GTP-Cyclohydrolase I deficiency presenting as malignant hyperphenylalaninemia, recurrent hyperthermia and progressive neurological dysfunction in a South Asian child – a case report

Kavinda Chandimal Dayasiri 1*, Nayani Suraweera 1, Deepal Nawarathne 1, U. E. Senanayake 2, B. K. T. P. Dayanath 2, Eresha Jasinge 1 and Kumudu Weerasekara 1

Abstract

Background: Tetrahydrobiopterin (BH4) deficiencies are disorders affecting phenylalanine homeostasis, and catecholamine and serotonin biosynthesis. GTP-Cyclohydrolase I deficiency (OMIM 600225) is an extremely rare variant of inborn error of BH4 synthesis which exists in recessive and dominant forms. The recessive form presents with complex neurological and autonomic dysfunction whilst the dominant form presents as Dopa-responsive dystonia.

Case presentation: We describe a South Asian child who initially presented with neurological dysfunction and recurrent vomiting and later developed recurrent hyperthermia for several months. The child did not have screening for hyperphenylalaninemia at birth and was found to have marked hyperphenylalaninemia after clinical presentation at 5 months. Further evaluation revealed BH4 deficiency. GTP-Cyclohydrolase I deficiency (GTPCH) was identified based on normal dihydro pteridine reductase activity and markedly reduced neopterin in dried blood spot test. After institution of treatment and control of high phenylalanine levels, clinical deterioration decelerated yet with noticeable residual neurological dysfunction.

Conclusion: To authors’ knowledge, this is first report of GTPCH deficiency in a South Asian child. The case highlights practical issues regarding diagnosis of GTPCH deficiency, especially in countries without broader universal newborn screening programs for early detection of inherited metabolic disorders. Testing for GTPCH deficiency should be considered for patients with unexplained neurological and autonomic symptoms following initial metabolic screen.

Keywords: GTPCH deficiency, Recurrent hyperthermia, South Asian child
Background
Tetrahydrobiopterin (BH$_4$) deficiencies comprises a heterogeneous group of disorders caused by mutations at one of the genes encoding enzymes involved in the biosynthesis (GTP cyclohydrolase I or 6-pyruvyltetrahydropterinsynthase) or regeneration (pterin-4a-carbinolamine dehydratase or dihydropteridine reductase) of BH$_4$ [1]. In addition to hyperphenylalaninemia, BH$_4$ deficiency leads to dopamine and serotonin depletion in the central nervous system [2]. Most late-diagnosed and untreated BH$_4$-deficient patients develop progressive neurological dysfunction from early infancy [3]. Consequences of delayed diagnosis and treatment are devastating and affected children develop clinical features such as mental retardation, seizures, dystonia, drowsiness, irritability, recurrent hyperthermia without infections, hypersalivation, and swallowing dysfunction [4]. Most of these clinical manifestations occur secondary to deficiencies of dopamine, noradrenaline, and serotonin.

GTP-Cyclohydrolase I Deficiency (GTPCH – 1) Disorder, a very rare inherited metabolic disorder, is one of the causes of malignant hyperphenylalaninemia due to tetrahydrobiopterin deficiency. The disorder is caused by mutation(s) in the GCH1 gene that encodes for the enzyme GTP Cyclohydrolase I. Currently there are two forms of GTPCH – 1 Deficiency. The first and more common is the autosomal dominant form, also known as Segawa Disease. This form typically responds well to dopamine replacement therapy. The second form is rare and is an autosomal recessive form which does not respond as well to treatment for currently unknown reasons. In countries which offer universal newborn screening for inherited disorders, patients with these rare metabolic diseases are suspected based on the presence of hyperphenylalaninemia.

We describe a South Asian infant who presented with progressive neurological dysfunction secondary to malignant hyperphenylalaninemia and in whom tetrahydrobiopterin deficiency was confirmed and autosomal recessive GTPCH-1 was identified based on normal dihydropteridine reductase activity and very low neopterin levels. His sibling, who had similar clinical features, succumbed following severe neurodevelopmental regression.

Case presentation
Five month old boy born to second degree consanguineous parents was brought for evaluation of global developmental delay since birth, and remittent fever, recurrent seizures and vomiting since three months of age. The pregnancy had been unplanned. Though the antenatal period was uncomplicated child had a low birth weight- 2.2 kg (<−3SD) and had evidence of symmetrical intrauterine growth retardation (OFC - 33 cm/ <5th centile, length – 46 cm/ (-2) - (-3) SD). He had recurrent vomiting since two months of age associated with poor weight gain. The clinical course was complicated with recurrent seizures since three months and the child had developmental regression with poor visual fixation and loss of social smile. He had remittent fever for several months with repeatedly negative septic screen following which a central cause for irregularities in thermoregulation was suspected. Later in the clinical course, he developed marked dystonia and dyskinetic movements suggesting extrapyramidal nervous system involvement. His elder sibling who had developmental regression and epileptic encephalopathy, died at 1 ½ years of age following aspiration pneumonia whilst being evaluated for a neuro-metabolic disorder.

Clinical examination at five months revealed severe growth retardation: weight – 5 kg (<−3SD), length – 59 cm (<−3SD), OFC- 39 cm (<5th centile). He had four limb spasticity and exaggerated reflexes. Electroencephalography revealed encephalopathy. Brain MRI showed multiple areas of increased T2 signal intensity with diffusion restriction involving brain stem, basal ganglia and white matter tracts and suggested widespread demyelination. Urine FeCl$_3$ test was positive for phenylketonuria. Plasma amino acid profile revealed elevated Phenylalanine – 1245.71 μM (range 25–120 μM). Plasma Phenylalanine/ Tyrosine ratio was 21.87 (range 0.4–2.2). Blood Neopterin levels were very low – 0.01 nmol/g Hb (range: 0.19–2.93 nmol/g Hb, Haemoglobin – 9.8 g/dl) and Biopterin were not detectable (range: 0.08–1.20 nmol/g Hb, Haemoglobin – 9.8 g/dl). Dihydro Pteridine reductase activity was normal – 2 mU/mg Hb (range - > 1.1 mU/mg Hb). Plasma acylcarnitine profile and screening for other metabolic disorders were negative. Genetic studies were not performed due to lack of facilities and as the biochemical tests were sufficient enough to make the diagnosis of GTPCH 1 deficiency (Figs. 1, 2 and 3).

Child was commenced on Phenylalanine restricted diet with supplementation of other essential amino acids by special formula milk. Micronutrients were also supplemented. Breast feeding was continued and complementary feeds were commenced with a carbohydrate rich and phenylalanine restricted diet. L-Dopa was commenced after detection of BH$_4$ deficiency and Tetrahydrobiopterin and 5-hydroxytryptophan were requested as they were not available. Multidisciplinary care was arranged with involvement of paediatrician, nutritionist, metabolic specialist, neurologist and geneticist. Since parents wished for a third child they were offered genetic counseling. Plasma Phenylalanine levels were monitored monthly to assess biochemical improvement. Plasma Phenylalanine level and Phenylalanine/ Tyrosine ratio at 9 months were 18.6 μM and 0.35 respectively.

Discussion and conclusions
The dried blood spot test analysis in this child revealed markedly reduced neopterin and undetectable biopterin...
confirming the diagnosis of tetrahydrobiopterin deficiency. Normal dihydro pteridine reductase activity and markedly reduced neopterin identified the defect in GTP Cyclohydrolase 1 pathway by ruling out Dihydro Pteridine reductase deficiency and 6-pyruvoyl-tetrahydropterinsynthase (PTPS) related BH₄ deficiency. Family history of consanguinity and possibly affected previous sibling clinically suggested the more severe and autosomal recessive GTPCH deficiency rather than the less severe, autosomal dominant GTPCH deficiency (Segawa disease).

The child presented in this report had a sibling who had similar clinical features. Unfortunately, the diagnosis of the elder sibling could not be confirmed due to early demise. Lack of clinical vigilance given the rarity of tetrahydrobiopterin deficiencies in the local setting seemed to be a contributory reason for not establishing the diagnosis. Both children in the current report had early onset similar and severe neurological manifestations suggesting malignant hyperphenylalaninemia and severe neurotransmitter deficiencies in the elder sibling.

Most children with BH₄ deficiencies have uneventful births but present with early onset development delay...
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The use of dried blood spot test is more practical and allows for measurements of pterins, dihydro pteridine redact activity and amino acids from a single speci-
men [9]. These tests are essential because they allow for the differentiation of all defects of BH4 metabolism that present with hyperphenylalaninemia. Hyperphenylala-
ninemia (plasma phenylalanine > 120 μmol/L) [10, 11], is considered a cardinal feature of classic autosomal reces-
sive GTPCH deficiency.

Several studies have suggested that diagnosis within the first month of life is essential, and the age at which treatment begins determines the prognosis [12, 13]. Studies from developed countries recommend that sele-
ctive screening for BH4 deficiency is essential in every newborn with even slightly elevated phenylalanine levels [14]. This case highlights practical issues regarding diagnosis of GTPCH deficiency, especially in countries without broader universal newborn screening programs for early detection of inherited metabolic disorders. Authors would like to emphasize the need of neonatal screening for hyperphenylalaninemas and research for BH4 deficiencies even in patients with slight hyperphenylalaninemia. Testing for GTPCH defi-
ciency should be considered for patients with hyperphe-
nylalaninemia who present unexplained neurological and autonomic symptoms.

Abbreviations
BH4: Tetrahydrobiopterin; GTPCH: Guanosine Triphosphate Cyclohydrolase; OFC: occipital frontal circumference; OMIM: Online Mendelian Inheritance in Man; SD: standard deviation

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KD, NS, DN and US drafted the manuscript. BD and EJ carried out biochemical analysis. KW and EJ critically evaluated manuscripts and lead medical management of the patient. All authors have agreed and approved the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available due to patient confidentiality of such data.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the proband’s parents for the publication of all personal information contained in this case report. A copy of the written consent is available for review by the corresponding author.

Competing interests
The authors declare that they have no competing interests.

Author details
1Lady Ridgeway Hospital for Children, Colombo, Sri Lanka. 2North Colombo Teaching Hospital, Ragama, Sri Lanka.

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