Molecular Genetics and Metabolism 104 (2011) 23–26

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Non-PKU mild hyperphenylalaninemia (MHP) — The dilemma

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ARTICLE INFO

Article history:
Received 4 March 2011
Received in revised form 10 May 2011
Accepted 10 May 2011
Available online 14 May 2011

Keywords:
Phenylketonuria
Tetrahydrobiopterin
Non-PKU mild hyperphenylananinemia
Hyperphenylalaninemia
Phenotypes
Neuropsychological executive function

ABSTRACT

Recent reviews have suggested that some patients with "non-PKU mild hyperphenylalaninemia" (MHP) might display neuropsychological executive function deficits and should be considered for treatment with tetrahydrobipterin (BH4) and/or phenylalanine (Phe) restricted diet.
Patients with phenylketonuria (PKU) — Classical and Mild/Atypical variants — appear to need "mean lifetime phenylalanine (Phe) levels" of 120–360 μmol/L for optimal results. MHP patients, on the other hand, have natural Phe levels of 200–600 μmol/L. Until recently this was thought to be a benign condition.
The available literature has been reviewed in detail and no good evidence, to date, has been uncovered to support treatment of MHP. It is suggested that more MHP subjects be tested to confirm this.
A plea is made to formulate a consistent world-wide classification of the PKU phenotypes.

Contents

1. The objective

The objective is to review the evidence for and against treatment of this phenylketonuria (PKU; OMIN 261600 and 261630) phenotype variant.

2. The problem

There is, unfortunately, no uniform, world-wide, agreed upon classification of the PKU phenotypes. This results in confusion for many of the uninitiated reading the literature. The most common classification used by the *vast majority* of authors [1] is shown in Table 1. Variations include that of Gulberg et al. [2] (Table 2), Lindner et al. [3] (Table 3), Singh et al. [4] (Table 4). Some authors call Mild/Atypical PKU "Mild PKU", others call non-PKU mild hyperphenylalaninemia (MHP) "Mild HPA" — and so on.

Basically, of course, hyperphenylalaninemia (HPA) is caused by either phenylalanine hydroxylase (PAH; EC 1.14.16.1) deficiency or a cofactor, tetrahydrobiopterin (BH4), deficiency. The term (HPA) should cover *all* the variants. Patients with HPA do not excrete phenylketones (phenylpyruvic acid, phenylacetic acid etc.) in their urine until blood levels are >600 μmol/L and not until they are 6–8 weeks of age. Hence the term "*non PKU mild hyperphenylalaninemia*" (MHP).

Early and well treated patients with PKU (Classical and Mild/Atypical phenotypes) have IQ's within the normal range (90–110) but are 5–15

Abbreviations: PKU, phenylketonuria; Phe, phenylalanine; HPA, hyperphenylalaninemia; MHP, non-PKU mild hyperphenylalaninemia; MPKU, maternal phenylketonuria; PAH, phenylalanine hydroxylase; BH4, tetrahydrobiopterin.

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doi:10.1016/j.ymgme.2011.05.007

Table 1
Classification of PKU phenotypes (Guttler [1]). (The most common).

	Blood Phe levels μmol/L (untreated)
1. Classical PKU	>1200
2. Atypical/mild PKU	600–1200
3. Non-PKU mild hyperphenylalaninemia (MHP)	200–600
4. Biopterin deficiency	Varies

points, on average, below their unaffected sibs and parents [5], often have neuropsychological (frontal lobe function) deficits [6] and/or emotional/psychological/psychiatric problems [7,8].

Patients with MHP, whose phenylalanine (Phe) levels *virtually never* rise above 600 μmol/L (even when metabolically stressed) and are on unrestricted diets, have normal IQ's and normal neuropsychological function [9–11]. This, apparently well established premise, has now come under question (the reason for this review).

Confusion has arisen because recommended Phe blood levels in *treated* PKU in infancy and childhood (to age 12) are, in most jurisdictions, 120–360 μmol/L [12]. There seems little doubt that "lifetime mean Phe levels" must remain below 360 μmol/L to preserve intellectual function in *treated* PKU [13,14] — at least up to age 12 years and perhaps beyond.

This discrepancy has puzzled clinicians for some years.

Anastasoaie et al. [15] have recently claimed that "spiking" of Phe levels in treated PKU during critical periods is the cause of these "suboptimal" results. Their data *did not reach statistical significance* but showed a "*trend*".

Perhaps the very vulnerable neonatal brain, where blood/brain Phe ratio is 1:1 [16] vs 3:1, 4:1 in older children and adults, is a factor.

3. What is the prevalence of MHP?

Unfortunately the literature is frustratingly unclear. This is partly due to the discrepancy in phenotype classifications mentioned above. It likely varies from country to country. PKU occurs worldwide but is most frequent in European Caucasians — where prevalence ranges from 1:4500 to 1:10,000 births [17] (except in Finland — 1:100,000–1:200,000 — one new case every 2–4 years [18]). The severe forms occur more often in Northern and Eastern Europe (e.g. 70% have Classical PKU in Poland [19]) with increasing numbers of the milder variants in Southern Europe (e.g. higher incidence of the milder phenotypes in Spain [20]). The North American prevalence of PKU is about 1:15,000 [12]. There is evidence of very high occurrence in some Middle Eastern Muslim countries (as high as 1:3672) related to consanguinity [21]. Frequency is lower in Blacks, Aboriginals and Asians (e.g. Taiwan [22] 1:19,412 — 6% Classical PKU, 26% Mild/Atypical PKU, 52% MHP, 16% Biopterin deficiency). In Israel Ashkenazi Jews have *only* MHP while Sephardic Jews and Arabs have a mixture (overall prevalence 1:11,000) [23]. Levy et al. [9] estimated that as many as 50% of HPA patients in Massachusetts have MHP.

A review of newborn PKU screening results from the province of Ontario, Canada from 1965 to 1998 (Minutes of the Advisory Committee on Newborn Screening to the Ontario Ministry of Health — 1999, Attachment #2) — 385 cases diagnosed — revealed 64% with Classical PKU and 22% with MHP.

We have been unable to find other breakdowns of the frequency of phenotypic variants — especially since the recent resurgence of PKU publications: most related to the trials of the new synthetic cofactor tetrahydrobiopterin (BH4, Sapropterin, Kuvan) formulation and numerous review articles.

Table 2
Classification of PKU phenotypes (Gulberg [2]).

	Blood Phe levels μmol/L (untreated)
1. Classical PKU	>1200
2. Moderate PKU	900–1200
3. Mild PKU	600–900
4. MHP	<600

Table 3
Classification of PKU phenotypes (Lindner [3]).

	Blood Phe μmol/L (untreated)
1. Classical PKU	>1200
2. Mild PKU	360–1200
3. Non PKU HPA	<360

4. To treat or not to treat — the evidence

4.1. Pro

Diamond et al. [24] reported that infants and young children with Phe levels of 400–600 μmol/L performed at lower, *although not statistically significant*, levels than did children without MHP, on tasks of executive function abilities dependent on prefrontal cortex.

Costello et al. [25] reported deficits in "milder" cases but a closer review of the publication reveals that patients with Phe levels up to 900 μmol/L were included.

Gassio et al. [26] claim some neuropsychological deficits in their "HPA" subjects. According to our interpretation, their classification of PKU phenotypes only recognizes 2 categories — "PKU" (baseline Phe levels >360 μmol/L) and "HPA" (baseline Phe levels <360 μmol/L). They reported on 35 patients with "HPA"(mean age 7.3 years (SD 2 months, range 2.75 to 12.75 years)). The authors state in the Discussion "however, we should take into account that the average age of the individuals with 'HPA' was lower than that of the control participants in our study, probably explaining the poorer performance of those with 'HPA' compared with control individuals".

4.2. Con

The earlier literature has presented observations on MHP [9,23,27].

In 1970 Berman and Ford [27] reviewed 13 patients with untreated MHP and found the mean IQ scores were no different than their unaffected sibs.

Szeinberg et al. [23] examined 8 patients with untreated MHP and found normal development.

In 1971 Levy et al. [9] reported on 13 individuals with "persistent mild hyperphenylalaninemia". None had been treated with Phe restricted diets. Age ranged from 3.1 to 26 years (mean 7.7 years). The initial Phe (3–6 days) was 242–606 μmol/L, peak was 485–727 μmol/L and subsequent levels were 242–485 μmol/L. The mean IQ of the 13 subjects was 115 (85–137). The mean IQ of 11 unaffected sibs was 100.9 (81–123). Of the 6 at school one had excellent marks, and 5 had "good" grades. None of the patients excreted phenylketones in the urine.

In 1980 Guttler [1] described 11 patients with MHP on normal diets: their median IQ was 109 (98–123) and compared favorably with 34 PKU patients on diet — median IQ 105 (87–143).

Table 4
Classification of PKU phenotypes (Singh et al. [4]).

	Blood Phe μmol/L (untreated)
1. Classic PKU	>1000
2. HPA	<1000