Neurocognitive function in mild hyperphenylalaninemia

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ABBREVIATIONS

HPA	Hyperphenylalaninemia
mHPA	Mild hyperphenylalaninemia
PKU	Phenylketonuria

AIM The purpose of this review was to provide an update on cognitive function in individuals with mild hyperphenylalaninemia (mHPA), the most clinically and biochemically benign form of phenylketonuria.

METHOD A review was conducted of the existing literature on mHPA. Individuals with mHPA, whose plasma phenylalanine concentration had always remained lower than 360μmol/L without dietary restriction, were considered.

RESULTS The review of the literature indicated that there is no consensus concerning the definition of mHPA. There are few studies regarding the cognitive functions of individuals with mHPA, results are contradictory, and samples are difficult to compare from one study to another. Most studies focus only on descriptions of IQ when assessing cognitive functions. The existing literature indicates that, in general, children with mHPA do not show significant cognitive impairments, but usually achieve scores between those of individuals with phenylketonuria and those of comparison groups with regard to the cognitive functions assessed.

INTERPRETATION When assessing cognitive functions in individuals with hyperphenylalaninemia, it is not enough to measure only IQ, as deficits in executive functions can be present even when an individual's IQ is within a normal range. Further studies are needed of individuals with mHPA, using consistent selection criteria, in order to make it possible to exclude the presence of cognitive impairment and to establish a consensus regarding the level of phenylalanine that necessitates dietary treatment.

The primary cause of hyperphenylalaninemia (HPA) is phenylketonuria (PKU), an inborn error of metabolism in which there is a persistent increase in the plasma concentration of phenylalanine owing to a total or partial decrease in the activity of the enzyme phenylalanine hydroxylase (PAH).[1]

The treatment of PKU is based on a phenylalanine-restricted diet that aims to maintain plasma phenylalanine levels within a safety range of 120 to 360μmol/L in order to prevent the risk of learning disability* or other neurological impairment. Nonetheless, despite dietary treatment, individuals with PKU who have a typical intellectual capacity have lower IQ scores than comparison groups and show deficits in attentional and executive functions such as strategic planning, inhibitory control, working memory, and cognitive flexibility.[2–17]

Two hypotheses have suggested a cause of this dysfunction. The first points to a decrease in dopamine synthesis in the prefrontal cortex caused by reduced availability of its precursor, tyrosine.[7] The second is based on impairment of the maintenance of myelin production.[18]

Deficits in executive functions are usually associated with high concurrent phenylalanine levels.[2,6–8,13,15,16,19–21] However, high levels of phenylalanine during the first years of life may adversely affect the intellectual capacity of individuals.[6,9,14,22,23]

HPA CLASSIFICATION

HPA shows extensive genetic and clinical variability. Over 500 mutations[24,25] have been described in the *PHA* gene. Most individuals with HPA are heterozygotes and generate numerous gene combinations that contribute to clinical heterogeneity.

Although it is one of the most common inborn errors of metabolism and, at the same time, one of the most studied, there is no general consensus on the classification of HPA (Fig. 1).[26,27]

Based on plasma concentrations at diagnosis and on phenylalanine tolerance (i.e. the amount of phenylalanine in the diet capable of maintaining concentrations at 300μmol/L), this review considers four categories of HPA: classic PKU, moderate PKU, mild PKU, and mild HPA (mHPA; Table I).[28,29]

*North American usage: mental retardation.

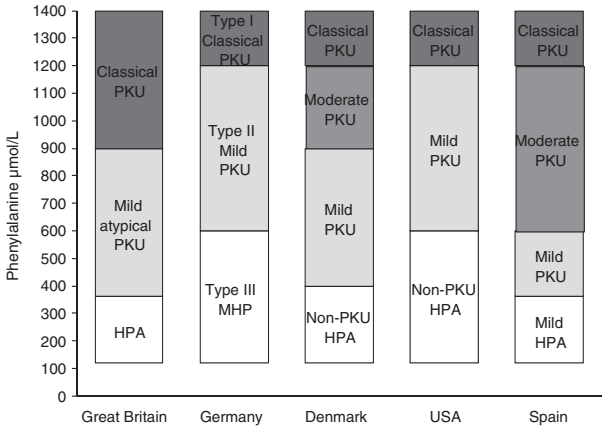

Figure 1: Classification of hyperphenylalaninemia (HPA) in five countries. Modified from Gramer et al.[26] PKU, phenylketonuria.

NEUROCOGNITIVE AND BEHAVIOURAL FUNCTION IN MHPA

There are few studies examining the cognitive functions of individuals with mHPA, and among these studies results are contradictory and samples are difficult to compare,[7,14,30–34] especially because of varying selection criteria (i.e. varying ages of participants) and a lack of consistency regarding the phenylalanine level considered (in most studies, the phenylalanine levels considered are <600µmol/L).

The first authors to warn about the possible risk of cognitive impairment in individuals with mHPA who were not receiving dietary treatment to maintain phenylalanine levels, were Costello et al.[30] In a study of 82 individuals with mild PKU (phenylalanine levels below 900µmol/L), IQ was examined at the age of 4 years using the Stanford–Binet test. Of these individuals, only 24 had not received dietary treatment. The IQ of the group as a whole and of the 24 untreated individuals was significantly lower than the estimated average IQ for the population, with deficits of 4.5 and 9 points respectively. The conclusion drawn was that individuals with phenylalanine levels ≥400µmol/L should begin dietary treatment.

Diamond et al.[7] conducted a longitudinal study lasting 4 years on children aged 6 months to 7 years (37 children with PKU who were treated early and continuously and 25 children with mHPA who had phenylalanine levels between 240µmol/L and 600µmol/L). They found that children with PKU whose phenylalanine levels were between 360µmol/L and 600µmol/L performed worse than the comparison groups, children with PKU who had lower phenylalanine levels, their own siblings, and children from the general population, on tasks that required working memory and inhibitory control, which are skills dependent upon the dorsolateral prefrontal cortex. With respect to children with mHPA whose phenylalanine levels were between 360µmol/L and 600µmol/L, performance on tests was halfway between that of children with PKU with similar phenylalanine levels and that of the comparison groups. In general, children with mHPA did not show significant cognitive impairment. General intelligence was measured at the age of 4 years using the Stanford–Binet test and indicated that all of the children with mHPA had an IQ equal to or greater than 80. The children with PKU whose phenylalanine levels were near the upper limit of the range that is considered safe (360–600µmol/L) had a significantly lower IQ than the comparison groups (90.4 vs 110 respectively). The mean IQ of the children with mHPA whose phenylalanine levels were between 360µmol/L and 600µmol/L was 100, which is in between that of the children with PKU with similar phenylalanine levels and that of the comparison groups. The mean IQ of children with mHPA whose phenylalanine levels were lower than 360µmol/L was 109. The conclusion reached was that phenylalanine levels that are three to five times higher than typical values are not as benign as they initially appeared. It is recommended that children with mHPA maintain a low-phenylalanine diet that is strict enough to keep phenylalanine levels between 120µmol/L and 360µmol/L.

Weglage et al.[31] studied a group of 31 adolescents and adults with mHPA who had phenylalanine levels between 360µmol/L and 600µmol/L and followed an unrestricted diet. The group had a mean age of 19 years (age range 11–30y) and a mean phenylalanine level during the study of 452µmol/L. The cognitive functions assessed were IQ (using the Wechsler scales according to age), selective and sustained attention, and fine motor skills. No statistically significant difference was found between the group with mHPA and the comparison group, whose mean IQs were 103 and 104 respectively. Previously, using a smaller group of individuals with mHPA (n=24), Weglage et al.[32,33] had also studied reaction time using a simple

What this paper adds

- This review highlights the lack of consensus on how to classify individuals with mHPA and PKU.
- It confirms that there are very few studies regarding cognitive functions in individuals with mild hyperphenylalaninemia.
- In the assessment of cognitive functions, individuals with mHPA achieved scores between those of individuals with PKU and those of non-affected comparison groups

Table I: Hyperphenylalaninemia (HPA) classification

Type	Mean enzyme activity (%)	Mean blood phenylalanine (µmol/L)	Phenylalanine tolerance (mg/day)	Treatment recommended
Classic PKU	<1	>1200	<350	Yes
Moderate PKU	<10	600–1200	350–400	Yes
Mild PKU	<10	360–600	400–600	Yes
Mild HPA	10–35	<360	>600mg	No

PKU, phenylketonuria.

task and executive functions and had not found any statistically significant differences between the group with mHPA and the comparison group. The authors concluded that individuals with phenylalanine levels between 360μmol/L and 600μmol/L are not at risk of developing cognitive impairment.

Smith et al.,[34] in a study involving 19 patients with mHPA (who had phenylalanine levels below 600μmol/L without dietary restriction) with a mean age of 14 years (age range 6–28y) and a mean phenylalanine level of 315μmol/L (SD 115), did not find significant differences in IQ, executive function measures, spatial memory, or face recognition with respect to the comparison group. The mean IQ in the group with mHPA was 104, and in the comparison group was 106. Smith et al.[34] concluded that small increases in phenylalanine and, therefore, small decreases in dopamine synthesis are not enough to cause significant cognitive impairment.

Our group[14] studied cognitive functions in individuals with classic PKU and mHPA. The first group under study comprised 37 individuals with PKU (mean age 9y 9mo) who were treated early and continuously with a low-phenylalanine diet, and the second group comprised 35 individuals with mHPA (mean age 7y 10mo) whose phenylalanine levels were below 360μmol/L and who did not receive dietary treatment. All of the means of the functions assessed were within a typical range in the two groups. We did not observe differences between the group with mHPA and the comparison group, except for executive functions, in which case the group with mHPA made more perseverative errors, showing difficulties in inhibiting responses. It should be noted that, just as in the study by Diamond et al.,[7] the individuals with mHPA in general obtained scores that lay between those of the group with PKU and the comparison group with regard to the cognitive functions assessed.

Levy and Waisbren[35] were two of the first authors to describe intellectual capacity in adults with mHPA, specifically in adult females with mHPA who were not diagnosed until adulthood, in a study on the incidence of maternal PKU. Of 22 identified females, nine had mHPA with phenylalanine levels between 165μmol/L and 540μmol/L. The mean IQ of these females was 105. However, the mean IQ of the 13 females with PKU whose phenylalanine levels were between 594μmol/L and 1130μmol/L was 99. Waisbren et al.[36] expanded upon this information by assessing not only IQ but also personality traits and visuomotor performance in six of the females with mHPA, and no cognitive deficits or psychological problems were found. In a larger series of 41 mothers with a mean phenylalanine level of 408μmol/L (SD 114; range 198–600μmol/L), the mean IQ was 95μmol/L (SD 15; range 58–130μmol/L), while the mean IQ for the comparison group was 103μmol/L (SD 13; range 75–130μmol/L).[37]

In the Netley et al.[38] series of 21 children with mHPA who had phenylalanine levels between 65μmol/L and 908μmol/L without any dietary treatment and a mean age of 8 years 6 months, mean IQ was 104.

Koch et al.[39] presented the case of a 25-year-old female with mHPA who developed symptoms of depression and panic attacks and whose phenylalanine levels during childhood were between 600μmol/L and 720μmol/L. Owing to behaviour problems and difficulties at school, when she was 5 years old she began dietary treatment, at which point her IQ was 113. When her phenylalanine levels decreased to between 120μmol/L and 360μmol/L, her behaviour and school performance improved. Her diet was discontinued at 10 years old. At the age of 23 years, she started having symptoms of depression, which improved with tetrahydrobiopterin (BH4) treatment and decreasing phenylalanine levels to 360 to 480μmol/L.

DISCUSSION

The category referred to as mHPA is the most clinically and biochemically benign form of PKU and is caused by at least one mild mutation in the *PAH* gene.

After reviewing the existing literature, we have concluded that there are very few studies on cognitive function in individuals with mHPA and that most of the literature focuses solely on descriptions of IQ. There is no agreement concerning the limits used to define mHPA, and it is difficult to carry out a literature search and make comparisons among the different studies owing to inconsistent selection criteria.

Despite the fact that there is no general agreement, most authors recommend maintaining phenylalanine levels between 120μmol/L and 360μmol/L in individuals with PKU,[3,29,40–46] at least during the first years of life. In addition, it has been shown that phenylalanine levels above 360μmol/L can have negative effects on IQ[9,22,23,46] and executive functions.[7,19,21,47,48] It is clear that individuals with phenylalanine levels below 360μmol/L who have a free diet do not require treatment, whereas treatment is necessary when phenylalanine levels are above 600μmol/L. Controversy remains regarding at what level between 360μmol/L and 600μmol/L treatment may become necessary.

If recommendations for individuals with PKU who receive dietary treatment are to keep phenylalanine levels under 360μmol/L, it seems to be appropriate to define mHPA as phenylalanine levels between 120μmol/L and 360μmol/L without any therapy; if levels are above 360μmol/L, treatment should be started.

Another point to consider in mHPA is the monitoring of mothers with mHPA. During pregnancy, it is recommended that phenylalanine levels be maintained between 120μmol/L and 360μmol/L according to US guidelines[49] and between 60μmol/L and 240μmol/L according to European guidelines[50] to avoid fetal damage due to elevated maternal phenylalanine levels.

When assessing cognitive function in children with HPA, it is not enough only to measure IQ, as deficits in executive functions can also be present in these children, even though their IQ is within the normal range.[2,5] A larger study should be conducted in order to illustrate these deficits, which frequently are subtle (especially in individuals with mHPA) and can be responsible for academic and behavioural problems.

Further studies are needed of individuals with mHPA that use the same selection criteria and make it possible to safely exclude the presence of cognitive impairment and, at the same time, establish what phenylalanine levels require dietary treatment.

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