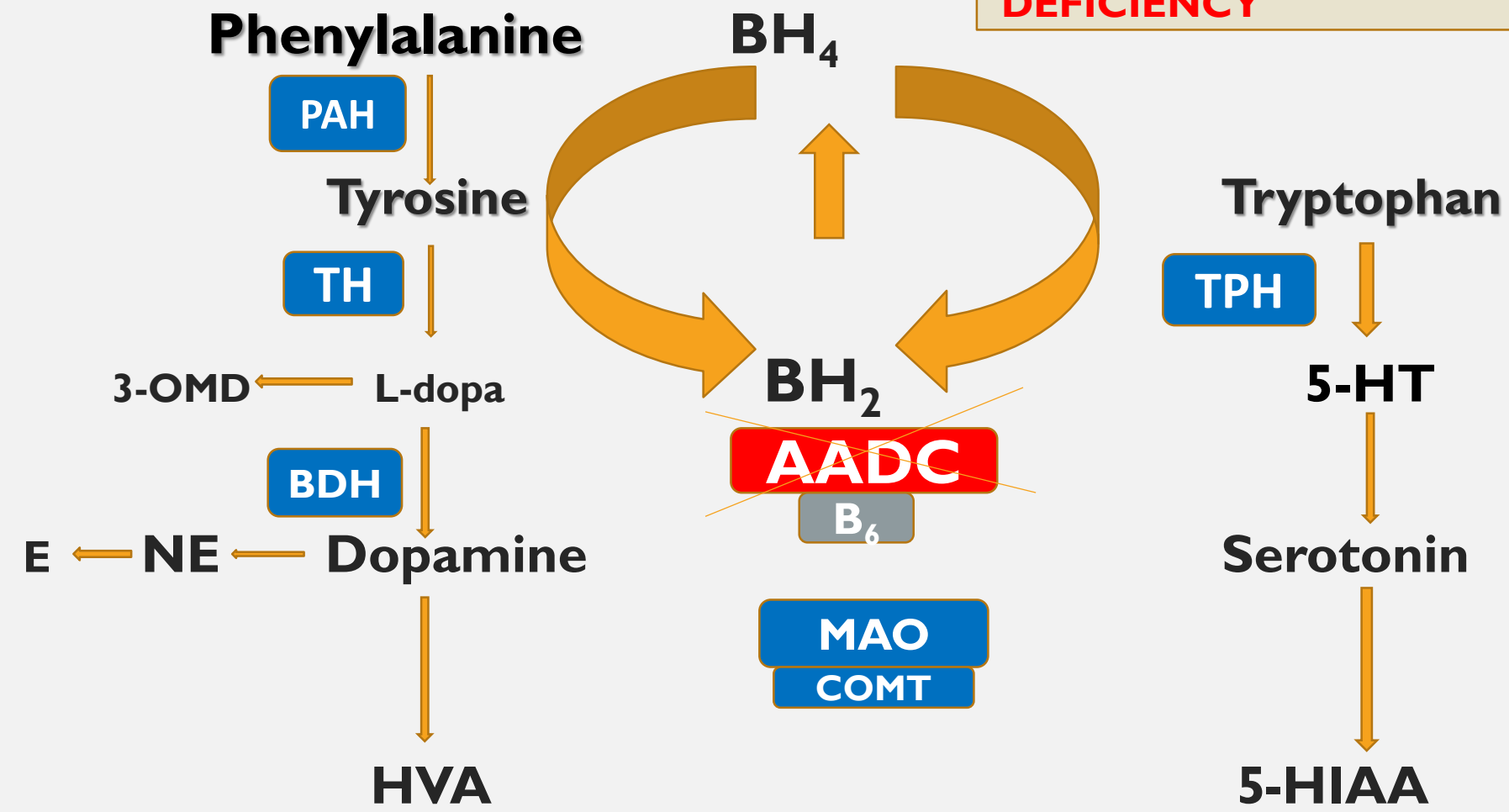
- abnormal concentration of biogenic amine metabolites in CSF

(very low concentration of HVA in CSF)

- normal pterin profile,
- normal phenylalanine loading test,

<u>Only</u> molecular study can be confirmation for the TH deficiency

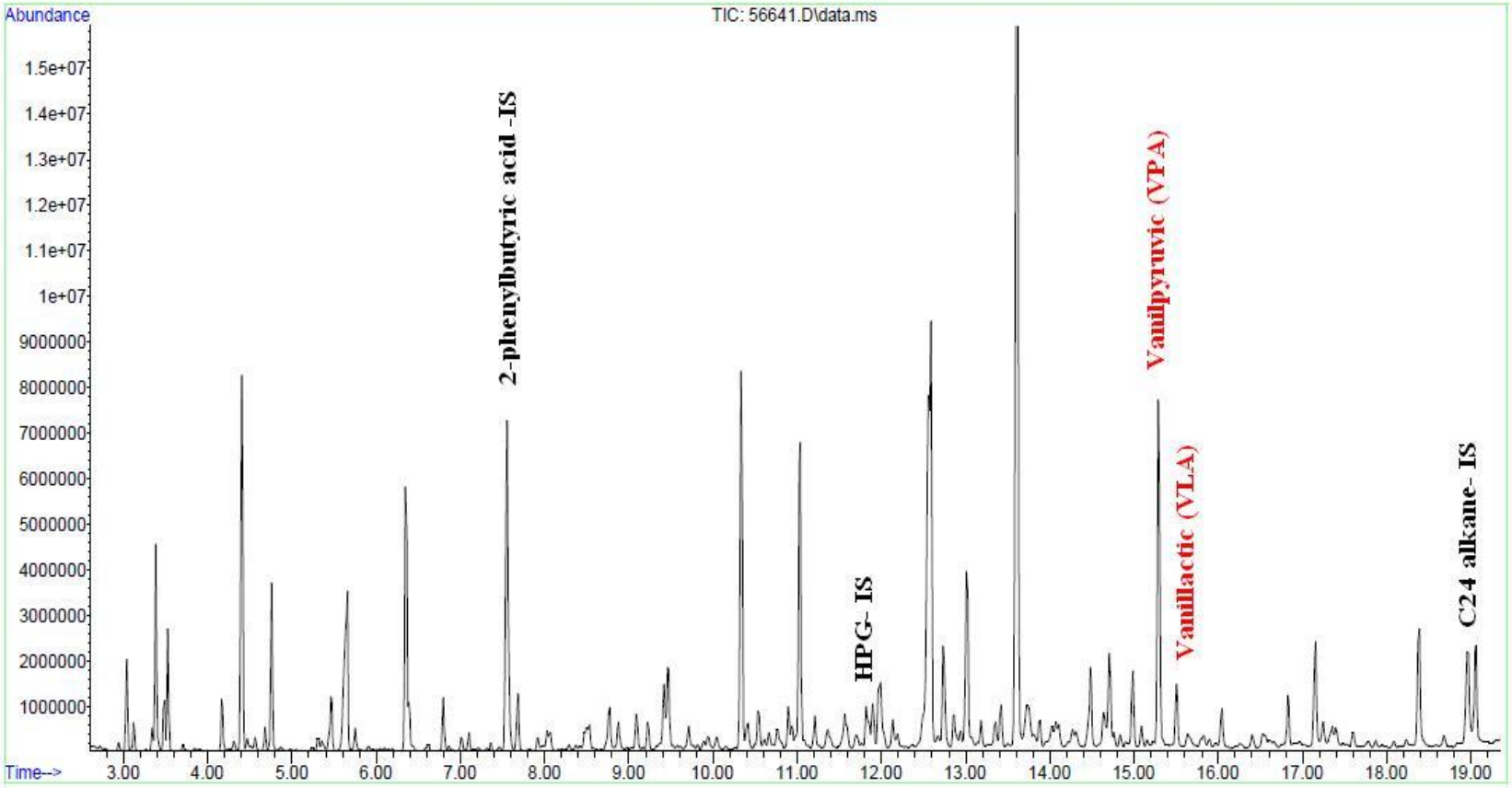
L-AROMATIC AMINO ACID DECARBOXYLASE DEFICIENCY



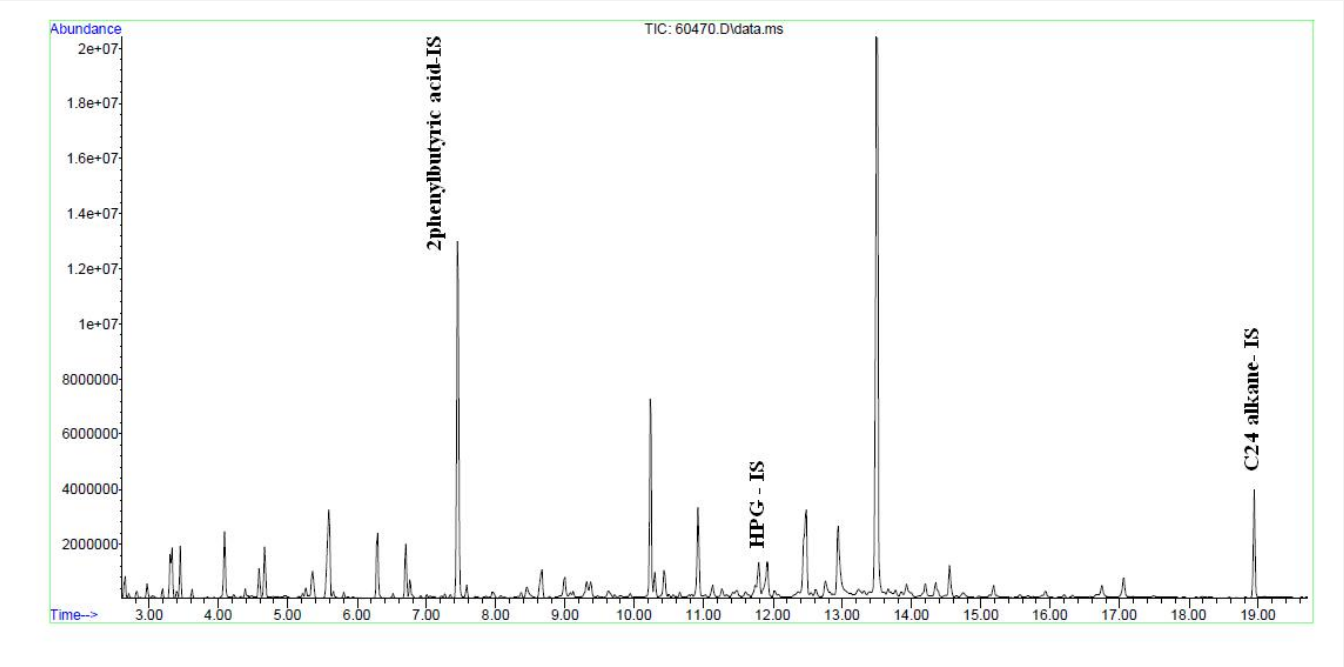
- Aromatic L-amino acid decarboxylase (AADC, EC 4.1.1.28) catalyzes the conversion of 5-hydroxytryptophan to serotonin in serotonergic neurons and of L- dopa to dopamine in catecholaminergic neurons and adrenal medullary cells.
- This enzyme thus plays a key role in the synthesis of both groups of neurotransmitter biogenic amines.

Biochemical findings in AADC deficiency:

- Organic acids profile in urine
- Prolactine in serum
- Biogenic amine metabolites in CSF
- 5-MTHF IN CSF
- Enzyme activity
- Molecular analysis



ORGANIC ACID PROFILE IN URINE – PATIENT WITH AADC DEFICIENCY



ORGANIC ACIDS PROFILE IN URINE - CONTROL

Biochemical findings for the patients with AADC deficiency

	Patient (8 m)	Control
5-HT [nmol/L] (CSF)	**380**	< 10
HVA [nmol/L] (CSF)	**54**	300 – 1000
5-HIAA [nmol/L] (CSF)	**46**	200 – 800
3-OMD [nmol/L] (CSF)	**1323**	< 100
5-MTHF	86	72 - 212
MHPG [nmol/L]	**nd**	5 - 50
Prolactine	**32**	2,7 – 19,7
Enzyme activity [mU/L]	**nd**	16 - 99

nd: not detectable

SUMMARY

AADC DEFICIENCY PRESENTS WITH:

- abnormal organic acids profile in urine

to present VLA,VPA – the metabolites of 3-OMD

- abnormal concentration of biogenic amine metabolites in CSF;
- increase prolactine concentration in serum;
- decreased /normal 5-MTHF concentration in CSF;

AADC deficiency

Fined in 1990

130 patients around the world

Clinical symptoms

MUSCLE TENSION	MOVEMENT DISORDERS
„Flappy baby”	DYSKINESIS/HYPERKINESIA
HYPOTONIA – MAINLY AXIALSŁABA	Chorea, athetosis
HYPERTONIA – MAINLY OF THE LIMBS	DYSTONIA
	Oculogyric crisis
	HYPOKINESIS-BRADYKINESIS
	MIOKLONIE
	TREMOR
	METAANALIZA Wassenberg et al. 2017

PSYCHOMOTOR DEVELOPMENT	BEHAVIORAL SYMPTOMS
ABNORMAL MOTOR DEVELOPMENT	IRRITABILITY
ABNORMAL COGNITIVE DEVELOPMENT	AUTISTIC FEATURES
ABNORMAL SPEECH DEVELOPMENT	DYSPHORIA / MOOD PROBLEMS
	CRYING

EYE SYMPTOMS	OTHER
PTOSIS	
SQUINT	EXCESSIVE SALIVATION
	EPILEPSY
	INSOMNIA
	TIREDNESS

METAANALIZA Wassenberg et al. 2017

Treatment

Agonist DOPAMINE	INHIBITORS MAO	OTHER
BROMOCRIPTINE PRAMIPEXOLE, ROPINIROLE, ROTIGOTINE	TRANYLCYPROMINE SELEGILINE	PYRIDOXAL PHOSPHATE (PLP) FOLIC ACID ANTICHOLINERGIC DRUGS MELATONINE
irritability, weight loss, vomiting, mild to severe dyskinesia	Side effects have been rarely reported	

METAANALIZA Wassenberg et al. 2017

GENE THERAPY

COOPERATION with prof. KRZYSZTOFEM BANKIEWICZ

From the UNIVERSITY of CALIFORNIA IN SAN FRANCISCO

- The first time in Poland
The first time in EUROPE

THE VIRUS, HARMFUL

TO HUMANS, IS INTRODUCED INTO THE BRAIN EQUIPPED WITH THE

GENE RESPONSIBLE FOR THE PRODUCTION OF THE AADC ENZYME

PROF. KRYSTOF BANKIEWICZ

UCSF Benioff Children's Hospital San Francisco

UCSF STUDY TEAM

- **Krzysztof Bankiewicz (PI)**
- Nalin Gupta (Clinical PI)
- Jill Imamura-Ching
- Waldy San Sebastian
- Amy Viehoever
- Ana Grijalvo-Perez

Gene for AADC + VIRAL VECTOR

SUMMARY

AADC DEFICIENCY PRESENTS WITH:

- abnormal organic acids profile in urine

to present VLA,VPA – the metabolites of 3-OMD

- abnormal concentration of biogenic amine metabolites in CSF;
- increase prolactine concentration in serum;
- decreased /normal 5-MTHF concentration in CSF;

Conclusions:

1. Cerebrospinal fluid (CSF) analysis of biogenic amines is a screening of neurotransmitter defects and need other investigations.

2. Investigations of neurotransmitter defects should be included in the diagnostic evaluation of any child suffering from a progressive infantile encephalopathy of unknown etiology.