Clinical aspects of pterin disorders

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Introductory words

Brain function depends on the capacity of neurons to excite and inhibit within connecting neuronal circuits.

Excitation and inhibition are achieved through synaptic transmission mediated by neurotransmitters.

Neurotransmitter “translate” an electrical signal to a chemical signal and back.
Tetrahydrobiopterin (BH$_4$)

Involved in a number of biological processes

- degradation of phenylalanine
- neurotransmitter synthesis

Defects in BH$_4$ synthesis or recycling results in

- dopamine and serotonine (neurotransmitter) deficiency
- hyperphenylalaninemia
Clinical aspects of pterin disorders
BH₄ deficiencies

BH₄ deficiencies with hyperphenylalaninemia

- Ar GTPCH deficiency ➔ Missing HPA!
- PTPS deficiency
- DHPR deficiency
- PCD deficiency

BH₄ deficiencies without hyperphenylalaninemia

- Ad GTPCH deficiency (Segawa; dopa responsive dystonia)
- SR deficiency
BH$_4$ deficiencies: Frequency

- SR; 31
- DHPR; 217
- PTPS; 355
- GTPCH; 31
- PCD; 23

Opladen, et al. JIMD 2012
Premature infants and low birth weight

Opladen, et al. JIMD 2012
Major clinical findings

- Psychomotor retardation
- Muscular hypotonia
- Dystonia and further extrapyramidal symptoms
- Autonomic dysfunction
- (Epilepsy)
Clinical aspects of pterin disorders with hyperphenylalaninemia
Asymptomatic patients

Asymptomatic patients (before treatment)

- DHPR
- PTPS
- GTPCH

- Neonates: 43%
  - DHPR: 36%
  - PTPS: 25%
  - GTPCH: 25%

- Infants: 19%
  - DHPR: 10%
  - PTPS: 25%
  - GTPCH: 4%

- Children: 0%
  - DHPR: 13%
  - PTPS: 0%
  - GTPCH: 0%

Opladen, et al. JIMD 2012
Clinical presentation (arGTPCH)

- Autonomic dysfunction: 25%
- Convulsions: 20%
- Movement disorder w/o dystonia: 30%
- Dystonia: 20%
- Muscular hypertonia: 40%
- Muscular hypotonia: 80%
- Retardation: 20%

GTPCH Neonates

GTPCH Infants

GTPCH Children

Opladen, et al. JIMD 2012
Clinical presentation (PTPS)

PTPS Neonates
- Autonomic dysfunction: 17.9%
- Convulsions: 8.9%
- Movement disorder w/o dystonia: 5.4%
- Dystonia: 7.1%
- Muscular hypertonia: 16.1%
- Muscular hypotonia: 37.5%
- Retardation: 25.0%

PTPS Infants
- Autonomic dysfunction: 16.92%
- Convulsions: 35.38%
- Movement disorder w/o dystonia: 12.31%
- Dystonia: 12.31%
- Muscular hypertonia: 24.62%
- Muscular hypotonia: 49.23%
- Retardation: 30.77%

PTPS Children
- Autonomic dysfunction: 31.58%
- Convulsions: 36.84%
- Movement disorder w/o dystonia: 21.05%
- Dystonia: 23.68%
- Muscular hypertonia: 23.68%
- Muscular hypotonia: 36.84%
- Retardation: 50.00%

Opladen, et al. JIMD 2012
Clinical presentation (DHPR)

- **DHPR Neonates**
  - Autonomic dysfunction: 14.29%
  - Movements disorder w/o dystonia: 7.14%
  - Dystonia: 4.12%
  - Muscular hypertonia: 14.29%
  - Muscular hypotonia: 14.29%
  - Retardation: 14.29%

- **DHPR Infants**
  - Autonomic dysfunction: 19.59%
  - Movements disorder w/o dystonia: 9.28%
  - Dystonia: 4.12%
  - Muscular hypertonia: 23.71%
  - Muscular hypotonia: 50.52%
  - Retardation: 32.99%

- **DHPR Children**
  - Autonomic dysfunction: 27.9%
  - Movements disorder w/o dystonia: 25.58%
  - Dystonia: 11.63%
  - Muscular hypertonia: 18.60%
  - Muscular hypotonia: 37.21%
  - Retardation: 72.09%

Opladen, et al. JIMD 2012
Clinical aspects of pterin disorders without hyperphenylalaninemia
## Age at diagnosis

<table>
<thead>
<tr>
<th></th>
<th>DHPR deficiency</th>
<th>GTPCH deficiency</th>
<th>PCD deficiency</th>
<th>PTPS deficiency</th>
<th>SR deficiency</th>
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<tbody>
<tr>
<td>Mean age at diagnosis [years]</td>
<td>1.9</td>
<td>1.3</td>
<td>1.9</td>
<td>1.8</td>
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<td>Lowest age at diagnosis [days]</td>
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Clinical presentation (SR)

- Cognitive delay
- Motor delay
- Speech delay
- Oculogyric crises
- Dystonia
- Diurnal fluctuation
- Hypotonia
- Paroxysmal stiffening
- Spasticity/pyramidal signs
- Hypersomnia
- Stiffness
- Sleep benefit
- Dysarthria
- Vegetative symptoms, e.g. sweating
- Dysphagia
- Parkinsonian tremor
- Ataxia
- Worsening on excitement
- Tongue tremor
- Disturbed sleep

Dill et al: Neurology 2012
ad GTP Cyclohydrolase deficiency

- **Synonym:**
  - Dopa-responsive Dystonia
  - DYT 5
  - Segawa Disease (1971 “hereditary basal ganglia diseases with diurnal fluctuation”)

- Autosomal-dominant, incomplete penetrance (!)
- No hyperphenylalaninemia
GTP Cyclohydrolase deficiency

Clinical presentation:

- Presentation occurs within the first decade of life (*mean age 7 years*; ♀ 3x > ♂)
- First symptom is usually a *postural dystonia of one leg* with progression to all limbs
- Followed by *action dystonia* and *hand tremor*
- In older children the first signs may start in the arms or by torticollism or writer’s cramp
- *Diurnal fluctuation* is normally present, with symptoms improving after nighttime sleep or bed rest.
- Presentation is not limited to childhood!
- *Normal cognition*
GTPCH: Behavioural and psychiatric aspects

- Role of serotonin?

- Psychiatric manifestations expanded clinical phenotype \([n=18, > 20\text{y}]\):
  - Depression (50%), obsessive–compulsive disorder (25%), sleep disturbances (50%)

- Neuropsychiatric symptoms and intelligence quotient (2 families; 7 adult and 7 paediatric patients):
  - Depression, anxiety, and obsessive–compulsive symptoms were NOT more common
  - Impulsivity in 7 adults (BIS-11); mild mental retardation IQ in 9 individuals, sleep disturbances in 4 individuals
  - 3 paediatric patients under L-Dopa treatment had a normal IQ. Role of dopamine in morphogenesis and development of neuronal networks for higher cortical functions such as cognition

Van Hove et al; J Neurol Neurosurg Psychiatry, 2006
López-Laso et al; J Neurol, 2011
GTPCH: Residual signs

Dopa-Responsive Dystonia Revisited

Diagnostic Delay, Residual Signs, and Nonmotor Signs

Vera Tadic, MD; Meike Kasten, MD; Norbert Brüggemann, MD; Sophie Stiller, MSc; Johann Hagenah, MD; Christine Klein, MDeta

Arch Neurol. Published online September 17, 2012.

- MEDLINE Search (352 cases) / pilot study (23 patients) with proven DRD
- Residual motor sign under therapy 28% (literature) and 39% (pilot study)
  - dystonic (20%) and parkinsonian (11%) symptoms
- Nonmotor signs in 70 patients (literature).
  - 34% had depression, 19% anxiety, and 9% obsessive-compulsive disorder.
- 6 patients (pilot study, 32%)
  - 1 or more nonmotor signs including depression and migraine.
Treatment of pterin disorders
Principles of treatment:

- Normalisation of neurotransmitter deficiency in CNS
- Supplementation of missing cofactor
- Correction of hyperphenylalaninemia
- Correction of decreased 5MTHF in CNS
## Treatment recommendations

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<td><strong>Diet</strong></td>
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Summary

- Pterin deficiencies are treatable disorders
- Hyper Phe in newborn screening in most BH₄ deficiencies
- Further differentiation by pterine in urine or dried blood spot as well as determination of DHPR enzyme activity must follow!
- First clinical symptoms are characterized by muscular hypotonia, stiffness of extremities and retardation
- Good treatment results. Early treatment improves outcome