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Long-term follow-up of Chinese patients who received delayed treatment for 6-pyruvoyl-tetrahydropterin synthase deficiency

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Abstract

Objectives: 6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency is the most important type of BH4 deficiency related to hyperphenylalaninemia. PTPS deficiency may not only cause a typical phenylketonuric phenotype, but is also accompanied by various neurological signs and symptoms due to impaired synthesis of catecholamines and serotonin. Reports of the long-term outcomes of these patients, especially after delayed onset of therapy, are few.

Study design: We reviewed the characteristics of 10 PTPS-deficient patients whose treatment onset with tetrahydrobiopterin, L-DOPA, and hydroxytryptophan had been delayed. The relationships among clinical manifestations, biochemical findings, genotypes, and long-term outcomes were analyzed.

Results: We classified eight patients as having severe forms, and two as having moderate forms of PTPS deficiency. Improvements in neurological status and intelligence/developmental quotient (IQ/DQ) were observed in all patients, up to approximately 15 years of follow-up. One patient began walking and talking after 4 years of treatment. In patients with severe disease, the mean initial IQ/DQ was 45.40 ± 13.94, and the final full-scale intelligence quotient (FIQ) score was 62.8 ± 13.06 ($p = 0.042$), with a mean increment of 17.4 ± 5.27 over 15.86 ± 4.85 years of follow-up. Two patients with moderately severe disease had FIQ increases from 75 to 77 and from 76 to 80 points, respectively.

Conclusions: The administration of neurotransmitters based on clinical response and adverse effects was beneficial in patients whose treatment of PTPS deficiency was delayed. Sustained clinical improvements were observed up to 15 years of follow-up.

Keywords: 6-Pyruvoyl-tetrahydropterin synthase deficiency; Atypical phenylketonuria; Hyperphenylalaninemia; Tetrahydrobiopterin; L-DOPA; hydroxytryptophan

Hyperphenylalaninemia (HPA) is the most common inherited disorder of amino acid metabolism. It may be caused by a deficiency of phenylalanine hydroxylase (PAH) or tetrahydrobiopterin (BH4), an important cofactor involved in the biogenic syntheses of tyrosine, L-DOPA, 5-hydroxytryptophan (5-HTP), nitric oxide, and glycerol [1]. A deficiency of BH4 in humans may not only produce the classical phenylketonuric phenotype, but may also be the source of neurological signs and symptoms due to impaired syntheses of L-DOPA and serotonin [1–3]. BH4 is synthesized from guanosine triphosphate by the enzymes

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guanosine triphosphate cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), and sepiapterin reductase (SR) in a three-step pathway. After reacting with the aromatic amino acid hydroxylase as an active cofactor, BH4 is oxidized to pterin-4α-carbinolamine (4α-OHBH4). It is then regenerated by pterin-4α-carbinolamine dehydratase (PCD) and dihydropteridine reductase (DHPR) to BH4 (Fig. 1). BH4 deficiency may be caused by defects in the enzymes involved in either its biosynthesis or its regeneration. In Caucasians, the overall prevalence of HPA attributable to BH4 deficiency is only 1–2% of all HPA [4,5]. According to the BIODEF database, which includes patients with BH4 deficiency of different ethnicities, PTPS deficiency (MIM #261640) represents about 60% of all BH4 deficiencies [6]. The treatment of PTPS deficiency consists of replacement with BH4 and the neurotransmitters L-DOPA and 5-HTP. Descriptions of the outcomes of patients with BH4 deficiency, particularly over long periods of observations, remain scarce. The proper amount of neurotransmitter replacement should be based on the levels of cerebrospinal fluid (CSF) neurotransmitter metabolites. However, these measurements are not available here. Furthermore, the parents of our patients were often reluctant to allow us to perform a lumber puncture on their children. Therefore, the administration of each agent was based only on the clinical response and development of adverse effects at our clinics. We have been concerned that replacement of neurotransmitters guided by clinical observations may not be the most appropriate for these patients, and that long-term undertreatment may be the source of subtle brain damage and gradual neurological dysfunction, particularly in patients with pre-existent brain damage.

In Taiwan, PTPS deficiency is the cause of approximately one-third of all cases of HPA. The prevalence of PTPS deficiency in this country (1/132,000) is considerably higher than in Caucasian populations (1/1,000,000) [7,8]. This provides us with more opportunities to observe and treat this form of illness within a single medical center.

This report describes 10 PTPS-deficient patients whose treatment had been delayed, most of whom were followed at our hospital for >15 years. We have analyzed the relationships among their clinical manifestations, biochemical findings, genotypes, and long-term outcomes.

Patient population and methods

We retrospectively reviewed the characteristics of seven male and three female patients from eight unrelated families, whose treatment of PTPS deficiency had been delayed. The 1st patient was detected by newborn screening for hyperphenylalaninemia and was placed elsewhere on a phenylalanine-restricted diet without replacements of BH4 and neurotransmitters. He was admitted to our hospital at two years and third months of age for evaluation and treatment of severe psychomotor retardation and progressive neurological deterioration. The other nine patients were born before the creation of our national newborn screening program. Seven of these nine patients (#2 to #8) were referred by pediatricians for evaluation of neurological symptoms. Patients #3 and #4 were sister and brother from one family, and patients #7 and #8 were brothers from another family. The diagnosis in patient #9 was made by an HPA screening program at a school for mentally handicapped children. In patient #10, the diagnosis was made after his sibling was found to have PTPS deficiency by newborn screening.

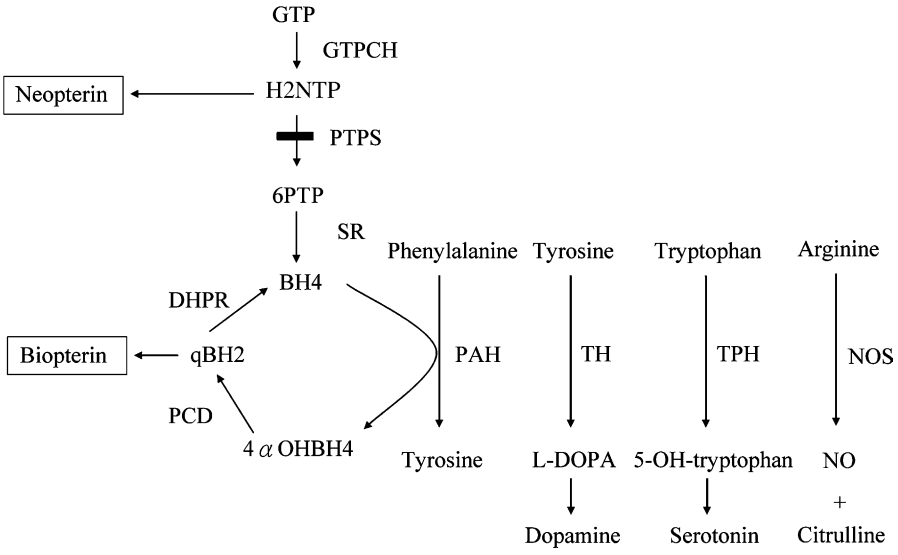

Fig. 1. The biochemical pathway of tetrahydrobiopterin (BH4) metabolism. 4α OHBH4, pterin-4α-carbinolamine; 6PTP, 6-pyruvoyl-tetrahydropterin; BH4, tetrahydrobiopterin; H2NTP, dihydroneopterin triphosphate; DHPR, dihydropteridine reductase; GTP, guanosine triphosphate; GTPCH, guanosine triphosphate cyclohydrolase I; NO, nitric oxide; NOS, nitric oxide synthase; PAH, phenylalanine hydroxylase; PCD, pterin-4α-carbinolamine dehydratase; PTPS, 6-pyruvoyl-tetrahydropterin synthase; qBH2, quininoid dihydrobiopterin; SR, sepiapterin reductase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase. This figure is modified from figure in http://www.bh4.org/.