



Cognitive functioning in mild hyperphenylalaninemia



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ABSTRACT

Background: Hyperphenylalaninemia is a hereditary metabolic disorder that causes elevated blood phenylalanine (Phe). Hyperphenylalaninemia is classified as Phenylketonuria PKU (Phe > 6 mg/dL) or mild hyperphenylalaninemia (mHPA) (Phe 2–6 mg/dL). This study examines the cognitive functioning of early diagnosed children with mHPA compared with early diagnosed and treated children with PKU.

Sample and methods: Psychomotor development (BSID-II) at 12 and 36 months of age, and cognitive performance at 4 and 7 years of age (WPPSI and WISC-R), were assessed in 118 PKU and 97 mHPA patients. Cognitive profile analysis of WISC-R subscales in school age children was performed and results were compared between the two groups.

Results: Both groups performed within the average range. Scores were significantly higher in the mHPA group. The mean Mental Development Index (MDI) at 12 months of age was 98.1 in the mHPA group and 92.3 in the PKU group ($p < 0.0002$). At 36 months the MDI was 94.6 in the mHPA group and 84.7 in the PKU group ($p = 0.0001$). At age four years the mean Full Scale IQ was 106.5 (mHPA group) and 95.9 (PKU group) ($p < 0.0001$). At age seven years the mean Full Scale IQ was 100.9 (mHPA group) and 89.9 (PKU group) ($p < 0.005$). The pattern of deficits was similar in both groups, with relative weaknesses in working memory and attention.

Conclusions: Children with mHPA achieved cognitive performance well within the average range and attained significantly higher scores than children with PKU. However, they appeared to have relative weaknesses in working memory and attention, similar to children with PKU.

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1. Introduction

Hyperphenylalaninemia is a recessive inherited metabolic condition, caused by the inability of the body to convert phenylalanine (Phe) to tyrosine, due to the total or partial absence of the enzyme phenylalanine hydroxylase. Phenylalanine is an essential amino acid found in protein-rich foods. Phe levels increase when not converted into Tyrosine, causing neuroanatomical and neurophysiological alterations, affecting cognitive development and functioning. Based on blood Phe levels, Hyperphenylalaninemia is classified as phenylketonuria (PKU; Phe > 6 mg/dL) and mild hyperphenylalaninemia (mHPA; Phe 2–6 mg/dL). PKU patients left untreated exhibit intellectual impairment, hyperactivity, irritability, convulsions, depigmentation and a characteristic odor. Diagnosis of PKU during the first days of life along with early treatment, (restrictive protein intake and specialized formula supplementation), prevents the more serious consequences of PKU. However, even early diagnosed and treated children exhibit intellectual

performance lower than siblings, peers or children with mHPA control groups [1,2,3,4].

Some research studies indicate that PKU children have poorer performance in visuo-spatial organization, perceptual reasoning and information processing speed compared with performance on verbal tasks [5]. Specific cognitive functions have been found to be compromised in PKU children with normal IQ. Multiple studies report alterations in selective attention, sustained attention, inhibitory control and working memory. These are described as executive functions generally thought to reflect functioning of the prefrontal cortex [6,7,8,9,10].

These cognitive deficits have been associated with anatomical and functional changes in the central nervous system. Neurotoxic effects of Phe have been reported, including frontal lobe effects, subcortical white matter demyelination, reduced connectivity within the prefrontal cortex and other brain regions, as well as, depletion of the dopaminergic system because of the interruption in the conversion of phenylalanine to tyrosine (a dopamine precursor) and/or reductions in hematoencephalic passage of tyrosine across the blood:brain barrier [11,12,13,14,15].

There are few studies examining cognitive functioning in mHPA. One reason for this is the lack of consensus regarding the definition of mHPA. Clinicians in Germany and the United States define mHPA as

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elevated plasma Phe concentrations at diagnosis up to 10 mg/dL (600 μmol/L). In most other countries Phe concentrations up to 4 or 6 mg/dL constitute mHPA [16].

Most previous studies report that patients with mHPA perform within the normal cognitive range with no significant differences when compared with control groups in executive functioning (specifically working memory and recognition memory), selective and sustained attention, fine motor skills and academic performance [17, 18,19]. Similar findings were noted even in untreated children with blood Phe levels between 6 and 10 mg/dL [3]. On the other hand, some investigators reported significant differences in executive functions in children with mHPA when compared with a control group [2].

The incidence of classic and moderate PKU in Chile is 1/18,916 births and 1/10,198 births for mHPA. Since 1992, Chile has carried out a National Neonatal Screening Program for phenylketonuria that covers 100% of newborns. Diagnosed children enter a follow up program for HPA at the Institute of Nutrition and Food Technology (INTA), University of Chile, National Reference Center. The follow-up program for PKU and mHPA children includes regular measurements of Phe and tyrosine levels, as well as specialized assessments by a multidisciplinary team of pediatricians, nutritionists, neurologists, and psychologists.

The aim of this study is to examine the development and cognitive functioning of early diagnosed children with mHPA compared with early diagnosed and treated children with PKU.

2. Sample and methods

This study is a retrospective single-center study. Subjects included children with classic and mild PKU (Phe > 6 mg/dL) and children with mHPA (Phe 2–6 mg/dL) diagnosed through newborn screening. All children participated in the follow-up program at INTA, University of Chile.

Data were collected from 118 children with PKU with a confirmed diagnosis by a mean of 15.3 (SD 8.9) days of life and average Phe 21.3 mg/dL (SD 7.5, range 6–46.1 mg/dL). The 97 children with mHPA, had a mean Phe level of 3.7 mg/dL (SD = 1.4) at diagnosis.

All PKU and mHPA children diagnosed through the national screening program between 1992 and 2009 were included in the sample, regardless of treatment compliance. Two children were excluded due to associated pathologies. As can be seen in Tables 1 and 2, age cohorts varied, because it was not possible to assess the complete sample at every age.

We present data from psychometric assessments of children with PKU and mHPA at 12 and 36 months, and 4 and 7 years of age.

2.1. Instruments

- The Bayley Scales of Infant Development Second Edition (1993) [20] assesses psychomotor development from the first month of life until 31/2 years of age. Standard scores are derived for a Mental Development Index (MDI) and a Motor Development Index (PDI) (mean = 100, SD = 15).
- The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [21] provides a Verbal IQ (VIQ) and Performance IQ (PIQ) for children 4 to 6 years of age, with standard score means of 100 (SD = 15). The

Wechsler Intelligence Scale for Children, Revised (WISC-R) [22] was administered to children 7–16 years of age in our sample and also provides a VIQ and PIQ (mean = 100, SD = 15). The WISC-R also provides subtest scale scores and composite scores for Verbal Comprehension (VC), Perceptual Organization (PO) and Freedom from Distractibility (FDF) with scores of 8–12 representing the average range. The WPPSI and WISC-R Spanish versions were used. The Bayley instructions to the child were translated since a Spanish Version has not been published. The WISC-R was used because validated WISC-III and WISC-IV versions were not available in Chile when the evaluations took place. For all tests, norms based on a Chilean sample were used.

Student's t test was used to compare results between PKU and mHPA groups in psychomotor and intellectual development. Differences were considered significant if $p < 0.05$.

3. Results

3.1. Psychomotor development

As noted in Table 1, the mHPA group and PKU group at 12 and 36 months demonstrated psychomotor development within the average range. However, the mHPA group attained significantly higher scores than the PKU group. By 36 months of age the mean MDI for the PKU group was more than one standard deviation below the normative mean and 12.6% of the children with PKU received scores indicating significant developmental delay with MDI < 70 (two standard deviations below the mean). In the mHPA group only one child (1.5%) attained an MDI < 70 (Table 1).

3.2. Intellectual performance

Intellectual performance of preschool and school-age children with mHPA and PKU was within the normative range for intelligence in the verbal (VIQ) and performance (PIQ) domains and for full scale IQ (FSIQ). The results for the PKU group whose FSIQ was below the normative range (<80) was the same as expected in the general population. For the PKU group, the percentage of children whose FSIQ was below the normative range was double that expected in the general population (Table 2).

As illustrated in Fig. 1, the PKU and mHPA groups exhibited similar profiles in terms of strengths and weaknesses on the WISC-R subtests, although the PKU group received lower scores compared with the mHPA group. Particular difficulties were noted on the Digit Span subtest (measuring auditory attention and working memory). In this subtest children must repeat orally a digit series in order and then a series of digits in reverse. Performance on the Information subtest was also relatively low in both groups. This test evaluated knowledge acquired by the child from his or her social and educational environment which may reflect the child's ability to pay attention to presented stimuli as well as educational opportunities.

Statistically significant differences between the PKU and mHPA groups were noted in performance subtests measuring visuospatial

Table 1

Mental and motor performance scores as assessed with Bayley's Scales for Infant Development in PKU and mHPA groups at 12 and 36 months of age.

Age	12 months			36 months		
	PKU N = 104	mHPA N = 66	p	PKU N = 97	mHPA N = 65	p
MDI	92.3 ± 11.3	98.1 ± 8.9	<0.0002	84.7 ± 14.9	94.6 ± 13.7	<0.0001
PDI	84.1 ± 13.6	88.2 ± 10.3	<0.04	86.9 ± 14.7	94.7 ± 15.7	<0.002
MDI < 70	3 (2.8%)	0 (0%)		12 (12.6%)	1 (1.5%)	

MDI: Mental Development Index; PDI: Motor Development Index.

Table 2
Intellectual performance of PKU and mHPA groups at preschool and school ages (assessed with WPPSI at 4 years of age and WISC-R at 7 years of age).

	Preschool (4 year olds)			School (7 year olds)		
	PKU N = 87	mHPA N = 53	<i>p</i>	PKU N = 75	mHPA N = 28	<i>p</i>
VIQ	96.9 ± 13.1	103.7 ± 12.5	<0.004	93.3 ± 14.9	101.3 ± 15.3	<0.03
PIQ	95.5 ± 15	108.1 ± 11.2	<0.0001	87.3 ± 15.3	99.1 ± 9.8	<0.002
FSIQ	95.9 ± 14.1	106.5 ± 12.1	<0.0001	89.5 ± 14.7	100.2 ± 13	<0.005
FSIQ 70–79	9 (10.3%)	0 (0%)		8 (10.7%)	1 (3.5%)	
FSIQ < 70	3 (3.4%)	0 (0%)		6 (8%)	0 (%)	

VIQ: Verbal Intellectual Quotient, PIQ: Performance Intellectual Quotient, FSIQ: Full Scale Intellectual Quotient.

Table 3
Verbal comprehension (VF), perceptual organization (POF) and freedom from distractibility factors (FDF) in PKU and mHPA groups at school ages.

Factor	PKU (n = 75)	mHPA (n = 28)	<i>p</i>
Verbal (VF)	9.0 ± 2.4	10.4 ± 2.5	N.S.
Perceptual organization (POF)	8.2 ± 2.4	10.0 ± 1.9	<0.0009
Freedom distractibility (FDF)	7.8 ± 2.4	9.3 ± 1.4	<0.002

VF: information, similarities, vocabulary, comprehension. POF: picture completion, picture arrangement, block designs and object assembly. FDF: arithmetic, digit span and coding.

organization and reasoning (Picture Arrangement, Picture Completion, Block Design and Coding). A significant difference was also observed in the Arithmetic subtest of the verbal scale, which also has a working memory component.

In terms of the composite factors, the PKU group received scores significantly lower than the mHPA group in the Perceptual Organization Factor (POF). This is consistent with the Performance IQ. Yet, the factor that is most affected in the PKU group is the Freedom from Distractibility Factor (FDF). The FDF includes Arithmetic (in which tasks are orally presented and must be mentally solved) and Digit Span. Both subtests require attention, immediate memory and working memory. The third subtest of the FDF is Coding that measures concentration and visual processing speed Table 3.

No statistically significant differences were observed in the factors measuring reasoning and verbal comprehension.

4. Discussion

Consistent with international studies [1,2,3], psychomotor development and intellectual performance in children with PKU identified

through neonatal screening and receiving early treatment are within the normative population range, although significantly lower than children with mHPA.

Unexpectedly, children with mHPA and PKU in our sample had similar performance profiles on the WISC-R subtests. This may indicate that specific cognitive functions are affected by even modest elevations in Phe.

The present study is consistent with the recommendation by Campistol et al. in 2011 that when assessing cognitive function in children with mHPA, it is not enough to measure only IQ, as deficits in executive functions can also be present even when IQ is within the normative range [16].

Attention, immediate auditory memory and working memory abilities should be assessed using other instruments in order to validate these results, especially in the mHPA group, for which fewer studies have taken place. Future research studies should also consider other variables, such as dietary intake, genotype, and psychosocial factors that might influence neurocognitive outcomes in both groups. A comparison group comprised of unaffected siblings would also provide worthwhile information.

The results of the present study indicate that mHPA might affect cognitive functioning, yet it does not offer a definitive answer to the question regarding whether mHPA should be treated. However the degree of deficits observed does not appear to justify treatment. On the other hand, alternative treatments, such as sapropterin dihydrochloride (BH4 therapy or Kuvan®) and moderate adjustments in protein intakes might be considered for individual children experiencing difficulties. Moreover, recognition of possible working memory and attention problems in mHPA children should be taken into account when providing healthcare follow-up and supportive services at school and at home.

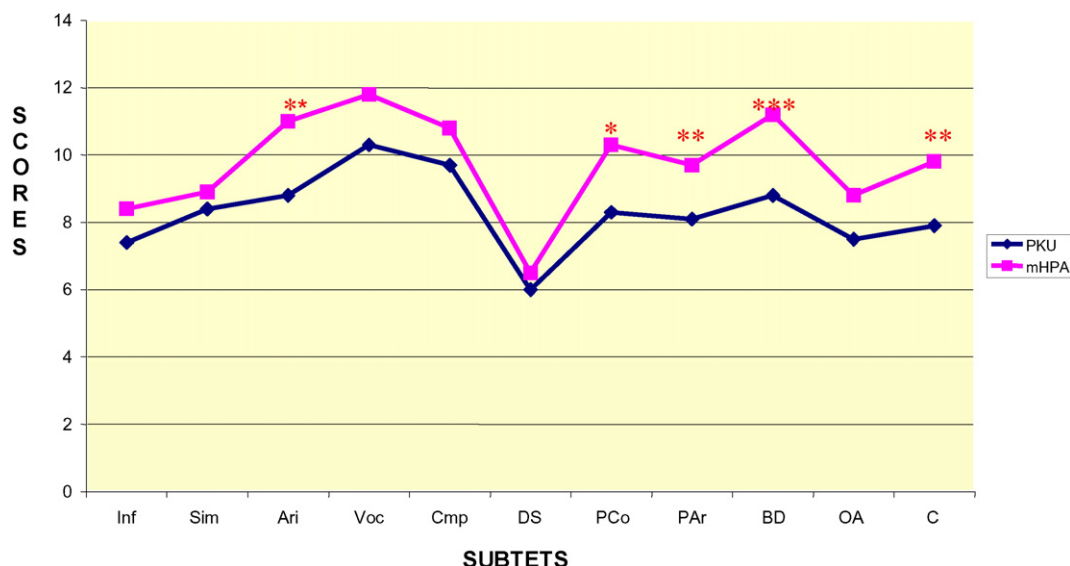


Fig. 1. WISC-R subtest scaled scores profile for PKU and mHPA.

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