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6-Pyruvoyl-tetrahydropterin synthase deficiency: The first Tunisian case

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Abstract

We detected a first case of 6-Pyruvoyl-tetrahydropterin synthase deficiency in Neuropediatric department mongi Ben Hmida of Tunisia. Genetic analyses of PTS gene demonstrated a homozygous mutation; treatment had been started at the age of 3 years.

Introduction

Tetrahydrobiopterin BH4 acts as a cofactor for phenylalanine hydroxylase as well as for tyrosine hydroxylase and tryptophan hydroxylase, which are required for the synthesis of dopamine and serotonin, respectively [1]. BH4 synthesis from GTP in humans requires some enzymes including dihydropterin redustase (DHPR) and 6-Pyruvoyl-tetrahydropterin synthase (PTS; EC 4.6.1.10; MIM# 261640) [2]. PTS deficiency is a major cause of BH_4-deficient hyperphenylalaninemia (HPAP) [3]. It also causes neurotransmitters synthesis decline [4]. The biological profile is characterized by high blood phenylalanine concentration, low urinary total biopterin and high neopterin:biopterin ratio, as well as decreased neurotransmitter metabolites homovanillic acid and 5-hydroxyindoleacetic in the cerebrospinal fluid [5]. Diagnosis is confirmed by measuring PTS activity in erythrocytes and identification of PTS gene mutation [6-8]. In this study, we report the first Tunisian case with PTS deficiency.

Case report

A one years old boy presented to Neuropediatric department with psychomotor delay. He is the second child of first degree consanguineous healthy parents. His sister died at the age of 18 months from a similar illness. He had a personal history of perinatal asphyxia, recurrent respiratory infections and hyperthermia. Examination showed irritability, axial hypotonia, spastic tetraparesis, dystonia, oculogyre crisis and increased sweating. Brain MRI showed frontal cortical atrophy and periventricular T2 hyperintensity (Figure 1).

Laboratory findings on admission were as follows: Guthrie test showed elevated blood phenylalanine, 31 mg/dL (normal values, < 3). Urinary pterin concentrations measured by high performance liquid chromatography with low biopterin, 194 nmol/mmol creatinine (normal values, 3500-5000), high neopterin, 24556 nmol/mmol creatinine (normal values, 3000-5000) and elevated neopterin:biopterin ratio, 127 (normal values, ≤ 1.22). Blood activity of DHPR was normal, 1.6 nmol/min/mg hemoglobin (normal values, 1-5). Genetic analysis of PTS gene demonstrated a homozygous mutation c.169_171del GTG (Val57del) confirming the diagnosis of PTS deficiency.

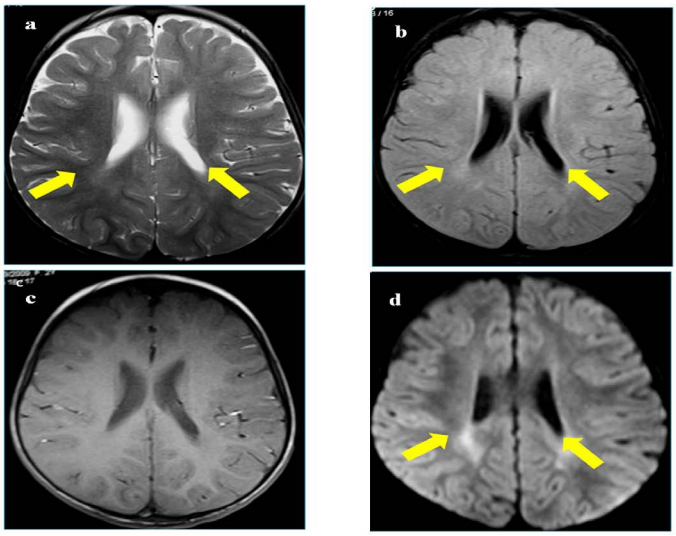

Figure 1. a. Cerebrospinal MRI showing an hypersignal T2; **b**. FLAIR; **c.** prominent periventricular white matter posteriorly and appearing in isosignal T1; **d**. with restriction of ADC on the weighted diffusion sequence as b1000

The Patient underwent BH_4 treatment (5mg/kg/j) at the age of 3 years resulting in a mild clinical improvement. Blood phenylalanine was reduced under treatment to less than 1 mg/dL at age of 4 years. No abnormalities in height or weight were observed in our patients.

The three-nucleotide deletion identified in this patient was assigned as 169-171del GTG. Such deletion leads to an in-frame deletion of

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valine at codon 57 (V57del) and had been identified in Caucasian and Chinese patient [9-11].

In absence of neonatal screening in Tunisia, diagnosis of PTS deficiency should be considered in children with phenylketonuric phenotype associated to neurological signs and symptoms related to impaired catecholamines and serotonin synthesis (movement disorders, microcephaly, seizures, dysautonomic signs). Early diagnosis allows initiation of appropriate therapy and genetic counseling.

Declaration of interest

The authors declare no conflict of interest.

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