Evaluation of Attention-deficit/Hyperactivity Disorder in Referred Patients to the PKU Clinic in Yazd, Iran

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Abstract

Objective

The imbalance of phenylalanine (PA) to tyrosine level and decreased dopamine brain level in patients with phenylketonuria (PKU) may have a role in their susceptibility of them to attention-deficit/hyperactivity disorder (ADHD). This study aimed to evaluate the frequency of ADHD in referred patients to PKU Clinic in Yazd, Iran.

Materials & Methods

In this cross-sectional analytical study, all patients older than three years with PKU who were referred to the PKU Clinic of Shahid Sadoughi Hospital, Yazd, Iran, in 2018 were evaluated, and ADHD symptoms in them were assessed via parent face-to-face interview. The patients were diagnosed with ADHD if they scored at least of 20 on ADHD diagnostic rating scale via parent interview based on DSM-VI criteria.

Results

Fourteen boys and 21girls with a mean age of 9.55±1.8 years were evaluated. 51.5% of those diagnosed with PKU had ADHD. Accordingly, ADHD was more frequent in girls (77.8% vs. 41% in boys, P=0.03).

The mean age of diagnosis of PKU was significantly higher in patients with ADHD (52.54±15.65 months vs. 29.75±9.65 months, P = 0.03). The mean of PA level in the last six months (15.59±5.95 vs. 8.72+5.18, P= 0.005) and mean of the last six PA levels (14.76±4.71 vs. 8.96±3.86, P= 0.03) were significantly higher in ADHD group.

Conclusion

The prevalence of ADHD in phenylketonuria patients in the present study was much more than in other studies. Late diagnosis of PKU and long-term high PA blood and brain level might be associated with increased neonatal screening. Hence, regular follow-up and continuous evaluation of patients with PKU for ADHD symptoms should be performed.

Keywords: Phenylketonuria; ADHD; Phenylalanine; Children

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Introduction

Phenylketonuria (PKU) is an autosomal recessive disease and the most common hereditary metabolic disorder in the world, causing deficiency of activity of the hepatic enzyme L-phenylalanine-4-hydroxylase (PAH) gene and impairment of phenylalanine (PA) conversion to tyrosine. The prevalence of PKU is globally one in 10,000 whites and one in 6000–8000 Iranians. (1) Deficiency of PAH activity causes a significant increase in PA blood level, a decrease of tyrosine and brain neurotransmitters such as serotonin, dopamine, noradrenaline, and alterations in cerebral myelin formation and protein synthesis. (2)

Chronic hyperphenylalaninemia (H-PHE) in untreated patients with PKU leads to adverse effects on brain development and irreversible brain damage, microcephaly, severe mental retardation, epilepsy, and severe behavioral problems. (3) Besides, it is one of the most typical causes of mental retardation. (4)

Dopaminergic pathways of dorsolateral prefrontal cortex neurons are effective in cognitive functions such as learning, retention, attention, and concentration. (5) In addition, an increased blood PA level and suppression of dopamine and serotonin brain turnover leading behavior disorders, such as autistic behaviors, aggression, hyperactivity, impulsive behavior, attention-deficit disorder, and disruptive stereotypic movements. (6)

Attention-deficit/hyperactivity disorder (ADHD), defined by inattention, increased distractibility and difficulty sustaining attention, motor hyperactivity and restlessness, poor impulse control, and decreased self-inhibitory capacity, is the most common neurobehavioral disorder of childhood. (7)

ADHD may be associated with decreased tyrosine and tryptophan levels in these patients' brains. (8)

Some studies tested this hypothesis that patients with ADHD and PKU have low dopamine levels in the frontal cortex and striatum. This hypodopaminergic condition suggests a possible link between the two diseases, and patients with PKU may be more susceptible to developing ADHD. (9)

Based on the newborn screening of PKU, the prevalence of PKU in Iran was estimated to be 16.5/100,000, according to a systematic review and meta-analysis. (10) Absence of pervasive PKU screening programs in Iran until a few years ago and problems with feeding with a low PA diet have

caused numerous late-diagnosed PKU patients with severe behavioral problems. (11)

This study evaluated signs and symptoms of attention-deficit/hyperactivity disorder in patients with PKU older than three years who were referred to the PKU Clinic of Shahid Sadoughi University of Medical Sciences (SSUMS), Yazd, Iran.

Materials & Methods

In a cross-sectional analytical study, patients with PKU older than three years diagnosed with the newborn-screening program or later in evaluating pediatric endocrinologist or pediatric neurologist were referred to PKU Clinic of SSUMS, Yazd, Iran, in 2018, were enrolled.

For all patients, immediately after diagnosis, PA free diet was initiated and followed up regularly. Patients who had irregular visits to the PKU clinic in the past six months or had definite neurological, psychological, or other genetic disorders were excluded.

Face-to-face parents interview was accomplished, and ADHD symptoms of their children were assessed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria with a parent ADHD diagnostic rating scale. (12) In this questionnaire, the parents were asked about 18 symptoms that were rated on a scale of zero to three on a Likert scale (zero: Never and Rarely, one: Sometimes, two: Often, three: More times or Permanently). A child with at least a score of 20 on the ADHD diagnostic rating scale was considered to have ADHD. (12)

The data were analyzed using Statistical Package for the Social Sciences version 17 (SPSS, Chicago, Illinois, USA) statistical software.

Recorded data were assessed for normal distribution using the Kolmogorov-Smirnov test, the Chi-square test was used for data analysis of categorical variables, and continuous and mean variables were compared using an independent t-test between the two groups. Differences were considered significant at P values of less than 0.05.

Informed consent was taken from the children's parents before enrolling in this study. Besides, the Ethics Committee of SSUMS, Yazd, Iran, has approved this study.

Results

Information of 46 children was available in the PKU Clinic; 35 children older than three years, including 21 girls and 14 boys with a mean age of 9.55±1.8 years, were evaluated.

Eighteen (51.5%) children of PKU patients had ADHD.

Table.1 shows a comparison of sex distribution, mean of age, and mean age of diagnosis of PKU in two groups and indicates that the mean age of patients in the two groups was not statistically significant. Nevertheless, AHDH was more frequent in girls, and the age of PKU diagnosis was significantly higher in PKU patients with ADHD.

A comparison of the mean of PA level at different times in both groups is shown in Table2. Accordingly, the mean PA level in the first six months of diagnosis was not statistically significant in both groups. However, the mean PA level in the last six months and the mean of the last six PA levels were significantly higher in the ADHD group.

Table 1. Comparison of sex distribution, mean of age and mean age of diagnosis of PKU in two groups

Data \ Groups		With ADHD	Without ADHD	P. value
Sex	Female	14(77.8%)	7(41%)	0.03
	Male	4(22.2%)	10(59%)	
Age in years (mean ± SD)		10.03 ± 2.1	9.01 ± 1.41	0.4
Age of diagnosis of PKU in months (mean ± SD)		52.54±15.65	29.75±9.65	0.03

Table 2. Comparison of mean of phenylalanine (PA) level in different times in both groups

Data \ Groups	With ADHD	Without ADHD	P. value
PA level in the first 6 months of diagnosis (mean ± SD)	14.90±6.78	13.76±6.44	0.7
PA level in the last 6 months (mean ± SD)	15.59±5.95	8.72+5.18	0.005
Mean of the six recent PA level (mean ± SD)	14.76±4.71	8.96±3.86	0.003

Discussion

The PKU screening program in Iran was launched in 2006, and PA blood level will be measured three to five after birth by colorimetric screening and then by HPLC test in newborns with a PA level of 4 mg/dl or higher. Regular follow-up, a low PA diet, and supplements of iron, zinc, selenium, carnitine, vitamins, and essential fatty acids in children under two years old are essential. (1)

Neonatal screening and a low phenylalanine diet significantly reduce the risk of neurobehavioral disorders of PKU. However, even patients with optimal management still face some neurological and behavioral manifestations. (13) In a study in Tehran, Iran, 70% of patients with PKU referred to Mofid Children's Hospital had white matter involvement in brain MRI and 20% had brain atrophy. (14)

In the present study in Yazd, Iran, 51.5% (18 of 35) of older than three years patients with PKU diagnosed with the newborn-screening program or later evaluated by pediatric endocrinologists or neurologists had ADHD. Nevertheless, the prevalence of ADHD among 6-year-old children in Yazd, Iran, was 16.3% in Karbasi et al. study (15). In the study of mental illness epidemiology in children and adolescents in Iran (IRCAP), 1035 samples of children aged 6-18 years were studied, and the prevalence of ADHD in Yazd was 1.6% and 4% in the whole country. (16) This means that the prevalence of ADHD in patients with PKU was more than in the general population. Therefore, ADHD is an essential behavioral disorder in patients with PKU and may be present in them at a higher-than-expected rate in the general population. (17)

In a study in Santa Catarina, Brazil, 6-18 years of patients with PKU diagnosed with newborn-screening tests and low PA diet was begun before 60 days of life, and they had permanently PA

level less than 6 mg/dL evaluated; 38% of them had ADHD by Swanson, Nolan, and Pelham Questionnaire. (5)

In a study in Sohag, Egypt, 88.5% of 110 patients with PKU that only three of them diagnosed by neonatal screening, had ADHD. (18)

In another study in Rio de Janeiro, Brazil, Child Behavior Checklist evaluated 36 6–18-year-old patients with early-treated PKU. The mean of the Attention Problem Scale was significantly more than the controls. However, the mean of the scores of DSM-IV/ADHD scale of patients was not significantly different in patients and controls, and attention problems and hyperactivity were more prevalent in non-adherent to treatment PKU patients. (19) These studies confirm the hypothesis of a direct link between ADHD and PKU. The rate of ADHD in patients with PKU is almost twice that of the general population. (20)

In the general population, 5-7% of school-age children have ADHD, and the rate of ADHD in males is higher than in females, with a male-to-female ratio of about 3:1 in community-based samples. (21)

However, in this research, in patients with PKU, AHDH was more frequent in girls.

In a study in Brazil, a significant percentage of patients with ADHD and PKU missed at least one year of schooling. Educational problems in children and adolescents with PKU may be a function of ADHD. (5)

An increase in phenylalanine during embryonic development might influence the rate of further ADHD symptoms, and an increase in the duration of exposure to high PA levels can affect the expression of ADHD symptoms. Late diagnosis and treatment of PKU cause PA levels to be higher than average for a more extended period and increases the chance of developing ADHD, which is dose-dependent toxicity. (22)

The incidence of ADHD symptoms in patients with PKU treated early was significantly lower than in patients treated late. (23)

In Antshel and Waisbren's study, the prevalence of ADHD in classical PKU children and maternal PKU offspring was more than in controls. (24)

In the present study, PA levels were measured every three months in patients with PKU, and the mean of PA levels in the last six months and the mean of the six current PA levels in the group with ADHD were significantly more than those without ADHD. The obtained results confirm that the duration of H-PHE and long-term brain exposure to high PA levels may influence the presentation of ADHD symptoms and a dose-dependent relationship between PA levels and ADHD symptoms; a more significant number of ADHD symptoms were associated with a higher level of PA exposure. (24-26)

In Conclusion

Based on the obtained results, ADHD was more prevalent in patients with PKU, and its frequency is much more than in other studies. Late diagnosis of PKU and long-term high PA blood and brain level might be associated with increased neonatal screening; regular follow-up and continuous evaluation of patients with PKU for ADHD symptoms should be performed.

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Author's contributions

Dr. Mahtab Ordoei: Editing the manuscript
Dr. Abolfazl Shafii ronizi: Gathering the data
Dr. Dr. Razieh Fallah: Writing the manuscript

Conflicts of interest

The authors declare no conflicts of interest.

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