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Intellectual and Developmental Status in Children With Hyperphenylalaninemia and PKU Who Were Screened in a National Program

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Abstract

Background: Hyperphenylalaninemia (HPA) and Phenylkeonuria (PKU) are metabolic errors caused by deficiency of phenylalanine hydroxylase enzyme, which results in increased level of phenylalanine. This increase is toxic to the growing brain.

Objectives: The purpose of this study was to compare the intellectual and developmental status in HPA and PKU children with normal population in national screening program.

Patients and Methods: In a historical cohort study, 41 PKU patients who had the inclusion criteria and 41 healthy children were evaluated. Wechsler preschool and primary scale of intelligence-3rd edition (WPPI-3) was used in order to assess the intellectual status of children 4 years and older and Ages and stages questionnaire (ASQ) was used to assess the developmental status of children 5 years and younger.

Results: In intellectual test comparison, the two groups showed significant difference in Wechsler's performance intelligence score and some performance subscales (P-value < 0.01). In comparison of developmental status, no significant difference was observed between the two groups (P-value > 0.05).

Conclusions: Even with early diagnosis and treatment of PKU patients, these children show some deficiencies intellectually compared to normal children. This study emphasizes on necessity for screening intellectual and developmental status of PKU patients so that effective medical or educational measures can taken in case of deficiencies.

Keywords: Hyperphenylalaninemia, PKU, Intelligence, Development

1. Background

HPA and PKU are metabolic errors caused by deficiency of the phenylalanine hydroxylase enzyme. This enzyme deficiency leads to defective metabolism of dietary proteins especially conversion of phenylalanine to tyrosine. Increasing phenylalanine is toxic for growing brain and causes disconnection of brain white matter pathways. Early diagnosis and ongoing and timely treatment (by restriction of phenylalanine diet) helps normalization of IQ (1-4).

It is observed that children with PKU who have high levels of phenylalanine (more than 6.6 milligrams per deciliter) and poor diet control have worse intellectual and functional status compared to those who have suitable diet (5, 6).

Following the diagnosis, metabolic center staffs are bound to support these patients, including their feeding program. Program setting should be coordinated by a physician and nutrition expert, and periodic testing of phenylalanine level and evaluation of nutritional status should be done during the life. It is better to evaluate these children weekly within the first year, and then monthly from one to five years old (7).

During the first six years, phenylalanine level is inversely proportional to intelligence, cognitive function and development. It is observed that PKUs under diets are lower than normal in terms of cognitive function and IQ (8). That is, early and continuous treatment does not necessarily cause normal IQ (9-11).

Screening helps provide early diagnosis and timely intervention (7) and it is emphasized that good metabolic control, especially during the first six years of life, is essential for prevention of defects in cognitive function and intelligence (8-15).

PKU screening program in Iran was initiated in 2006 and blood samples were taken from all newborns in third to fifth day of birth for the colorimetric screening. And those with phenylalanine as 4 mg/dL or above levels were referred to confirm the diagnosis by HPLC testing. Then, regular follow-ups are done for those who have phenylalanine levels of equal or more than 4 mg/dL and if the level of phenylalanine levels is 7 mg/dl and more, phenylalanine restriction diet starts (16), dietary supplements of iron, zinc, selenium, carnitine, vitamins and essential fatty acids are prescribed for all children with HPA and PKU up to 2 years of age, as the beneficial role of these materials in improvement of intellectual and functional status of these children has been proven (3, 17-25).

2. Objectives

This study compared intelligence and developmental status of children with PKU and HPA within the national screening program with normal population in Children's medical center in Tehran.

3. Patients and Methods

This is a historical cohort study. The study was conducted at Children's Medical Center, a governmental university referral center in Tehran, Iran during 2014 - 2015.

Case group sampling method was used as consensus. Patients with PKU detected in national screening program were referred to Children's medical center and were recruited in the study if they met all inclusion and exclusion criteria and their parental informed consent was obtained. The case group was composed of 41 children.

Control group sampling method was done randomly among children referred to Children's medical center for vaccinations or dental procedures as well as the hospital's kindergarten. Children of this group were selected similar to case group in terms of age and gender. In this group, 41 children were enrolled.

Inclusion criteria included:

- Lack of any acute or chronic disease
- Lack of use of any drug for any disease
- Lack of special diet

Exclusion criteria included:

- Those patients with no diagnosed HPA and PKU during neonatal screening
- Non-classical PKU patients
- PKU and HPA diagnosis was based on screening test in the third to fifth day after birth and its confirmation by HPLC.

The diet included phenylalanine restriction and early diet started upon diagnosis (i.e. during neonatal period). The diet observation level was measured based on the level of plasma phenylalanine. The last three measured levels of phenylalanine were recorded.

The developmental status of children 5 years of age and younger in both groups was measured by ASQ questionnaire. This is a valid and standard questionnaire including 30 questions written in plain language. The questions assess five scopes: communication, gross motor, fine motor, personal-social, and problem solving (26).

Intelligence in children at age 4 and older was measured by Wechsler preschool and primary scale of intelligence-3rd edition (WPPI-3), a standard and valid IQ test. This test consists of 11 subtests, which measure the child's verbal skills and performance. Each sub-test assesses the following (27):

A. Verbal Section

- Child's knowledge and awareness of the environment (Information)
- Understanding, learning, memory (Vocabulary)
- Cognitive ability (Similarities)
- The ability to calculate the real, personal and social problems (Arithmetic)
- Child's understanding of events and knowledge of the social environment (Comprehension)
- Familiarity with the term and its application (Sentences)

B. Performance Section

- Concentration, reasoning, visual attention, visual memory and visual-perceptual organization (Picture completion)
- Spatial orientation (Mazes)
- The ability of conceptual and visual-motor organization (Geometric design)
- Accuracy and attention (Block design)
- Speed, memory, target attention and concentration (Animal house).

Wechsler intelligence test was conducted for each person (in case or control group) during two 1.5 hour sessions by trained clinical psychology expert. The parents were asked to carefully answer and complete the ASQ questionnaire. If any questions were not clear enough, they were explained. Scoring was done by clinical expert and confirmed by child psychiatrist. Finally, case and control groups were compared.

Data analysis was performed by SPSS software. For quantitative variables, the mean and standard deviation, and for qualitative variables, frequency and percentage were used. Kolmogorov-Smirnov test was used for determining normal distribution of variables. t-test, Chi-square and ANOVA were used for testing hypotheses according to the type of data. P-value was considered as significant at < 0.05 in the tests and as significant at < 0.01 in sub-tests.

Parental consent was obtained from all subjects. This study was in compliance with the ethical principles of Helsinki. The study was approved by the ethics committee of Tehran university of medical sciences (code number: IR.TUMS.REC.1394.529).

4. Results

Overall 46 patients were investigated in case group, 5 of whom were excluded due to the non-classical PKU. In control group 50 children were investigated, 10 of whom

Table 1. Results of Wechsler Test for Comparison of Intelligence in Case And Control Group[a]

Variables (Subtests)	Case	Control	P-Value
Information	9.4 ± 3.09	11.3 ± 3.4	0.12
Vocabulary	12.2 ± 5.1	13.8 ± 3.4	0.33
Arithmetic	10.13 ± 4.2	11.06 ± 3.03	0.49
Similarities	11.4 ± 4.8	12.6 ± 3.5	0.44
Comprehension	11.4 ± 5.8	12.5 ± 3.3	0.54
Animal house	8.2 ± 5.01	12.8 ± 1.6	0.002
Picture completion	10.6 ± 2.8	13.5 ± 2.1	0.004
Mazes	9.9 ± 2.9	12 ± 1.4	0.02
Geometric design	9.4 ± 1.9	10.2 ± 2.04	0.32
Block design	10.9 ± 4.1	13.8 ± 2.9	0.03
Total IQ Score	102.9 ± 24.07	116 ± 12.2	0.05
Verbal IQ Score	102.6 ± 36.4	115.2 ± 18.07	0.24
Performance IQ Score	99.06 ± 20.2	116.6 ± 9.1	0.005

[a]Data are presented as mean ± SD.

Table 2. Results of ASQ Comparison Between Case and Control Groups[a]

Variables	Case	Control	P-Value
Communication score	53.8 ± 9.7	55.2 ± 8.7	0.52
Gross motor score	55.8 ± 7.7	53.9 ± 12.2	0.43
Fine motor score	52.9 ± 10.08	49.9 ± 11.22	0.25
Problem solving score	54.4 ± 9.3	54.3 ± 7.04	0.96
Personal-social score	55.7 ± 7.1	54.6 ± 7.4	0.54

[a]Data are presented as mean ± SD.

were excluded due to the acute disease and use of drug. Finally, data from 41 patients in case and 41 children in control group was analyzed.

In the patient group, 21 (51.2%) were female and 20 (48.8%) were male, and in control group, 25 (61%) were female and 16 (39%) were male (P = 0.3).

Mean age in patient group was 37.5 ± 20 months and 37.3 ± 19 months in control group (P = 0.9). The differences between two groups in terms of age and gender were not statistically significant.

Mean level of phenylalanine in the patient group was 4.7 ± 3.1 mg/dL.

Results of Wechsler test for comparison of intelligence for two groups are shown in Table 1.

Significant difference was observed between the two groups in the sub-tests of Animal House (P = 0.002), and picture completion (P = 0.004), as well as in total IQ score (P = 0.05) and performance IQ score (P = 0.005).

Comparison results of ASQ to assess the developmental status for two groups are shown in Table 2. No significant differences were found between the two groups (P > 0.05).

5. Discussion

The purpose of this study was to compare in framework of national screening program the intellectual and developmental status in HPA and PKU children with normal population. Current study is important because it investigated subtest of intelligence and developmental indexes in a group of PKU patients.

Our hypothesis was that PKU and HPA group is lower in terms of intelligence and development compared to the normal population. Current study showed that while significant differences were not found between the two groups in developmental indexes based on ASQ, the total IQ score was lower than normal in PKU group, and there were significant differences between them (P = 0.05). The performance IQ score in PKU group showed significant difference with the control group (P = 0.005). In relation with the sub-tests of performance IQ, animal house (P = 0.002) and Picture Completion (P = 0.004) tests showed significant difference between the 2 groups. The total score of verbal IQ and its sub-tests showed no significant difference between the two groups. Similar studies by other researchers showed a problem in the executive functions in this group of children.

Sherman and Rachael in a cohort study on 13 children with PKU, observed some mild defects in executive function. Half of these children showed defects in visuospatial skill and they had also a clear cut of the language understanding skills from age 6 to adolescence (4).

In the study by Leuzzi et al. 14 children with PKU were compared with 14 normal children by Wechsler test. All of them were normal in terms of IQ score. In order to evaluate executive functions (EF), subtests were also completed. All PKU patients showed lower scores than control group, which included sorting category, problem solving, planning, set shifting, attention and concentration (5).

Gassio et al. observed that PKU patients had significantly lower levels of spatial vision, visual memory, motor function and executive function compared to the control group (8).

In a study, 57 children with PKU were compared to normal population using Wechsler. Significant difference was observed in Wechsler sub-tests comparison between PKU group and normal group in terms of information, picture completion, object assembly, picture arrangement and coding. In other cases, i.e. the similarities, arithmetic, vocabulary and comprehension were not significantly different. In short, the two groups showed significant differences in performance sub-tests, but they showed no difference in verbal test except for information (9). The results of our study are almost in agreement with those of others.

Sajedi et al. compared problem-solving skills (related to ASQ) in the early treated PKU children with the control group, and showed a significant difference between the two groups regarding developmental indexes (17).

In another study by Nazi et al. (18), development of motor skills in 1 - 4 years old Iranian children with early treated PKU were studied. 70 early diagnosed children were compared to 100 healthy children. This study showed that in the area of fine and gross motor, there was a significant difference between the two groups; the difference was more obvious in the fine motor area. The peabody developmental motor scales (PDMS-2) was used. There are some differences in the results of our study on the developmental skills with other studies which may be due to low sample size in our study or possible weaknesses in the related test.

Small number of subjects is one of the limitations of this study, since it was conducted on children in national screening program referred to Children's Medical Center. It is suggested that future studies will be done on a larger level, for example in the metropolis of Tehran to obtain more generalized results. Confounding factors also were involved in the study like in any other study. Weaknesses of intelligence and development tests is also undeniable.

Even with early diagnosis and proper diet, some defects are observed in intellectual status such as performance IQ score in children with PKU and HPA. Thus, it is recommended that with implementing screening programs for development and intelligence, timely detection of weaknesses in children with PKU is possible and useful medical and educational measures will be provided.

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