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Short Communication

Non-responsive Dihydropteridine Reductase Deficiency

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Introduction

The BH_4 loading test is commonly used for the differential diagnosis of BH_4 defects.

The oral loading test was introduced by Niederwieser *et al.* (1) in 1979: oral administration of 7.5 mg BH_4 per kg is followed by a decrease of Phe levels within 4 to 6 hours, in patients with atypical PKU.

Although the BH_4 loading test is completely reliable in detecting BH_4 synthesis defects, it misses diagnosis of dihydropteridine reductase (DHPR) deficiency in some cases (2).

In the 1987 Ponzone *et al.* (3) reported that on administration of 7.5 mg/kg oral dose of BH_4 two patients showed no response but did show a decreased serum Phe levels after the administration of 20 mg/kg BH_4.

For this reason one DHPR-deficient patient known to be a non-responder to the dose of 7.5 mg BH_4 per kg was re-tested at 20 mg/kg.

Case Report

The clinical development and therapeutic aspects have been described previously (4, 5).

The patient was the third child of healthy non-related parents. One brother died in the first month of life with neurological symptoms.

Pregnancy and delivery were normal. Birth weight was 4500 g. The neonatal period was uneventful.

A delay in motor development was realized in the second half of the 1st year: the parents referred episodes of eye rolling from the age of 4 months.

The patient was first seen at our Department at the age of 20 months.

Neurological examination revealed hypotonia and severe psychomotory retardation (I.Q. = 48).

Biochemical findings are given in Table 1:

- Hyperphenylalaninemia with urinary excretion of phenylalanine metabolites;
- high urinary excretion of pterins;
- low levels of homovanillic acid (HVA) and 5-hydroxy-indole acetic acid (5HIAA) in CSF.

DHPR activity was absent in dried blood spots.

Phe plasma levels do not decrease after BH_4 loading at dose of 7.5 mg/kg. The child was re-tested at 20 mg/kg of BH_4.

Table 1. Biochemical findings in patient S. F.

	Patients	Controls	
Plasma Phe	845	42– 74	µmol/l
Urine Neopterin*	2.15	0.51	mmol/mmol Cr
Urine Biopterin*	10.7	1.5	mmol/mmol Cr
CSF HVA	117	250–880	nmol/l
CSF 5HIAA	12.1	110–360	nmol/l
CSF Neopterin	9.11	0– 20	nmol/l
CSF Biopterin	42	10– 34	nmol/l

* Urinary pterins are measured after BH_4 load.

Material and Methods

Plasma aminoacids were determined by ion-exhange chromatography; a BH_4 loading test was performed by oral administration of 7.5 mg/kg of body weight

after overnight fasting, measuring plasma Phe and Tyr at zero, 4th and 8th hr; urinary pterins, CSF HVA and 5HIAA were analyzed by HPLC; DHPR activity in liver biopsy and in dried blood spot was measured according to Arai *et al.* (3).

Results and Discussion

In Table 2 are reported the Phe levels before and after load with the differential dose of BH_4.

At 20 mg/kg Phe levels decreased from 1241 μmol/l to 440 μmol/l 8 hours later.

On the basis of our results we think that the dose of 20 mg/kg BH_4 represents the accurate basis to discriminate the responsiveness or non-responsiveness of the BH_4 load, as emphasized by Ponzone *et al.* (3).

Of course to define diagnosis pterins or enzyme assay are essential.

Table 2. Phenylalanine levels after loading with different doses of BH_4

	Phe levels (μmol/l)		
	0	+4 h	+8 h
BH_4 (mg/kg) 7.5	671	660	630
BH_4 (mg/kg) 20	1241	775	440

References

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