University Children's Hospital Zürich, Switzerland

Neurotransmitter Disorders
Clinical Presentation and Diagnosis

Nenad Blau

ERNDIM Meeting, 22-23 October 2009 – Basel - CH

Definition

Neurotransmitters are chemicals (biogenic amines, amino acids, purines, neuropeptides, etc.) that are released from neurons and that change the electrical activity of other neurons or of myocytes.

University Children's Hospital Zürich, Switzerland

Classification

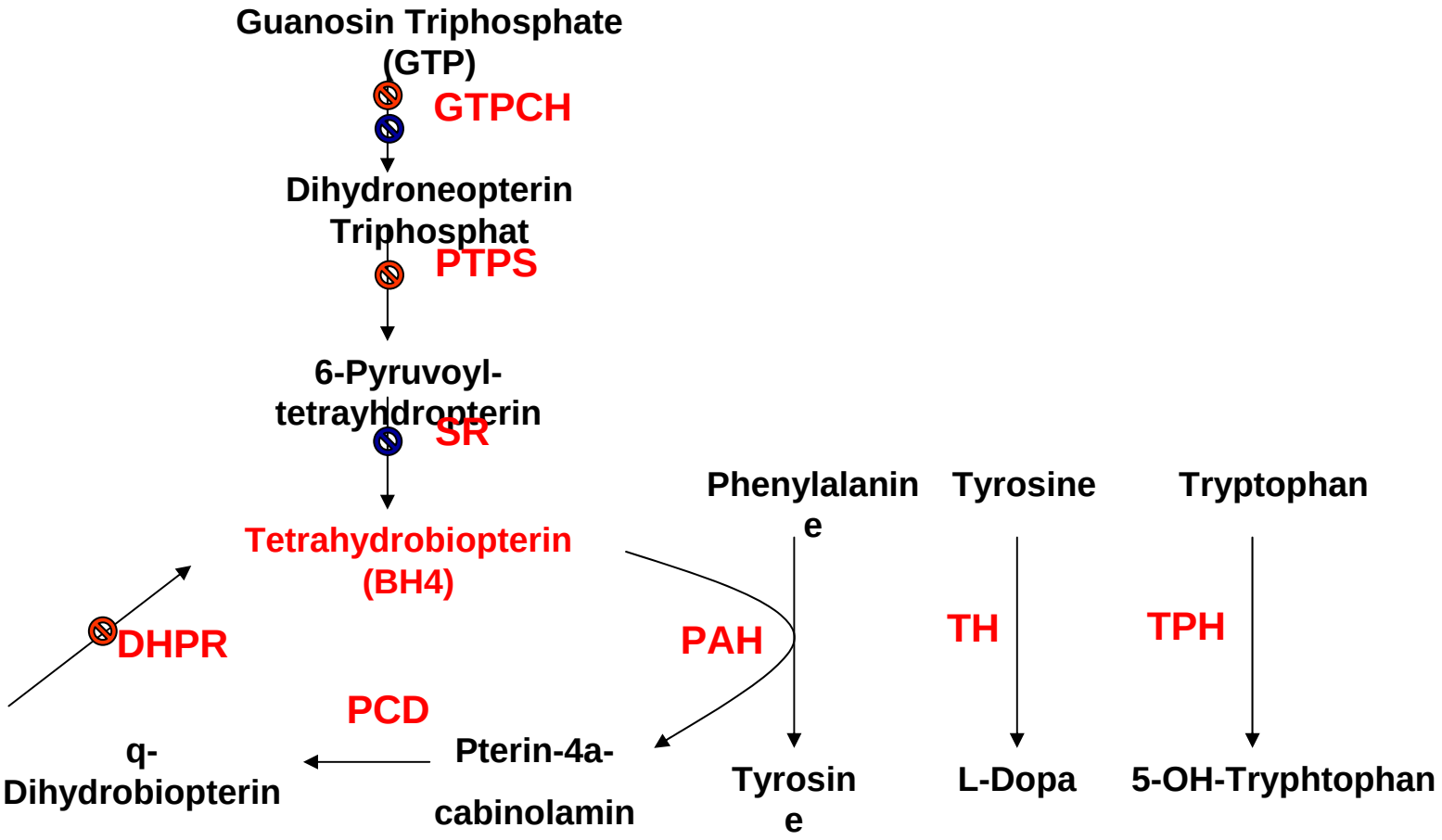
- Disorders of tetrahydrobiopterin (BH4)
- Disorders in catecholamines and serotonin metabolism
- Disorders of serine and glycine metabolism
- Disorders of glutamate and GABA
- Disorders of folate deficiency
- Disorder of B6 metabolism

Classification

- **Disorders of tetrahydrobiopterin (BH4)**
  - **<u>with</u> hyperphenylalaninemia**
    - GTP cyclohydrolase I (*ar*)
    - 6-Pyruvoyl-tetrahydropterin synthase
    - Dihydropteridine reductase
  - **<u>without</u> hyperphenylalaninemia**
    - GTP cyclohydrolase I (*ad*) -

University Children's Hospital Zürich, Switzerland

Tetrahydrobiopterin Metabolism

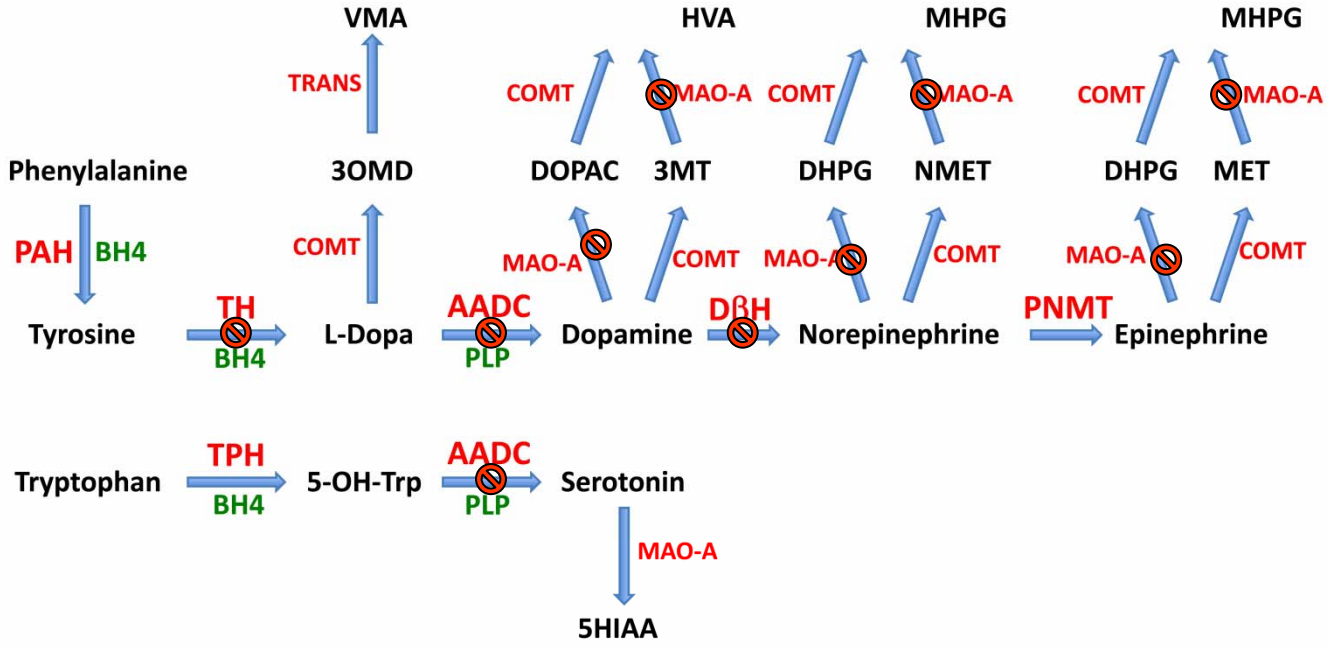


Classification

- **Disorders in catecholamines and serotonin metabolism**
  - Tyrosine hydroxylase
  - Aromatic amino acid decarboxylase
  - Monoamine A oxidase
  - Dopamine-β-hydroxylase

University Children's Hospital Zürich, Switzerland

Disorders in catecholamines and serotonin metabolism

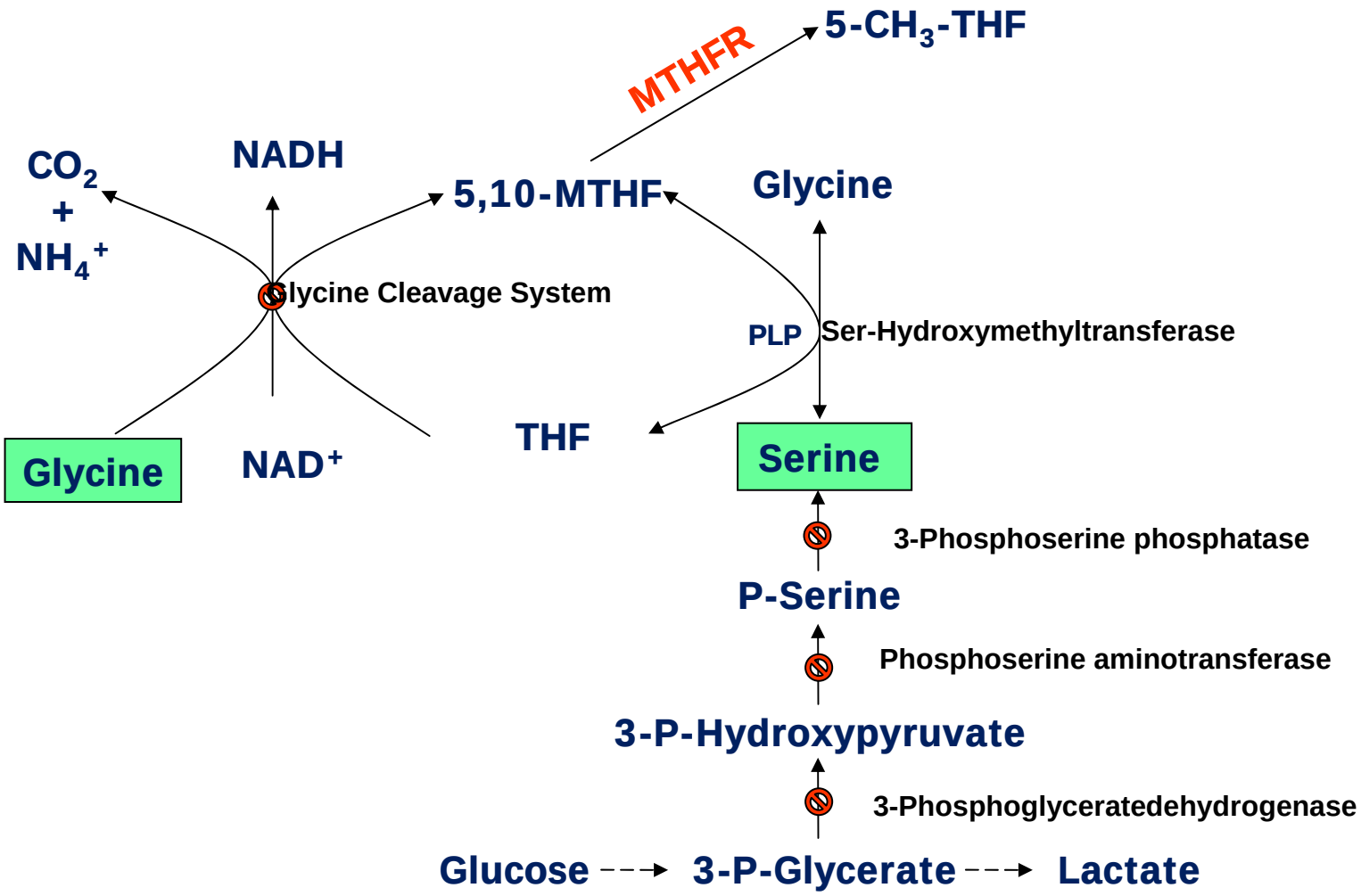


Classification

- **Disorders of serine and glycine metabolism**
  - 3-Phosphoglyceratedehydrogenase
  - 3-Phosphoserine phosphatase
  - Phosphoserine aminotransferase
  - Glycine cleavage system

University Children's Hospital Zürich, Switzerland

Disorders of glycine and serine metabolism

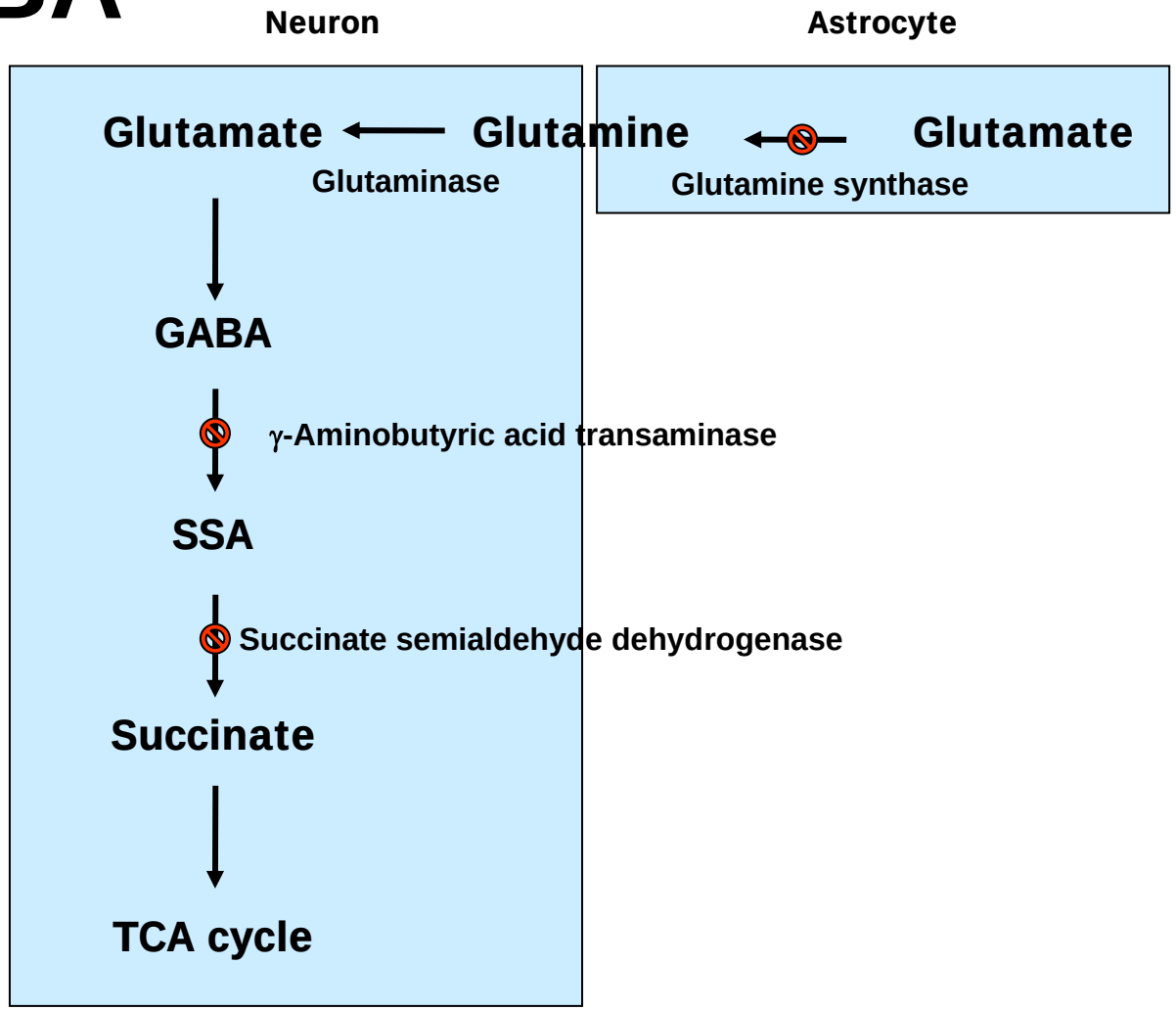


Classification

- **Disorders of glutamate and GABA**
  - Succinate semialdehyde dehydrogenase
  - γ-Aminobutyric acid transaminase
  - Glutamine synthase

University Children's Hospital Zürich, Switzerland

Disorders of glutamate and GABA

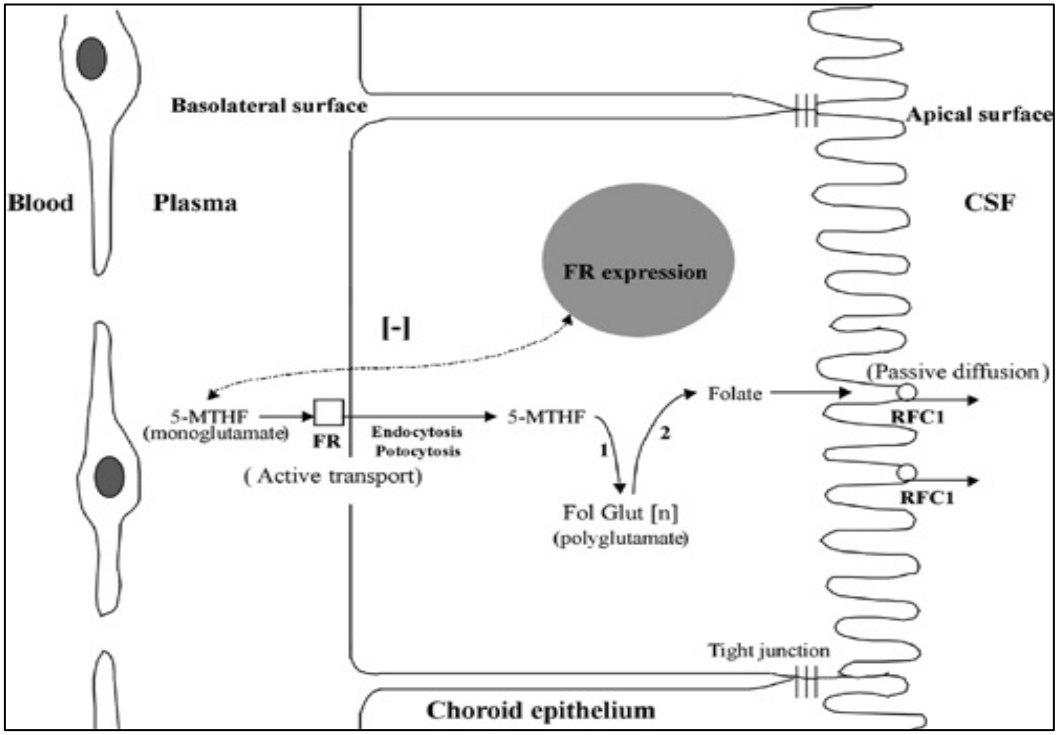


University Children's Hospital Zürich, Switzerland

Classification

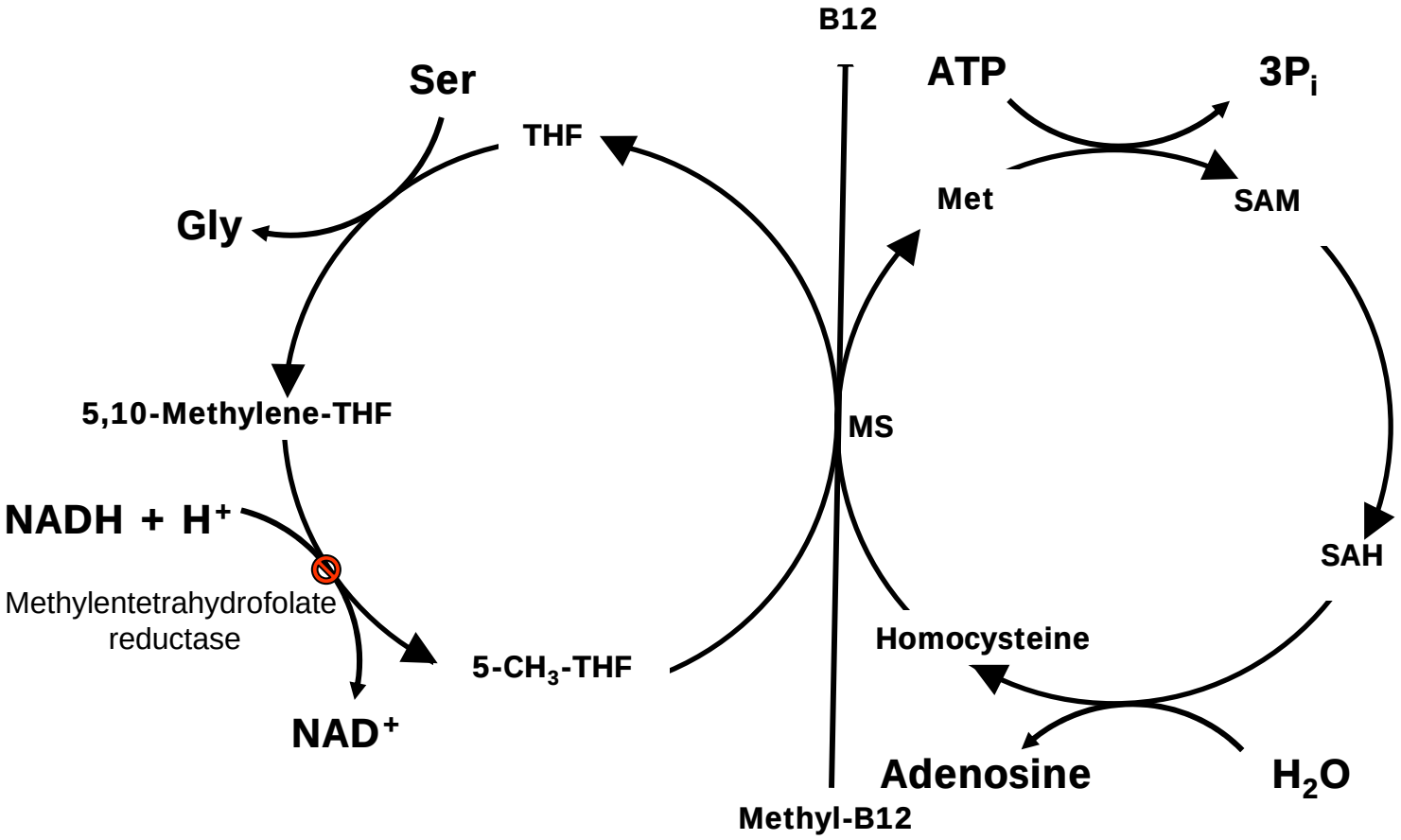
- **Disorders of folate deficiency**
  - Hereditary folate malabsorption
  - Methylentetrahydrofolate reductase
  - Folate receptor alpha
  - Cerebral folate deficiency

Disorders of folate transport



University Children's Hospital Zürich, Switzerland

Disorders of folate metabolism

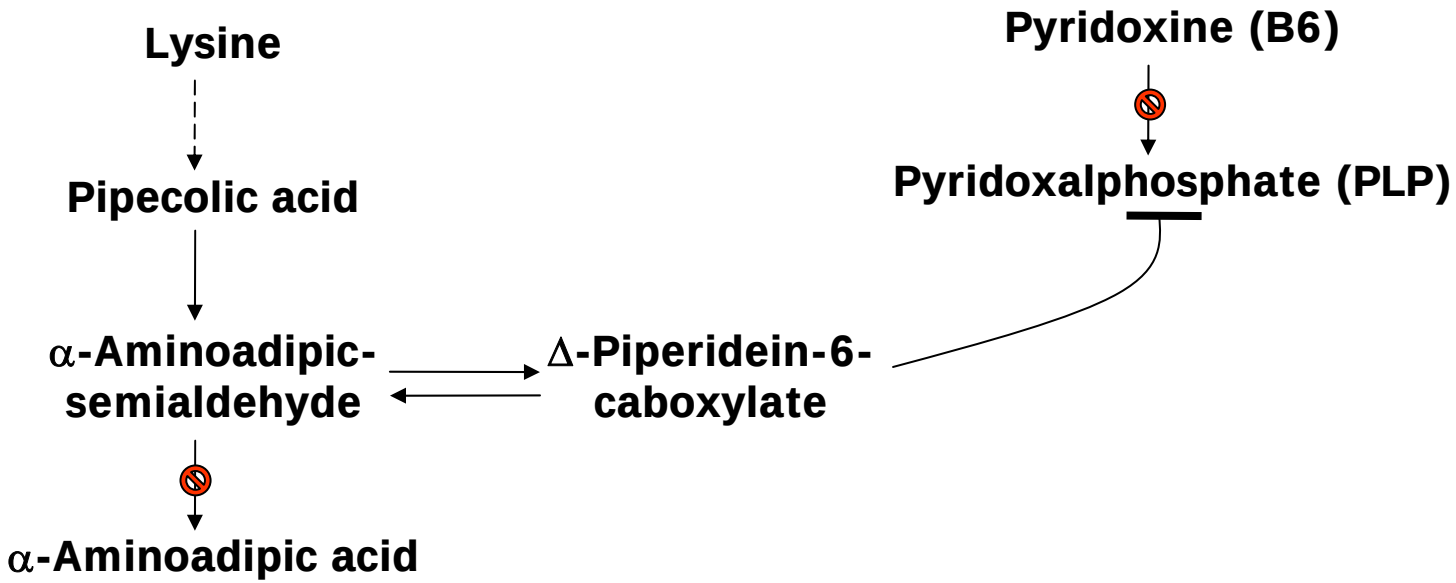


Classification

- **Disorders of B6 metabolism**
  - α-Aminoadipicsemialdehyde DH
  - Pyridoxamine-5'-phosphate oxidase

University Children's Hospital Zürich, Switzerland

Disorders of B6 metabolism



Secondary Biogenic Amine Deficiencies

Primary

- **Defects in biosynthesis (non-HPA)**

  Enzyme deficiencies
  GTP cyclohydrolase I
  Tyrosine hydroxylase
  Tryptophan hydroxylase
  Aromatic amino acid decarboxylase
  Dopamine β-hydroxylase

  Cofactor (BH_4) deficiency (HPA)

- **Defect in catabolism**

  Monoamine oxydase A

Secondary

- **Classical PKU**

  Competitive inhibition of TH and TPH

- **Lesch-Nyhan syndrome**
- **Rett syndrome**
- **Arginase deficiency**
- **Menkes disease**
- **Viral infections**
- **Familial erythrophagocytic lymphohistiocytosis**

University Children's Hospital Zürich, Switzerland

Guidelines for the Screening

Newborn screening normal

'Missed' cases

No HPA or not tested

'Undiagnosed neurological disease'

Central and/or peripheral nervous system dysfunction with either/and/or:

Typical

- Hypokinesia
- Distal chorea
- Myoclonic epilepsy
- Temperature disturbance
- Hypersalivation

Non-specific

- Mental retardation
- Microcephaly
- Developmental delay
- Pinpoint pupils
- Irritability
- Convulsions
- Oculogyric crises
- Hyper- or hypotonia
- Swallowing difficulties
- Dystonia (diurnal variations)

Biogenic amine and metabolite analysis (P, CSF or U)

University Children's Hospital Zürich, Switzerland

SIGNS & SYMPTOMS

+

TREATMENT

Patients‘ pictures and movies removed from the presentation

University Children's Hospital Zürich, Switzerland

Symptoms Related to Specific Biogenic Amine Deficiency

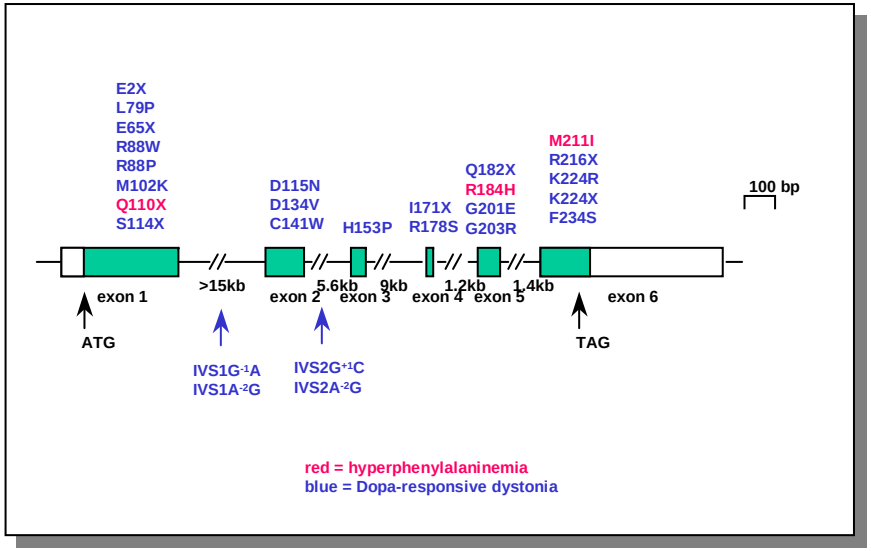
Dopamine	Serotonin	Norepinehrine
Immobility	Depression	Axial hypotonia
Parkinsonism	Altered thermogenesis	Cerebellar symptoms
Sleepiness	Insomnia	Ptosis
Dystonia		
Eye rolling		
Hypersalivation		
Swallowing difficulties		

University Children's Hospital Zürich, Switzerland

Dopa-responsive Dystonia (DRD)

Dopa-responsive Dystonia (DRD) - GTP Cyclohydrolase I Deficiency

Inheritance autosomal dominat (14q22.1-q22.2)



Signs & Symptoms

Onset: neonatal - adolescence
Dystonia
Diurnal variation of symptoms
Parkinsonism
Spasticity
Hyperreflexia
Rigidity
Pyramidal signs

Diagnosis

CSF: HVA ↓ ; 5HIAA n - ↓ ; Neo & Bio ↓
Oral : Phe (100 mg/kg); L-Dopa/Carbidopa

Treatment

L-Dopa/Carbidopa (2-5 mg/kg/d)

Disorders Catecholamines

Therapy: L-dopa/Carbidopa

Table 2.1. Tyrosine hydroxylase deficiency [10]

System	Symptoms/ markers	Neonatal	Infancy	Childhood
Characteristic clinical findings	Truncal hypotonia		+	+
	Chorea/athetosis		+	+
	Ptosis of eyelids		+	+
	Parkinsonian symptoms		+	+
	Tremor		+	+
	Hypokinesia		+	+
Routine laboratory	Glucose ↓	±	±	±
Special laboratory	MRI/CT		n or cerebral/ cortical atrophy	n or cerebral/ cortical atrophy
	Prolactin (P)		↑	↑
	Norepinephrine (U)		↓–n	↓–n
	Dopamine (U)		↓–n	↓–n
	VMA (U)		↓–n	↓–n
	HVA (U)		↓–n	↓–n
	HVA (CSF)		↓↓	↓↓
	MHPG (CSF)		↓↓	↓↓

Disorders of Serotonin and the Catecholamines

Table 2.2. Aromatic L-amino acid decarboxylase (AADC) deficiency [15]

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence
Characteristic clinical findings	Oculogyric crises		+	+	+
	Hypotonia	+	+	+	+
	Sweating		+	+	+
	Retardation		+	+	+
	Temperature instability	+	+		
	Chorea		+	+	+
	Ptosis of eyelids	+	+	+	+
Special laboratory	MRI/CAT		± cerebral atrophy		
	Prolactin		↑		
	Norepinephrine (P)		↓	↓	
	Epinephrine (P)		↓	↓	
	L-Dopa (P, U, CSF)		↑	↑	
	3OMD (P, U, CSF)		↑↑↑	↑↑↑	
	5HTP (P, U, CSF)		↑	↑	
	Serotonin (BL)		↓↓	↓↓	
	L-Dopa decarboxylase (P)		↓↓↓	↓↓↓	
	HVA (CSF)		↓↓↓	↓↓↓	
	5HIAA (CSF)		↓↓↓	↓↓↓	
	Organic acids (U) (vanillactic acid)		↑		
Eye	Oculogyric crises		+	+	+
	Ptosis	+	+	+	+
	Miosis	+	+		

University Children's Hospital Zürich, Switzerland

Most common signs and symptoms in patients with AADC deficiency

	Symptoms*	%	All patients	Infancy ≤18months	Childhood ≤10years	Adolescence ≥11 years	Adulthood
Characteristic features	Hypotonia	95	74/78	35/38	33/33	3/4	3/3
	Oculogyric crises	86	67/78	33/38	28/33	3/4	3/3
Other neurological signs	Sweating	65	51/78	20/38	26/33	2/4	3/3
	Developmental retardation	63	49/78	22/38	24/33	1/4	2/3
	Dystonia	53	41/78	21/38	16/33	1/4	2/3
	Hypertonia	44	35/78	14/38	18/33	1/4	2/3
	Feeding/swallowing difficulties	42	33/78	17/38	16/33	0/4	0/3
	Dysarthria/speech difficulties	41	32/78	9/38	20/33	1/4	2/3
	Hypersalivation	41	32/78	12/38	17/33	1/4	2/3
	Ptosis	39	30/78	18/38	10/33	2/4	0/3
	Insomnia	37	29/78	11/38	17/33	1/4	0/3
	Irritability	35	27/78	12/38	12/33	1/4	2/3
	Hypokinesia	32	25/78	8/38	14/33	1/4	2/3
	Nasal congestion	31	24/78	10/38	12/33	2/4	0/3
	Temperature instability	29	23/78	12/38	9/33	1/4	1/3
	Head control poor	28	22/78	10/38	9/33	2/4	1/3
	Athetosis	27	20/78	8/38	11/33	0/4	1/3
	Eye fixation poor	26	19/78	10/38	9/33	0/4	0/3
	Chorea	22	17/78	7/38	9/33	1/4	0/3
Brain imaging	Abnormal MRI	28	22/78				
	Abnormal EEG	14	11/78				
	Abnormal CT	6	5/78				

Diagnosis, outcome, and long-term follow-up of 78 patients with aromatic L-amino acid decarboxylase deficiency: Lesson from the international database of pediatric neurotransmitter disorders. Brun L et al. (2009) Neurology, submitted

University Children's Hospital Zürich, Switzerland

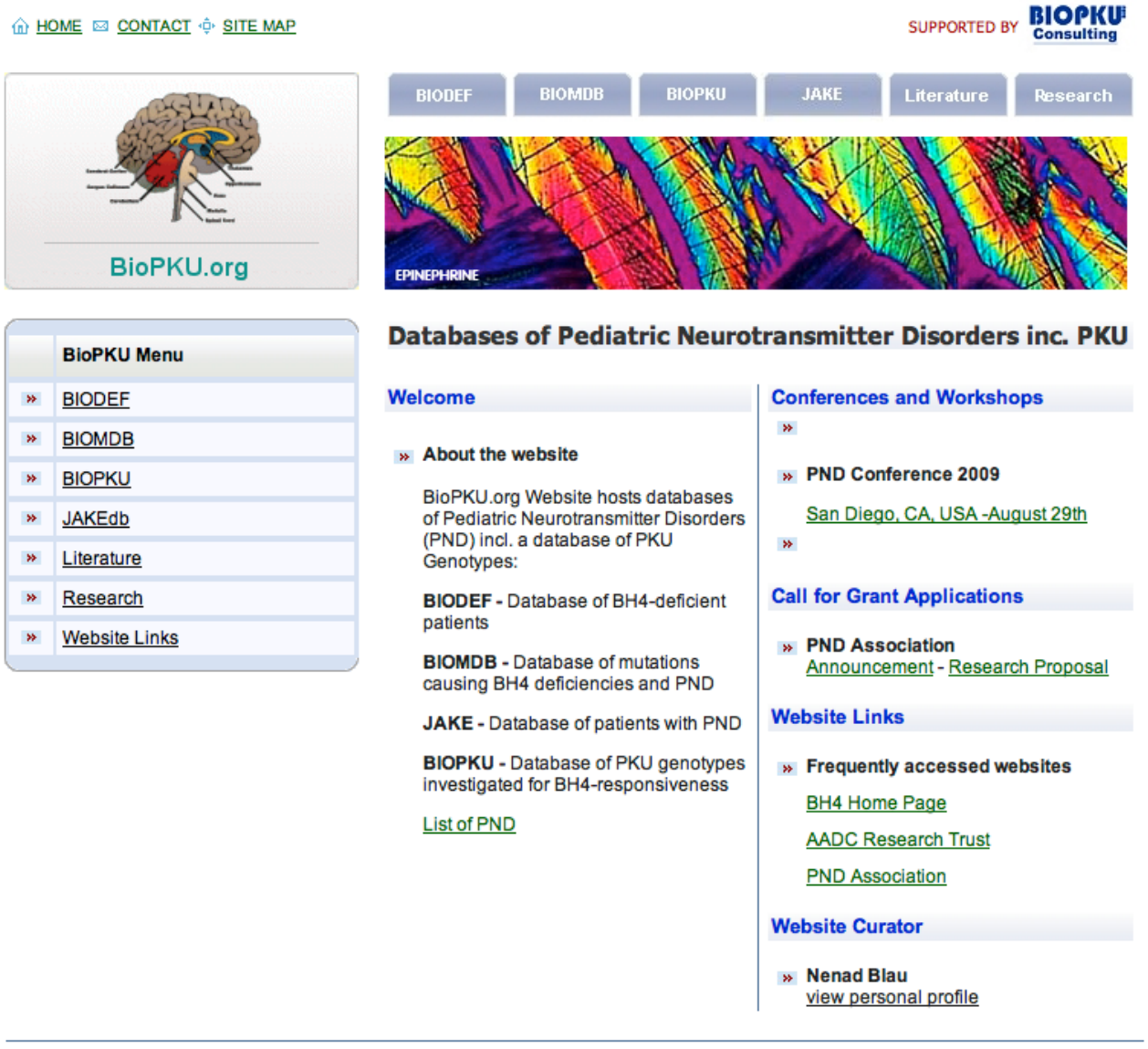
Most frequently used medications in patients with AADC deficiency.

Medication	Dosage	No. of patients	%
Pyridoxine (B6)	40-1800 mg/d or 4.0-81 mg/kg/d	55/78	71
Bromocriptine	1.0-45.5 mg/d or 0.013-4.0 mg/kg/d	38/78	49
Tranylcypromide	1.5-54 mg/d or 0.4-0.5 mg/kg/d	22/78	28
Seligiline	0.1-6.0 mg/d or 0.03-1.5 mg/kg/d	19/78	24
Trihexyphenydyl	0.231-4.62 mg/d or 0.3-0.5 mg/kg/d	15/78	19
Pergolide	0.3-1.5 mg/d or 0.006-0.75 mg/kg/d	12/78	15
L-Dopa	400-2250 mg/d or 11.2-54 mg/kg/d	10/78	13

University Children's Hospital Zürich, Switzerland

Databases of Pediatric Neurotransmitter Disorders

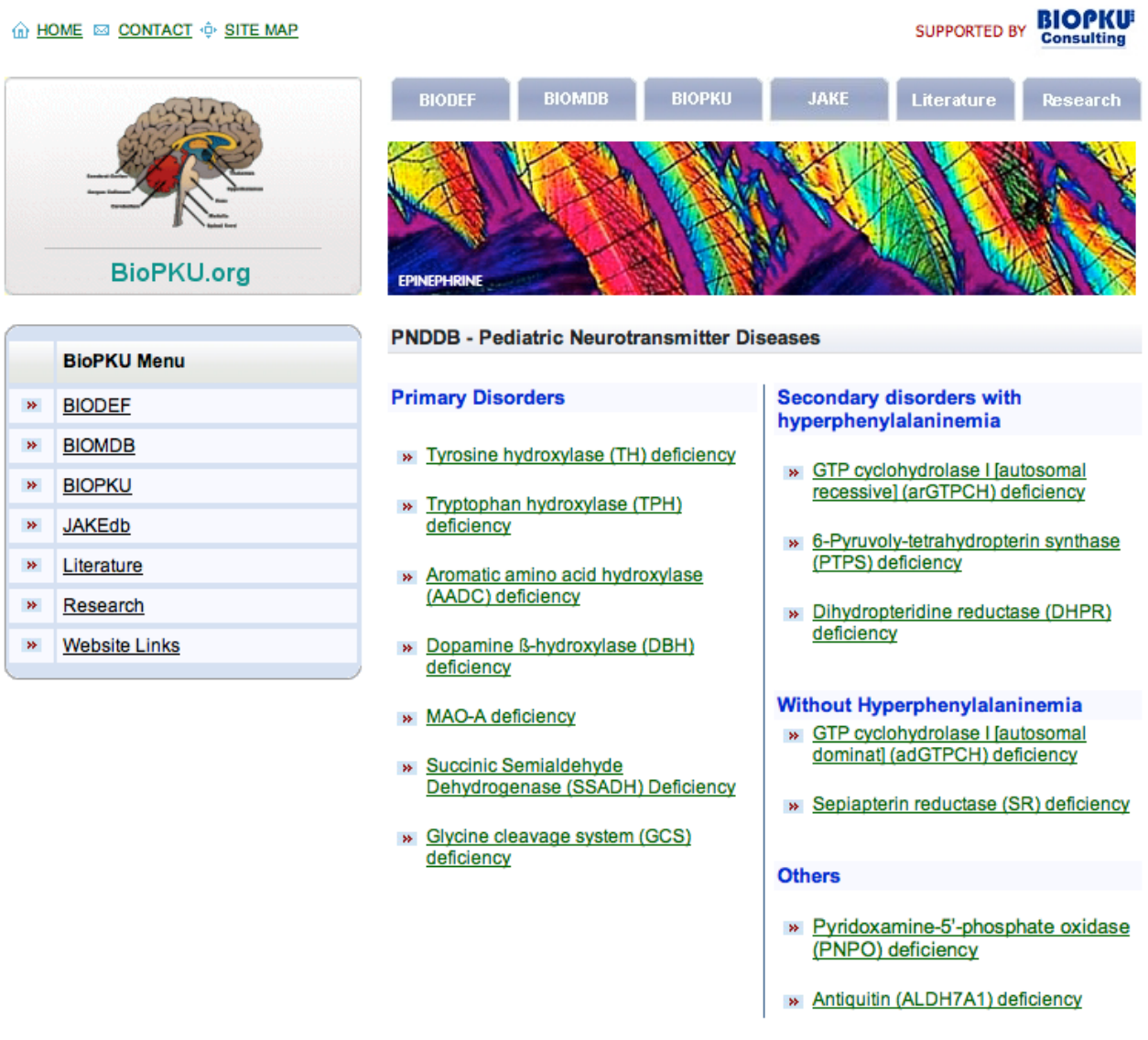
www.BIOPKU.org



University Children's Hospital Zürich, Switzerland

Databases of Pediatric Neurotransmitter Disorders

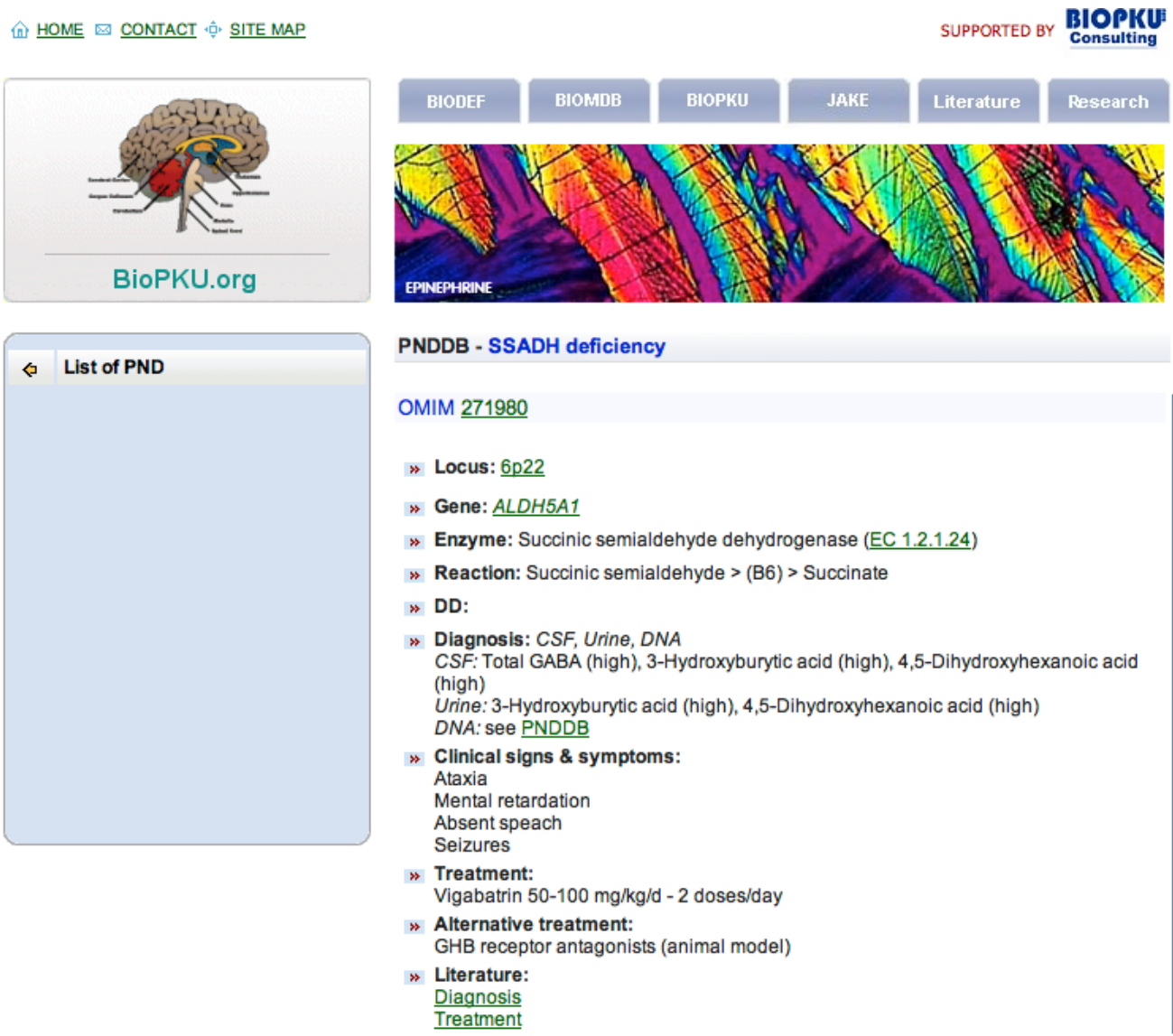
www.BIOPKU.org



University Children's Hospital Zürich, Switzerland

Databases of Pediatric Neurotransmitter Disorders

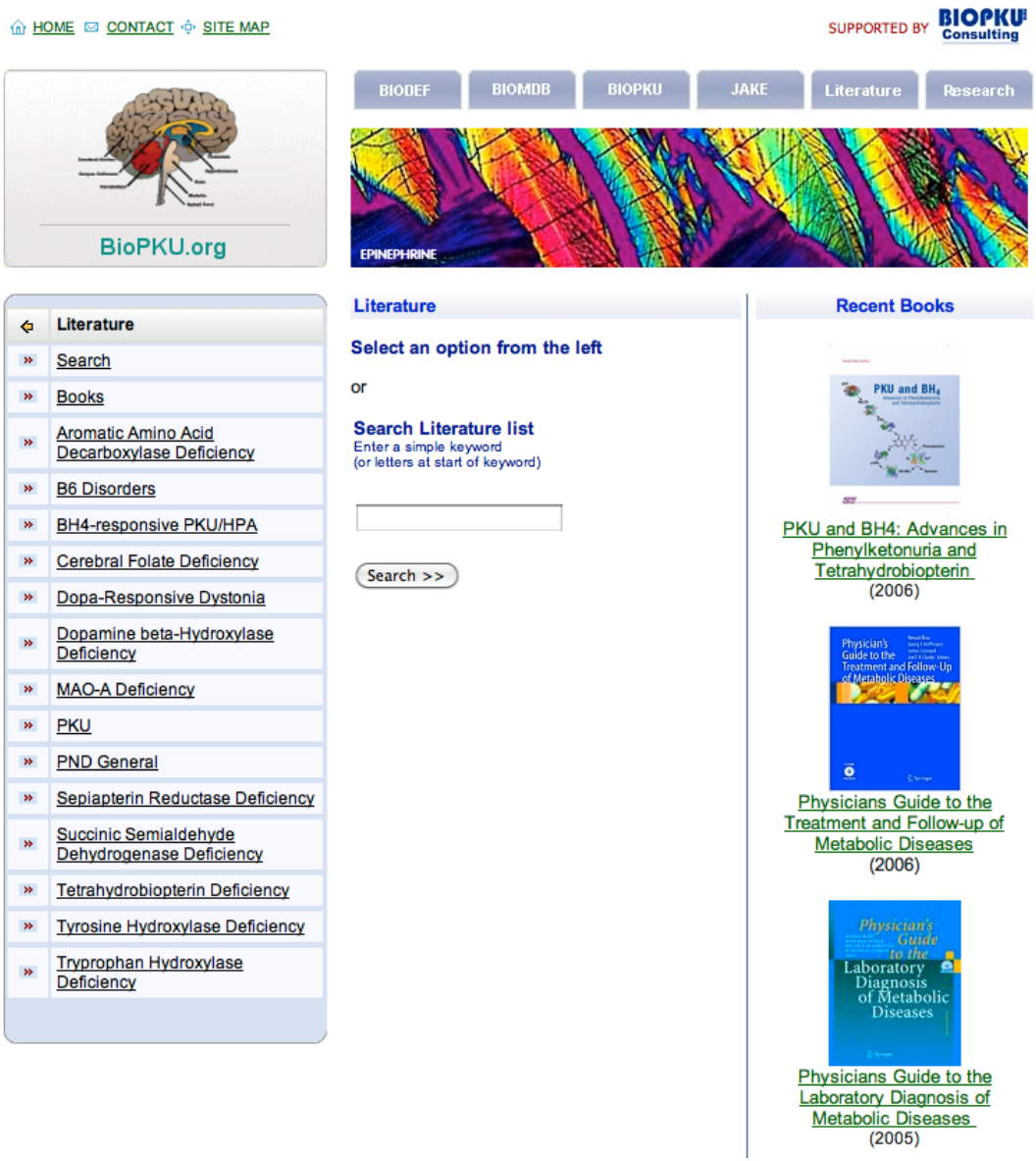
www.BIOPKU.org



University Children's Hospital Zürich, Switzerland

Databases of Pediatric Neurotransmitter Disorders

www.BIOPKU.org



University Children's Hospital Zürich, Switzerland

Conclusions

Patients with typical signs and symptoms of psychomotor retardation with hypo/dyskinesia, truncal hypotonia, ataxia, oculogyric crises and epileptic seizures should be tested for CSF neurotransmitter metabolites, amino acids and folates.

<u>Children's Hospital Zürich (1995 – 2009)</u>

5'100 CSF samples

5-6% pathological profile

1.8% with final diagnosis