
BIODEF: International Databases of Tetrahydrobiopterin Deficiencies

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Lomme cedex, France The BIODEF database is established as an information resource and retrieval system on the Web that includes clinical, biochemical, and molecular information on variants of BH₄ deficiency. Not included in the database are patients with the autosomal-dominant form of GTP cyclohydrolase I deficiency (DRD or Segawa's disease). The initial database was established in a collaboration with Prof. Jean-Louis Dhont, Lille, France (Blau, Barnes and Dhondt 1996).

Methods

Data collection

Data were collected from pediatric departments, departments of biochemistry, and screening laboratories worldwide over the last 30 years. Some of the data were obtained from the literature. The following information was provided with a questionnaire by the clinic:

- Patient's identification data including age, ethnic origin, consanguinity, parents' and siblings' information.
 - Birth information including data on weight, height, head circumference, and clinical status.
 - Screening data on hyperphenylalaninemia: age when screened, initial blood Phe level, loading test, diet tolerance etc.
 - Screening data about pterins in urine, plasma and CSF, and loading test with BH₄.
 - Initial concentrations of neurotransmitters and folates in the CSF.
 - Measurements of related enzyme activities in tissue and blood cells.
 - Clinical symptoms before and after initiation of treatment including EEG, CT and MRI data.
 - Treatment and follow-up of therapy including therapy protocols, clinical examinations, and neurochemical investigations in the CSF.
 - Clinic and physician's directory.
 - Literature references.
 - DNA analysis entry is linked to the BIOMDB database (see corresponding chapter).
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Software

Patient data are maintained in the Microsoft Access 2003 database. Anonymous patients' data are exported in the MSQL format and installed on the server. BIODEF database is linked with the BIOMDB mutations database (see chapter by Thöny and Blau). Both databases are accessible through the BH₄ homepage (www.bh4.org).

URL: <http://www.bh4.org/biodef1.html>

Search options

The following search options are available: Type of BH₄ deficiency (i.e. GTPCH, PTPS, SR, PCD, DHPR), Subtype (i.e. mild/peripheral, severe, transient), Sex, Country, and Ethnic origin. Extended search allows sorting patient by up to three clinical signs or symptoms, in addition to main search criteria.

System	Symptoms	Neonatal <30 days	Infancy <18 m	Childhood <10 y
Characteristic features	progressive psychomotor retardation despite treatment for PKU	±	+	+
Other neurological signs and symptoms	hypotonia/hypertonia/dystonia	+	+	+
	temperature instability	+	+	+
	seizures – myoclonic		+	+
	microcephaly	+	+	+
	hypersalivation	+	+	+
	mental retardation		+	+
	feeding difficulties	+	+	+

Table 1: Signs and symptoms in patients with autosomal recessive GTPCH deficiency.

Results and Discussion

495 patients with BH₄ deficiency have been diagnosed as a result of selective screening carried out during the last 30 years. Of these 490 patients, 286 suffered from PTPS deficiency, 152 from DHPR deficiency, 22 with PCD deficiency, 18 with GTPCH deficiency, and 9 are still unclassified (Figure 1). 47 out of 286 patients with PTPS deficiency are defined as mild/peripheral variants requiring no neurotransmitters substitution. Since the

introduction of a routine screening program for BH₄ deficiency in 1989, an average of 15 patients per year have been detected worldwide.

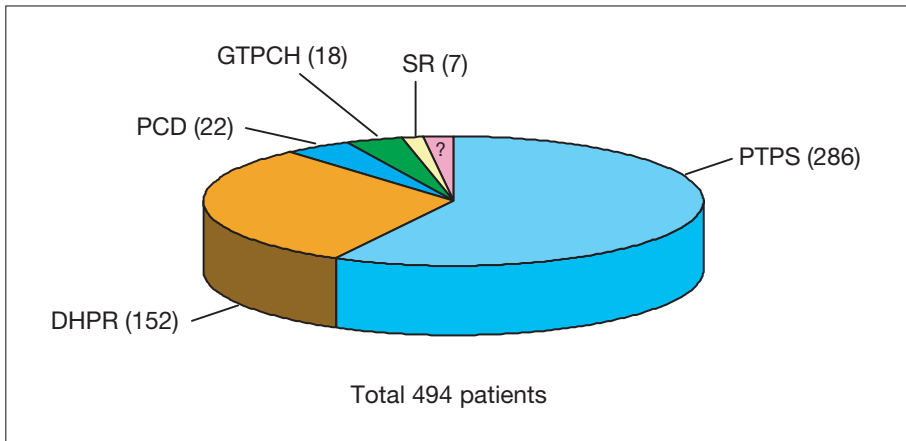


Figure 1: Summary of patients registered in the international BIODEF database.

System	Symptoms	Neonatal <30 days	Infancy <18 m	Childhood <10 y	Adolescence >11 y
Characteristic features	progressive mental and physical retardation despite dietary phenylalanine restriction	±	+	+	+
Other neurological signs and symptoms	myoclonic or tonic clonic seizures	+	+	+	
	temperature instability	+	+	+	
	hypersalivation	+	+	+	+
	lethargy and irritability		+	+	
	hypotonia/hypertonia/dystonia	+	+	+	+
	retardation and regression	+	+	+	+
	choreoathetosis		+	+	
	feeding difficulties	+	+	+	

Table 2: Signs and symptoms in patients with PTPS and DHPR deficiency.

Selective screening for BH₄ deficiency was performed following the positive newborns' Guthrie test (classical or tandem mass-spectrometry) (plasma Phe >120 µmol/l) by urinary pterins analysis, measurement of DHPR activity in blood on filter paper, and BH₄ loading

test. Typical levels of neopterin, biopterin, and primapterin in urine of patients with different forms of BH₄ deficiency are shown in Figure 2A.

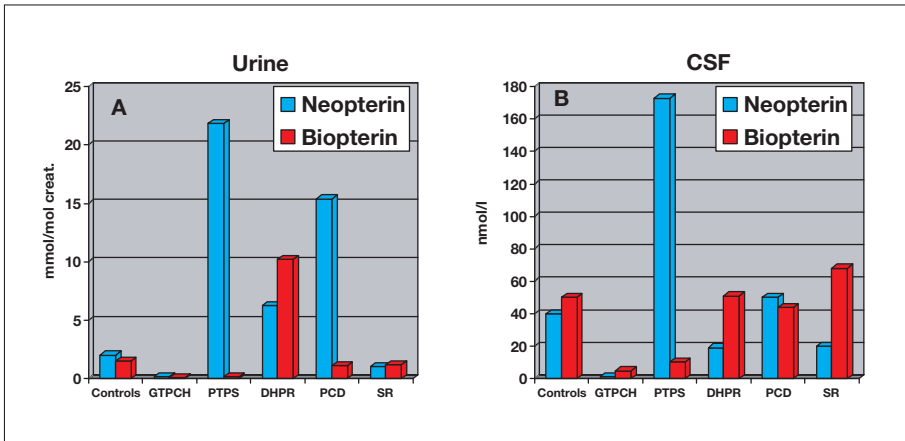


Figure 2: Typical mean values of urinary (A) and CSF (B) pterins, in patients with BH₄ deficiency and control persons (data obtained from the BIDEF database).

An almost identical pterin pattern is observed in the CSF (Figure 2B). Differentiation between the mild (atypical) and severe (typical) form of BH₄ deficiencies was done by analysis of neurotransmitter metabolites 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) in the CSF (Fig 3). While distribution of the 5HIAA and HVA is similar in patients with a PTSP, DHPR, and SR deficiency, patients with a GTPCH deficiency showed a lower HVA/5HIAA ratio (Figure 3).

BIODEF data reveals that the mortality rate is higher in patients with a DHPR deficiency than in those with a PTSP deficiency; however, some DHPR-deficient patients who died were born in the 1970s (data not shown). They were diagnosed late and probably not treated adequately.

Symptoms can manifest during the first weeks of life but usually are noted at about 4 months of age. The variable but common symptoms in patients with severe form of GTPCH, PTSP, and DHPR deficiencies are: truncal hypotonia, hypertonia of extremities, temperature instabilities, seizures (myoclonic or tonic clonic), microcephaly, hypersalivation, lethargy, and irritability. In PTSP- and DHPR-deficient patients additional findings of chorea, athetosis, rash, and pneumonia are noted. Some of these patients died suddenly. The most common clinical signs and symptoms, tabulated from the BIODEF database, are summarized in Tables 1–3.

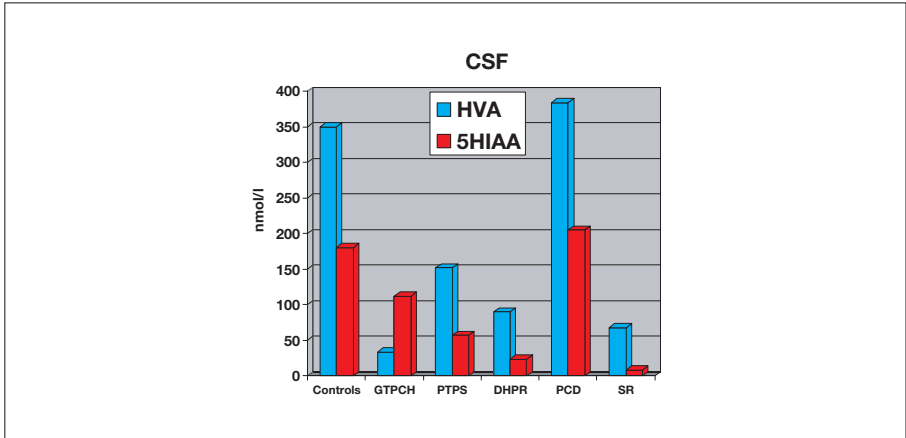


Figure 3: CSF neurotransmitter metabolites 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) in patients with BH_4 deficiency, PKU patients, and control persons (data obtained from the BIDEF database).

System	Symptoms	Neonatal <30 days	Infancy <18 m	Childhood <10 y Adolescence >11 y
Characteristic features	Progressive psychomotor retardation	++	++	++
	Dystonia	+	+	+
	Spasticity	+	+	+
Other neurological signs and symptoms	Microcephaly	+	+	+
	Hypersalivation	+	+	+
	Hypotonia of the trunk	+	+	+
	Hypertonia of the limbs	+	+	+
	Tremor		+	+
	Extrapyramidal signs		+	+
	Seizures		±	±
	Hypersomnolence			
	Oculogyric crises		±	±
	Diurnal fluctuations of dystonia			±
Cortical atrophy				+

Table 3: Signs and symptoms in patients with SR deficiency.

The frequency of all BH₄ deficiencies is approximately 2% of all hyperphenylalaninemias. However, data from newborn and selective screening reveal regional variations in frequency. The incidence is particularly high in Turkey (15%), Taiwan (20%), and Saudi Arabia (60%). Most patients documented in BIODÉF are of Caucasian origin (63%). About 3% are Africans, 6% Japanese, 12% Chinese, 15% Arabs and there is no information for about 12% of registered patients.

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REFERENCES:

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