

Neurotransmitter Disorders Clinical Presentation and Diagnosis

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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.



Classification

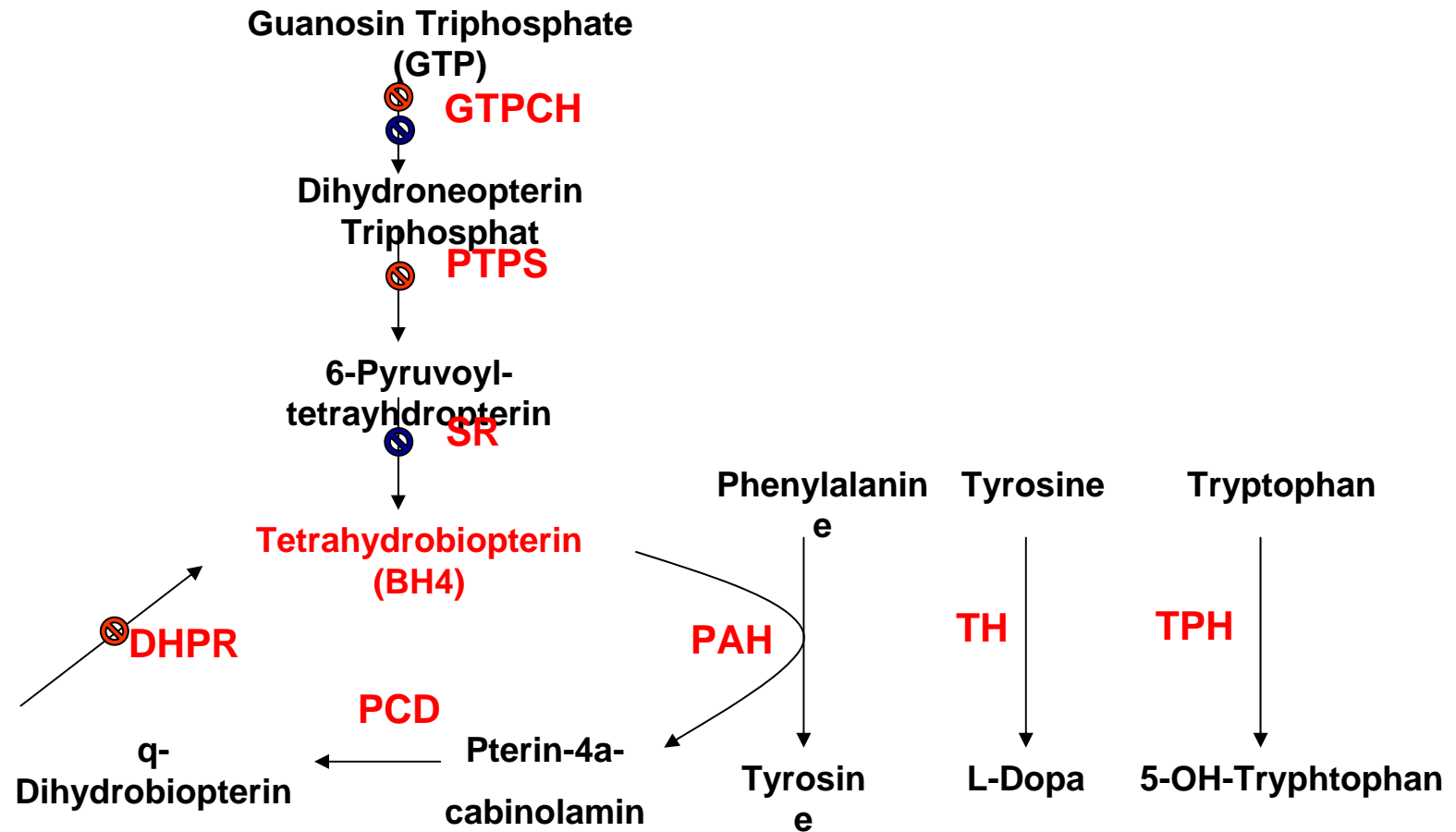
- Disorders of tetrahydrobiopterin (BH₄)
- Disorders in catecholamines and serotonin metabolism
- Disorders of serine and glycine metabolism
- Disorders of glutamate and GABA
- Disorders of folate deficiency
- Disorder of B₆ metabolism



Classification

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

Tetrahydrobiopterin Metabolism



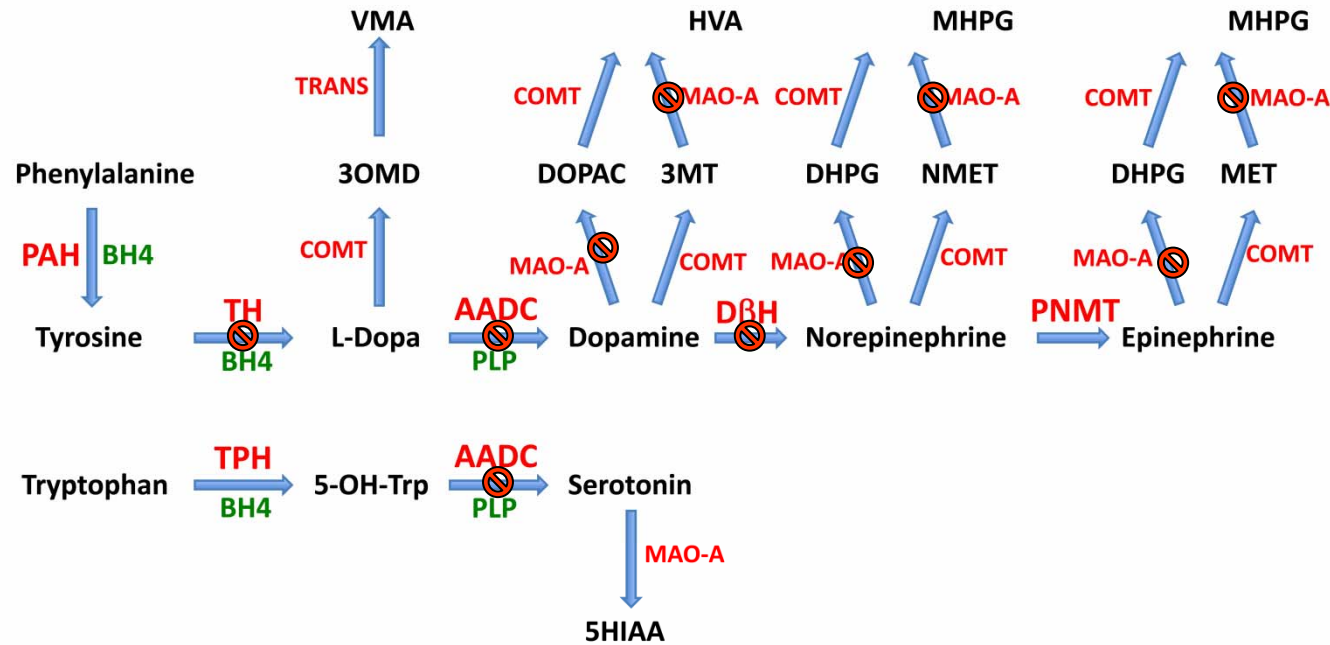


Classification

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



Disorders in catecholamines and serotonin metabolism



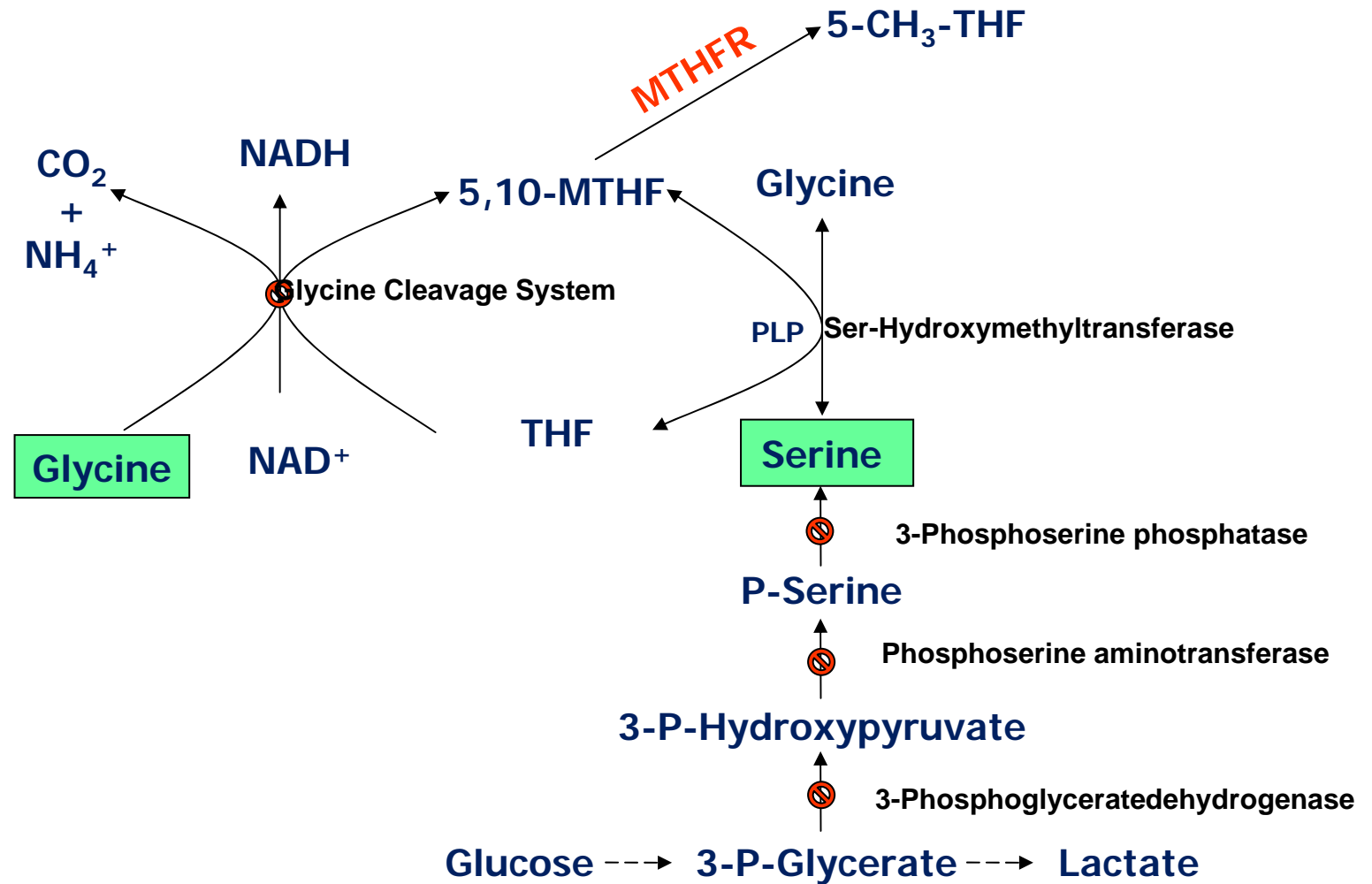


Classification

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



Disorders of glycine and serine metabolism



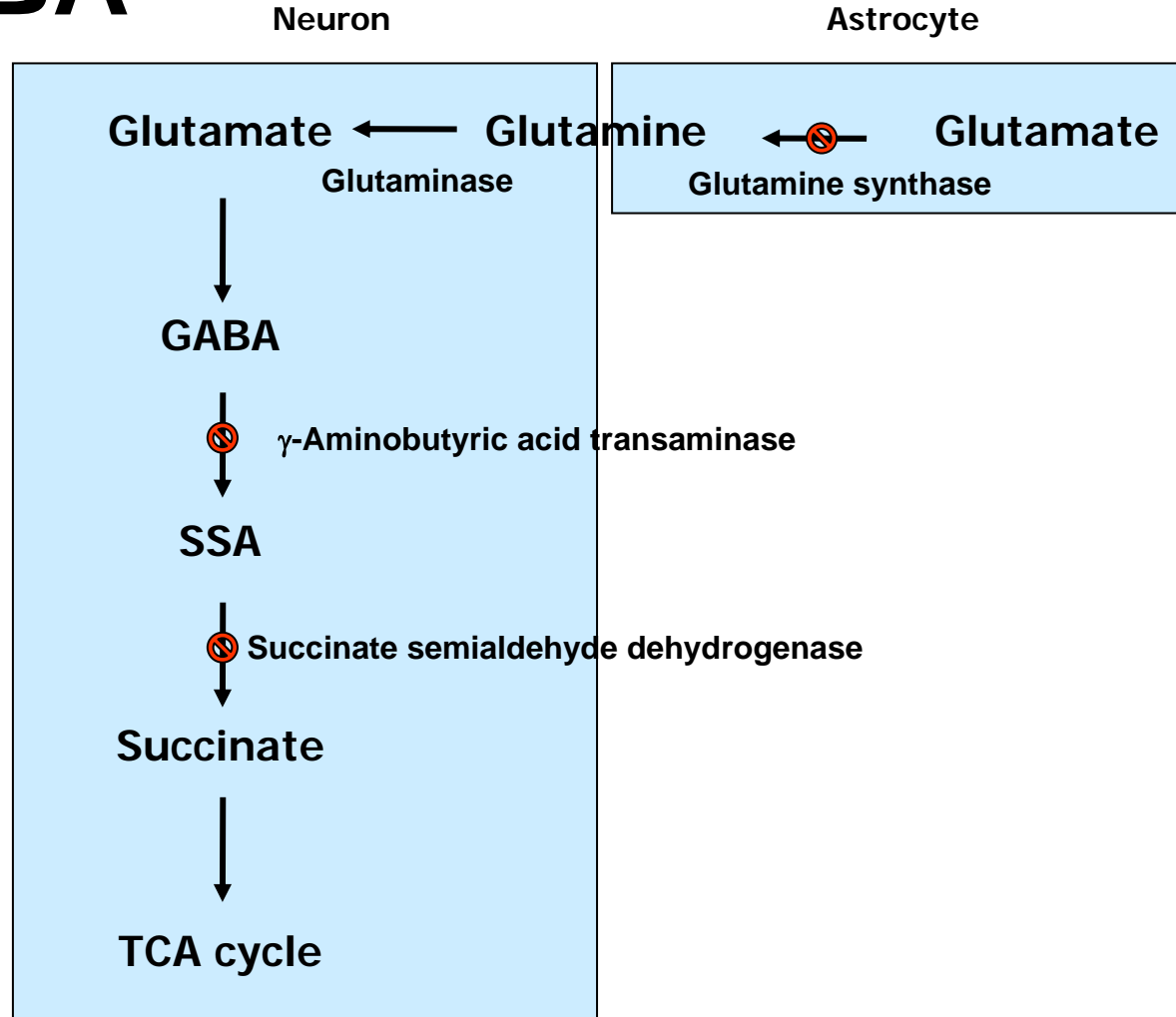


Classification

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



Disorders of glutamate and GABA



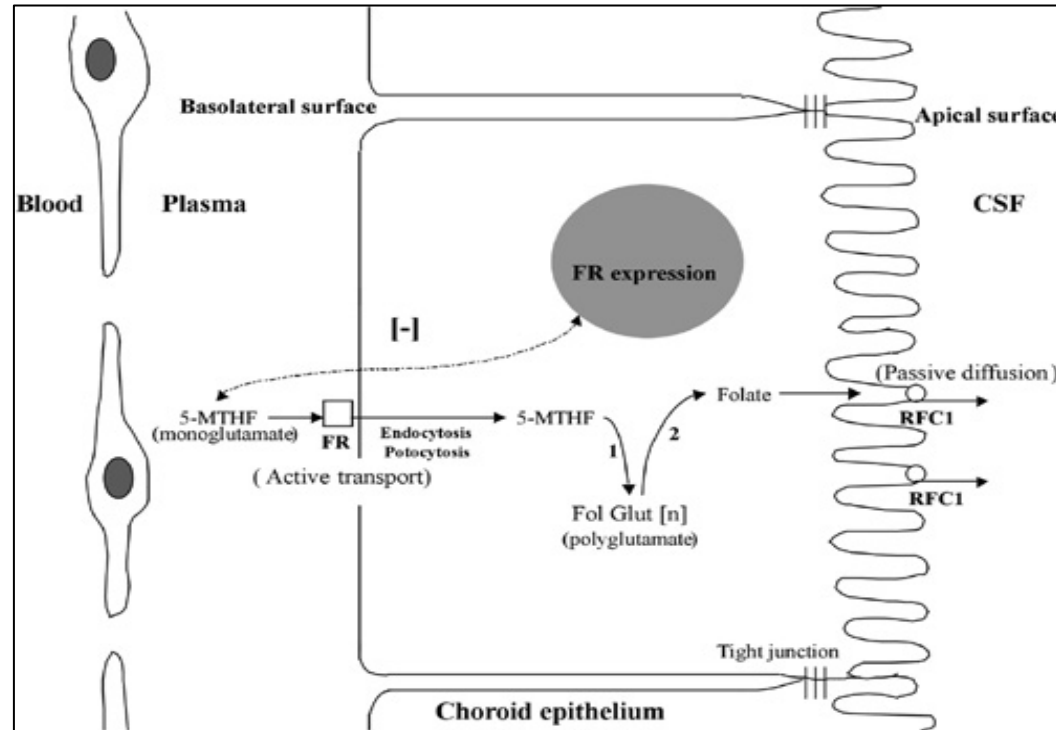


Classification

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

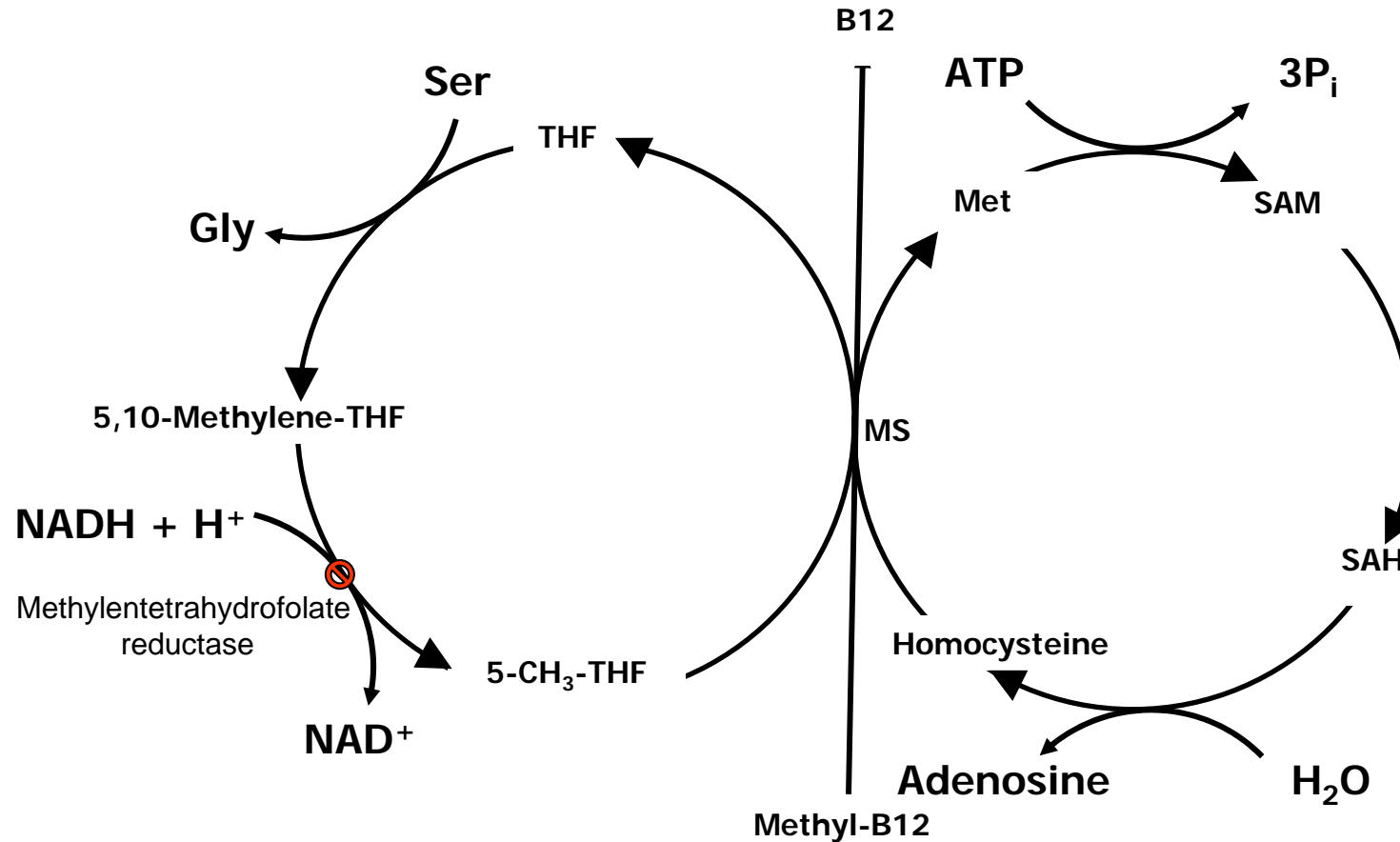


Disorders of folate transport





Disorders of folate metabolism

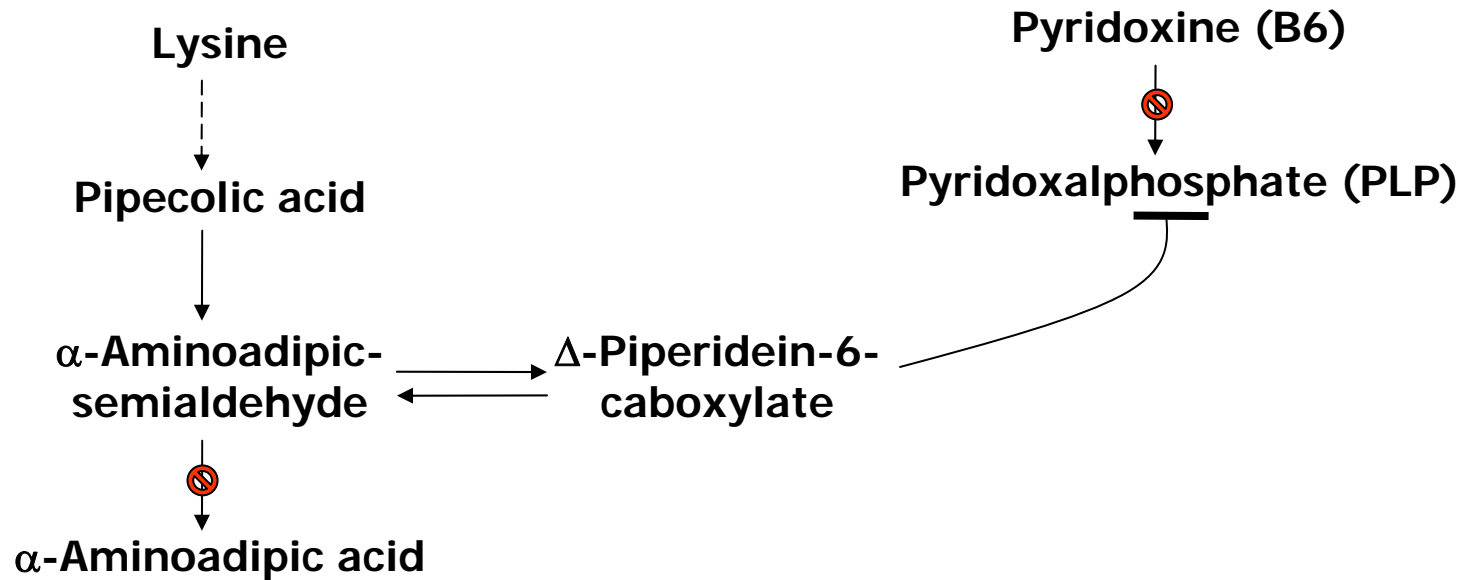




Classification

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

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 (BH₄) deficiency (HPA)

- Defect in catabolism

Monoamine oxydase A

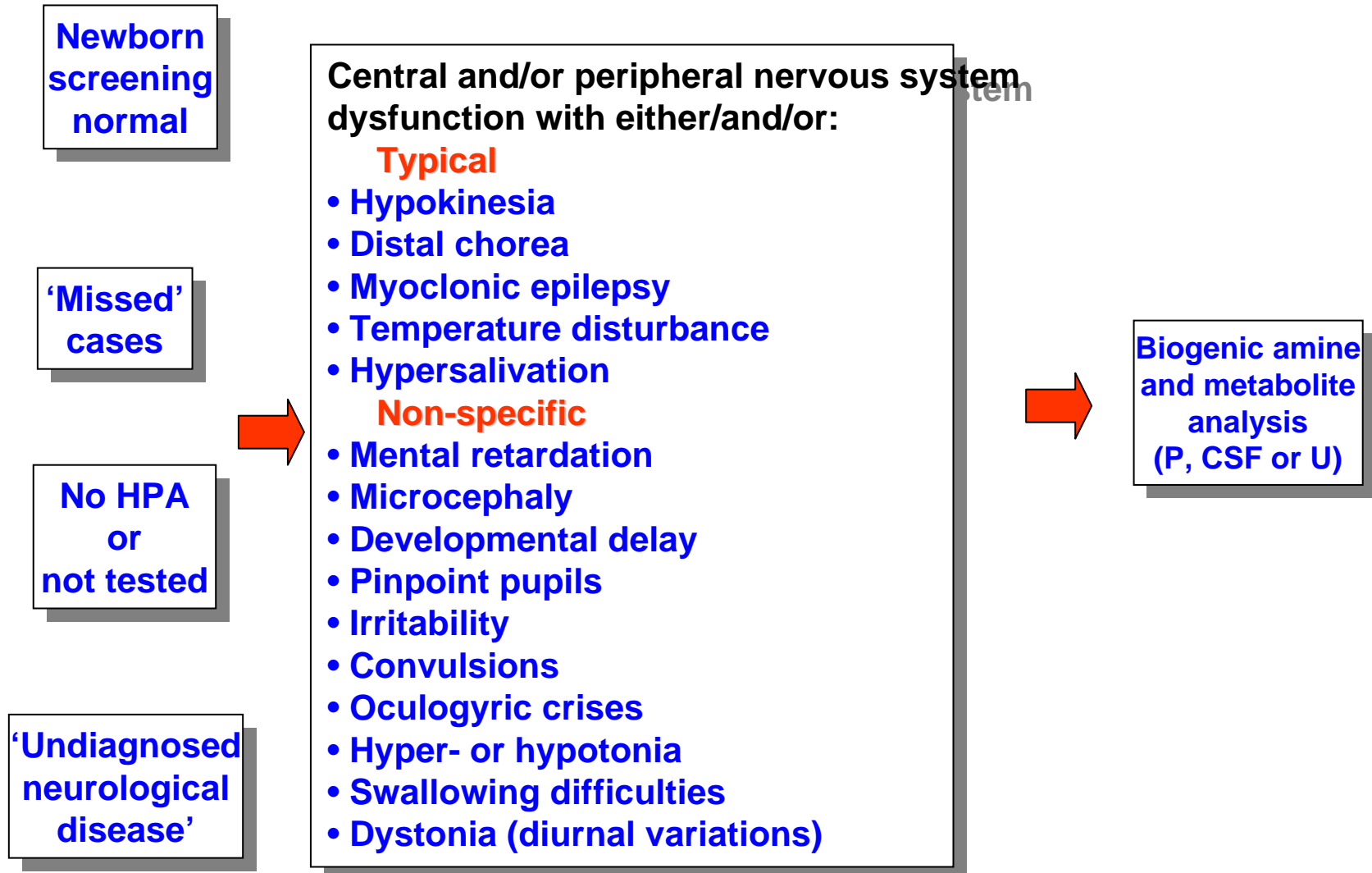
Secondary

- Classical PKU

*Competitive inhibition of TH and
TPH*

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

Guidelines for the Screening





SIGNS & SYMPTOMS

+

TREATMENT

Patients' pictures and movies removed from the presentation



Symptoms Related to Specific Biogenic Amine Deficiency

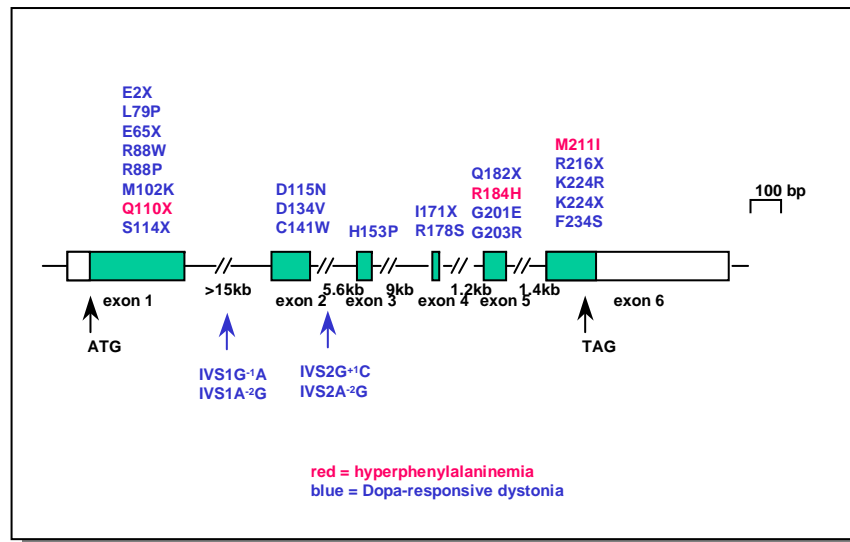
Dopamine	Serotonin	Norepinehrine
Immobility	Depression	Axial hypotonia
Parkinsonism	Altered thermogenesis	Cerebellar symptoms
Sleepiness	Insomnia	Ptosis
Dystonia		
Eye rolling		
Hypersalivation		
Swallowing difficulties		

Dopa-responsive Dystonia (DRD)

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

Inheritance autosomal dominant (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) (vanillic acid)		↑		
	Eye	Oculogyric crises		+	+
Ptosis		+	+	+	+
Miosis		+	+		

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
Brain imaging	Chorea	22	17/78	7/38	9/33	1/4	0/3
	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

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
Tranlycypromide	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
Trihexyphenydydyl	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

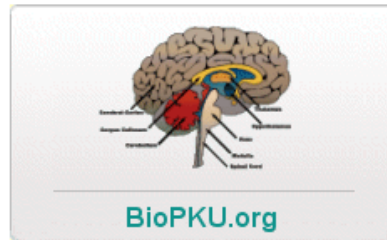
Databases of Pediatric Neurotransmitter Disorders



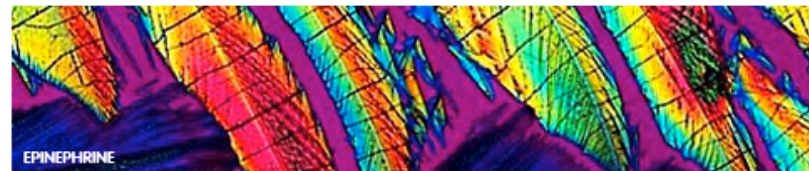
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Databases of Pediatric Neurotransmitter Disorders inc. PKU

Welcome

» About the website

BioPKU.org Website hosts databases of Pediatric Neurotransmitter Disorders (PND) incl. a database of PKU Genotypes:

BIODEF - Database of BH4-deficient patients

BIOMDB - Database of mutations causing BH4 deficiencies and PND

JAKE - Database of patients with PND

BIOPKU - Database of PKU genotypes investigated for BH4-responsiveness

[List of PND](#)

Conferences and Workshops

»

» PND Conference 2009

[San Diego, CA, USA -August 29th](#)

»

Call for Grant Applications

» PND Association

[Announcement - Research Proposal](#)

Website Links

» Frequently accessed websites

[BH4 Home Page](#)

[AADC Research Trust](#)

[PND Association](#)

Website Curator

» Nenad Blau

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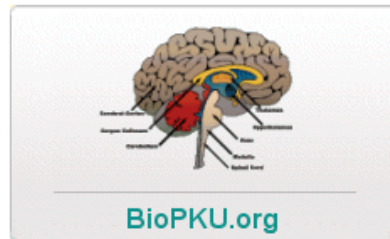
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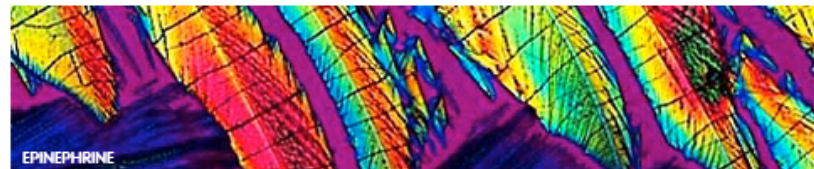
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PNDDDB - Pediatric Neurotransmitter Diseases

Primary Disorders

- » [Tyrosine hydroxylase \(TH\) deficiency](#)
- » [Tryptophan hydroxylase \(TPH\) deficiency](#)
- » [Aromatic amino acid hydroxylase \(AADC\) deficiency](#)
- » [Dopamine β-hydroxylase \(DBH\) deficiency](#)
- » [MAO-A deficiency](#)
- » [Succinic Semialdehyde Dehydrogenase \(SSADH\) Deficiency](#)
- » [Glycine cleavage system \(GCS\) deficiency](#)

Secondary disorders with hyperphenylalaninemia

- » [GTP cyclohydrolase I \[autosomal recessive\] \(arGTPCH\) deficiency](#)
- » [6-Pyruvoly-tetrahydropterin synthase \(PTPS\) deficiency](#)
- » [Dihydropteridine reductase \(DHPR\) deficiency](#)

Without Hyperphenylalaninemia

- » [GTP cyclohydrolase I \[autosomal dominant\] \(adGTPCH\) deficiency](#)
- » [Sepiapterin reductase \(SR\) deficiency](#)

Others

- » [Pyridoxamine-5'-phosphate oxidase \(PNPO\) deficiency](#)
- » [Antiquitin \(ALDH7A1\) deficiency](#)

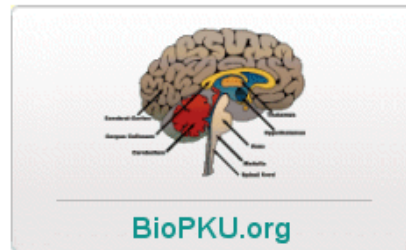
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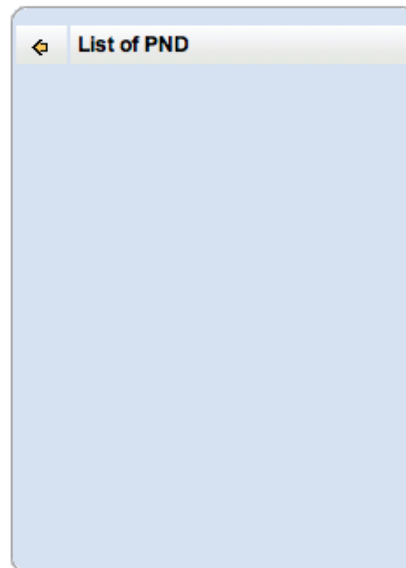
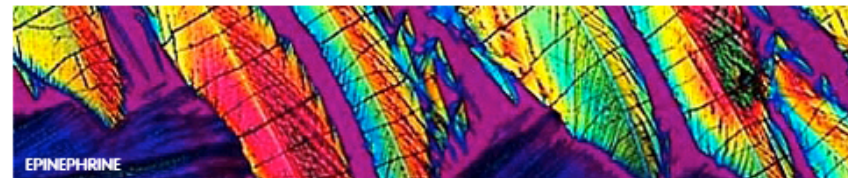
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PNDDB - SSADH deficiency

OMIM [271980](#)

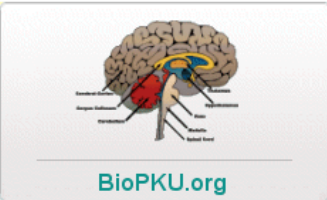
- » **Locus:** [6p22](#)
- » **Gene:** [ALDH5A1](#)
- » **Enzyme:** Succinic semialdehyde dehydrogenase ([EC 1.2.1.24](#))
- » **Reaction:** Succinic semialdehyde > (B6) > Succinate
- » **DD:**
- » **Diagnosis:** CSF, Urine, DNA
 CSF: Total GABA (high), 3-Hydroxybutyric acid (high), 4,5-Dihydroxyhexanoic acid (high)
 Urine: 3-Hydroxybutyric acid (high), 4,5-Dihydroxyhexanoic acid (high)
 DNA: see [PNDDB](#)
- » **Clinical signs & symptoms:**
 Ataxia
 Mental retardation
 Absent speech
 Seizures
- » **Treatment:**
 Vigabatrin 50-100 mg/kg/d - 2 doses/day
- » **Alternative treatment:**
 GHB receptor antagonists (animal model)
- » **Literature:**
[Diagnosis](#)
[Treatment](#)

Databases of Pediatric Neurotransmitter Disorders



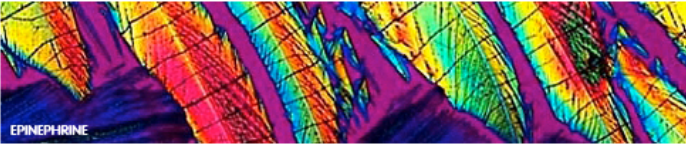
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Literature


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Recent Books



[PKU and BH4: Advances in Phenylketonuria and Tetrahydrobiopterin](#)
(2006)



[Physicians Guide to the Treatment and Follow-up of Metabolic Diseases](#)
(2006)



[Physicians Guide to the Laboratory Diagnosis of Metabolic Diseases](#)
(2005)



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.

Children's Hospital Zürich (1995 – 2009)

5'100 CSF samples

5-6% pathological profile

1.8% with final diagnosis