ORIGINAL ARTICLE

Clinical, Biochemical, and Radiologic Profiles of Filipino Patients with 6-Pyruvoyl-Tetrahydrobiopterin Synthase (6-PTPS) Deficiency and their Neurodevelopmental Outcomes

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ABSTRACT

Background. Six-pyruvoyl-tetrahydrobiopterin synthase (6-PTPS) deficiency is an inherited metabolic disorder which results in tetrahydrobiopterin (BH4) deficiency causing hyperphenylalaninemia.

Objective. This study aimed to describe the clinical, biochemical, and radiologic profiles, and neurologic and developmental outcomes of patients diagnosed with 6-pyruvoyl tetrahydrobiopterin (PTPS) deficiency through newborn screening and confirmed by BH4 loading test, pterin analysis, and gene sequencing who were following-up with the metabolic team.

Methods. The research was a single-center descriptive case series study design that was done at the Philippine General Hospital, a tertiary government hospital. The clinical, biochemical, radiologic profiles and neurodevelopmental evaluation of each patient were described.

Results. Nine patients from 1 year 2 months to 14 years 5 months of age were enrolled in the study. Clinical manifestations before treatment were hypotonia, poor suck, and seizure. The most common clinical manifestation even after treatment initiation was seizure. The mean phenylalanine level on newborn screening was 990.68 umol/L, but after treatment was started, mean levels ranged from 75.69 to 385.09 umol/L. Two of the patients had focal atrophy of the posterior lobe on brain imaging. Pathogenic variants on molecular analysis were all missense, with two predominant variants, c.155A>G and c.58T>C. Eight of the nine patients had varying degrees of developmental delay or intellectual disability, while the remaining patient had signs of a learning disorder.

Conclusion. Newborn screening has played a crucial role in the early identification and management of patients with hyperphenylalaninemia due to 6-PTPS deficiency. Confirmation of diagnosis through determination of DHPR activity, urine pterins and/or molecular analysis is necessary for appropriate management. However, despite early initiation of treatment, neurodevelopmental findings of patients with 6-PTPS deficiency were still unsatisfactory.

Keywords: 6-PTPS deficiency, hyperphenylalaninemia, tetrahydrobiopterin

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INTRODUCTION

Hyperphenylalaninemia refers to the elevated level of phenylalanine in the blood. One of the most common inherited metabolic disorders causing hyperphenylalaninemia is phenylketonuria. This is due to the deficiency of phenylalanine hydroxylase, which catalyzes the hydroxylation of phenylalanine to tyrosine.[1] However, this reaction also needs a cofactor, Tetrahydrobiopterin (BH_4). This cofactor is also essential for enzymes involved in the biosynthesis of neurotransmitters dopamine and serotonin (Figure 1).[2-4] Six-pyruvoyl-tetrahydrobiopterin synthase (6-PTPS) is an enzyme important in the synthesis of BH_4. Hence, its deficiency may cause not only hyperphenylalaninemia, but also neurologic manifestations associated with the impaired synthesis of the neurotransmitters.[3-5]

The prevalence of 6-PTPS deficiency varies widely with an estimated prevalence of 1 in 1,000,000 in Caucasian population up to about 1 in 132,000 in Taiwan.[6,7] It is a pan-ethnic disorder with mainly Chinese, Caucasians, and Arabs and uncommon in Africans and Hispanics based on International Database of Tetrahydrobiopterin Deficiencies (BIODEF).[1] In the Philippines, 6-PTPS deficiency has an estimated prevalence of 1 in 1,488,031 based on newborn screening.[8] This data was obtained since the Philippines has been screening for increased phenylalanine since the beginning of the newborn screening program and has been able to diagnose patients with this condition and refer them for treatment.

Studies describing the clinical, biochemical, and radiologic factors, as well as neurodevelopmental outcomes of 6-PTPS-deficient patients have been published. Several factors (phenylalanine concentration, genotype, birth weight percentile, and age at onset of treatment) and their relation to neurological or developmental status of 6-PTPS-deficient patients vary in different populations. For instance, long-term follow-up (15 years) of 6-PTPS-deficient patients in China who received delayed treatment had significant improvements in intelligence and development quotient.[9] On the other hand, long-term follow-up of patients in Taiwan who received early treatment showed no correlation between age at time of treatment and full-scale intelligence quotient of the patients.[7]

Description of Filipino patients with 6-PTPS deficiency has not been done before. Thus, this study aimed to describe the clinical, biochemical, and radiologic profiles, and neurologic and developmental outcomes of patients diagnosed with 6-PTPS deficiency in the Philippines.

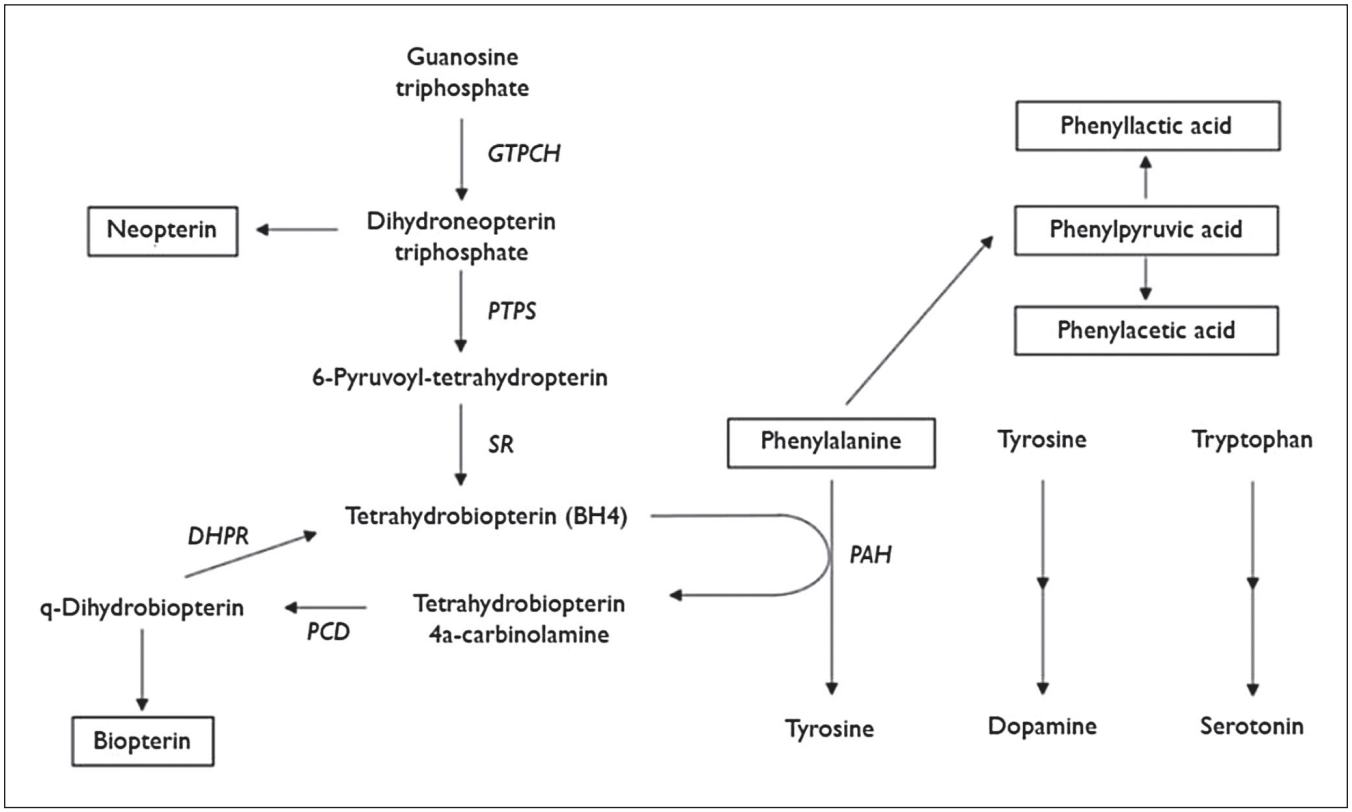

Figure 1. The biochemical pathway of tetrahydrobiopterin metabolism (BH4).[4]

GTPCH – GTP cyclohydrolase I, PTPS – 6-pyruvoyl tetrahydropterin synthase, SR – sepiapterin reductase, DHPR – dihydropteridine reductase, PCD – pterin-4a-carbinolamine dehydratase

METHODS

This was a single-center descriptive case series study at the Philippine General Hospital, a tertiary government hospital. A total of 13 patients (from 1996-2021) diagnosed with 6-pyruvoyl tetrahydrobiopterin (PTPS) deficiency through newborn screening and confirmed by BH_4 loading test, pterin analysis, and gene sequencing who were following-up with the metabolic team were included in the study.

Informed consent was obtained from the patient's parents/guardians after fulfilling the inclusion criteria. Sociodemographic data and other relevant information from the patients' medical records were collected. Participation in the study was entirely voluntary, however it was either full or partial in nature (online participation with no face-to-face procedures or consultations). There were no participant withdrawals in this study.

Baseline phenylalanine levels of all patients were determined and subsequently, the patients underwent monthly or quarterly monitoring of their phenylalanine and prolactin levels. Phenylalanine and prolactin levels were obtained from extracted blood samples. They underwent cranial magnetic resonance imaging (MRI) with contrast. Radiologic films and reports were obtained and evaluated. Patients were also referred to a developmental pediatrician and a pediatric neurologist for the evaluation of their developmental and neurologic status, respectively. The demographic, clinical, biochemical, radiologic profiles and neurodevelopmental evaluation of each patient were described.

Cases of 6-PTPS deficiency were described according to the clinical, biochemical, radiologic profiles, and neurodevelopmental outcomes. Descriptive statistics were used to summarize socio-demographic data of the patients. Categorical variables were summarized as proportions and frequency distributions were obtained. Continuous variables were summarized using mean or median, standard deviation, and range (minimum and maximum values). For dichotomous factors (e.g., most common clinical manifestations, cranial MRI findings, DNA mutation) and neurodevelopmental outcomes (e.g., global developmental delay or intellectual disability), two-by-two tables were generated and the crude odds ratios (ORs) were reported. For quantitative factors [e.g., age at diagnosis, phenylalanine level, prolactin level, urine pterins, dihydropteridine reductase (DHPR) activity] and dichotomous neurodevelopmental outcomes, the difference in the mean values were reported. The data set generated was considered a population data set since all diagnosed cases of 6-PTPS deficiency in the country were included in the study.

The study adhered to the principles provided by the National Ethical Guidelines for Health and Health-Related Research (2017) and was approved by the UP Manila Research Ethics Board under registration number 2020-732-01. All data gathered for all patients were kept confidential. All sociodemographic information and results of blood tests, imaging studies, and neurodevelopmental evaluation of each patient were recorded in a master file using software from a computer which was password-protected. All patients were anonymized and assigned a corresponding code for reference.

RESULTS

A total of 13 patients were listed with the diagnosis of 6-PTPS deficiency under the records of the University of the Philippines- Philippine General Hospital Department of Clinical Genetics. Six of these patients enrolled for full participation, three patients enrolled for partial involvement (online participation only with no face-to-face procedures or consultations), two patients refused participation, and two patients had died prior to the study initiation.

Participants enrolled in the study were aged 1 year 2 months to 14 years 5 months. The mean age of newborn screening was 5.5 days [5.9 days standard deviation (SD)]. Of the nine patients, one was diagnosed after clinical presentation at 11- 12 months old. The mean age of diagnosis and initiation of treatment was 84.3 days (115.1 days SD) or 2.8 months (3.8 months SD). Clinical manifestations before treatment were hypotonia (4/9), poor suck (3/9), and seizure (2/9) (Table 1). The most common clinical manifestation even after treatment initiation was seizure (6/9) 66.67%. Two patients did not present with any clinical manifestations. The mean phenylalanine level on newborn screening was 990.68 umol/L, but once treatment was started, mean levels for each of the different patients in the study ranged from 75.69 to 385.09 umol/L (Table 2). For those who underwent collection of DHPR activity, level was not deficient. For urine pterins, neopterin was elevated and biopterin was low. Meanwhile, the lowest mean prolactin level was 30.41 and the highest was 1452.21 ng/ml.

Out of the nine patients in this cohort, five were diagnosed with focal or generalized epilepsy, while all nine patients had intellectual disability in varying degrees of severity (Table 2). Out of the four patients with brain MRI studies in this series, two had unremarkable results while two had focal atrophy of the posterior lobe. Pathogenic variants in this cohort were all missense, seen in 14 alleles of seven patients. The predominant variants were c.155A>G (7/14) and c.58T>C (5/14).

DISCUSSION

Patients with 6-PTPS deficiency may be detected via newborn screening through the presence of hyperphenylalaninemia. From the patients included in the study, one patient did not undergo newborn screening and was subsequently diagnosed after presenting with symptoms. Another patient, however, was managed late because the patient was initially diagnosed as having phenylketonuria. The remaining seven patients underwent newborn screening and subsequent confirmatory work-up.

Table 1. Biochemical and Clinical Profile of Patients with 6-PTPS Deficiency at Diagnosis

Patient Number	Phenylalanine on NBS (umol/L)	Age on NBS (days of life)	DHPR Activity (RV: 5.2-11.5 nmol/min/mg Hb)	Urine Pterins		Age at Diagnosis and Treatment Initiation (days)	Clinical Manifestations	
				Neopterin (RV: 0.9-7.49 mmol/mol creatinine)	Biopterin (RV: 1.73-3.68 mmol/mol creatinine)		before treatment	on treatment
PTPS 1	1077.60	17	–	18.17	0.88	30	seizure	seizure
PTPS 2	no NBS	–	13.9	34.14	0.41	358	seizure, poor suck, and hypotonia	seizure
PTPS 3	2383.9	2	7.0	16.80	<0.01	17	none	none
PTPS 4	934.48	2	7.9	20.73	0.13	19	poor suck and hypotonia	seizure
PTPS 5	379.20	10	6.8	52.97	0.04	60	none	none
PTPS 6	350	1	–	18.48	0.07	180	hypotonia	seizure
PTPS 7	380.68	2	8.9	9.86	0.07	18	hypotonia	seizure
PTPS 8	1465.58	1	7.1	23.57	0.07	17	none	none
PTPS 9	954	9	–	6.56	0.23	60	poor suck	seizure
Median (SD)	990.68 ± 690.25	5.5 ± 5.9				84.3 ± 115.1		

RV – Reference value

Table 2. Neurodevelopmental Outcomes and Molecular and Radiologic Profiles of 6-PTPS-Deficient Patients

Patient Number	Age	Mean Phenylalanine Level (umol/L) + SD	Mean Prolactin Level (ng/mL) + SD	Neurologic Assessment	Developmental Assessment (DSM-5 Criteria)*	Cranial MRI Findings	Mutational Analysis
PTPS 1	8 years 8 months	194.89 ± 362.38	536.99 ± 707.99	Focal epilepsy	Intellectual disability	Polysinus disease otherwise unremarkable MRI	c58T>C homozygote
PTPS 2	10 years 6 months	270.55 ± 339.26	90.29 ± 129.16	Generalized epilepsy	Intellectual disability	not done	c.155A>G homozygote
PTPS 3	13 years	385. 09 ± 525.86	84.43 ± 127.26	Asymptomatic	Probable learning disorder (Math, Reading Comprehension, Written Expression)	not done	c.58T>C and c.382T>A
PTPS 4	11 months	75.69 ± 23.46	242.86 ± 362.77	To consider Seizure disorder	Global developmental delay	unremarkable MRI	c.200C>T and c.115A>G
PTPS 5	1 year 3 months	76.05 ± 34.92	511.41 ± 734.71	Asymptomatic	Global developmental delay	Focal atrophy of the posterior lobe Mastoid disease, right	c.155A>G homozygote
PTPS 6	14 years 5 months	346.56 ± 535.29	30.41 ± 14.54	Focal epilepsy	Intellectual disability	Focal atrophy of the posterior lobe Mastoid disease, right	c58T>C homozygote
PTPS 7	1 year 2 months	153.17 ± 228.63	424.34 ± 341.73	Focal epilepsy	Global developmental delay	not done	c.155A>G homozygote
PTPS 8	4 years 3 months	384.01 ±526.46	90.29 ± 129.16	Asymptomatic	Global developmental delay	not done	not done
PTPS 9	7 years 9 months	185.72 ± 266.89	1452.21 ± 583.24	Focal epilepsy	Intellectual disability, probably mild	not done	not done

**DSM-5 Criteria – The Diagnostic and Statistical Manual of Mental Disorders, 5th ed.*

In the Philippines, the diagnostic work-up of BH_4 deficiencies, of which 6-PTPS deficiency is the most common, includes the analysis of urine pterins (neopterin, biopterin) and the measurement of DHPR activity in dried blood spots (DBS). These are sent to a partner laboratory in Taiwan that does the analysis. Oral BH_4-loading test (20 mg/kg) which is also part of the diagnostic work-up is done locally. These are consistent with the recommended diagnostic examinations based on the Consensus Guidelines which are also followed by other countries.[5] The confirmation of diagnosis also includes mutational analysis of the *PTS* gene and cerebrospinal fluid (CSF) analysis of neurotransmitter

metabolites, 5-hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA), and PTPS enzyme activity in fibroblasts.[7,10] Analysis of either the urine or via dried blood spots for increased neopterin and decreased biopterin, and analysis of DHPR activity on DBS are essential for the exact diagnosis of 6-PTPS deficiency.[11] The BH_4 loading test was initially used to discriminate between patients with hyperphenylalaninemia due to PAH deficiency or PKU and BH_4 deficiencies like 6-PTPS deficiency.[12] It must be noted that due to financial constraints and the invasive nature of some tests, other diagnostic examinations are no longer performed. It has been deemed by the metabolic experts in the country that the current tests are sufficient to confirm the diagnosis of 6-PTPS deficiency.

As with any laboratory test, the turn-around time remains a challenge especially with specialized tests. One way to expedite the process is by doing the test locally. However, other factors must be considered such as the cost of the test, infrastructure and the number of samples that will be analyzed. While awaiting the results of the confirmatory testing, patients are put on a phenylalanine restricted diet. Once the diagnosis is confirmed, patients are put back on a regular diet and started on tetrahydrobiopterin (2-4 mg/kg/day), 5-HT (5 mg/kg/day), and levodopa (10-15 mg/kg/day) based on the protocol by Liu et al.[7]

All patients had some degree of intellectual disability which were noted on formal assessment by a developmental pediatrician and two thirds of patients had seizure even after the initiation of treatment. On diagnosis, 55% presented with hypotonia. This is similar to the findings in a study on Arab population where 11 out of 20 (55%) presented with hypotonia while five out of 20 (25%) had seizures.[1] In another study, the most frequent manifestations of 6-PTPS deficiency have been reported to be developmental delay, axial hypotonia, epilepsy, cognitive and speech impairment, and peripheral hypertonia.[5] These are supported in this study, where six out of nine patients were diagnosed with focal or generalized epilepsy, while all nine patients had intellectual disability in varying degrees of severity despite majority of the patients were diagnosed and managed in the neonatal period. There are two recognized phenotypes of 6-PTPS deficiency: the mild phenotype and the severe phenotype.[1] Patients with the mild phenotype are usually asymptomatic and CSF neurotransmitters are normal on diagnosis. These patients usually are just managed with BH_4 monotherapy. The severe phenotype, on the other hand, may have symptoms such as mental retardation, hypotonia, and seizures. Patients with the severe phenotype are managed with BH_4, L-dopa, and 5-hydroxytryptophan (5-HT).[1,11] Factors noted to contribute to adverse neurodevelopmental outcomes include compliance to therapy and timing of management initiation. Although early management (treated <2 months of age) is clearly associated with better outcomes, early treated patients may still have some concerns on maintaining movement rhythm even with external cues.[1,13]

In the Philippines, the treatment protocol followed was adapted from Taiwan which Liu et al. had previously described.[7] This involved administration of BH_4, and restoration of neurotransmitter homeostasis by giving oral amine precursors such as L-dopa and 5-HT. Carbidopa, an inhibitor of peripheral aromatic amino-acid decarboxylase, is also given to reduce the therapeutic dose of L-dopa.[14] Due to low dopamine, plasma prolactin also becomes elevated in patients with BH_4 deficiencies.[1] Thus, during treatment, aside from phenylalanine level monitoring, prolactin level is also evaluated. None of the patients are maintained on a low-phenylalanine diet. Staring dose of L-dopa is at 0.5 mg–1 mg/kg BW/day and analysis of CSF HVA for dose adjustment is considered.[5] In the Philippines, dose adjustment is guided by the prolactin levels. For 5-HT, starting dose is at 1–2 mg/kg BW/day and instead of analysis of CSF 5-HIAA, we are guided by clinical picture and side effects.

Homozygous and compound heterozygous pathogenic variants in the PTS gene causing 6-PTPS deficiency were noted in our patients. Pathogenic variants in this cohort were all missense, seen in 14 alleles of seven patients. The predominant variant was c.155A>G (p.Asn52Ser), which is a common variant in different Asian populations.[1,15] The second most common variant is the c.58T>C(p.Phe20Leu), which has been reported in Japanese and Filipino populations.[1] There are no consistent reports, however, about the genotype-phenotype correlation in 6-PTPS deficiency.[5]

Other studies have shown that patients with 6-PTPS deficiency have non-specific electroencephalogram (EEG) changes, and frequent and early brain or cerebral atrophy on brain imaging.[7] Out of the four patients with brain MRI studies in this series, two had unremarkable results while two had focal atrophy of the posterior lobe. In published studies, patients with 6-PTPS deficiency may have neuroradiologic abnormalities like delayed myelination, periventricular hyperintensities, brain atrophy, and calcifications.[10,16]

For our patients, there was no robust association between the MRI findings and the clinical and biochemical characteristics of the patients. This may be because of the limited number of patients who had cranial imaging done. This is consistent with the study of Wang et al. that cranial MRI of patients with 6-PTPS deficiency show large areas of abnormalities in all patients investigated but were not related to clinical findings.[17] Also, these abnormal findings detected on MRI did not relate to the severity of neurological manifestations.[17]

CONCLUSION

Newborn screening has played a crucial role in the early identification and management of patients with hyperphenylalaninemia due to 6-PTPS deficiency. Determination of DHPR activity, urine pterins, and molecular testing are crucial for early diagnosis and treatment. However, despite early management, patients were noted to still present with

neurodevelopmental manifestations. Compliance to the medications is something that needs to be investigated and given the small number of patients, findings on outcomes may change in the future.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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