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Brain & Development 36 (2014) 268–271

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Early replacement therapy in a first Japanese case with autosomal recessive guanosine triphosphate cyclohydrolase I deficiency with a novel point mutation

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Received 30 December 2012; received in revised form 9 April 2013; accepted 10 April 2013

Abstract

Autosomal recessive guanosine triphosphate cyclohydrolase I (GTPCH) deficiency is an inborn error of tetrahydrobiopterin (BH4) synthesis from GTP. GTPCH deficiency causes severe reduction of BH4, resulting in hyperphenylalaninemia (HPA) and decreased dopamine and serotonin synthesis. Without treatment, a patient with GTPCH deficiency develops complex neurological dysfunctions, including dystonia and developmental delays. The first Japanese patient with GTPCH deficiency was discovered by HPA during asymptomatic newborn screening. The phenylalanine level at the age of 5 days was 1273 μmol/L (cutoff value, 180.0 μmol/L). The high serum phenylalanine level was decreased to normal after adequate BH4 oral supplementation. Serum and urinary pteridine examination revealed very low levels of neopterin and biopterin. Sequence analysis of *GCH1* revealed compound heterozygous point mutations, including a novel point mutation (p.R235W). Replacement therapy with BH4 and L-dopa/carbidopa were started at the age of 1 month, and 5-hydroxytryptophan (5-HTP) was started at the age of 5 months. At 10 months of age, the patient showed slight dystonia but no obvious developmental delay. Cerebrospinal fluid should be examined to determine the appropriate dosage of supplement drugs. In conclusion, it is important to control the serum phenylalanine level and perform early replacement of neurotransmitters to prevent neurological dysfunction.

Keywords: Autosomal recessive guanosine triphosphate cyclohydrolase I (GTPCH); Tetrahydrobiopterin (BH4); Hyperphenylalaninemia; Early replacement therapy

1. Introduction

Tetrahydrobiopterin (BH4) is an essential cofactor in the enzymatic hydroxylation of phenylalanine, tyrosine, and tryptophan. The BH4 loading test is performed to distinguish BH4 deficiency from hyperphenylalaninemia (HPA) during newborn screening. BH4 deficiency causes HPA and decreased production of the neurotransmitters dopamine and serotonin. Five types of enzyme deficiencies have been reported in BH4 deficiency: guanosine triphosphate cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), sepiapterin reductase (SR), dihydropteridine reductase (DHPR), and pterin-4a-carbinolamine dehydratase (PCD) [1]. GTPCH deficiency is an error of BH4 synthesis. *GCH1*, the gene

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http://dx.doi.org/10.1016/j.braindev.2013.04.003

symbol of GTPCH, is located on chromosome 14q22.1-q22.2 and comprises six exons. GTPCH deficiency has autosomal dominant and autosomal recessive forms. The autosomal dominant (AD) form is known as dopa-responsive dystonia (DRD, Segawa disease), whereas the autosomal recessive (AR) form results in swallowing difficulties, truncal hypotonia, seizures, mental retardation, and developmental delays. The residual GTPCH enzyme activity is thought to be the cause of clinical severity between the AD and the AR form. The AR form is so rare that only 17 cases are listed in the BIOMDB Database [1], and no case has been reported in Japan. The combination of BH4 replacement and neurotransmitter precursor supplementation of both L-dopa/carbidopa and 5-hydroxytryptophan (5-HTP) is a common therapeutic approach.

We experienced the first Japanese case of autosomal recessive GTPCH deficiency with HPA during newborn screening. We herein describe the clinical symptoms and treatments with a review of previous reports.

2. Case report

The patient was the first child of healthy, nonconsanguineous parents. He was born in the 40th week of pregnancy by spontaneous delivery (birth weight, 2744 g; birth height, 50 cm). At the age of 11 days, the patient was hospitalized because of HPA detected by newborn screening. The phenylalanine level measured by Guthrie test at the age of 5 days was 1273 μmol/L (cutoff value, 180.0 μmol/L). There were no abnormalities on physical or neurological examinations. Laboratory examinations showed HPA. The serum phenylalanine level was 2206 μmol/L (reference interval, 61.2 ± 14 μmol/L). A BH4 loading test with 10 mg/kg of sapropterin hydrochloride was performed. The serum phenylalanine level was decreased to normal 8 h after adequate BH4 oral supplementation (Fig. 1). Serum and urinary pteridine examination revealed very low levels of neopterin and biopterin. The serum levels of neopterin and biopterin were 5.76 nM (reference interval, 33.8 ± 4.9 nM) and 3.31 nM (reference interval, 15.0 ± 1.6 nM), respectively. The urinary level of neopterin and biopterin were 0.14 mmol/mol creat. (reference interval, 2.09 ± 0.52 mmol/mol creat.) and 0.64 mmol/mol creat. (reference interval, 1.08 ± 0.36 mmol/mol creat.). The cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA) was 114 nmol/L (reference interval, 746 ± 207 nmol/L), and that of homovanillic acid (HVA) was 21 nmol/L (reference interval, 1083 ± 339 nmol/L) (Table 1); both were reduced.

Molecular genetic analysis of *GCH1* revealed compound heterozygous point mutations in exon 5 of *GCH1* (p.R184H) and exon 6 of *GCH1* (p.R235W) (Fig. 2). His father was heterozygous for p.R184H, and his mother was heterozygous for p.R235W. The

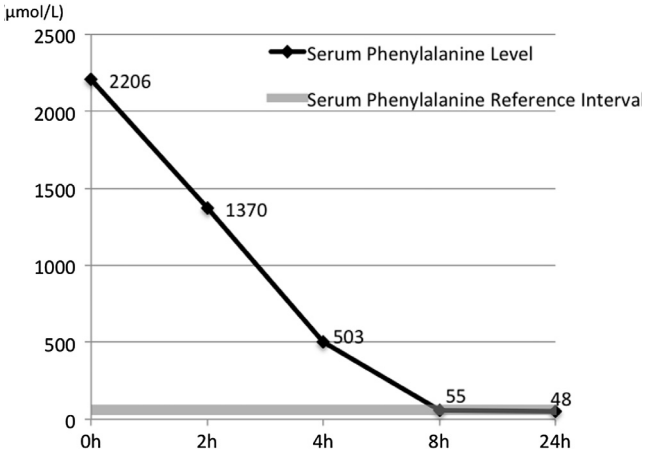

Fig. 1. Response of serum phenylalanine level by oral BH4 loading. Serum phenylalanine level was decreased to reference interval (61.2 ± 14 μmol/L) at the 8 h after BH_4 supplement.

p.R235W has not been previously reported in patients with GTPCH deficiency.

At the age of 1 month, treatments with L-dopa/carbidopa and BH4 were started, with initial doses of 2 and 5 mg/kg/day, respectively. Mild dystonia appeared at the age of 3 months. It was slightly improved by increasing the dose of L-dopa/carbidopa supplementation. Because 5-HTP is not an approved medicine in Japan, we began supplemental therapy with 5-HTP at the age of 5 months (4 mg/kg/day) after approval by our hospital ethics committee. We adjusted the dose of BH4 according to the level of serum phenylalanine, L-dopa/carbidopa according to the clinical symptom of dystonia and serum prolactin and CSF HVA levels, and 5-HTP according to the CSF 5-HIAA level. At 8 months of age, a brain MRI was normal, and the CSF concentrations of 5-HIAA and HVA were improved (5-HIAA, 143 nmol/L; HVA, 403 nmol/L). In the most recent examination at 10 months old, he still had slight dystonia but no obvious developmental delay (sitting without support and playing toy with babbling) under treatment with BH4 (5 mg/kg/day), L-dopa/carbidopa (16 mg/kg/day), and 5-HTP (4 mg/kg/day).

3. Discussion

We herein report the first Japanese case of autosomal recessive GTPCH deficiency detected by newborn screening and presenting as HPA. We identified a novel point mutation of *GCH1*. The patient had no family history, and his parents were asymptomatic carriers. Although five *GCH1* mutations (p.Q110X (exon 1), p.R184H (exon 5), p.M213T (exon 6), p.M211V (exon 6), and p.M211I (exon 6)) have been reported in patients with HPA (BIOMDB Database) [2], there seem to be no obvious phenotype or genotype correlations.