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Clinical aspects of pterin disorders

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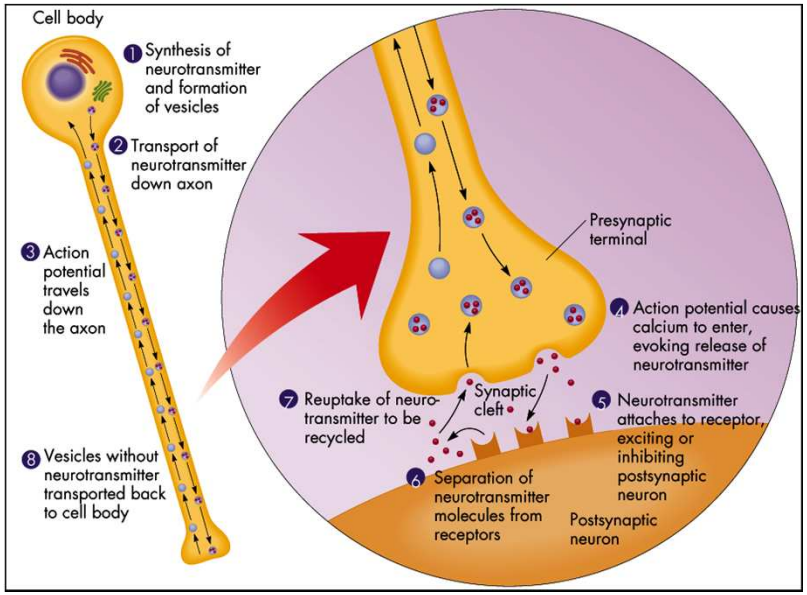
Introductory words

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



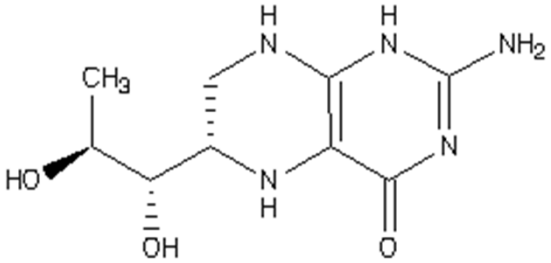
Tetrahydrobiopterin (BH_4)

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



5,6,7,8 Tetrahydrobiopterin

Werner; Biochem J; 2011

Clinical aspects of pterin disorders

BH_4 deficiencies

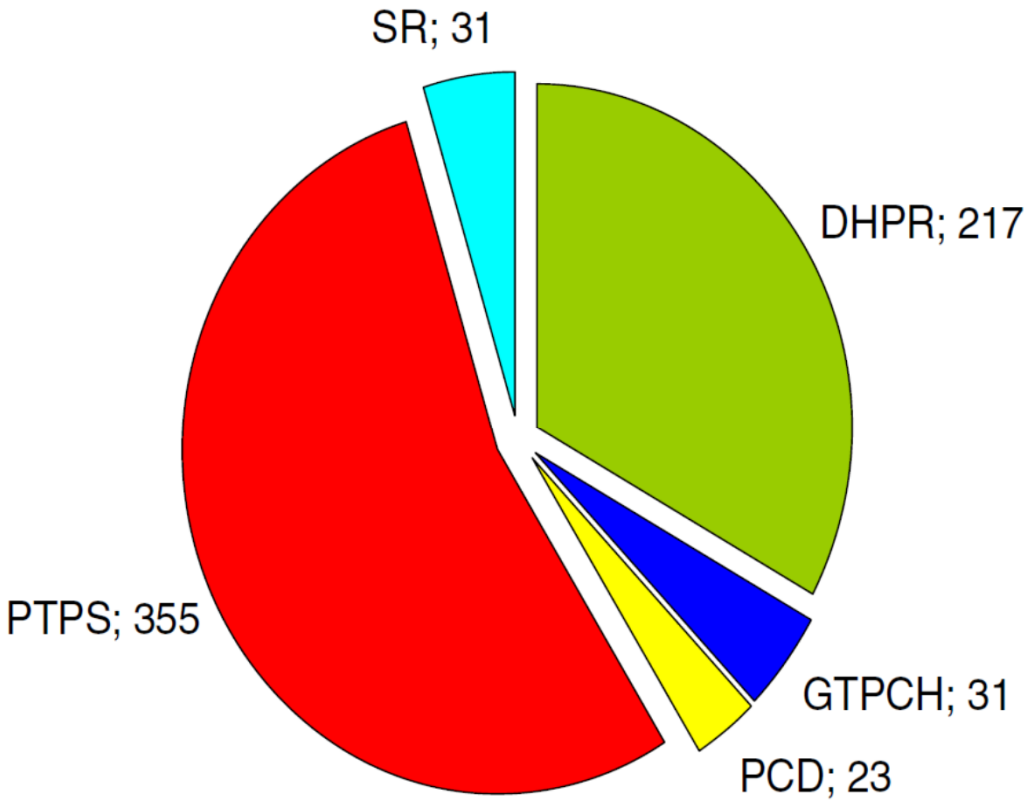
BH_4 deficiencies <u>with</u> hyperphenylalaninemia

- ar GTPCH deficiency → Missing HPA! 
- PTPS deficiency
- DHPR deficiency
- PCD deficiency

BH_4 deficiencies <u>without</u> hyperphenylalaninemia

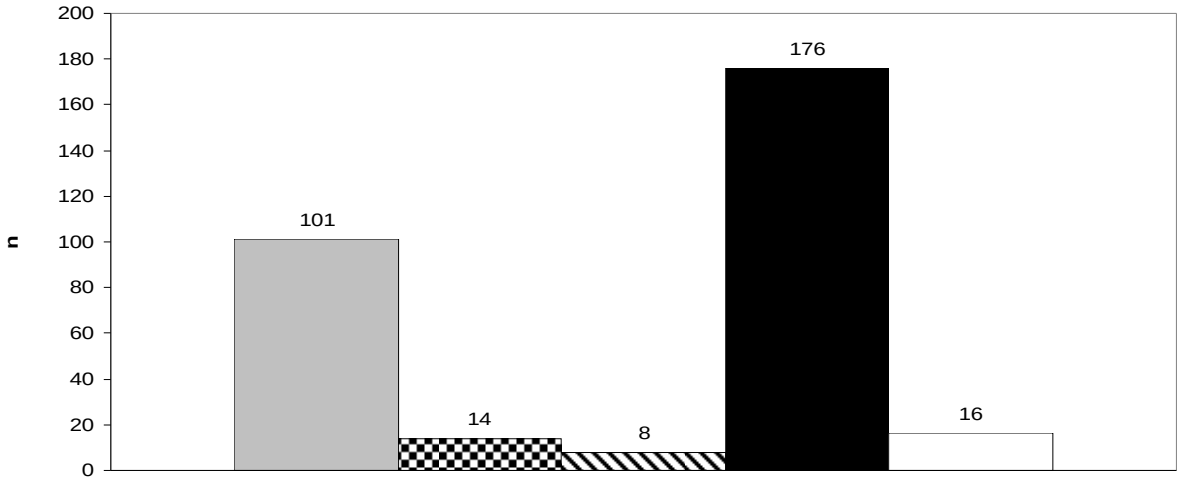
- ad GTPCH deficiency (Segawa; dopa responsive dystonia)
- SR deficiency

BH_4 deficiencies: Frequency

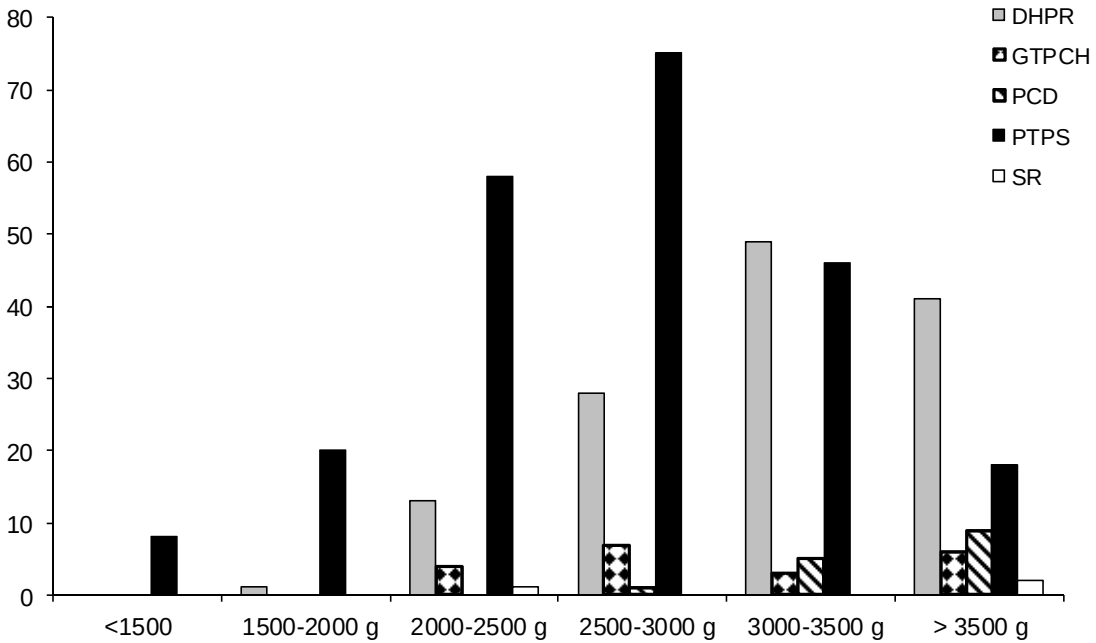


Opladen, *et al. JIMD 2012*

Premature infants and low birth weight



Preterm babies



Opladen, *et al. JIMD 2012*

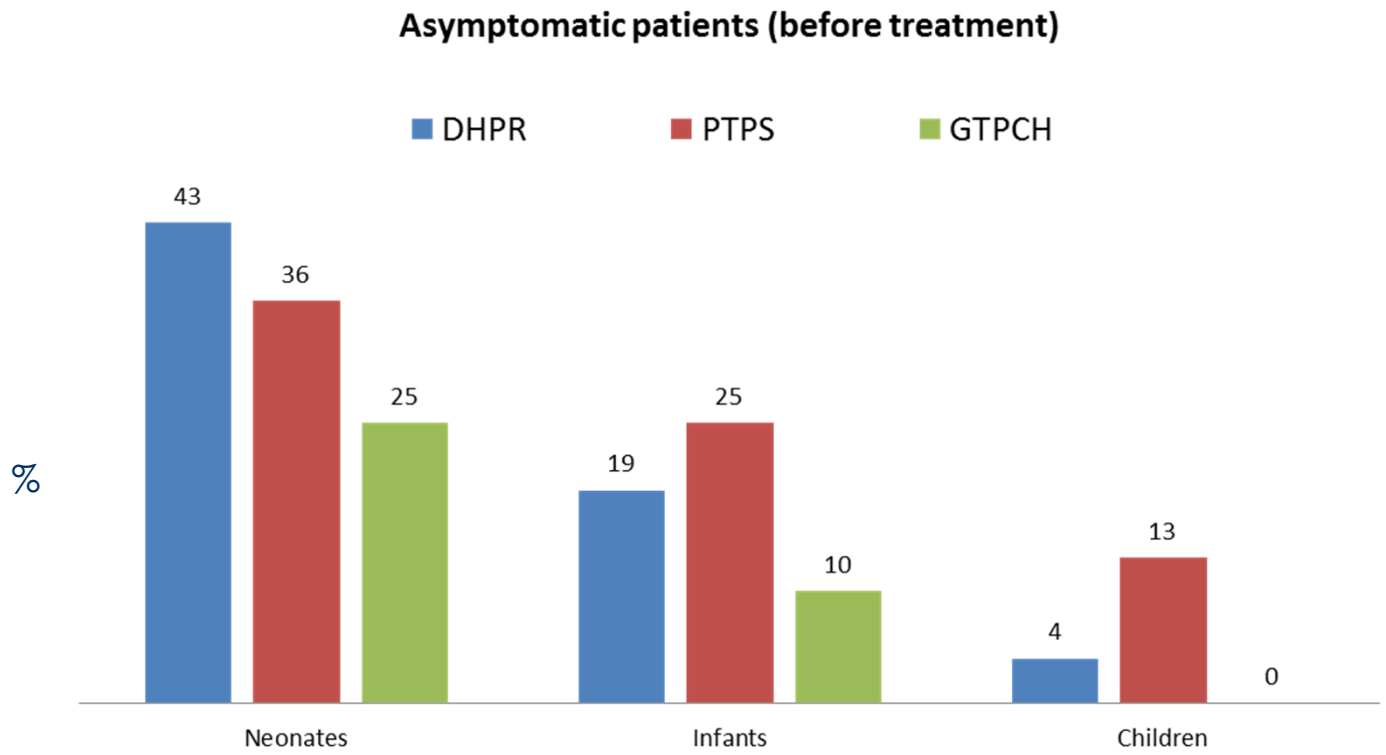
Major clinical findings

- Psychomotor retardation
- Muscular hypotonia
- Dystonia and further extrapyramidal symptoms
- Autonomic dysfunction
- (Epilepsy)

Opladen, *et al. JIMD 2012*

Clinical aspects of pterin disorders with hyperphenylalaninemia

Asymptomatic patients



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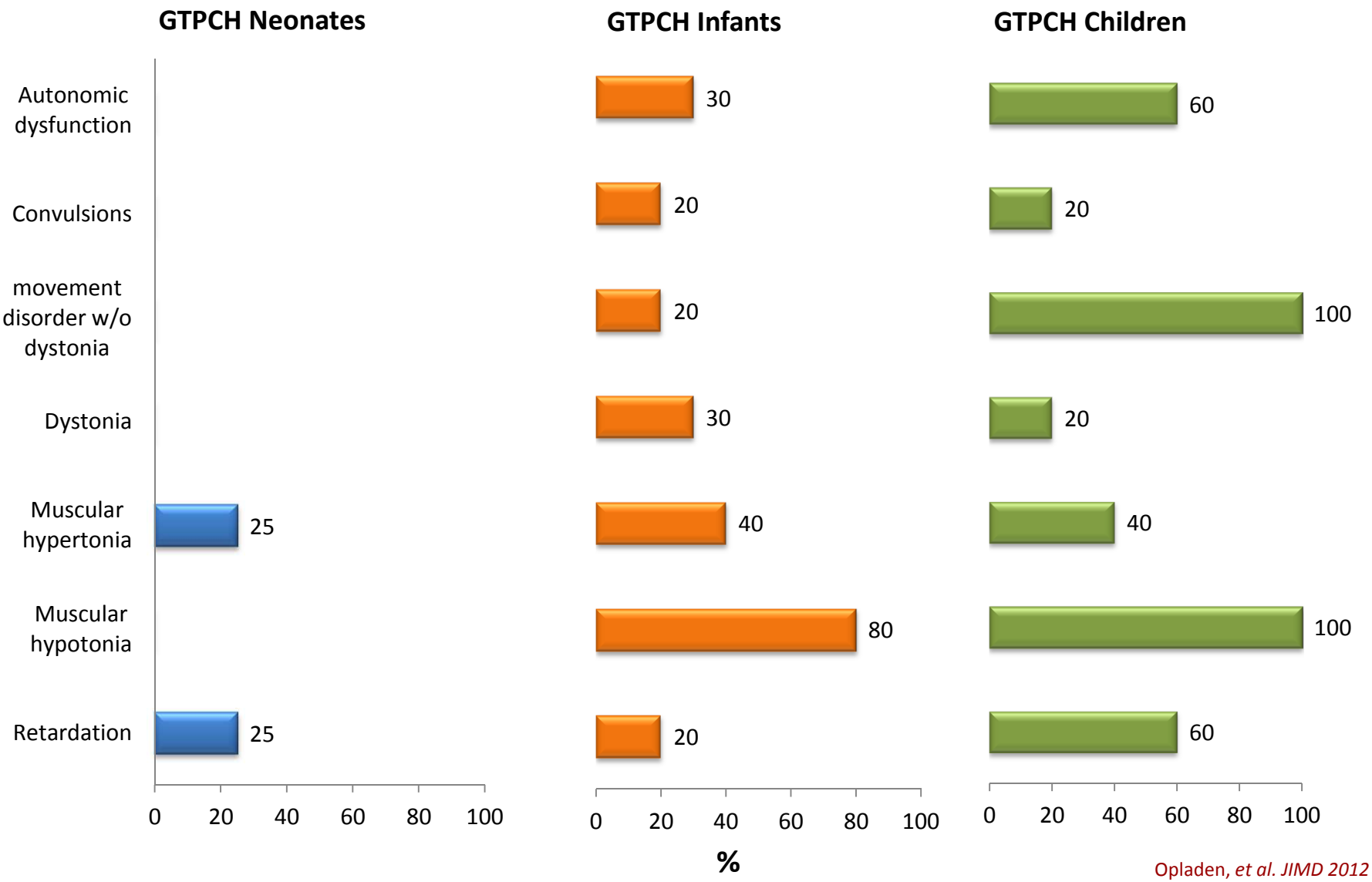
Clinical presentation (arGTPCH)



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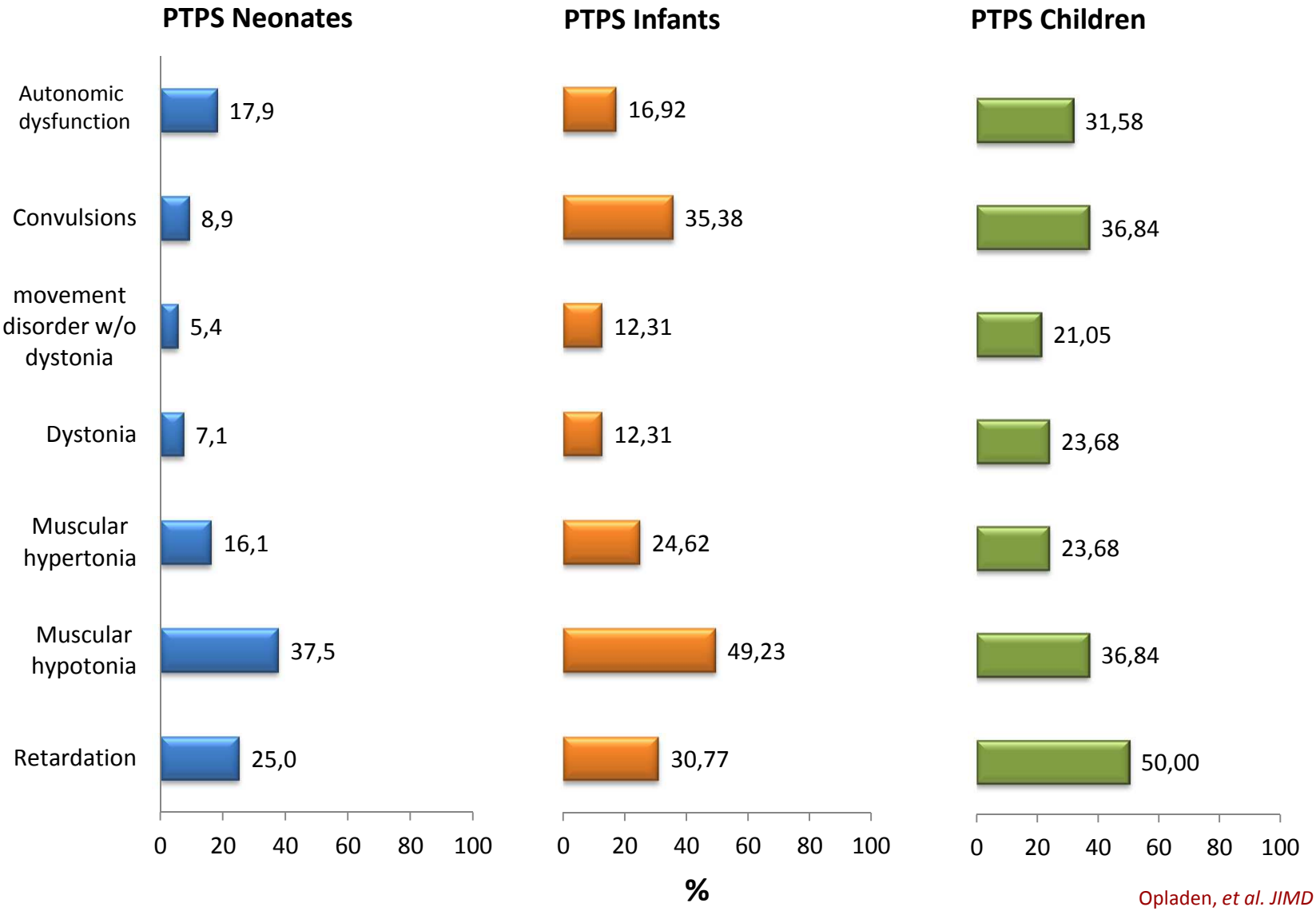
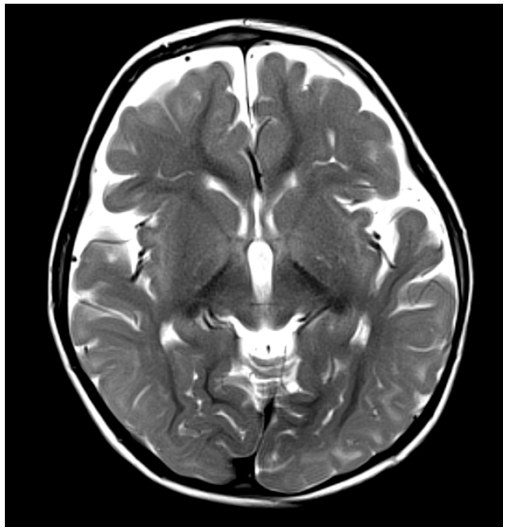
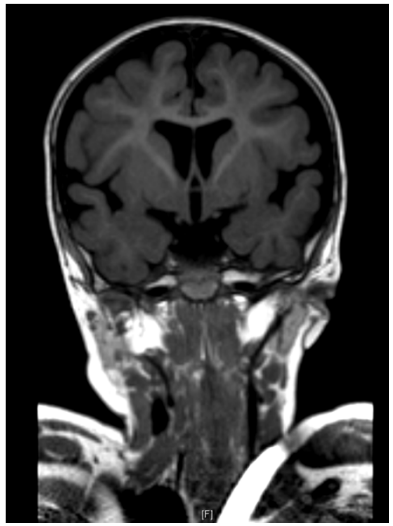
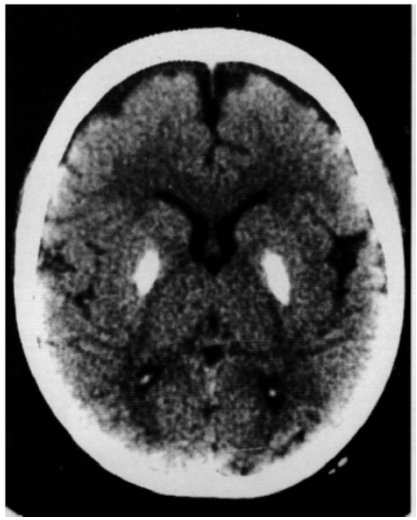
Clinical presentation (PTPS)



Opladen, *et al. JIMD 2012*

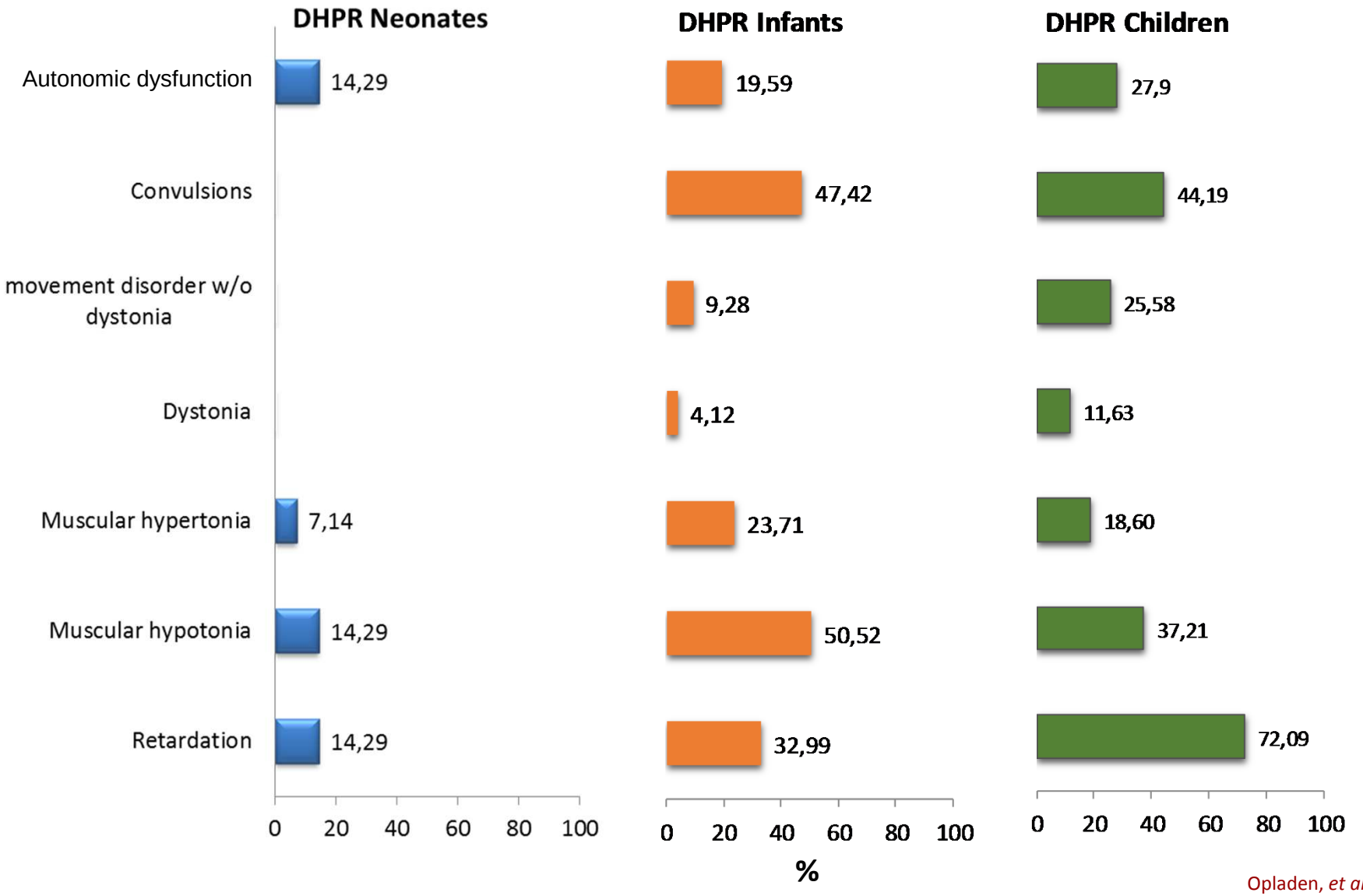






CCT

Clinical presentation (DHPR)



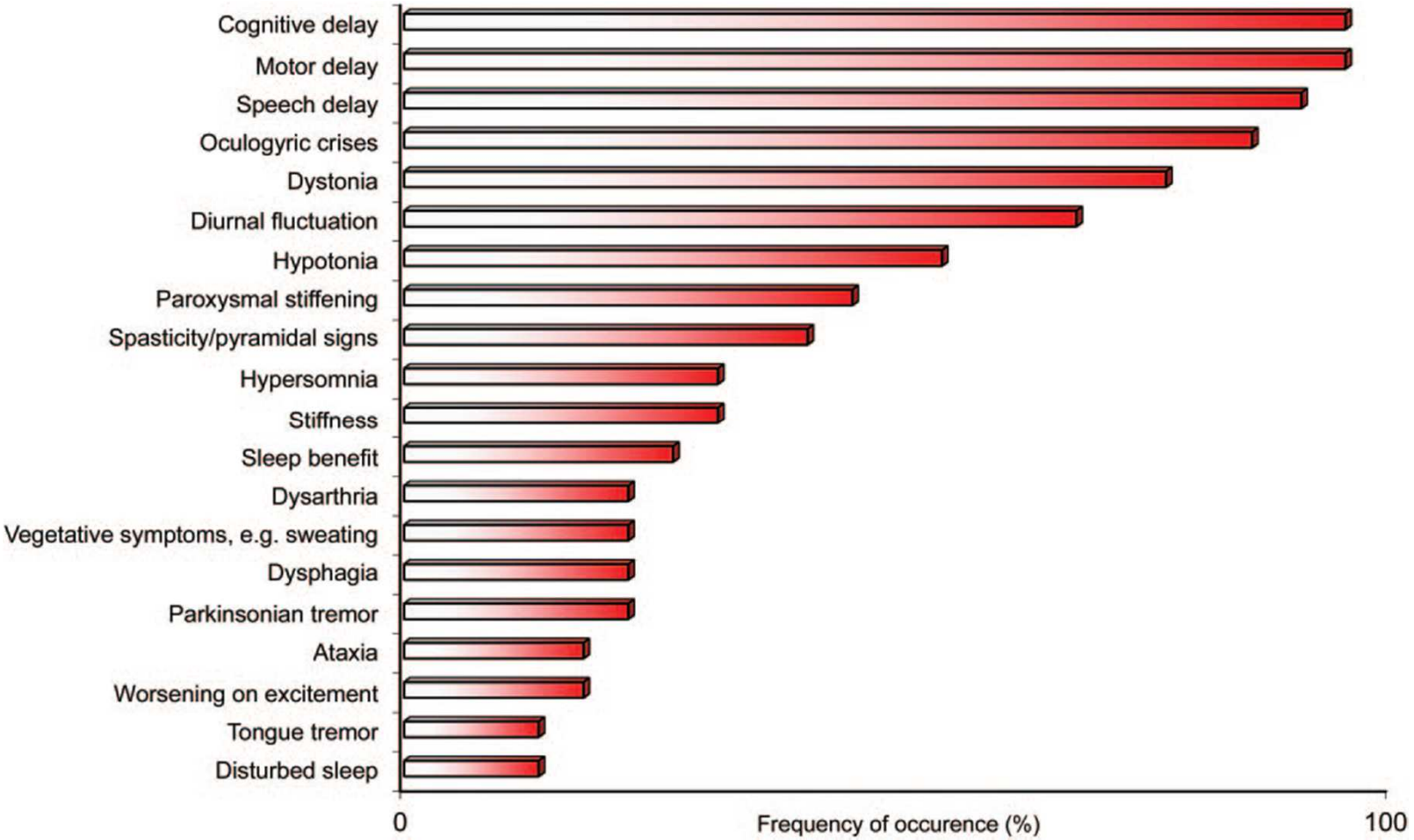
Opladen, *et al. JIMD 2012*

Clinical aspects of pterin disorders without hyperphenylalaninemia

Age at diagnosis

	DHPR deficiency	GTPCH deficiency	PCD deficiency	PTPS deficiency	SR deficiency
Mean age at diagnosis [years]	1.9	1.3	1.9	1.8	8.4
Lowest age at diagnosis [days]	2	14	7	2	336

Clinical presentation (SR)



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

Dr. Masaya Segawa

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, > 20y]:
  - 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.
doi:10.1001/archneurol.2012.574

- 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

	arGTPCH	PTPS	SR	DHPR
L-dopa/carbidopa	✓	✓	✓	✓
5-hydroxytryptophan	✓	✓	✓	✓
BH_4	✓	✓		
Diet		✓		✓
Folinic acid				✓

Summary

- Pterin deficiencies are treatable disorders
- Hyper Phe in newborn screening in most BH_4 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