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Original Article

6-Pyruvoyltetrahydropterin Synthase Deficiency: Review and Report of 28 Arab Subjects

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ABSTRACT

Background: Tetrahydrobiopterin is an essential cofactor for the hydroxylation of aromatic amino acids phenylalanine, tyrosine, and tryptophan. Therefore, tetrahydrobiopterin deficiency results in hyperphenylalaninemia as well as dopamine and serotonin depletion in the central nervous system. The enzyme 6-pyruvoyltetrahydropterin synthase catalyzes the second step of *de novo* synthesis of tetrahydrobiopterin, and its deficiency is the most frequent cause of tetrahydrobiopterin metabolism disorders.
Method: We conducted a retrospective chart review of 28 subjects from 24 families with molecularly confirmed 6-pyruvoyltetrahydropterin synthase deficiency from six centers in three Arab countries. We reviewed clinical, biochemical, and molecular data. We also reviewed previously published cohorts of subjects with 6-pyruvoyltetrahydropterin synthase deficiency.
Results: Similar to previous observations, we show that early treatment (less than two months) is associated with better outcome. We identify eight PTS variants in 24 independent families. The most common variant is (c.238A>G; p.M80V) with an allele count of 33%. We also identify one novel variant (c.2T>G; p.?).
Conclusion: The deficiency of 6-pyruvoyltetrahydropterin synthase is relatively common in the Arab population and should be considered in individuals with hyperphenylalaninemia. More natural history studies with comprehensive biochemical and molecular genetics data are needed for a robust base for the development of future therapy.

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Introduction

Phenylketonuria (PKU; OMIM #261600), which was first reported by Asbjörn Fölling in 1934, is one of the most common inborn errors of metabolism with an estimated prevalence of 1 in 10,000 in the European population[1]. PKU was the first disorder for which newborn screening was established through bacterial inhibition assay by Robert Guthrie and Ada Susi in 1963.[2] PKU is caused by the deficiency of phenylalanine hydroxylase, which catalyzes the hydroxylation of phenylalanine to generate tyrosine (Fig). As a result, phenylalanine will accumulate to toxic levels causing irreversible intellectual disability (ID).

Hydroxylation of phenylalanine to tyrosine through phenylalanine hydroxylase requires the essential cofactor tetrahydrobiopterin (BH4) that was first identified in the 1960s.[3] More than a decade later, a subgroup of individuals with PKU who developed progressive neurological deterioration despite early dietary management was identified.[4] The term *malignant hyperphenylalaninemia* was then used to describe subjects who were found to have deficiency in BH4, the cofactor for phenylalanine hydroxylase.[5]

BH4 is synthesized *de novo* from guanosine-5′-triphosphate (GTP) through a sequence of three reactions carried out by guanosine-5′-triphosphate cyclohydrolase I, 6-pyruvoyltetrahydropterin synthase (PTPS), and sepiapterin reductase. During hydroxylation of aromatic amino acids, BH4 is oxidized to pterin-4α-carbinolamine. BH4 is then recycled through the action of two enzymes, pterin-4α-carbinolamine dehydratase and dihydropteridine reductase[6] (Fig). Defects in any of these enzymes will result in BH4 deficiency. Sepiapterin reductase deficiency and autosomal dominant form of guanosine-5′-triphosphate cyclohydrolase I deficiency present, however, without hyperphenylalaninemia (HPA).[7]

In addition to its role in phenylalanine hydroxylation, BH4 is also an essential cofactor for tyrosine and tryptophan hydroxylases, which are rate-limiting enzymes in catecholamine and serotonin biosyntheses, respectively. Therefore, besides HPA, BH4 deficiency also results in dopamine and serotonin depletion in the central nervous system.[8] This accounts for the progressive neurological deterioration in that subset of individuals with HPA despite early dietary management. Finally, BH4 is also an essential cofactor for the three isoforms of nitric oxide synthase.

Disorders of BH4 metabolism account for only 1% to 2% of patients with HPA in Europeans,[8] whereas they are more common in some other ethnic groups. For example, BH4 deficiency accounts for more than 10% of HPA patients in some countries in East Asia[9,10] reaching up to one-third of cases in some reports.[11] In a cross-sectional study from Iran, 76 of 617 (12%) with HPA have BH4 deficiencies.[12] In one old report from south Brazil, PTPS deficiency alone represents 17% of cases with HPA.[13]

Methods

We reviewed the electronic and paper medical records of 28 subjects with molecularly confirmed PTPS deficiency from four centers in Saudi Arabia, one center in Oman, and one center in Qatar. We used a case report form to collect the demographic characteristics of the subjects, the age and pattern of the initial presentation, the clinical phenotype, and the biochemical, radiological, and molecular features. Literature review was conducted using PubMeb search (https://www.ncbi.nlm.nih.gov/pubmed/). The nomenclature of variants is according to the Human Genome Variation Society recommendations. This study was approved by King Fahad Medical City Institutional Review Board (Institutional Review Board registration number H-01-R012).

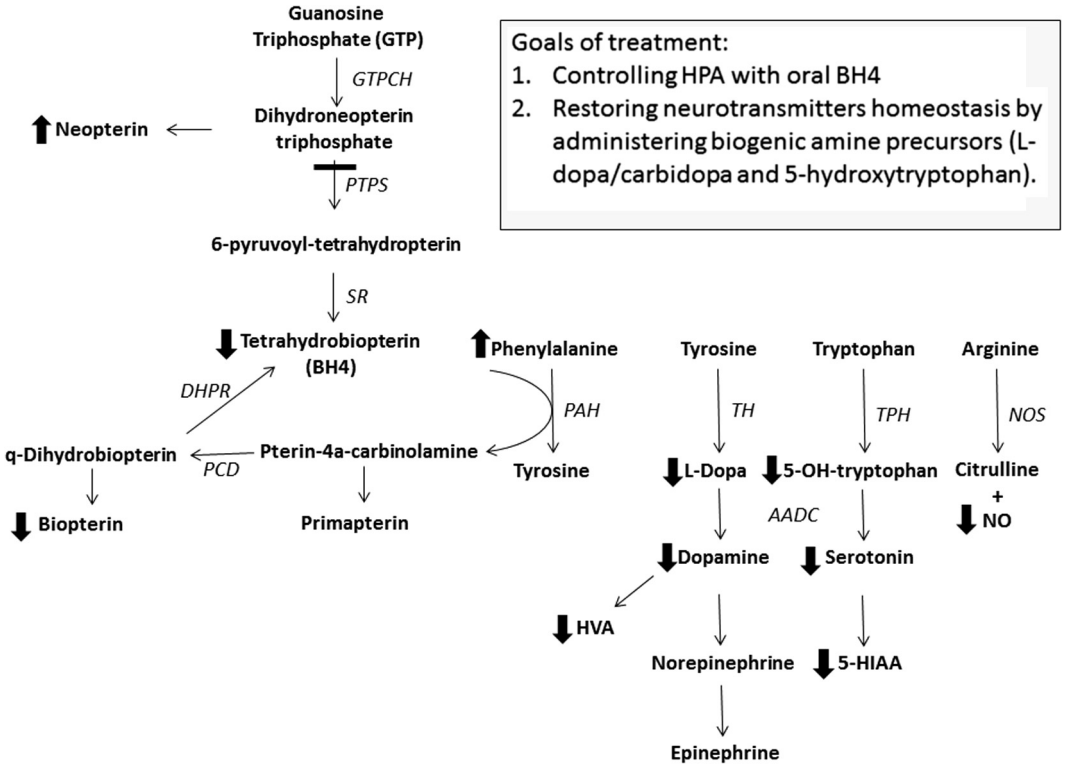

FIGURE. Biosynthesis of BH4 and consequences of defect in PTPS. AADC, aromatic L-amino acid decarboxylase; DHPR, dihydropteridine reductase; GTPCH, GTP cyclohydrolase I; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; NOS, nitric oxide (NO) synthase; PCD, pterin-4α-carbinolamine dehydratase; PAH, phenylalanine hydroxylase; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase.

Results and discussion

Local experience: report of 28 Arab subjects

A total of 28 individuals with PTPS deficiency have been identified and included in this study. All are Arabs, but they belong to different geographical regions including Saudi Arabia (n = 21), Oman (n = 5), Egypt (n = 1), and Sudan (n = 1). There is an equal distribution of males and females (46%:54%). Most individuals in our cohort were born to consanguineous parents (89%). Prematurity was evident in 15% of the subjects, whereas 40% were born small for gestational age. The birth weight range was 1.25 to 3.0 kg (mean 2.3, median 2.25). Microcephaly was evident in 10 of 20 subjects (50 %).

Ten subjects were diagnosed by newborn screening (NBS), 17 were symptomatic, and the remaining one was diagnosed early because of family history. Some of those who were diagnosed by NBS were already symptomatic in the neonatal period (Supplementary Table 1). The age range of diagnosis for those diagnosed symptomatically was neonatal period to 9 months (mean 2.6 months, median 1.5 months). Among subjects who presented with early symptoms, common presenting complaints include hypotonia (11 of 20: 55%), seizures (five of 20: 25%), and lethargy and irritability (four of 20: 20%). The age range of initiation of treatment for those diagnosed with NBS was two days to two months (mean 27 days, median 22 days), and for the rest of subjects, it was one month to three years (mean 11.5 months, median 10 months).

In regard to the biochemical profile on presentation, phenylalanine levels ranged between 201 and 2665 μmol/L (mean 1111, median 1039) in subjects diagnosed by NBS, and it was comparable to those of subjects diagnosed symptomatically, 360 to 2373 μmol/L (mean 1128, median 1037 [$P = 0.95$]). Pterin analysis on presentation is available for eight subjects (seven urine samples and one dry blood spot). All but one subject (subject #20) had high neopterin (range 3.9 to 29.3 mmol/mol Crea, mean 13.2, median 13.4; reference range 1.1 to 4), whereas biopterin and biopterin/total pterins ratio were low in all of them (Supplementary Table 1). In three additional subjects, only the ratio is available, and it was low in all. Only two subjects (subjects #11 and #21) had cerebrospinal fluid (CSF) studies available on presentation, and they showed typical pattern with high neopterin, low biopterin, low 5-hydroxyindoleacetic acid (5-HIAA), and low homovanillic acid (HVA). Plasma prolactin is available for 17 individuals on presentation (range 368 to 2890 mIU/L; mean 876, median 736).

The age range for individuals in this cohort at their last follow-up visit was five months to 18 years (mean 5.1 years, median 4.4 years). Phenylalanine levels on last follow-up ranged between 26 and 1677 μmol/L (mean 156, median 62) (note: the subject who had a value of 1677 was known to be noncompliant). Follow-up CSF studies on last follow-up are available for only two subjects (subjects #2 and #4, Supplementary Table 1). Plasma prolactin levels on last follow-up ranged between 25 and 10,788 (mean 1461, median 476).

In regard to treatment, all subjects but one (subject #20, noncompliant) are on BH4 (dose range 3.2 to 21 mg/kg/day, mean 11, median 10) and L-dopa (dose range 2 to 15 mg/kg/day (mean 7.7, median 6.3), 19 of 27 are taking 5-hydroxytryptophan (5-OH-Trp) (dose range 1.6 to 10 mg/kg/day; mean 5.5, median 6), and seven subjects are on folinic acid.

Most of our subjects (23 of 27; 85%) show variable degrees of developmental delay or ID. All subjects who were treated late (greater than two months) (n = 13; outcome not available in subject #28) have global developmental delay or ID, only one of them had an intelligence quotient (IQ) testing performed, and it was 50.

TABLE 1.
Patient Cohort Characteristics

Variable	Value
Number of subjects	28
Male: female (%)	46:54
Consanguinity	25 /28 (89%)
Ascertainment	Family history: 1 (3%) Positive newborn screening: 10 (36%)* Symptomatic: 17 (61%)
Age at presentation in subjects diagnosed symptomatically (n = 17)	Neonatal period-9 mo (mean 2.6 mo, median 1.5 mo)
Presenting complaints	Hypotonia (11/20, 55%), seizures (5/20; 25%), lethargy and decreased activity (4/20; 20%), irritability (4/20; 20%), oculogyric crisis (3/20; 15%), developmental delay (3/20; 15%)
Initial phenylalanine level (μmol/L) (n = 24)	201-2665 (mean 1120, median 1037)
Age at start of treatment	Diagnosed by NBS: 2 d-2 mo (mean 27 d, median 22 d) Diagnosed symptomatically: 1 mo-3 yr (mean 11.5 mo, median 10 mo)
Age at last follow-up	5 mo-18 yr (mean 5.1 yr, median 4.4 yr)
Most recent phenylalanine level (μmol/L)	26-1677 (mean 156, median 62)
Most recent prolactin level (mIU/L)	368-2890 (mean 876, median 736)
Treatment	
BH4 (mg/kg/day) (n = 27)	3.2-2.0 (mean 11 and median 10)
L-Dopa (mg/kg/day (n = 27)	2.0 -15.0 (mean 7.7, median 6.3)
5-OH-Trp (mg/kg/day) (n = 19)	1.6 -10.0 (mean 5.5, median 6)
Last clinical evaluation	
Global developmental delay or ID	18/27 (67%)
Mid developmental delay	5/27 (18%)
Normal development	4/27 (15%)
Truncal hypotonia	14/28 (50%)
Seizures	13/28 (46%)
Movement disorders	9/27 (33%)
Microcephaly	12/24 (50%)

* 3 subjects with abnormal NBS had early symptoms before diagnosis was made; see Supplementary Table 1.

On the other hand, the outcome is better in subjects who were treated early (≤ 2 months) (n = 14). Four of them have normal development, and five more have mild delays only. The remaining five subjects have global developmental delay; two of them have had IQ testing performed, and it was in the mild ID range (59 and 62). Peripheral hypertonia is commonly observed in our cohort (15 of 25; 60%), whereas truncal hypotonia is evident in half of the subjects. Seizures are observed in 13 subjects (46%). Nine subjects (33%) have movement disorders. Failure to thrive is observed in 14 subjects (52%), whereas 50% of them have microcephaly. Additional clinical characteristics are summarized in Table 1.

Neuroimaging is available for nine subjects only, and it is normal in five of them (obtained once, not repeated). Findings in the other four subjects include abnormal T2 hyperintensities within the posterior tegmental structures of the pons (subject #6, obtained at age two months), mild white matter volume loss along bilateral centrum semiovale (subject #12, obtained at six years), and white matter changes with mild cerebral atrophic changes (subjects #22 and #27).

Eight pathogenic variants have been identified in this report for 24 independent families (Table 2); all were in homozygous status. The most common variant is c.238A>G; p.M80V with an allele count of 33%, followed by the missense variant (c.342C>G; p.I114M) and the in-frame deletion (c.169_171del; p.V57del), both with an allele count of 17%. These variants were identified in subjects from Saudi Arabia only. One novel variant (subject #6) is identified in this report; (c.2T>G; p.?)

TABLE 2.
PTS Variants in This Report

DNA Nucleotide Change	Protein Amino Acid Change	# Homozygous (Families)	# Heterozygous (Families)	Total Allele Count (Families)	Origin
c.2T>G	p.?	1	0	2	Saudi
c.155A>G	p.N52S	1	0	2	Saudi
c.169_171del	p.V57del	4	0	8	Saudi
c.200C>T	p.T67M	2	0	4	Egyptian/Sudanese
c.238A>G	p.M80V	8	0	16	Saudi
c.342C>G	p.I114M	4	0	8	Saudi
c.367C>T	p.P123S	3	0	6	Omani
c.400G>A	p.E34K	1	0	2	Omani

PTPS deficiency is the most frequent BH4 metabolism disorder

Of the BH4 metabolism disorders, PTPS deficiency accounts for more than 60% of cases.[14] As of February 13, 2017, there are 1118 subjects in the International Database of Tetrahydrobiopterin Deficiencies (BIODEF), 735 (66%) of whom have PTPS deficiency (http://www.biopku.org/biodef/BIODEF_Start.asp).

PTPS deficiency is a pan-ethnic disorder. Chinese subjects represent 51% (372 of 735) of subjects listed in the BIODEF database, whereas Caucasians and Arabs represent 12% (86 of 735) and 8% (57 of 735), respectively. On the other hand, PTPS deficiency is uncommon in Africans and Hispanics. None of the subjects listed in the BIODEF database are of Jewish ancestry.

There are two recognized forms of PTPS deficiency. The mild or peripheral form is characterized by normal levels of CSF neurotransmitters in the initial stages, and a good response to BH4 monotherapy.[8] The other form, which is the severe, or the typical, form presents early and is characterized by developmental delay/ID, convulsions, and abnormal tone and movements. In one report, of 355 subjects with PTPS deficiency, one-fifth presented with the mild "peripheral" phenotype.[8]

PTPS deficiency can be diagnosed by finding HPA as part of standard newborn screening that is followed by proper evaluation to look for BH4 deficiencies as a potential cause for HPA. Alternatively, PTPS deficiency can be diagnosed either in symptomatic infants presenting with neurological deterioration who were diagnosed with HPA by NBS but were presumed to have phenylalanine hydroxylase deficiency and treated with diet only or in infants who did not have NBS or in whom the screen was false-negative. ID, hypotonia, and convulsions are the most common presenting symptoms in the severe phenotype of PTPS deficiency[8] (Table 3). Among disorders of BH4 metabolism, PTPS deficiency has the highest risk of prematurity and low birth weights.[8] Subjects with PTPS deficiency have significantly higher phenylalanine concentrations compared with other disorders of BH4 metabolism.[8]

Mutation spectrum in the PTS gene and geographical distribution

In 1986, 6-pyruvoyltetrahydropterin synthase was purified from human liver.[15] Thony et al. cloned and expressed the human cDNAs for the PTPS enzyme, which was subsequently mapped to the chromosomal region 11q22.3-q23.3.[16] *PTS* gene spans about eight kilobases and contains six exons.[17] In 1994, Thony et al. characterized, for the first time, three variants in two subjects with PTPS deficiency.[18] Since then, several pathogenic variants were identified, and 141 variants are currently listed in the Database of Gene Variants Causing BH4 Deficiencies and other pediatric neurotransmitter disease (PNDdb), distributed across all six exons and five introns (http://www.biopku.org/pnddb/home.asp; accessed on December 10, 2018). No hotspots for mutations are found,[19] although some of the reported pathogenic variants are more common in certain ethnicities. For example, in one study, molecular analysis of the *PTS* gene was performed on 176 subjects from East Asia, including the Han populations in Taiwan, Mainland China, and Malaysia, as well as the populations of Japan, South Korea, Thailand, and the Philippines. Five variants (c.155A>G, c.259C>T, c.272A>G, c.286G>A, and c.84-291A>G) were the most common, with the first two accounting for 15.6% and 37.5%, respectively, of the allele count. Two variants (c.58T>C and c.243G>A) were dominant in the Philippines and Okinawa, Japan, respectively, indicating founder events restricted to these isolated geographic regions.[9] From PNDdb, two variants (c.260C>T and c.407A>T) are commonly reported in Caucasian subjects. In our local cohort, the most common variant is c.238A>G with an allele count of 33%. Interestingly, all individuals with this variant belong to the same tribe in Saudi Arabia, indicating a founder effect, which is a common phenomenon in Saudi Arabia and Arabs in general.[20] The missense variant c.200C>T is reported in two individuals here, both originating from North Africa (Egyptian and Sudanese). This variant is also reported in seven subjects in the PNDdb with different ethnic backgrounds, including Caucasian, Chinese, and Tamil. One novel variant is identified in this report: c.2T>G. Pathogenic variants affecting the initiation codon (c.1A>G and c.3G>A) have been reported.[9,21]

Treatment and outcome

There are two main goals of treatment in subjects with PTPS deficiency: first is controlling HPA with oral BH4 and second is restoring neurotransmitter homeostasis by administering biogenic amine precursors (L-dopa/carbidopa and 5-OH-Trp). The recommended dose range for BH4 is 5 to 10 mg/kg/day, whereas for L-dopa and 5-OH-Trp, the recommended doses are slightly variable based on age. For children, the recommend dose is 8 to 15 mg/kg/day and 6 to 9 mg/kg/day, respectively.[8] Replacement therapy for dopamine is more difficult than replacing serotonin, mainly because of the short half-life of L-dopa and the associated adverse advents. In one study, it was shown that administering dopamine agonist, pramipexole, was associated with a reduction in L-dopa dosage and in potentiating the effects of L-dopa therapy[22]; high doses were associated with impulse control disorders, whereas low doses were safe and clinically effective.[23] Long-term L-dopa therapy may result in low 5-methyltetrahydrofolate levels in CSF, and therefore CSF folate should also be monitored and replaced in deficient subjects through folinic acid administration.[24]

Besides plasma phenylalanine levels and clinical evaluation, monitoring the efficacy of therapy in subjects with PTPS deficiency requires regular measurements of neurotransmitter metabolites (5-HIAA and HVA) in CSF. Low CSF5-HIAA and HVA values could be an indicator for the ongoing developmental impairment.[24] In a report of 36 patients, Jaggi et al. did not find clear correlation between CSF 5-HIAA and HVA values and clinical outcome.[24] CSF neurotransmitter testing is challenging as it requires invasive procedure and

TABLE 3.
Summary of Previous Cohorts of Subjects With PTPS Deficiency

	Dudesek et al., 2001	Liu et al., 2001	Chien et al., 2001	Lee et al., 2006	Wang et al., 2006	Jaggi et al., 2008
Number of subjects	5	5	10	10	31	26
Ethnicity	Turkish and German	Chinese	Taiwanese	Chinese	Chinese	Mixed
Prematurity	2/5	0/5	NA	NA	NA	4/26
Birth weight (kg)	2.18-3.5 (Mean 2.66, median 2.67)	2.7-3 (Mean and median 2.85)	2.66 ± 1.97	NA 3/10 born SGA	3.1 ± 0.5	1.4-3.3 (Mean 2.6, median 2.8)
Age at diagnosis of PTPS deficiency	18 d-7 yr (Mean 20 mo, median 3 mo)	10 mo-14 yr (Mean 43 mo, median 14 mo)	NA (all diagnosed through NBS)	8 mo-20 yr (Mean 6 yr, median 3.5 yr)	2 mo-47.5 mo (Mean 8.6 mo, median 5 mo)	1 wk-27 yr (Mean 9 mo, median 1 mo)
Presentation						
Developmental delay/intellectual disability	1/5	3/5	NA	NA	22/26	NA
Tone abnormalities	3/5	4/5	NA	NA	19/26	NA
Seizures	1/5	3/5	NA	NA	10/26	NA
Movement disorders	4/5	0/5	NA	NA	11/26	NA
Initial biochemical profile						
Phenylalanine level (μmol/L)	80-1398 (Mean 635, median 541)	236-1210 (Mean 830, median 938)	423-2280 (Mean 1316, median 1367	234-2340 (Mean 1211, median 1137)	181-2054 (Mean 964, median 960)	180-2117 (Mean 841, median 713)
Neopterin mmol/mol cr (1.1-4)	1.6-32.8 (Mean 17.6, median18.7)	NA	NA	5.92-5.92 (Mean 21.1, median 18.8)	1.5 -31 (Mean 7, median 4.5)*	2-40.5 (Mean 18, median 17)
Biopterin mmol/mol cr (0.5-3)	0-0.65 (Mean 0.2, median 0.1)	NA	NA	0.005-0.5 (Mean 0.18, median 0.16)	0.01-0.81 (Mean 0.2, median 0.14)*	<0.01-0.56
Phenotype	Severe 4/5 Mild 1/5	Severe 4/5 Mild 1/5	NA	Severe 8/10 Mild 2/10	NA	NA
Treatment						
BH4 (mg/kg/day)	2.1-6.5 (Mean 3.85, median 3.4) (4/5 taking)	NA	1.50 ± 0.44 (0.75-2.14)	NA	1.1-3 (Mean 1.9, median 1.8)	3-12 (Mean 6.5, median 6)
L-Dopa (mg/kg/day)	6.9 and 7.1 (2/5 taking)	NA	8.39 ± 3.67 (3.77-14.40)	NA	5.8-12.5 (Mean 9.3, median 8.8)	4-18 (Mean 9, median 9.5): (22/26 taking)
5-OH-Trp (mg/kg/day)	4.2 and 5.6 (2/5 taking)	NA	2.13 ± 1.76 (0.00-5.32)	NA	3.6-6 (Mean 4.7, median 4.3)	4-10 (Mean 6.8, median 7) (23/26 taking)
Developmental delay/ID on last follow-up (severity variable)	3/5	NA	10/10 Mean IQ 76 ± 14 (56-98)	10/10 IQ (<20-80)	7/26 had IQ less than 70 (57-115, Mean and median 80)	10/26

	Liu et al., 2008	Leuzzi et al., 2009	Opladen et al., 2012	Ye et al., 2013	Fernandez-Lainez et al., 2018	Souza et al., 2018
Number of subjects	12	19	335	240	5	4
Ethnicity	Taiwanese	Italian	Mixed	Chinese	Mexican	Brazilian
Prematurity	1/12	1/19	Gestational age 28-37 (Mean 35)	NA	2/5 Gestational age 35-38 (Mean 37, median 38)	NA
Birth weight (kg)	2-3.3 (Mean 2.6, median 2.65)	1.02 -3.5 (Mean 2.7, median 2.8)	<1.5 (3.6%) 1.5-2(8.9%) 2-2.5(25.8%) 2.5-3 (33.3%) - 3-3.4(20.4%) >3.5 (8%)	Mean (S.D.) birth weight was 3.1 (0.5) kg‡	1.8-3.3 (Mean 2.47, median 2.55) 3/5 born SGA	NA
Age at diagnosis of PTPS deficiency	Neonatal period Mean age of diagnosis 20.0 (6.3) d	8 d-32 yr (Mean 25 mo, median 1 mo)	Mean 1.8 yr	0.5-156 (Mean 11.5, median 3)	1-38 mo (Mean 17 mo, median 5 mo)	5-96 mo (Mean 27 and median 4.5)

Presentation						
Developmental delay/intellectual disability	NA	8/19	Neonates 30% † Infants 45%† Children 52%†	NA§	5/5	4/4
Tone abnormalities	NA	7/19	Neonates 40% † Infants 62%† Children 40%†	NA§	4/5	4/4
Seizures	NA	2/19	Neonates 10%† Infants 50%† Children 40%†	NA§	5/5	1/4
Movement disorders	NA	3/19	Neonates 10%† Infants 18%† Children 25%†	NA§	5/5	0/4
Initial biochemical Profile						
Phenylalanine level (μmol/L)	527-3426 (Mean 1963, median 2002)	151-2120 (Mean 1025, median 1051)	Severe phenotype 829 (121−2251) Mild phenotype 1111 (41−3805)	242-2724 (Mean 1035, median 974)	419-1027 (Mean 751, median 779)	538-2582 (Mean 1552, median 1544)
Neopterin mmol/mol cr (1.1-4)	NA	3.5-44.1 (Mean 17, median 13)	Severe phenotype 21 (1.6−134) Mild phenotype 17.1 (1.9−78)	0.08-70.7 (Mean 12.6, median 9.4)	4.69-11.88 (Mean 6.9, median 6.5)	NA
Biopterin mmol/mol cr (0.5-3)	NA	<0.01-0.55	Severe phenotype 0.2 (0−7.8) Mild Phenotype 0.3 (0−1.6)	0-2.69 (Mean 0.24, median 0.13)	0-0.07 (Mean and median 0.04)	NA
Phenotype	NA	Severe 13 Mild 6	84.9 % severe 15.1 % mild	NA	NA	NA
Treatment						
BH4 (mg/kg/day)	2-4	2-21	Neonates 5.6 (1.8−15) Infants 5.3 (0.5−16) Children 5.5 (0.4−20)	NA	NA	NA
L-Dopa (mg/kg/day)	10-15.5 (Mean 12, median 11.25	1-10	Neonates 5.9 (1−12) Infants 7.2 (0.1−44) Children 8.6 (0.3−49)	NA	NA	NA
5-OH-Trp (mg/kg/day)	1-5.8 (Mean 3.9, median 4)	1-8	Neo 4.5 (0.6−10) Infants 5.4 (0.5−42) Children 6.1 (0.5−37)	NA	NA	NA
Developmental delay/ID on last follow-up (severity variable)	IQ 86-111 (Mean 97, median 95)	8/19	NA	IQ 36-11 (Mean 79, median 80); available for 31 subjects	3/5	NA

Abbreviations:
Cr = Creatinine
DHPR = Dihydropteridine reductase
GTPCH = GTP cyclohydrolase I
ID = Intellectual disability
IQ = Intelligence quotient
NA = Not available or not applicable
NBS = Newborn screening
SGA = Small for gestational age

* nmol/l

† Out of subjects with severe phenotype

‡ Calculations included six subjects with DHPR deficiency and four subjects with GTPCH deficiency (total 250)

§ 73.6 % of patients presented with typical symptoms of BH4 deficiency (including hypotonia, apathy, drowsiness, low response, drooling, and retardation of motor development), 70.4 % with systemic symptoms of HPA (including yellow hair, white skin, characteristic body odor, convulsions, mental retardation, occasional tremors, and microcephaly), and 4.0 % with other symptoms (including eczema and vomiting).

specialized laboratory facilities to analyze the samples, which are not readily available. This was a challenge that we faced with our local subjects. Alternatively, plasma prolactin levels, which correlate inversely with hypothalamic dopamine levels, could be used,[25] as dopamine originating from the hypothalamic tuberoinfundibular tract is the major physiological inhibitor for prolactin.[26] Ogawa et al. described an individual with more significant correlation of L-dopa dose with serum prolactin levels than CSF HVA levels.[27] Similarly, in another study, monitoring serum prolactin was used successfully for optimizing the dosage of L-dopa.[28] However, prolactin levels do not reflect serotonin homeostasis and could also fluctuate due to external factors such as exercise and stress.[29] Prolactin secretion has marked diurnal variations, with lowest levels found shortly after awakening. Therefore, this time is chosen for the basal evaluation of prolactin secretion.[26]

Developmental outcome is worse in those who are treated late (i.e., greater than two months). In a report of 10 subjects from Taiwan, the average IQ score was 76 ± 14, and it was inversely correlated to the age of starting medication.[11] A similar observation was made in another report.[30] Wang et al. showed that subjects who were diagnosed by neonatal screening had much higher development quotient or IQ than those who were diagnosed symptomatically (88 versus 62, respectively).[30] Leuzzi et al. showed that only two of eight subjects with late (greater than two months) treatment had normal mental development, whereas all the others were neurologically impaired.[31] In a Chinese study, the median age at which treatment was started was significantly (P value 0.02) less in subjects with an IQ above 70 than in those with an IQ below 70.[32] Tanaka et al. showed that individuals with PTPS deficiency who were started on treatment after age 2.5 years performed poorly on tests of executive functioning, and they hypothesized that there is a critical level during which adequate neurotransmitter levels, especially dopamine, is required for the stable development of executive functioning.[33] Although early treatment is clearly associated with better outcomes, one report showed that early-treated subjects with PTPS deficiency may not maintain movement rhythm as well as normal subjects, even with external cues.[34]

Conclusion and future directions

PTPS deficiency is relatively common in the Arab population and should be considered in individuals with hyperphenylalaninemia. It is apparent from several studies that early treatment is associated with better outcome, so early diagnosis cannot be stressed enough. Although NBS is becoming widely available in different areas of the world, still there are missed cases owing to failure to recognize BH4 deficiencies, including PTPS deficiency, as a potential cause for HPA. Therefore, adding metabolites specific for BH4 deficiencies could help in early diagnosis. In fact, measuring neopterin and biopterin from direct blood spot for routine diagnosis of BH4 deficiencies proved to be useful in one study.[35] With wide availability of next-generation sequencing methods and reduced cost, these methods could also be utilized in newborn screening.[36]

In the near future, more therapeutic options could become available for PTPS deficiency. It was shown very early that gene delivery into primary patients' fibroblasts restored BH4 production.[37] Antisense oligonucleotides were used successfully to induce pseudoexon exclusion in fibroblasts of patients with splicing variants and restored PTPS enzyme activity and pterin profile.[38] Finally, given the relatively common prevalence of PTPS deficiency in our area, we need a regional collaborative effort to establish a specialized laboratory for BH4 deficiencies.

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Supplementary data

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