Disorders of Dopamine & Serotonin Metabolism

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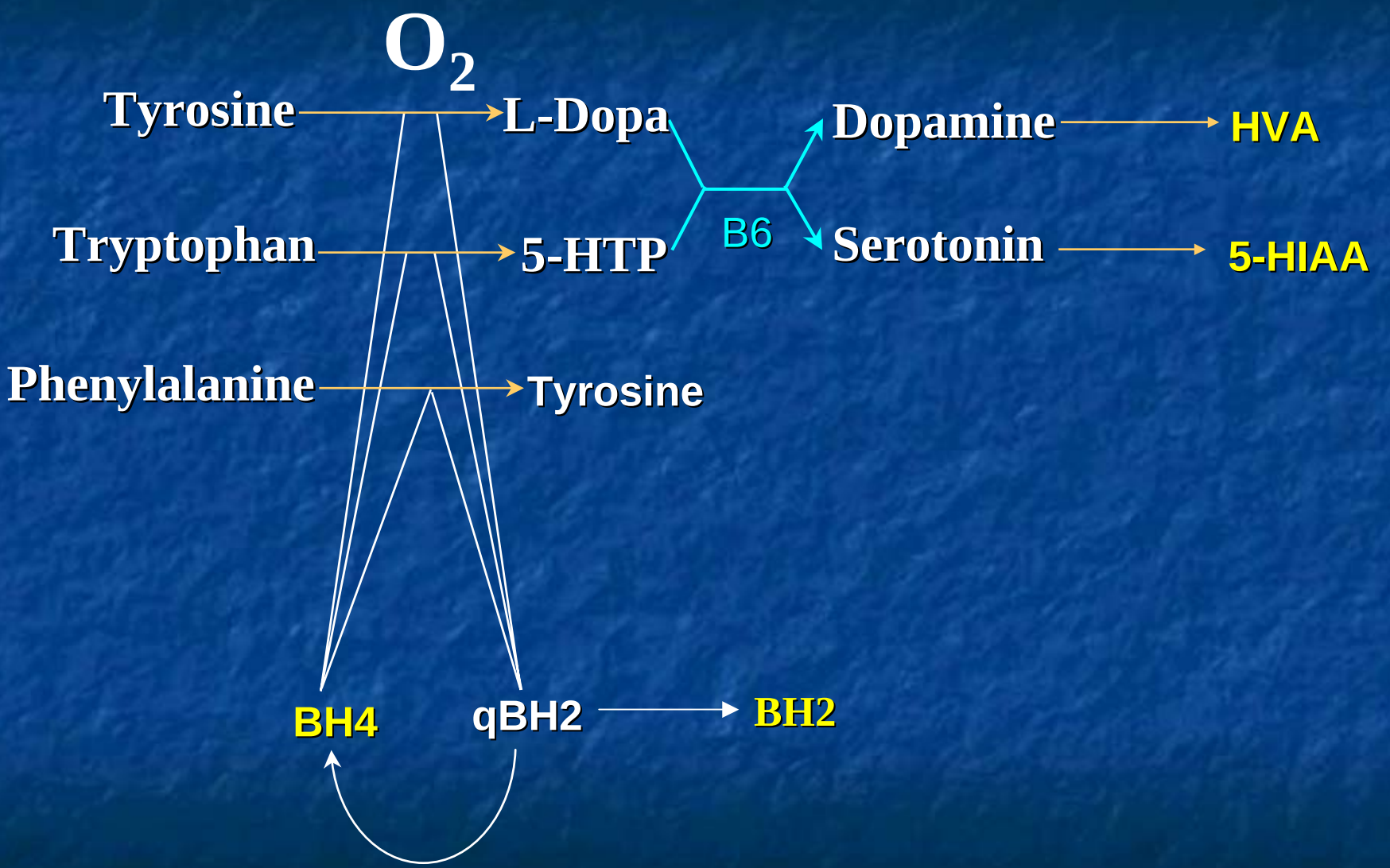
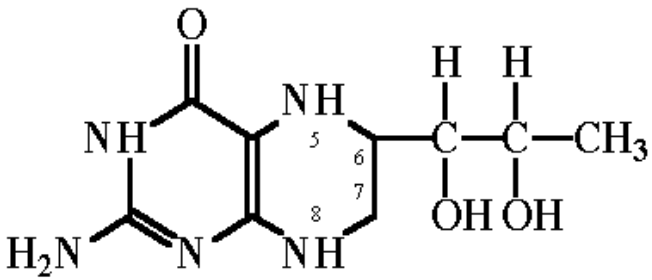
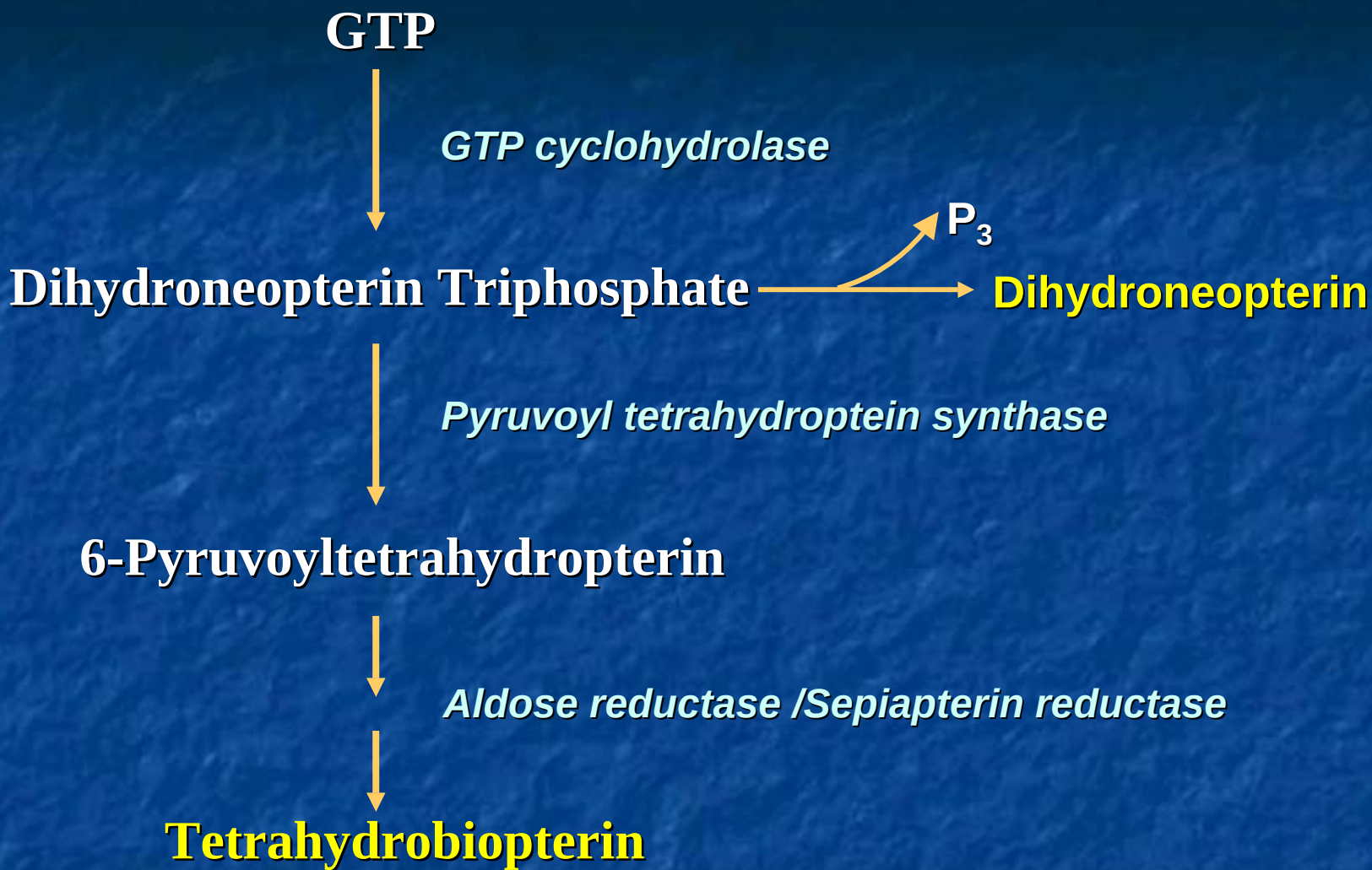
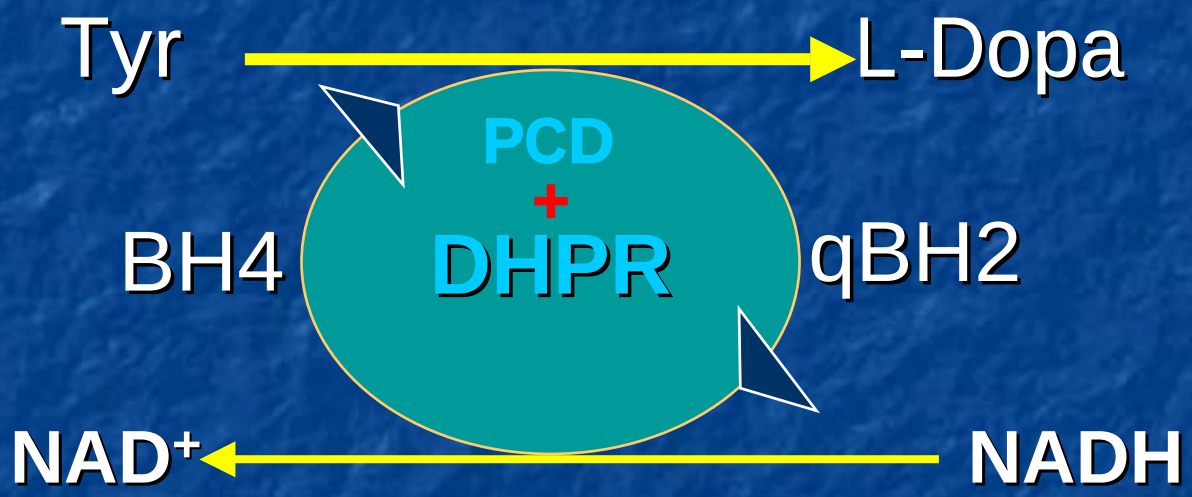

O2
Tyrosine
L-Dopa
Dopamine
HVA
Tryptophan
5-HTP
B6
Serotonin
5-HIAA
Phenylalanine
Tyrosine
BH4
qBH2
BH2



5,6,7,8-Tetrahydrobiopterin


GTP
GTP cyclohydrolase
Dihydroneopterin Triphosphate
P_3
Dihydroneopterin
Pyruvoyl tetrahydroptein synthase
6-Pyruvoyltetrahydropterin
Aldose reductase /Sepiapterin reductase
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

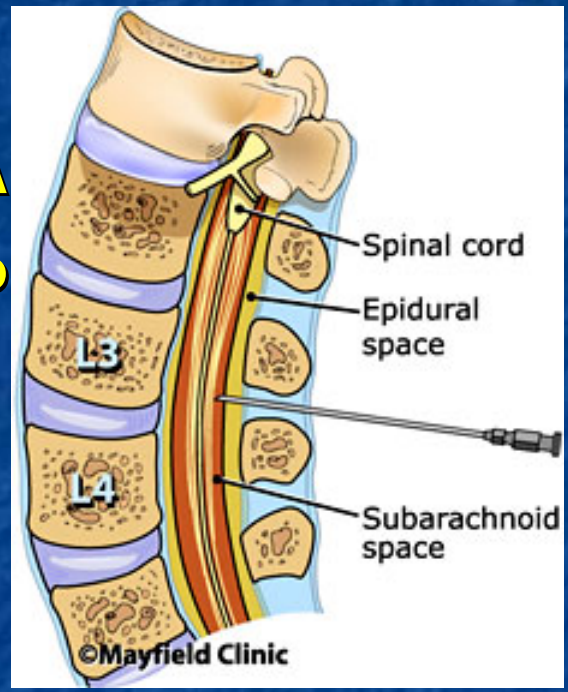
Neurochemical Evaluation - CSF

- 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 !)

		nmol/L	
Metabolite	Age (years)	Mean	Range
HVA	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
5-HIAA	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

		nmol/L	
Metabolite	Age (years)	Mean	Range
BH4	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
BH2	ALL	5.6	0.4-13.9
NH2	ALL	19	7-65

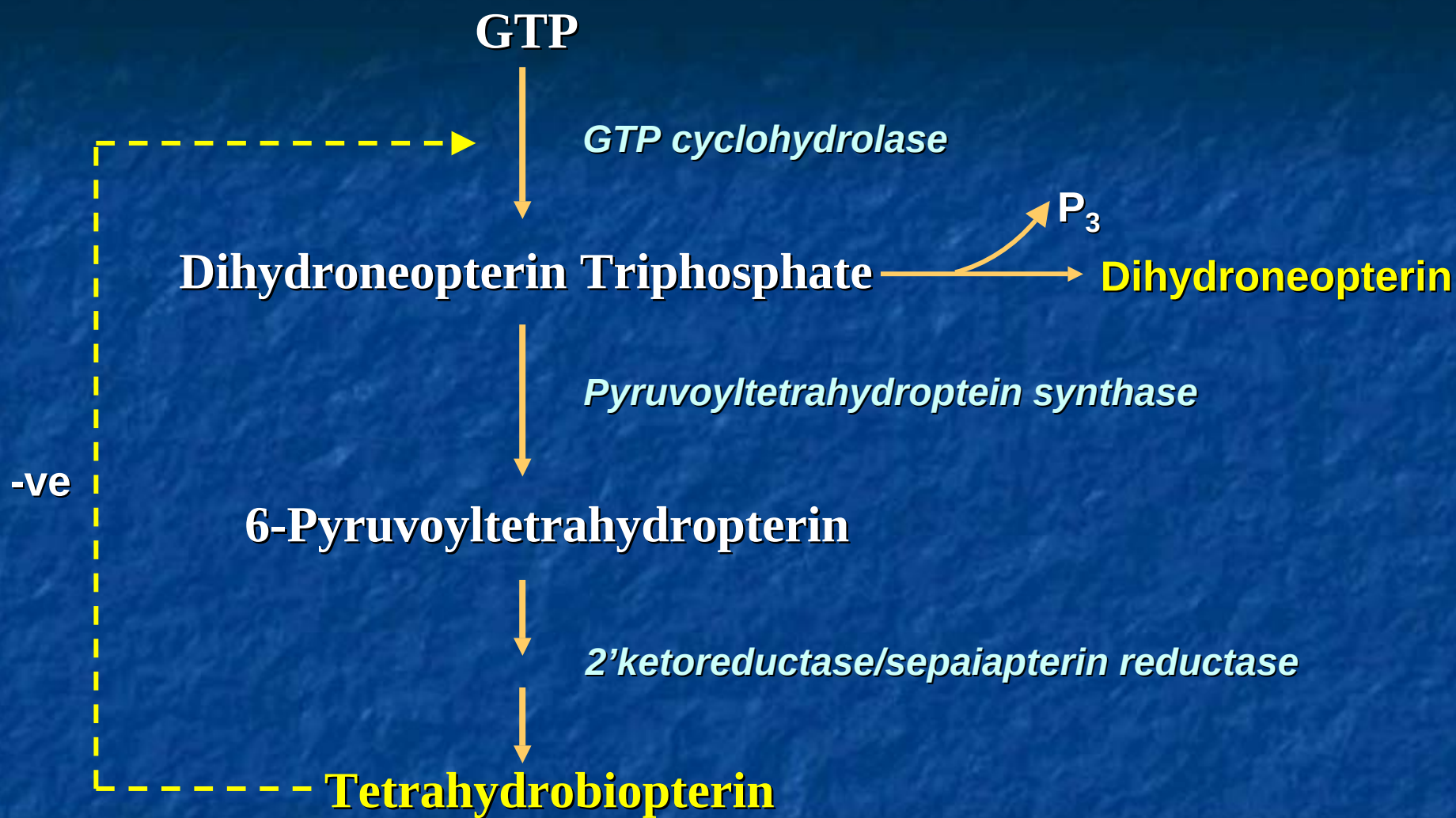
Pediatr Res (1993) 34, 10-14

CSF - Results

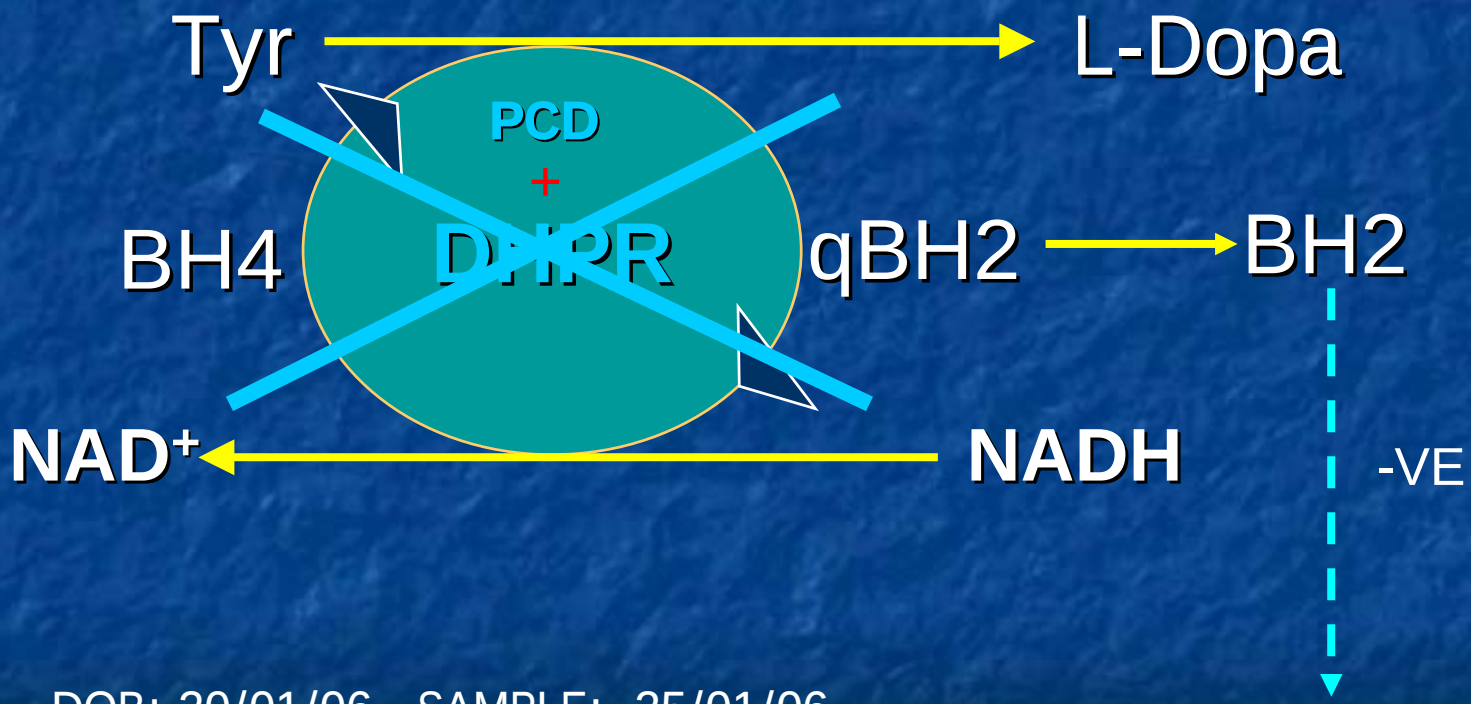
↓ HVA & 5-HIAA + Pterins → GTP Cyclohydrolase def

↓ HVA & 5-HIAA
↓ BH4
↑ NH2 → PTP Synthase def

↓ HVA & 5-HIAA
↑ BH2 → DHPR def


GTP
GTP cyclohydrolase
Dihydroneopterin Triphosphate
P3
Dihydroneopterin
Pyruvoyltetrahydroptein synthase
-ve
6-Pyruvoyltetrahydropterin
2'ketoreductase/sepaiapterin reductase
Tetrahydrobiopterin

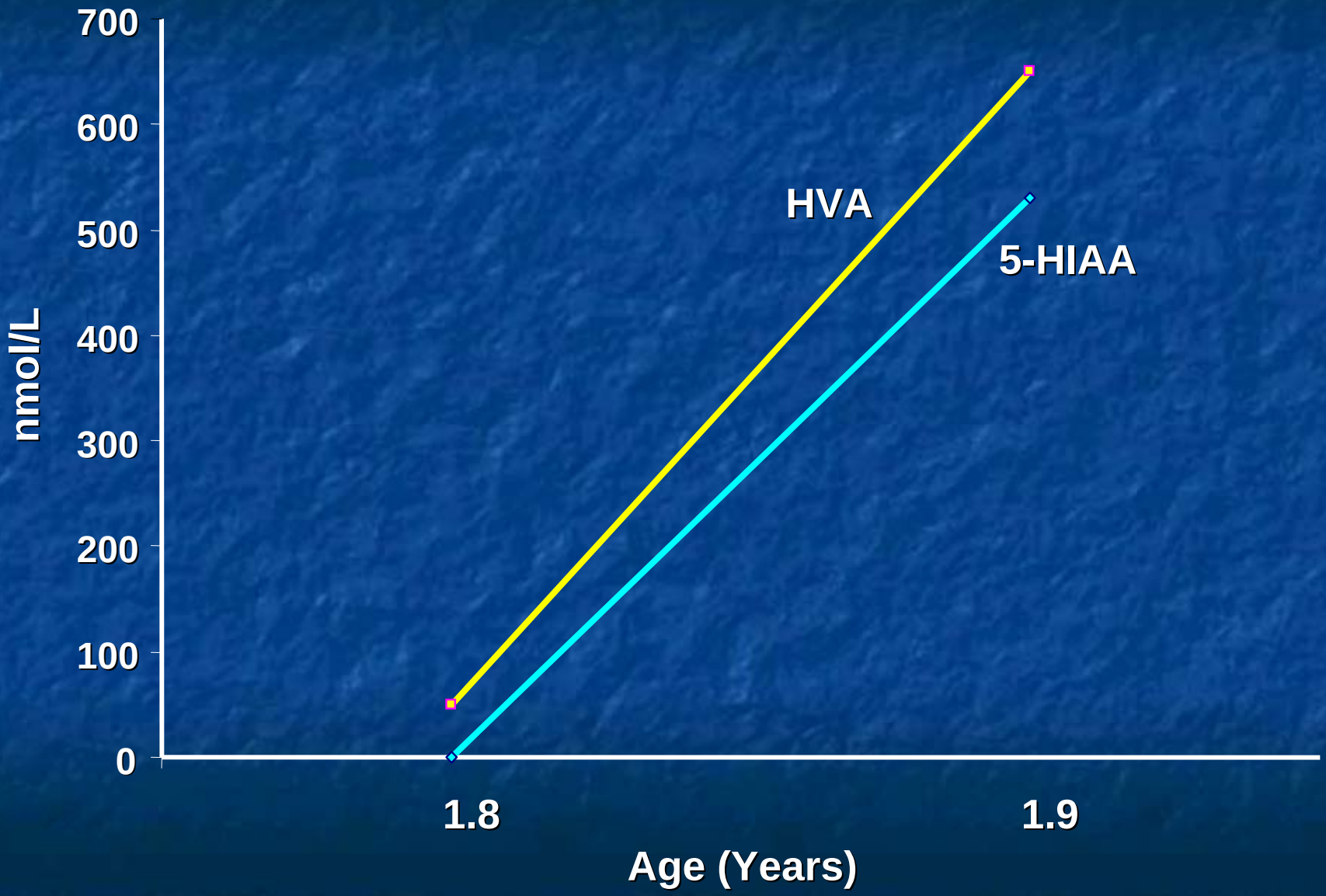
DHPR Deficiency



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

Folate Metabolism
Monoamine Metabolism

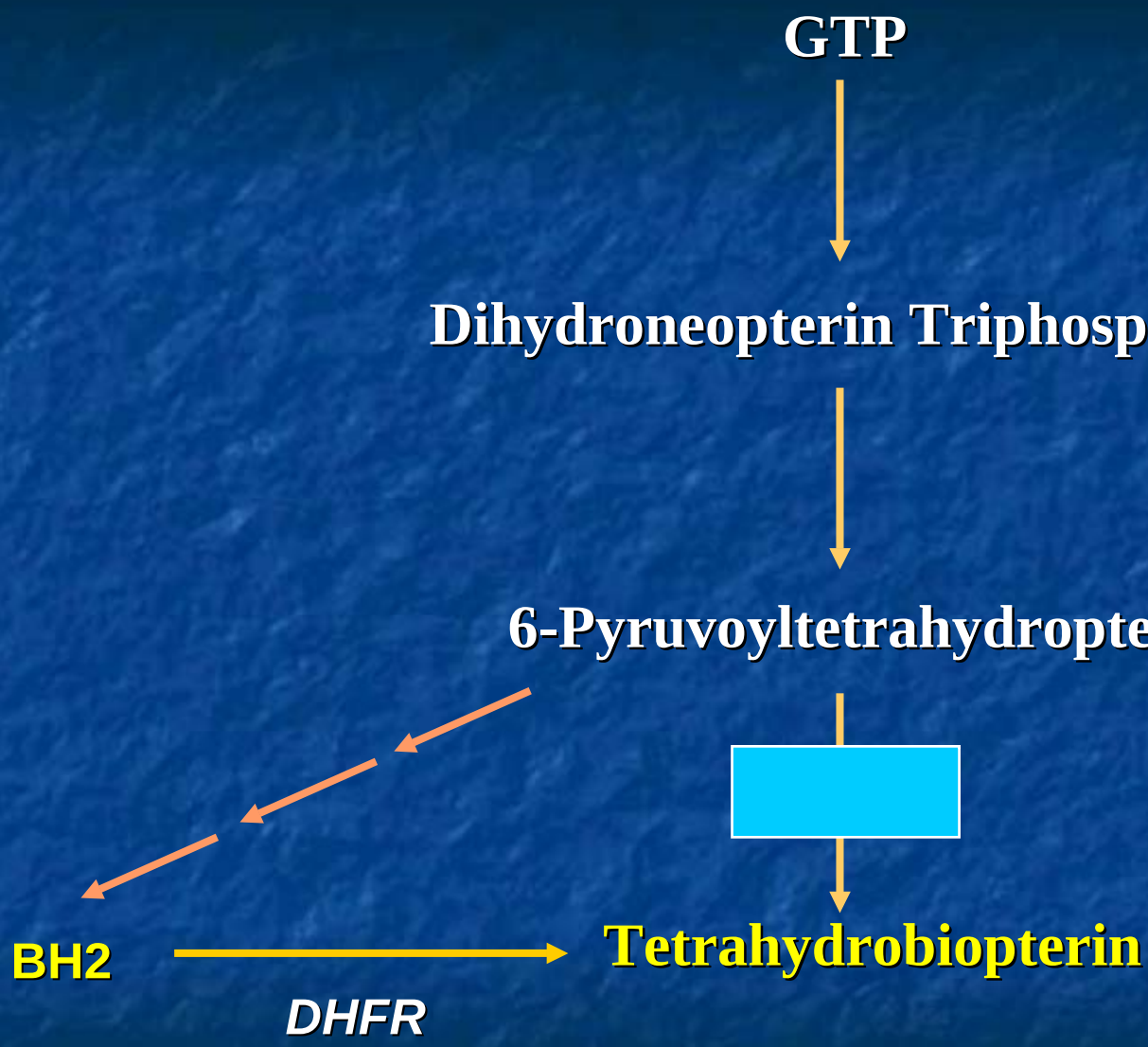
DHPR Deficiency – Response to Treatment



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.

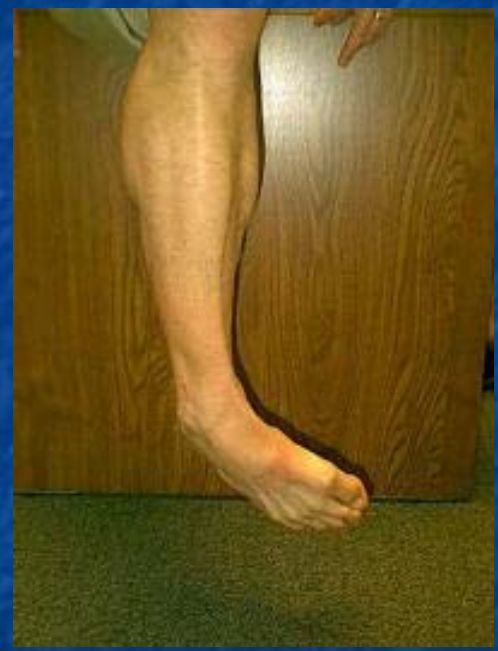
HVA:	**23**	**(71-565 nmol/L)**
5-HIAA:	**2**	**(58-220 nmol/L)**
BH4:	**11**	**(9-39 nmol/L)**
BH2:	**64**	**(0.4-13.9 nmol/L)**
Total Neopterin:	**19**	**(7-65 nmol/L)**

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 causitive 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 :-**

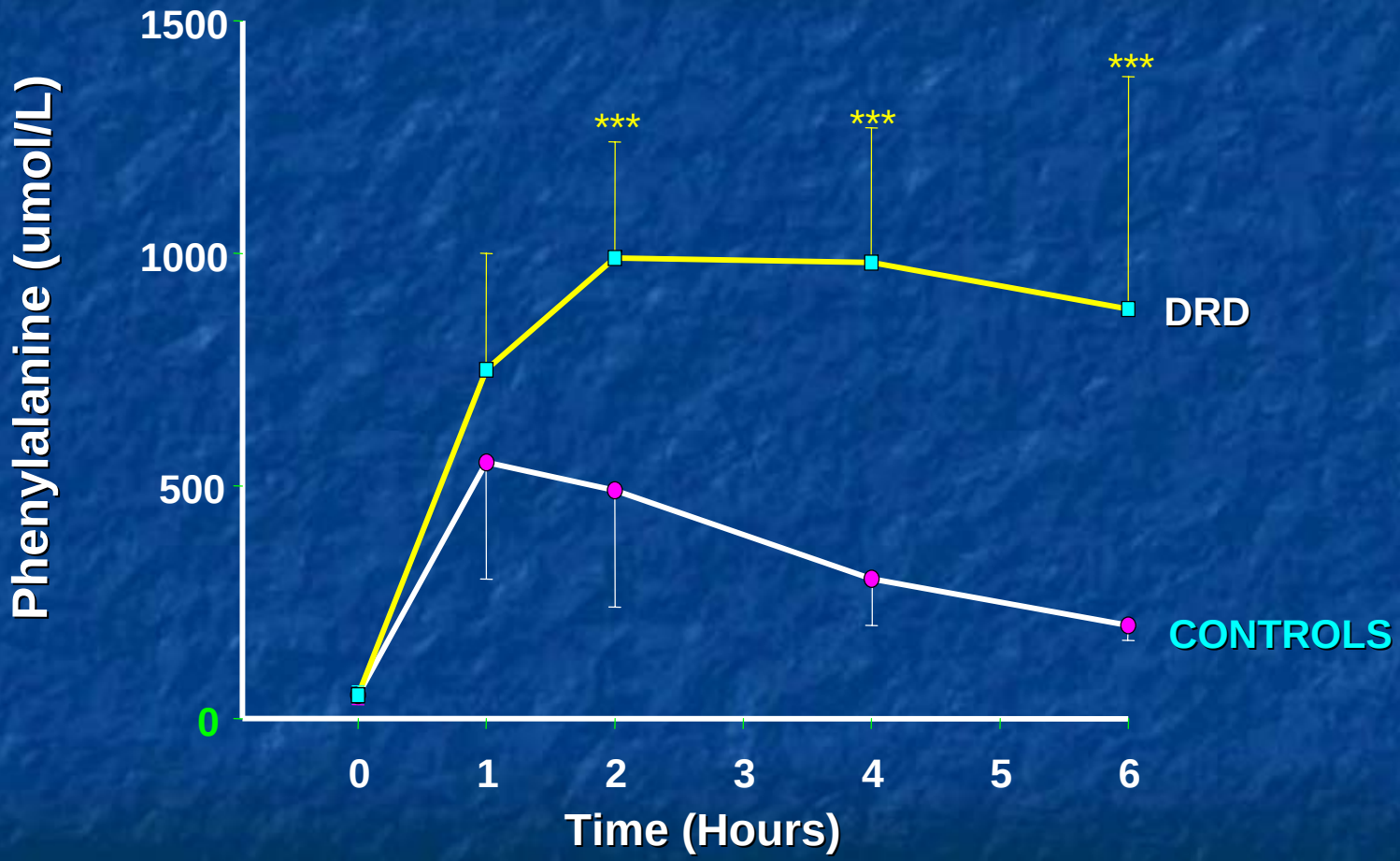
  BH4

  Neopterin.

  HVA.

- **Impaired phenylalanine tolerance.**

Plasma Phenylalanine after 100mg/kg oral Phenylalanine



Tyrosine Hydroxylase Deficiency

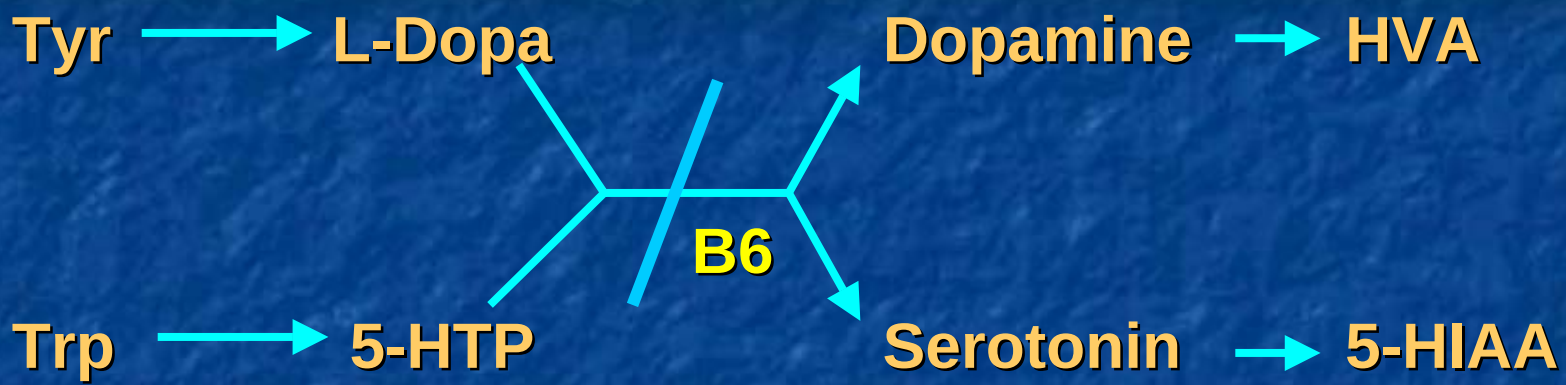
- **Parkinsonian, ptosis, drooling, myoclonic jerks, severe head lag and trunkal hypotonia.**
- **L-Dopa → marked and sustained improvement in hypokinesia and parkinsonian symptoms.**
- **Identified from *CSF analysis*; *Normal pterin & 5-HIAA concentration. Very low HVA. Mutation analysis also available.***

Tyrosine Hydoxylase 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

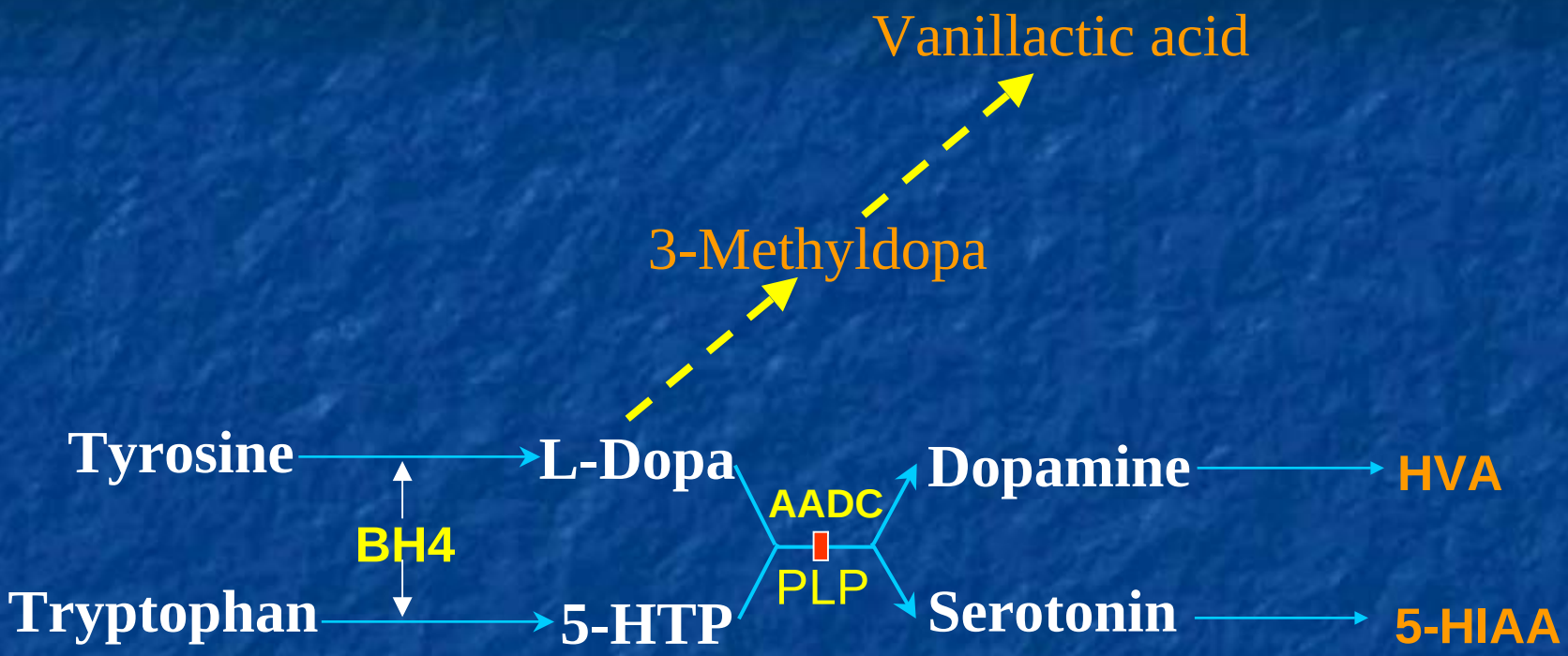


Clinical features resemble those of recessive BH4 deficiency; hypotonia, oculogyric crises, ptosis and paucity of spontaneous movement. Can be fatal

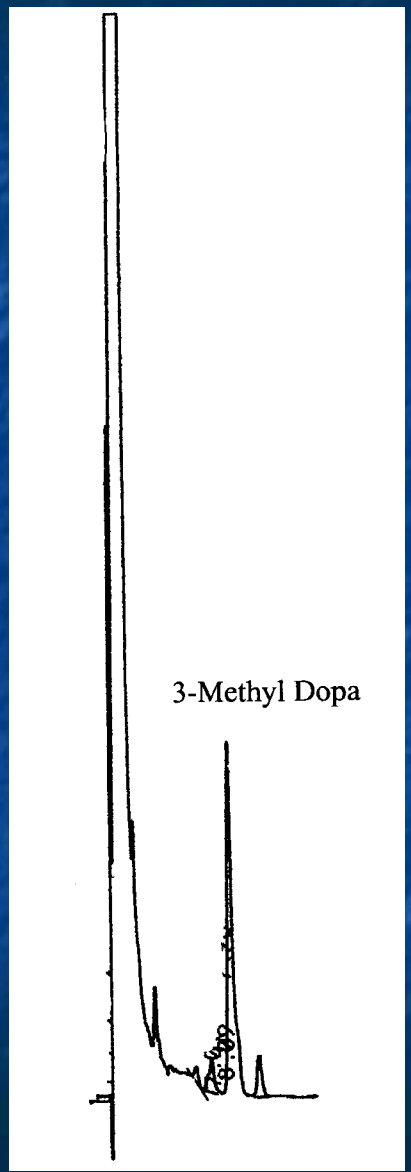
Urine: Vanillactic acid

***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.


Vanillactic acid
3-Methyldopa
Tyrosine
L-Dopa
Dopamine
HVA
AADC
BH4
PLP
Tryptophan
5-HTP
Serotonin
5-HIAA

Aromatic Amino Acid Decarboxylase Deficiency



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

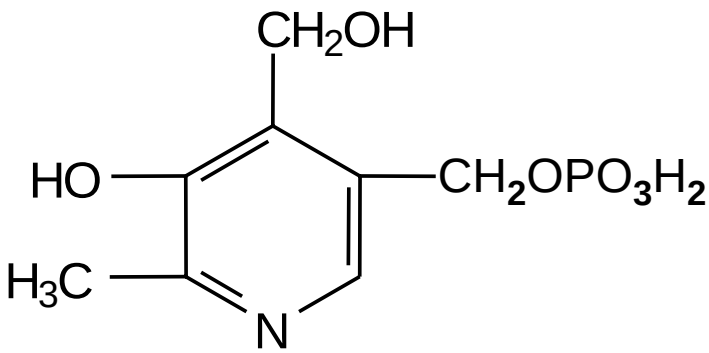
HVA
52 (154-867 nmol/L)

5-HIAA
22 (89-367 nmol/L)

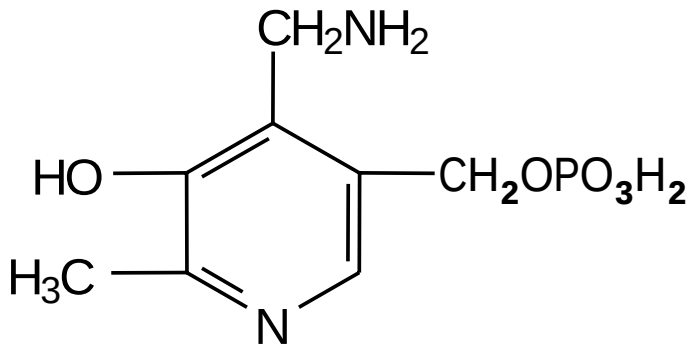
3-Methyldopa
589 (< 50 nmol/L)

Pyridox(am)ine-5'-Oxidase Deficiency

Pyridoxine-5'- phosphate



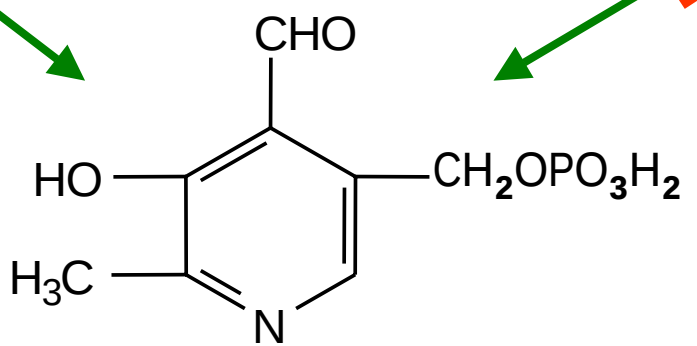
Pyridoxamine-5'- phosphate



PNPO

PNPO

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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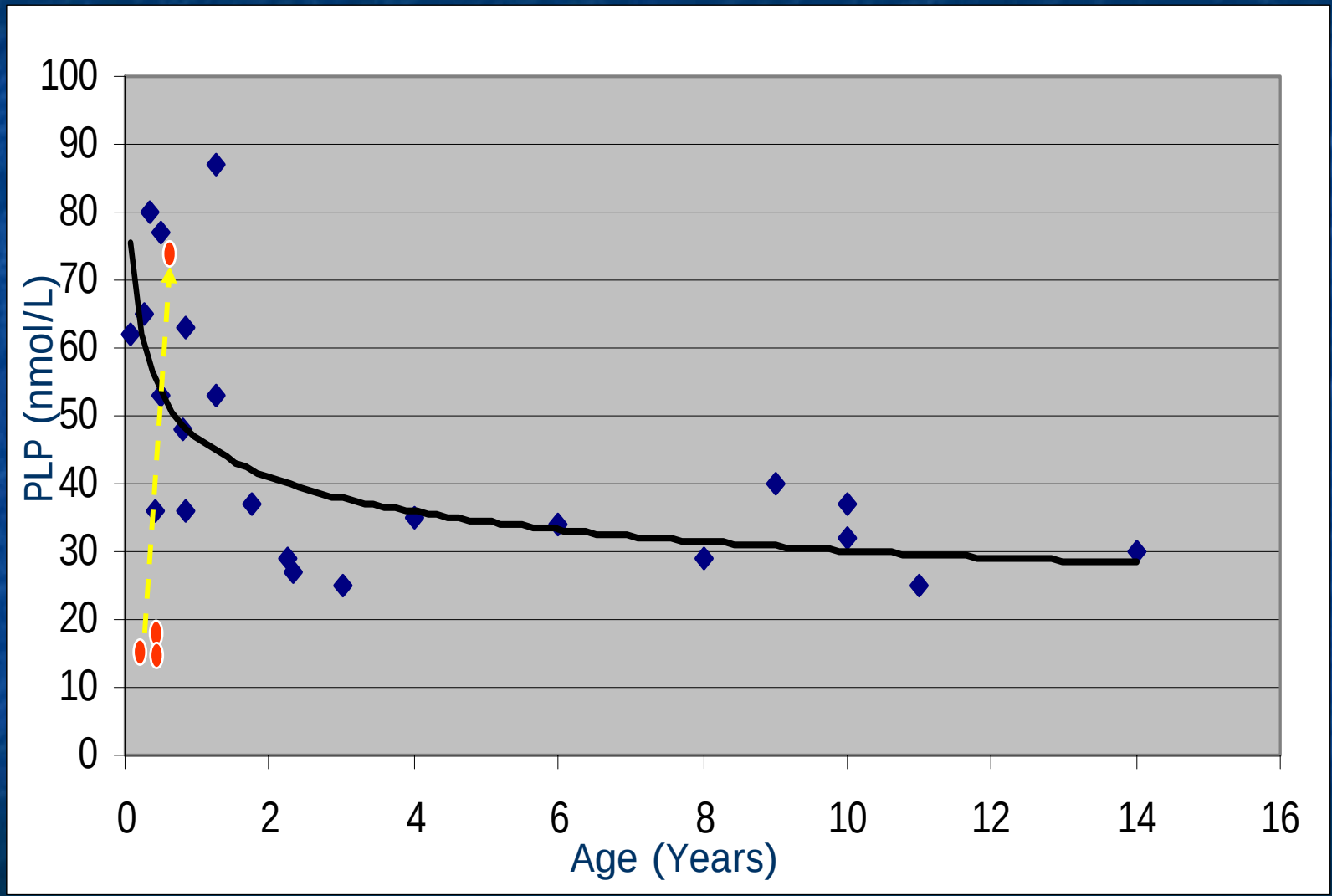
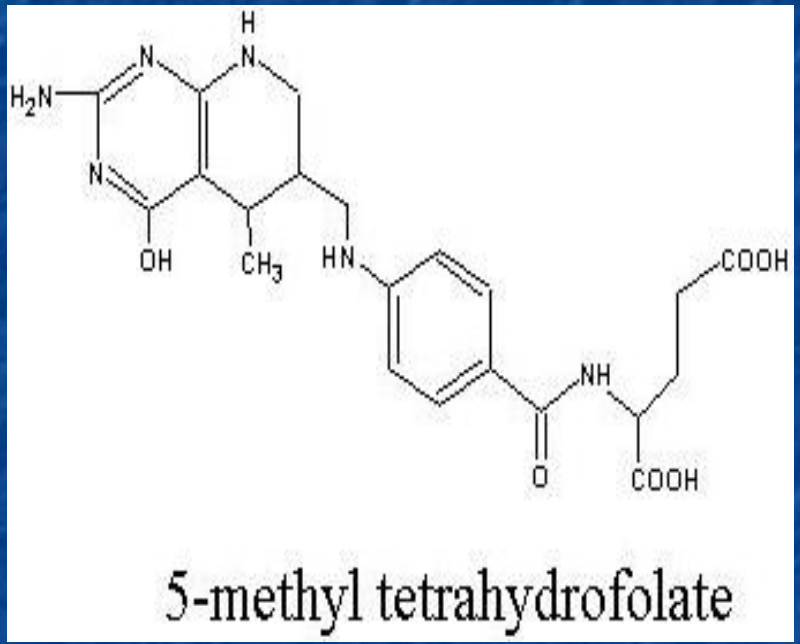
CSF (PLP)


PLP (nmol/L)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
Age (Years)

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 and Metabolism
www.elsevier.com/locate/ymgme

Brief communication

Cerebral folate deficiency: life-changing supplementation with folinic acid

Flemming Juul Hansen[a], Nenad Blau[b,*]

[a] *Division of Pediatric Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[b] *Division of Clinical Chemistry and Biochemistry, University Children's Hospital, Zurich, Switzerland*

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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 !**

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