



# *Disorders of Dopamine & Serotonin Metabolism*

*Simon Heales*

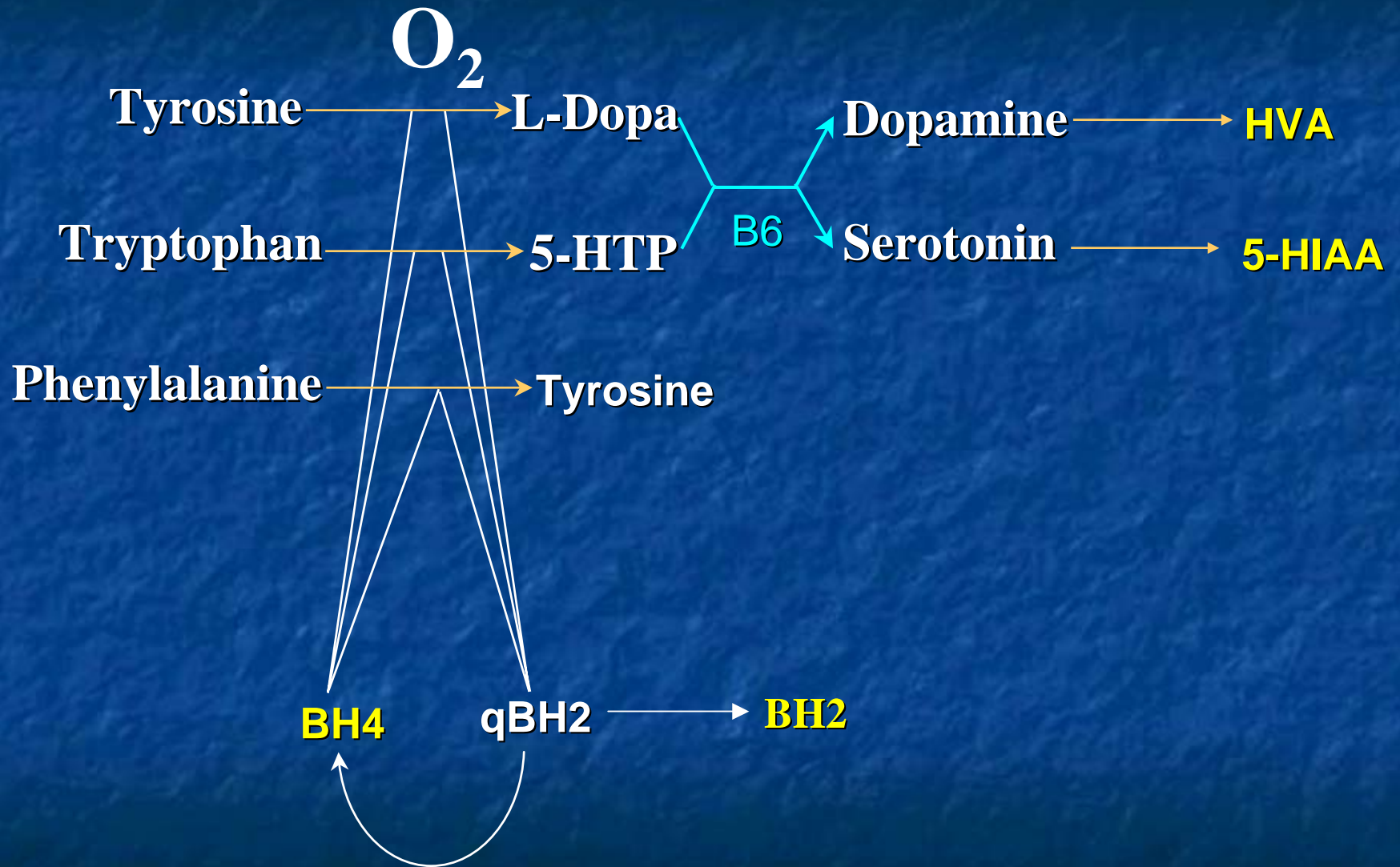
*Neurometabolic Unit*

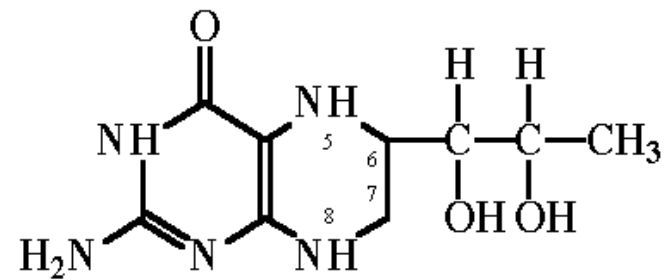
*A CPA accredited & SAS Laboratory*

*National Hospital (UCLH Trust)*

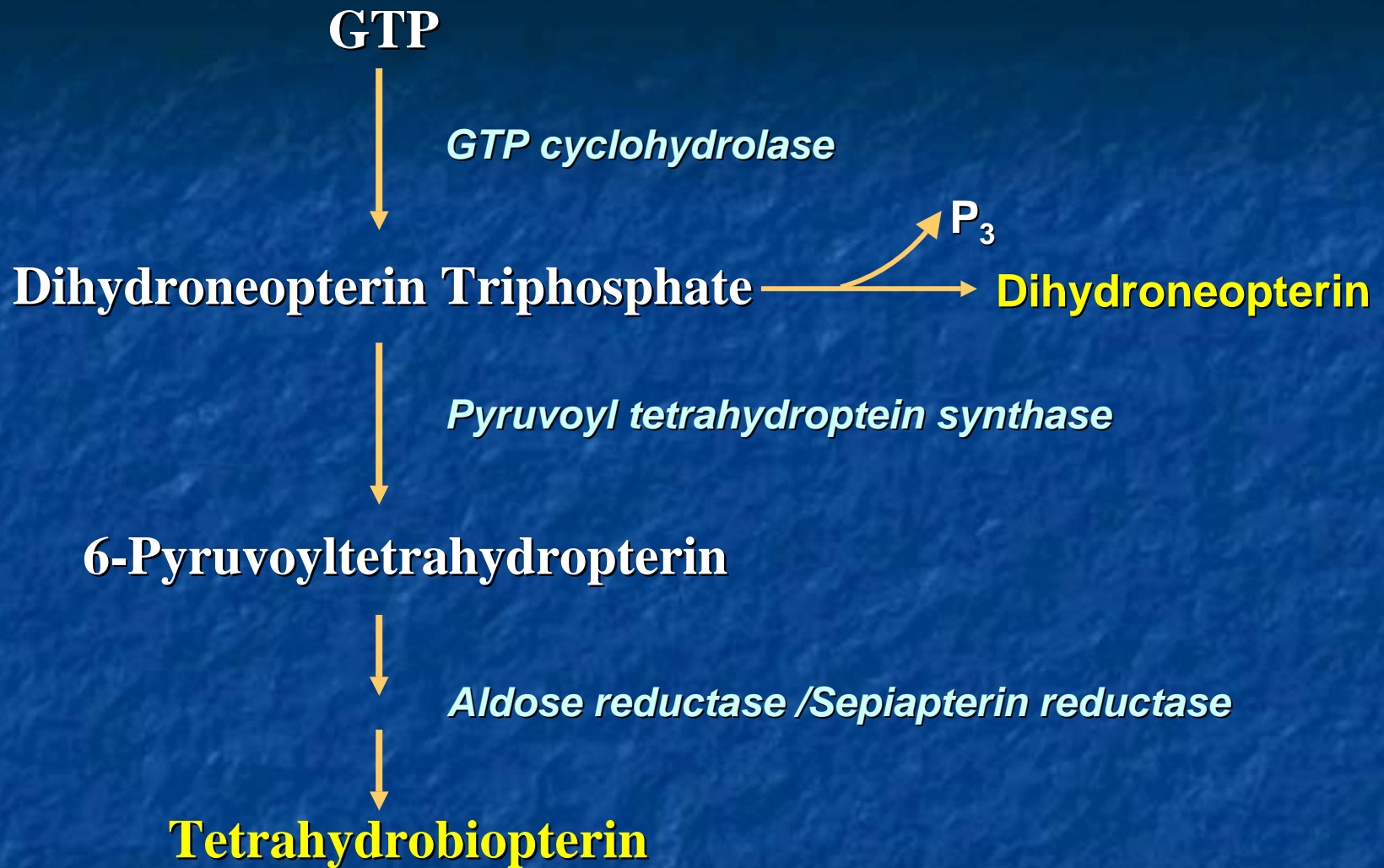
*Queen Square*

*London WC1N 3BG*

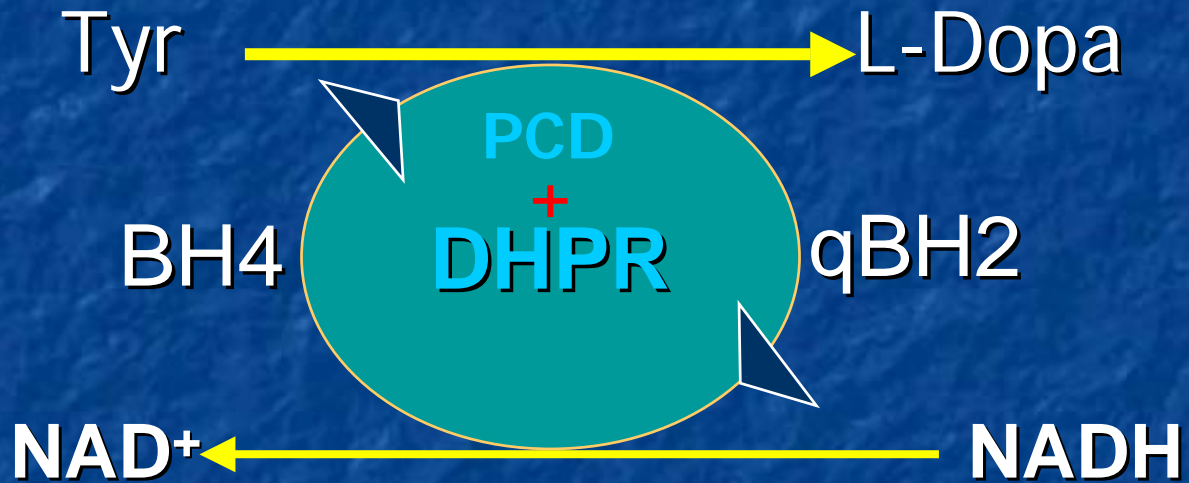




**5,6,7,8-Tetrahydrobiopterin**



# BH4 Salvage



PCD = pterin carbinolamine dehydratase  
DHPR = dihydropteridine reductase

# BH4 Deficiency

- Decreased spontaneous movements, mental retardation, convulsions, disturbances of tone and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia, hypersalivation, swallowing difficulties, diurnal fluctuations of alertness, microcephaly

# BH4 Deficiency

- Hyperphenylalaninaemia.
- Neurological impairment due to :-
  - Decreased DA and 5-HT metabolism.
  - Impaired NO metabolism ?
- Treatment; Phe restriction.
  - Monoamine replacement.
  - Folinic acid (DHPR deficiency)
  - BH4

# Diagnosis

- Detection of hyperphenylalaninaemia
- Plasma/urine pterin profile
- Serum prolactin
- Blood Spot DHPR

Caution – isolated CNS deficiency  
*Sepiapterin Reductase Deficiency*

- Enzymatic and mutation analysis

*CSF Analysis*

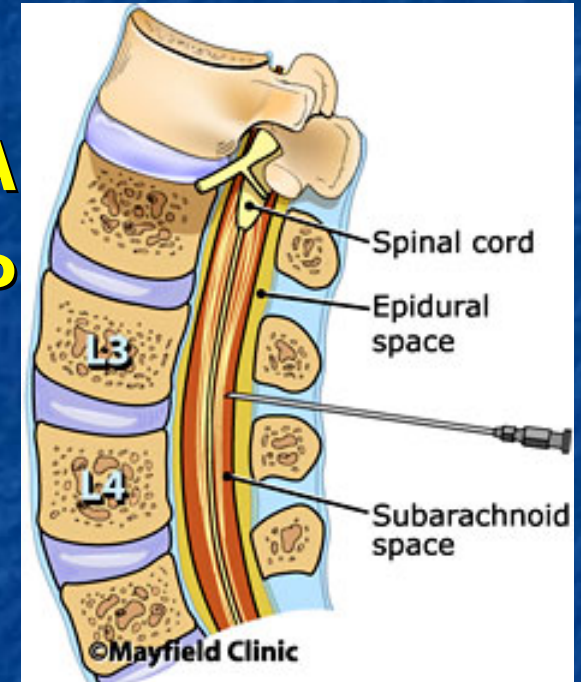


# Neurochemical Evaluation - CSF

- Determines degree of CNS pterin & monoamine deficiency.
- Can identify pterin defects **plus** other disorders of monoamine metabolism.
- Monitors response to treatment.
- HPLC + Electrochemical Detection.

# CSF – Sample Requirements

- *Tube 1* 0.5ml **HVA & 5-HIAA**
- *Tube 2* 0.5ml **5-MTHF & PLP**
- *Tube 3* 1.0ml **Pterins**  
(DTE/DETAPAC)



***Collect at bedside and freeze immediately (not the form !)***

Metabolite	Age (years)	nmol/L	
		Mean	Range
<b>HVA</b>	0 - 0.33	714	324-1098
	0.34 - 0.66	587	362-955
	0.67 - 1.00	508	176-851
	1.10 - 5.00	465	154-867
	5.1- Adult	281	71-565
<b>5-HIAA</b>	0 - 0.33	417	199-608
	0.34 - 0.66	271	63-503
	0.67 - 1.00	250	68-451
	1.10 - 5.00	185	89-367
	5.1- Adult	98	58-220

*Pediatr Res (1993) 34, 10-14*

Metabolite	Age (years)	nmol/L	
		Mean	Range
<b>BH4</b>	0 - 0.33	67	27-105
	0.34 - 0.66	37	23-55
	0.67 - 1.00	38	19-56
	1.10 - 5.00	33	8-57
	5.1- Adult	23	9-39
<b>BH2</b>	ALL	5.6	0.4-13.9
<b>NH2</b>	ALL	19	7-65

*Pediatr Res (1993) 34, 10-14*

# CSF - Results

↓ HVA & 5-HIAA + Pterins → GTP Cyclohydrolase def

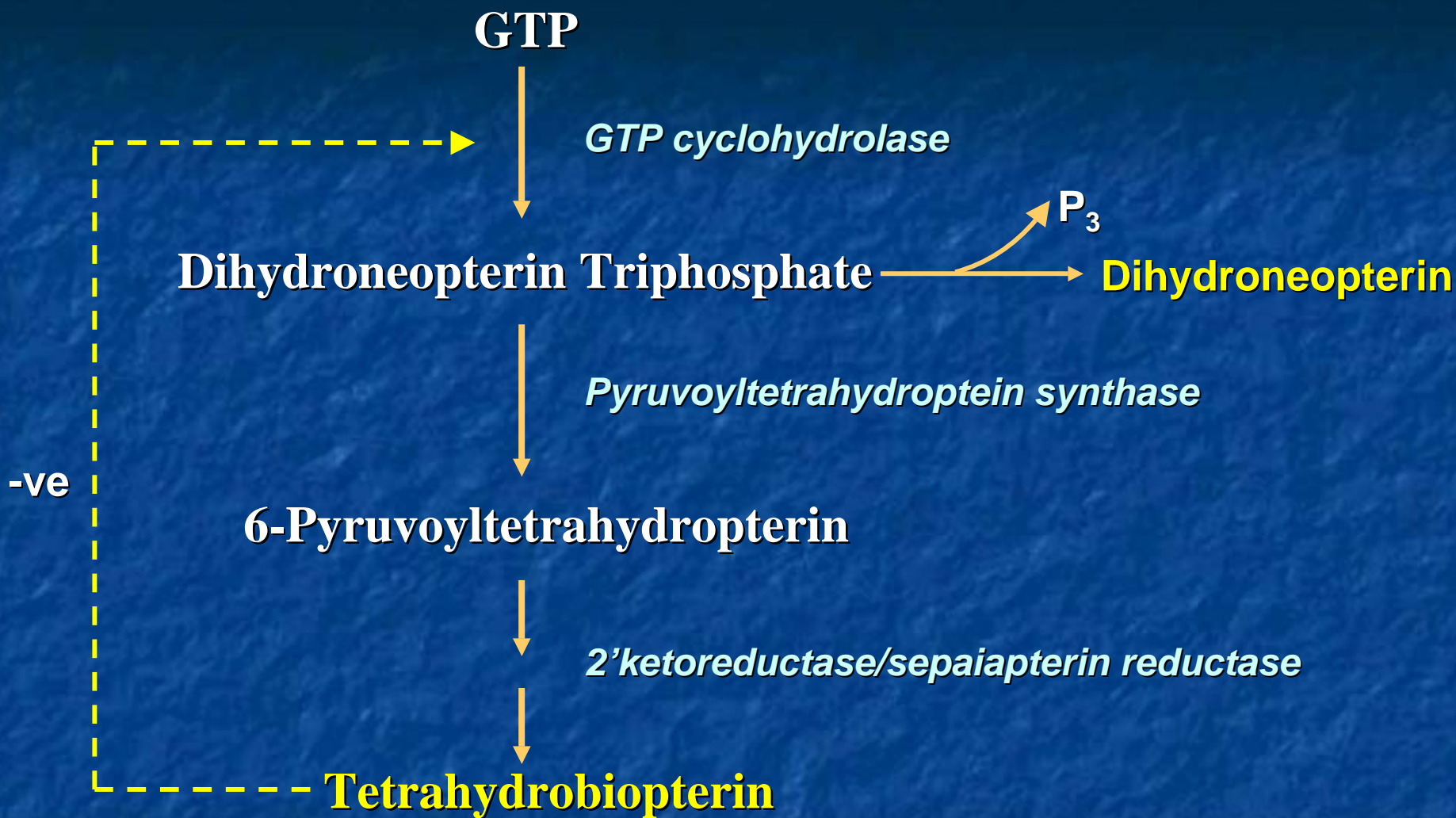
↓ HVA & 5-HIAA

↓ BH4 → PTP Synthase def

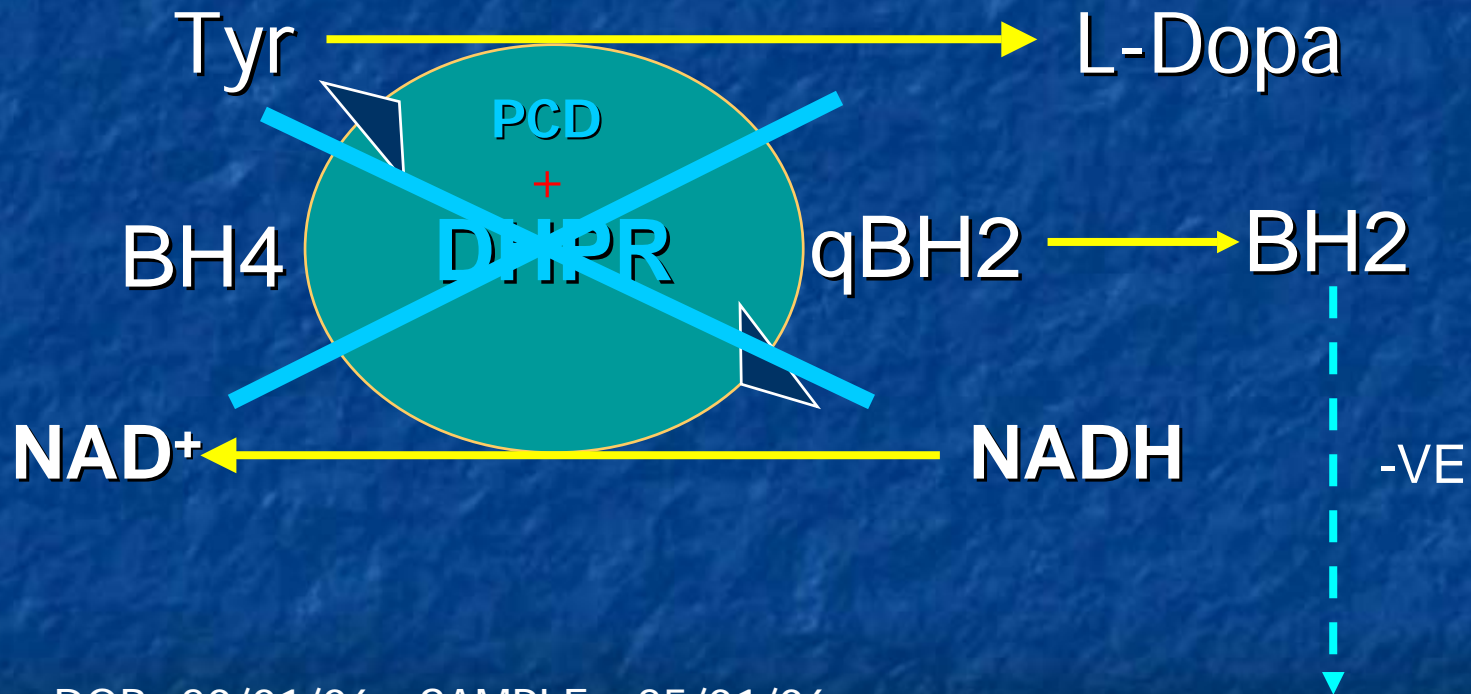
↑ NH2

↓ HVA & 5-HIAA

↑ BH2 → DHPR def



# DHPR Deficiency



DOB; 20/01/06 . SAMPLE; 25/01/06  
BH2; 106 (<0.4 – 13.9 nmol/L)

Folate Metabolism  
Monoamine Metabolism

# DHPR Deficiency – Response to Treatment





# Sepiapterin Reductase Deficiency

- 2 patients (14 & 9 year old males)
- Progressive psychomotor retardation, dystonia
- No Hyperphenylalaninaemia
- Normal urinary pterins
- **Low CSF HVA, 5-HIAA. Elevated BH2**

*Am. J. Hum Genet. (2001) 69, 269-277*

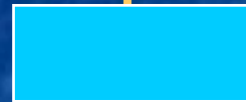
**GTP**



**Dihydroneopterin Triphosphate**



**6-Pyruvoyltetrahydropterin**



**BH2**



**DHFR**

**Tetrahydrobiopterin**



# Sepiapterin Reductase Deficiency

Sex; Male. Dob; 31/12/1987. Sample; 09/05/2003. Dystonia responsive to L-DOPA. No hyperphenylalaninaemia. DHPR normal.

HVA:	<b>23</b>	(71-565 nmol/L)
5-HIAA:	<b>2</b>	(58-220 nmol/L)
BH4:	<b>11</b>	(9-39 nmol/L)
BH2:	<b>64</b>	(0.4-13.9 nmol/L)
Total Neopterin:	<b>19</b>	(7-65 nmol/L)

# Outcome of Current treatment

- **Restoration of monoamine turnover by L-DOPA & 5-HTP**
- **Resolution of major but not all neurological signs**
- **Some cases severe developmental delay persists**
- **Poor response and variation may be due to**
  - **Severity of metabolic defect**
    - **Irreversible brain damage occurring *in utero***
    - **Failure to Correct primary defect**
    - **NO Metabolism**

# L-Dopa Responsive Dystonia

- Typical onset in first decade - dystonic equinus posturing of the feet that spreads to other extremities.
- Can present later with parkinsonian features.
- Marked diurnal fluctuation.
- Response to L-Dopa appears complete and enduring.
- Has been misdiagnosed as cerebral palsy.



# L-Dopa Responsive Dystonia

- Hereditary progressive dystonia (Segawa et al., 1971).
- Autosomal Dominant – Female predominance (4:1).
- GTP cyclohydrolase – a causative gene (Ichinose et al., 1994)

*Mutations in gene cause at least 2 disorders:-*

**AR** – present within 6 months, hyperphenylalaninaemia & neurological dysfunction.

**AD** - DRD. Residual activity 2-20%.

# L-Dopa Responsive Dystonia

- *Lowish* CSF concentrations of :-

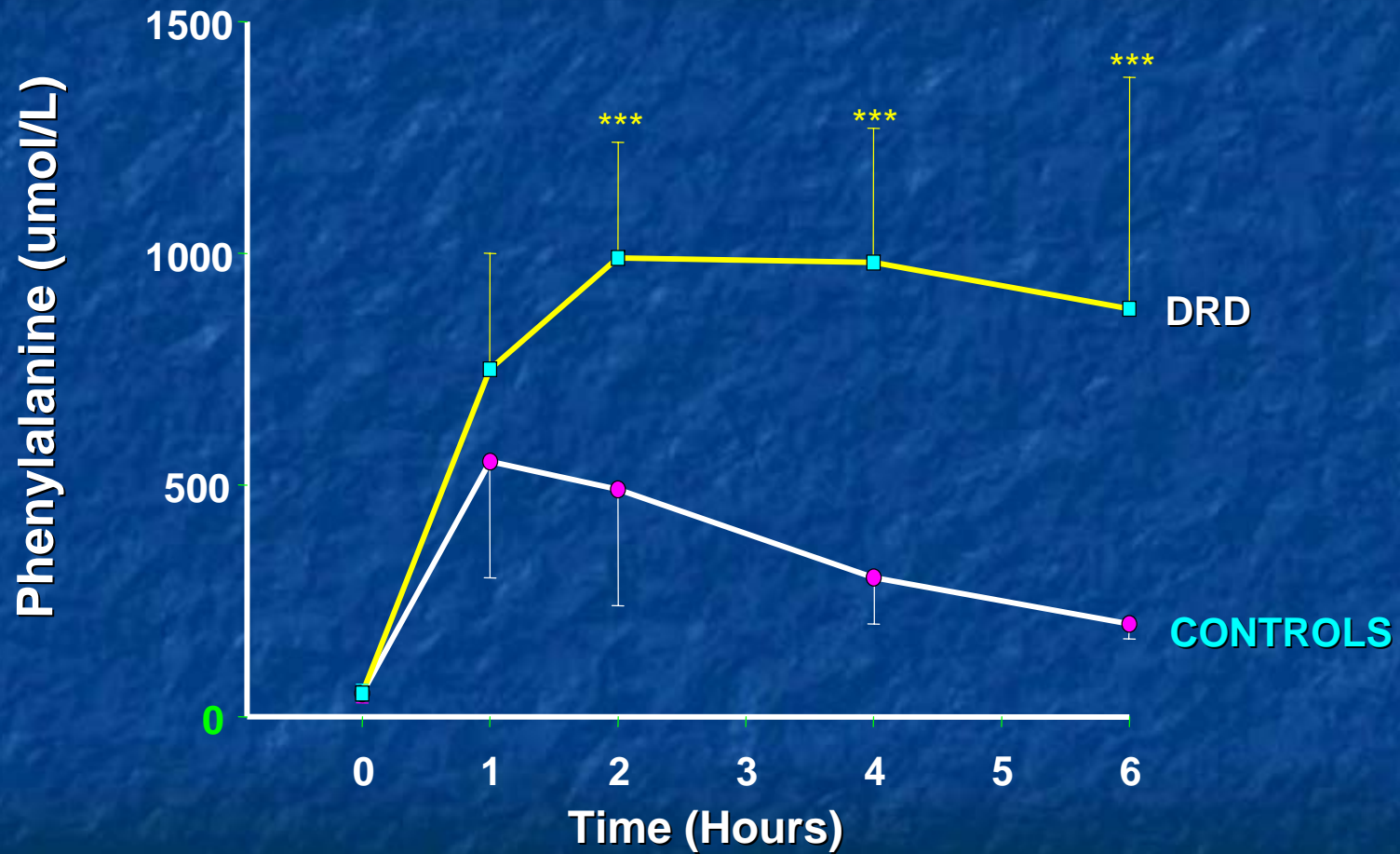
**BH4**

**Neopterin.**

**HVA.**

- Impaired phenylalanine tolerance.

# Plasma Phenylalanine after 100mg/kg oral Phenylalanine





# Tyrosine Hydroxylase Deficiency



- Parkinsonian, ptosis, drooling, myoclonic jerks, severe head lag and trunkal hypotonia.
- L-Dopa  $\longrightarrow$  marked and sustained improvement in hypokinesia and parkinsonian symptoms.
- Identified from *CSF analysis; Normal pterin & 5-HIAA concentration. Very low HVA. Mutation analysis also available.*

# Tyrosine Hydroxylase Deficiency

Sex; Female. Dob; 12/04/2000. Sample; 14/12/2001

**HVA:**                    **22**      (154-867 nmol/L)

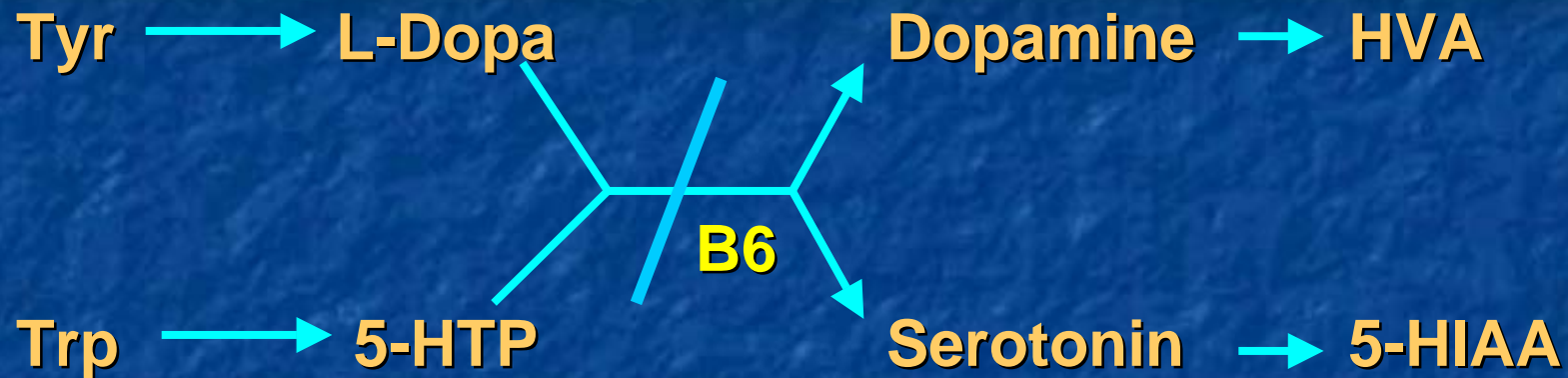
**5-HIAA:**                **165**    ( 89-367 nmol/L)

**BH4:**                    **47**      (8-57 nmol/L)

**BH2:**                    **10**      (0.4-13.9 nmol/L)

**Total Neopterin:** **11**      (7-65 nmol/L)

# Aromatic Amino Acid Decarboxylase Deficiency

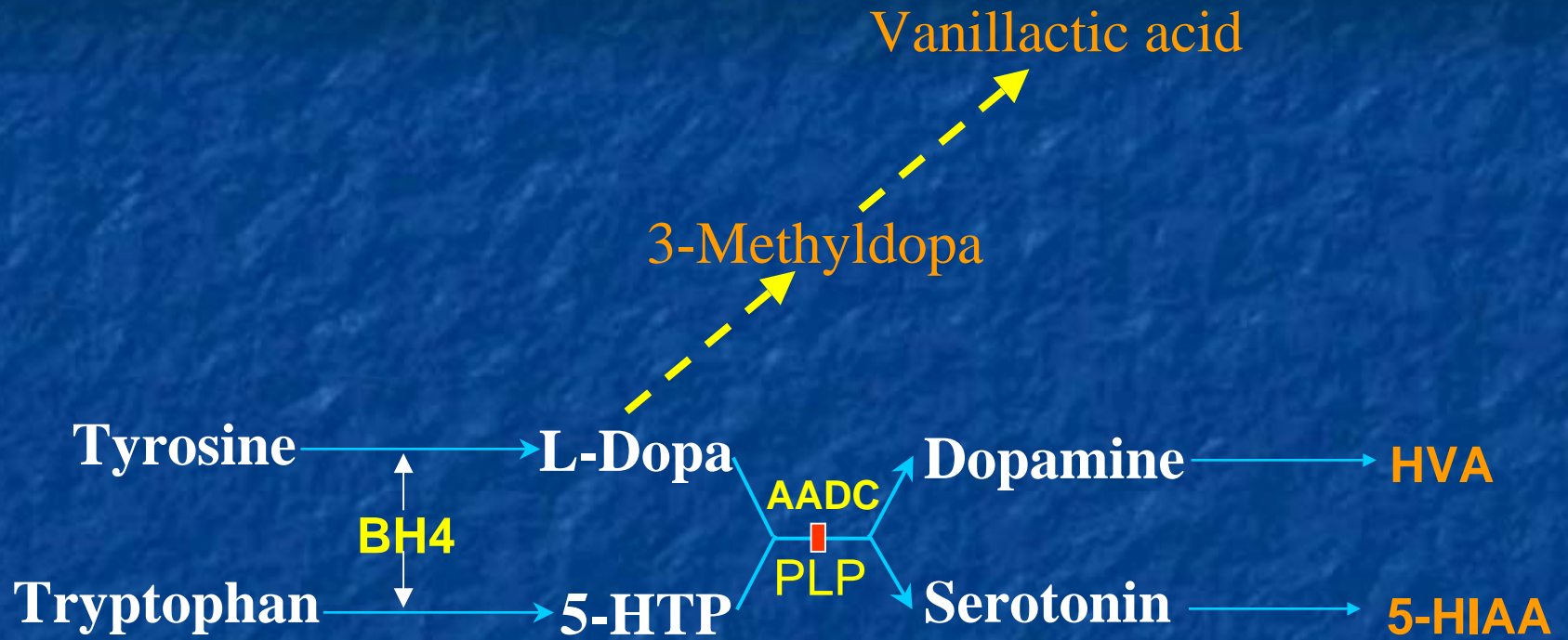


Clinical features resemble those of recessive BH4 deficiency; hypotonia, oculogyric crises, ptosis and paucity of spontaneous movement. Can be fatal

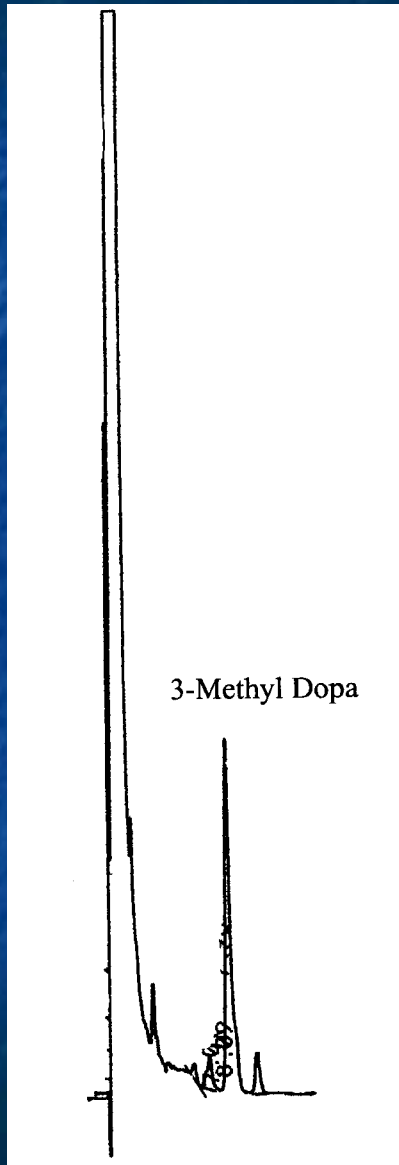
**Urine:** Vanillactic acid

**CSF:** Low HVA + 5-HIAA, but normal pterin profile and accumulation of 3-O-methyldopa. Enzymatic analysis possible on **plasma**.

Treatment; B6, MAOI & dopamine agonists.



# Aromatic Amino Acid Decarboxylase Deficiency



Sex; Male

Dob; 02/03/1998. Sample; 05/07/2001

HVA

**52** (154-867 nmol/L)

5-HIAA

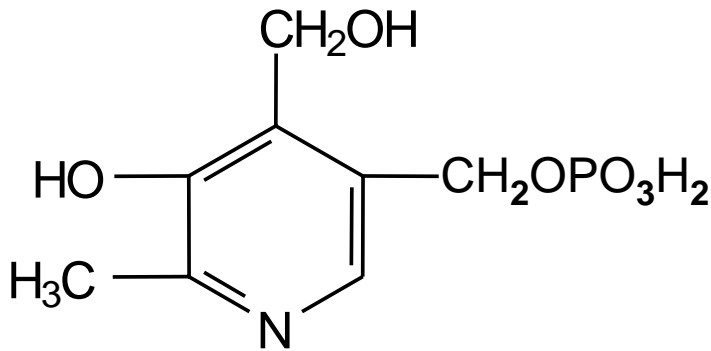
**22** (89-367 nmol/L)

3-Methyldopa

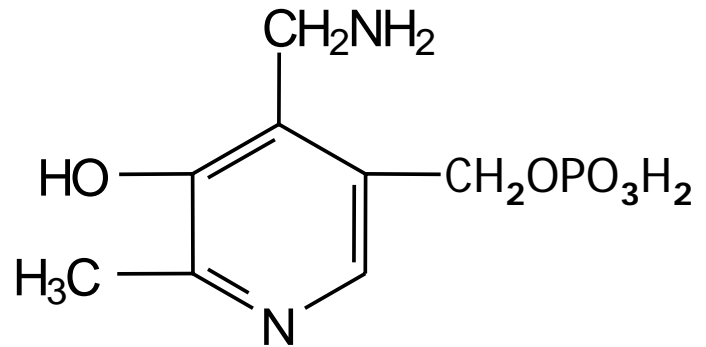
**589** (< 50 nmol/L)

# Pyridox(am)ine-5'-Oxidase Deficiency

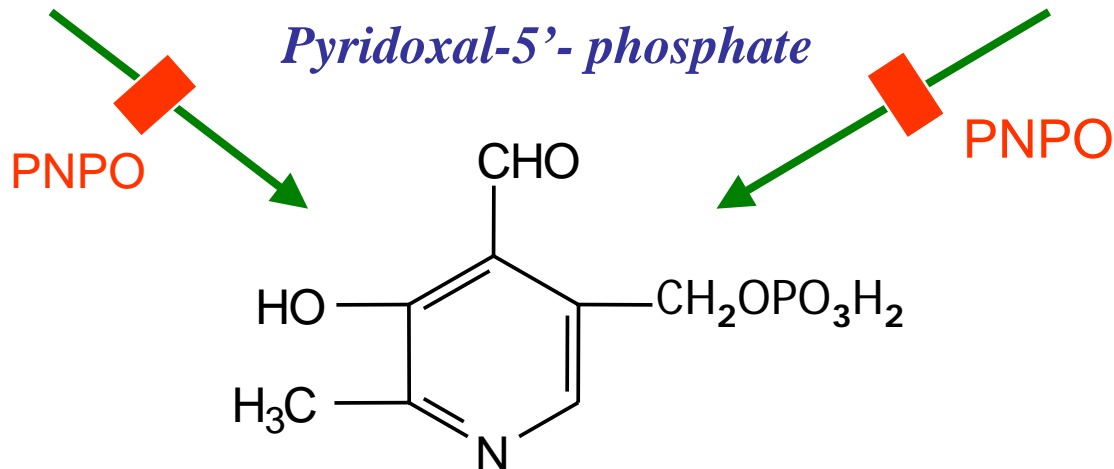
*Pyridoxine-5'-phosphate*



*Pyridoxamine-5'-phosphate*



*Pyridoxal-5'-phosphate*



PNPO = Pyridox(am)ine-5'-oxidase

# PNPO Deficiency

- Neonatal epileptic encephalopathy
- Fetal distress, prenatal seizures, low Apgar.
- ↑ Lactate (blood, CSF), pseudo AADC deficiency
- ↑ Glycine & Threonine (blood, CSF)
- ↓ Pyridoxal phosphate (CSF)

# PNPO Deficiency

J Inherit Metab Dis (2007) 30:96–99  
DOI 10.1007/s10545-006-0508-4

ORIGINAL ARTICLE

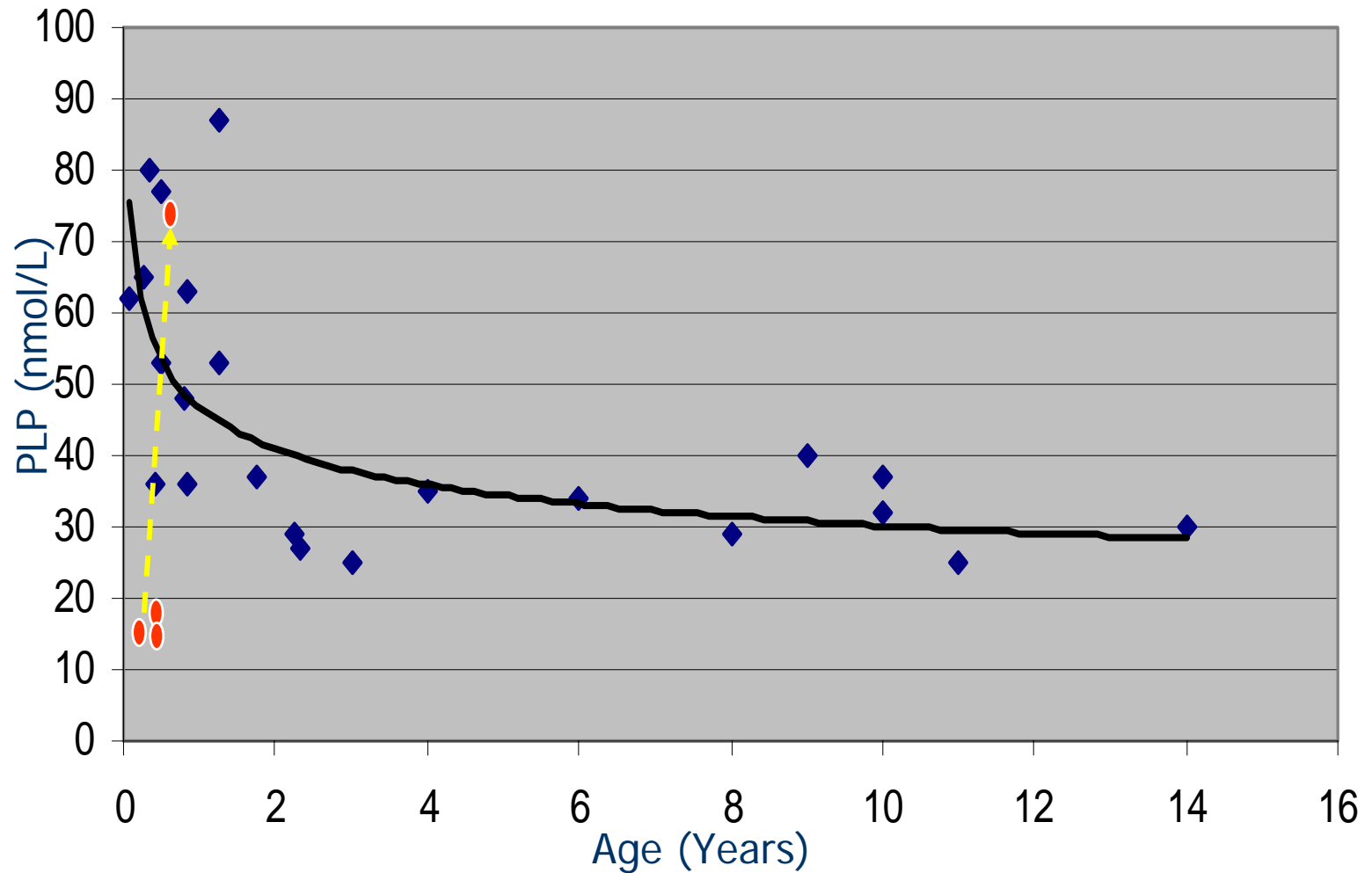
## Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy

G. F. Hoffmann · B. Schmitt · M. Windfuhr · N. Wagner · H. Strehl · S. Bagci ·  
A. R. Franz · P. B. Mills · P. T. Clayton · M. R. Baumgartner · B. Steinmann · T. Bast ·  
N. I. Wolf · J. Zschocke

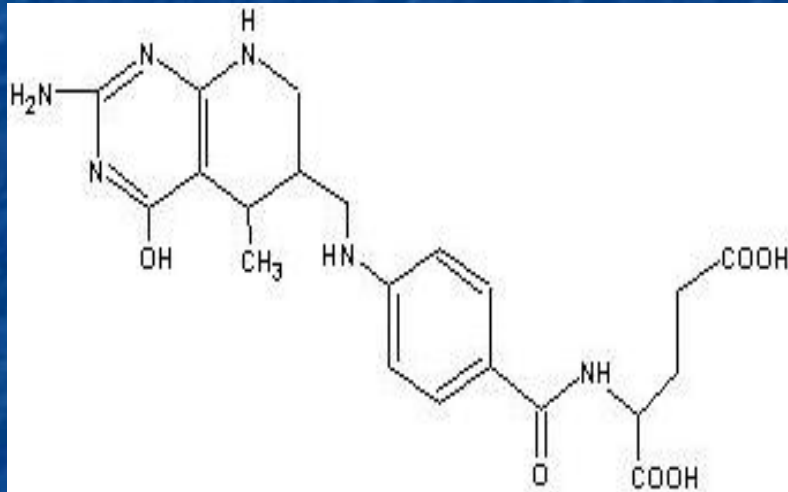
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# CSF (PLP)



# CSF 5-MTHF Deficiency



5-methyl tetrahydrofolate

- DHPR deficiency
- MTHFR deficiency
- AADC deficiency
- 3-Phosphoglycerate dehydrogenase def
- Rett syndrome
- Aicardi Goutieres
- Mitochondrial disorders
- L-dopa treatment
- Methotrexate
- Anticonvulsants
- Steroids
- Co-trimoxazole

# Cerebral Folate Deficiency

- Neurological syndrome associated with low CSF 5-MTHF and normal peripheral folate.
- Decreased transport/increased turnover ?
  - 20 children reviewed:
    - 4 months unrest, irritability, sleep disturbances followed by psychomotor retardation, cerebellar ataxia, spastic paraplegia & dyskinesia. Autistic features. Epilepsy in 33% of cases.*
    - Visual disturbances around 3 years.*
    - Imaging; atrophy of frontotemporal regions and periventricular demyelination in 7 children.*

Oral folinic acid associated with favourable clinical response



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Molecular Genetics and Metabolism 84 (2005) 371–373

Molecular Genetics  
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Brief communication

## Cerebral folate deficiency: life-changing supplementation with folinic acid

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Available online 22 January 2005

5-MTHF

34.4

42.0 – 119.6 nmol/L

# CSF Analysis

- Pterin defects + sepiapterin reductase def.
- Tyrosine hydroxylase deficiency.
- Aromatic amino acid decarboxylase deficiency.
- Disorders of B6 metabolism.
- 5-MTHF deficiency.
- Monitor response to treatment.
- Tryptophan hydroxylase deficiency ?
- Immune response activation (neopterin)
- **Be aware of secondary causes !**



*Hope for tomorrow  
begins today*



*the most precious gift in the world is the love of a child - when that life is so cruelly jeopardised by a PND you learn to cherish every waking moment and live in the hope that somebody, somewhere, somehow will find a cure...*

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