Cognitive and behavioral impairment in mild hyperphenylalaninemia

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Received: 5th March 2019, Revised: 7th March 2019, Accepted: 8th March 2019

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SUMMARY: Evinç SG, Pektaş E, Foto-Özdemir D, Yıldız Y, Karaboncuk Y, Bilginer-Gürbüz B, Dursun A, Tokatlı A, Coskun T, Öktem F, Sivri HS. Cognitive and behavioral impairment in mild hyperphenylalaninemia. Turk J Pediatr 2018; 60: 617-624.

As elevated phenylalanine (Phe) is detrimental to brain functions, determining a safe upper limit of blood Phe is important for initiation of treatment plans and setting Phe targets in hyperphenlalaninemic patients. It is accepted that Phe levels below 360 μmol/L does not impair brain function and hence does not require treatment. Therefore, we aimed to compare cognitive functions and attention-related problems among healthy children and untreated patients with hyperphenylalaninemia (HPA). This study included 41 hyperphenylalaninemic patients ("all HPA group") aged 6-16 years with untreated blood Phe between 240 and 600 μmol/L and 29 healthy controls. "All HPA group" was further divided into 2 subgroups according to their lifetime median blood Phe levels as "Phe 360-600 μmol/L" and "Phe 240-360 μmol/L" groups. Wechsler Intelligence Scale for Children–IV (WISC-IV), Conners' Continuous Performance Test (CPT), Strength and Difficulties Questionnaire (SDQ) and Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL) were performed as a comprehensive neurocognitive, attention and behavioral assessment. The study illustrated that "all HPA" patients had significantly lower scores on all WISC-IV indexes compared to controls, except for Working Memory. Both "Phe 360-600 μmol/L" and "Phe 240-360 μmol/L" subgroups had lower Full Scale intelligence quotient (IQ) and Verbal Comprehension scores compared to controls. "All HPA" patients also had longer reaction times and more peer problems than controls, indicating attention deficits and behavioral problems. Since the results demonstrated that children with untreated Phe levels between 240-360 μmol/L are at higher risk for cognitive and attention-related problems, lowering the "safe" upper Phe level should be considered.

Key words: hyperphenylalaninemia, cognitive functions, intelligence quotient.

Phenylketonuria (PKU, OMIM #261600) is an autosomal recessive metabolic disorder resulting from a deficiency of phenylalanine hydroxylase (PAH, E.C. 1.14.16.1), an enzyme that catalyzes the hydroxylation of the essential amino acid phenylalanine (Phe) to tyrosine (Tyr), causing increased levels of blood Phe.[1] Although high blood Phe and subsequent downstream alterations are believed to be responsible for the neurotoxicity in PKU, the underlying pathophysiology is currently not well-defined.[2] Phenylalanine hydroxylase deficiency can be classified according to treatment-naïve blood Phe levels as mild hyperphenylalaninemia (mHPA)-not requiring treatment (OMIM #617384) (120-360 μmol/L), mHPA-grey zone (in reference to the conflicting data on the effects on cognition and executive

function, 360-600 μmol/L), mild PKU (600-900 μmol/L), moderate PKU (900-1200 μmol/L) and classical PKU (>1200 μmol/L).[3]

Although PKU is the most commonly inherited disorder of amino acid metabolism, its incidence varies around the globe.[4,5] Turkey is one of the countries with high incidence of PKU (1:4500 live births) and therefore has a considerably large PKU population.[6]

Traditional management of PKU includes Phe-restricted diet with Phe-free amino acid supplementation and low-protein products. Pharmacological treatment with sapropterin dihydrochloride (Kuvan®), a synthetic version of tetrahydrobioptherin (BH4), has been more recently available to be used alone or in conjunction with diet in a subset of patients with BH4 responsive PKU.[4,5] Considering the detrimental effect of high blood Phe levels on brain development and its function, strategies to decrease Phe levels should be initiated as early as possible. Due to the lack of strong evidence as to the safe upper limit of blood Phe concentration in different age groups, inconsistencies are observed between the recent European and American PKU guidelines. Both guidelines agree that there is no need for treatment blood Phe levels between 120-360 μmol/L and recommend treatment of blood Phe higher than 600 μmol/L.[1,4,5] Current evidence for treating patients with blood Phe levels between 360 and 600 μmol/L is limited, with conflicting results. While some studies demonstrate normal clinical outcomes in these patients, others show subtle neurocognitive deficits.[7,8] The European guidelines recommend to treat blood Phe levels between 360 and 600 μmol/L only in the first 12 years of life and during pregnancy, stating that although the evidence to treat this group of patients is weak, these levels cannot be assumed to be safe in these populations, whereas the American guidelines recommend that blood Phe levels be kept between 120 and 360 μmol/L throughout life.[4, 5] Furthermore, there is some evidence from the literature that clinical outcomes may even be better when Phe levels are kept below 240 μmol/L.[9]

Therefore we aimed to compare cognitive functions and attention related problems among healthy children and untreated hyperphenylalaninemia patients with blood phenylalanine between 240-600 μmol/L.

Material and Methods

Subjects

This is a single center study performed at Hacettepe University Children's Hospital by the Section of Pediatric Metabolism and Department of Child and Adolescent Psychiatry. Hyperphenylalaninemic patients between 6 and 16 years of age with untreated blood Phe levels below 600 μmol/L, who had not received dietary or sapropterin dihydrochloride treatment were included. Patients with other underlying chronic diseases, disorder of BH4 metabolism or maternal hyperphenylalaninemia were excluded. All eligible patients and age- and sex-matched controls who consented to be included in the study were enrolled. Data were collected from 41 untreated hyperphenylalaninemia patients (all HPA group) and 29 healthy controls. Healthy controls were preferably selected from siblings, relatives or neighbors of the patients in order to obtain a similar socioeconomic background between patients and controls. Since mild hyperphenylalaninemia is not expected to cause intellectual disability, subjects with IQ scores lower than 70 were excluded from the study due to the possibility that they might have another underlying condition.

In order to obtain detailed results, the study group was also divided into 2 subgroups based on their lifetime median phenylalanine level. The first group consisted of 10 patients with median blood phenylalanine level between 360-600 μmol/L (Phe 360-600 μmol/L group) and the second consisted of thirty-one patients with median blood phenylalanine level between 240-360 μmol/L (Phe 240-360 μmol/L group).

Materials

Wechsler Intelligence Scale for Children –IV (WISC-IV) is a structured multi-dimentional tool measuring IQ and the cognitive abilities of children and youth between the ages of 6-16 years. WISC-IV is composed of four main indexes including 10 main and 5 substitute sub-tests, all of which are suggested to measure different intellectual abilities including learning difficulties, executive functions, measurements of capacity, intellectual disabilities and other neurological conditions.[10] Turkish standardization of the scale was conducted

by Uluç and his colleagues.[11]

Conners' Continuous Performance Test (CPT) is a computerized neuropsychological test. The subject is asked to sign the target stimuli (letter A) when it appears after another identified stimulus (letter Z). This task is taught to the child before starting the test and practiced until the tester is sure that the child has learned it. CPT contains four main scores, including correct detection, reaction time, omission errors and commission errors.[12] These scores give information about the subject's sustained attention, selective attention, and suppression.[13]

Strength and Difficulties Questionnaire (SDQ) was developed by Goodman in 1997.[14] This inventory aims to measure five dimensions; namely, attention problems, emotional problems, peer relationship, social behavior problems and hyperactivity.[14] In addition, externalization and internalization scores can be obtained. Güvenir et al[15] determined the validity and reliability of the inventory in the Turkish population.

Presence of attention-deficit hyperactivity disorder (ADHD) was determined by a semi-structured instrument, named 'Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL)'. The instrument was originally developed by Kaufman and colleagues[16] and adapted to Turkish by Gökler and her colleagues.[17]

Procedures

HPA patients, control group and their parents were informed about the study and volunteers and healthy controls were included. Informed consent was obtained from all subjects and their parents. The local ethics board approved the study (GO.15/213-18).

A psychologist and a child psychiatrist interviewed all children and their parents. Psychiatric diagnoses were screened by K-SADS-PL and intelligence scores of the children were determined by WISC-IV. In addition to WISC-IV, CPT was applied to all children with the aim of screening their cognitive abilities such as attention. Parents were given socio-demographic questionnaire and children were asked to complete the Strengths and Difficulties Questionnaire.

Statistics

All analyses were performed by SPSS 20.0. Chi-square was used to compare the groups on categorical demographic variables. Group differences on WISC-IV, CPT and SDQ were analysed by Mixed Method Analysis of Variance (ANOVA) with repeated measures on the last factor.

The study group consisting of HPA patients and the control group were compared on the test variables. The HPA group was further divided into two subgroups as described above (Subjects) and compared both with the control group and with each other. When the main effect or the interaction effect was significant, Tukey's HSD was conducted at .05 significance level to interpret the ANOVA results.

Additionally, in order to understand the association between blood Phe level and WISC-IV scores in more detail, separate hierarchical regression analyses were run for all WISC-IV scores. Demographic variables of the children were entered into the equation in the first step and demographic variables, which belong to the parents, were entered in the second step. In the third step, WISC-IV scores were entered.

Results

The female:male ratio of the subjects was 49:51 for the whole group and the groups did not differ significantly on gender. Among all subjects the age range was 72-187 months and the mean age was 116.7 months (102.54 for study group, 124.59 for control group). Among the whole group both mothers and fathers mostly had high-school education or higher. Groups did not differ on paternal education but mothers in the control group had higher education than the study group. The mean blood Phe level was 316.2 μmol/L (ranging between 240.6-487.2 μmol/L) among all HPA patients. Among the "Phe 360-600 μmol/L group" the mean blood Phe concentrations was 406.2 and among the "Phe 240-360 μmol/L group" mean blood Phe concentrations was 287.4 μmol/L.

Comparison of "all HPA group" and control group showed that the HPA patients had significantly lower scores on all WISC-IV indexes except for the Working Memory Index. Similarly, comparison of three groups
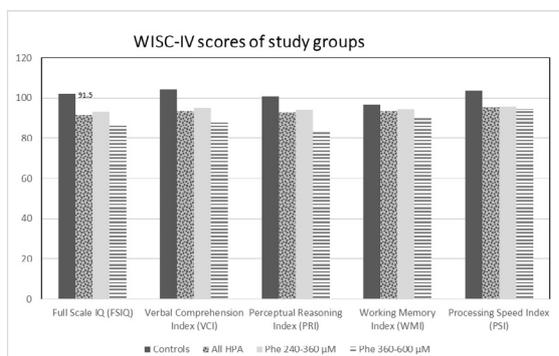
Fig. 1. Comparison of WISC-IV Scores. Mean full scale IQ and WISC-IV index scores of the control group with all HPA, Phe 240-360 μmol/L and Phe 360-600 μmol/L groups are presented.

Fig. 2. Comparison of CPT Results. Results of CPT tasks of the control group with all HPA, Phe 240-360 μmol/L and Phe 360-600 μmol/L groups.

(two study subgroups and control group) also yielded that the control group had higher Verbal Comprehension and Full Scale IQ score when compared to the two study subgroups (Fig. 1).

Regression analysis revealed that the age of the subject was associated with Full Scale IQ scores and Verbal Comprehension scores, and maternal age was associated with Perceptual Reasoning Scores. After controlling for demographic variables, blood Phe level predicted children's Full Scale IQ scores, Verbal Comprehension scores, Perceptual Reasoning scores and Processing Speed scores. Blood Phe level explained 13% of the variance for Full Scale IQ scores, 9% of the variance for Verbal Comprehension scores, 7% of the variance for Processing Speed scores, 6% of the variance for Perceptual Reasoning scores. According to these results, increase in blood Phe level was accompanied by increasing age and decreasing Full Scale IQ, Verbal Comprehension, Perceptual Reasoning and Processing Speed scores.

Analysis on Conners Performance Test revealed that "All HPA" group had higher reaction times and higher reaction time standard error than the control group, meaning that the HPA patients were slower on CPT tasks and that they had to spend more time to make a decision and they had greater inconsistency in the response speed compared to healthy controls (Fig. 2).

When three groups (control group and two study subgroups) were compared on CPT scores, results indicated that compared to the control group, "Phe 360-600 μmol/L group" had significantly lower correct detection and significantly higher omission and commission

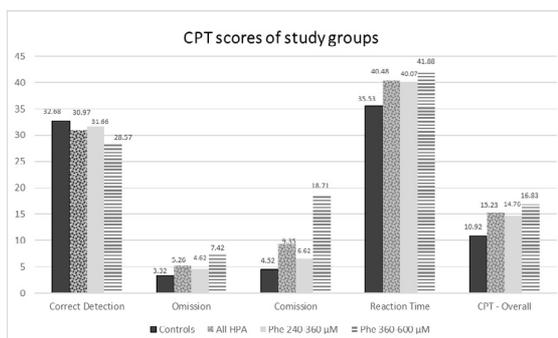errors. Similarly, "Phe 360-600 μmol/L group" also had higher commission errors compared to "Phe 240-360 μmol/L group". "Phe 240-360 μmol/L group" and controls did not differ significantly on any CPT scores (Fig. 2).

SDQ and K-SADS-PL were applied to children with the aim of investigating their psychological problems. Results on SDQ scores revealed that the control group had less peer problems compared to the whole study group. When the study group was divided into two subgroups ("Phe 240-360 μmol/L group" and "Phe 360-600 μmol/L group"), analysis of SDQ scores among these two subgroups and the control group did not yield significant differences. Psychiatric disorders were screened by K-SADS-PL and the results indicated that 61% (59% of study group, 66% of control group) of all children did not have a psychiatric disorder, 33% of the children had ADHD and %7 had other diagnoses (3% oppositional defiant disorder, 4% anxiety disorders). When the "all HPA" group and the control group were compared on the ADHD diagnosis, the analysis did not reveal a significant difference. According to these results, peer problems were more common among HPA patients, but psychiatric diagnoses in this group were not more common compared to healthy children.

Discussion

If left untreated, phenylketonuria is known to cause impairment in neuropsychological functioning. Although early diagnosis and treatment prevent severe deficits, there is some evidence that these patients may present with attention-related problems, deficits in executive

functioning and with poor memory.[18-25] Patients with untreated mild hyperphenylalaninemia are usually in good health, but there are studies suggesting that they may exhibit subtle neuropsychological deficits. Although current guidelines state that Phe levels above 360 μmol/L should be treated, there is limited evidence regarding the necessity of treatment for Phe levels between 360 and 600 μmol/L.[4,5,7,8] On the other hand, it has also been suggested that targeting Phe levels below 240 μmol/L may result in better outcomes.[9] One can hypothesize that it may be unsound to set a "safe" upper limit for a known neurotoxic compound at 360 μmol/L when the blood levels in healthy individuals are strictly kept between 30-90 μmol/L. Therefore, cognitive abilities and attention problems in an untreated hyperphenylalaninemia population were evaluated in the present study.

Since there is an established association between cognitive abilities and blood Phe levels in children and adolescents with PKU, neurocognitive assessment can be used to evaluate the toxic effects of high Phe levels on the developing brain.[21, 26] Therefore, WISC-IV, CPT, SDQ and K-SADS-PL were performed in order to obtain a comprehensive neurocognitive and behavioral assessment.

K-SADS-PL results showed that the prevalence of psychiatric disorders did not differ between healthy controls and HPA patients whereas Strengths and Difficulties Questionnaire (SDQ) suggested that "Phe 240-360 μmol/L" group had higher peer relation problems than controls. But perhaps the most striking finding in our study was the significantly lower full scale IQ scores and lower main index scores (except for the Working Memory Index) in children with HPA compared to healthy controls. Furthermore, when the study group was divided into two subgroups in order to get more detailed results, subjects in both subgroups of HPA (Phe 240-360 μmol/L and Phe 360-600 μmol/L groups) had significantly lower total IQ scores and lower Verbal Comprehension Index scores than healthy controls whereas the two subgroups did not differ from each other in terms of IQ scores. ANOVA also showed that the control group had higher IQ scores than the whole HPA group and the two HPA subgroups while the two HPA subgroups were not significantly

different from one another. However, regression analysis indicated that higher blood Phe levels predicted lower IQ scores. Moreover, regression analyses also demonstrated that as blood Phe level increased, all IQ scores -except for working memory- of HPA group decreased. "All HPA" group was also much slower while making a decision in CPT tasks. In other words, on the tasks of CPT, children with HPA spent more time to give the right response, i.e. reaction time was significantly longer, and this indicates that the rate of information processing is slow and the duration of motor response is prolonged in these patients, which is closely related to impaired executive functions. Furthermore, high response time variability suggests that the HPA group has considerable difficulty in maintaining sustainability. "Phe 240-360 μmol/L" group exhibited a more similar performance to healthy controls and had significantly less wrong detection and commission errors than "Phe 360-600 μmol/L" group. Significant increase in commission errors in parallel with the increase in Phe levels can be interpreted as 'high Phe levels in HPA cases may negatively affect the ability to plan, delay impulses, execute self-control, which in turn, it may increase impulsivity'. ANOVA statistics on CPT scores also showed that the group with higher Phe levels had worse performance. Based on these WISC-IV and CPT results, it is clear that as blood Phe level increases, cognitive performance decreases, but the decrease on some of the cognitive domains -related to executive functioning- do not reach significance before the blood Phe level exceeds 360 μmol/L. Still, contrary to current guidelines, phenylalanine levels between 240-360 μmol/L have an unexpected negative effect on intelligence and therefore, are not safe.

Previous studies have also addressed the relationship between cognitive functions and Phe levels, focusing on different aspects of intelligence and settling on different conclusions. Costello et al.[7] pointed out in 1994 that depending on the severity of hyperphenylalaninemia, children may exhibit some degree of neurological impairment. Later studies investigating the presence of cognitive impairment in mHPA have reached conflicting results: It has been suggested that adolescents and adults with untreated HPA between 360 and 600 μmol/L have

IQ scores that are comparable to healthy individuals.[8, 27] Meanwhile, it has also been proposed that while IQ scores of those with Phe levels below 360 μmol/L are comparable to controls, children with Phe levels below 240 μmol/L have IQ scores that are the closest to the healthy population.[28] Besides IQ scores, executive functioning and attention may also be impaired in mHPA with Phe levels below 360 μmol/L.[29-31] This discrepancy may be a result of the difference between the assessment tools that were used in different studies because different tools target different cognitive abilities. In addition, according to van Spronsen,[24] this inconsistency may also be the result of some methodological issues. van Spronsen[24] also reports that two of the studies -suggesting that Phe levels up to 600 μmol/L are safe- had problematic samples and one reference study -which suggests Phe levels below 400 μmol/L are safe- relied only on standard deviations of samples and not on statistical analyses. In our study, cognitive abilities were assessed by two assessment tools (WISC-IV and CPT) that are used worldwide and shown to be valid and reliable in our culture (see the methods section).

The results of our study suggest that executive functioning, attention and even intelligence can be impaired as Phe levels increase; and contrary to the literature, even patients with lifetime median Phe between 240 and 360 μmol/L had lower IQ scores and were found to be at higher risk for cognitive impairment such as difficulty in verbal comprehension. Lower IQ scores may be a direct toxic effect of Phe or may be a consequence of distractibility, impulsivity and prolonged reaction time. It can be suggested that impaired executive functions may also be mixed up with poor IQ, learning difficulties and deficiencies in attention skills. In any case, the striking difference in total IQ scores between both HPA groups and healthy controls is alarming and requires further study. Similar to the study of Diamond et al,[28] our data also suggest that the cut-off level for initiating treatment should be decreased.

It is interesting that children with HPA were not clinically diagnosed with ADHD more frequently than healthy controls. This suggests that they may not have ADHD –a heritable attentional and behavioral disorder beginning at early childhood- more frequently than their peers. In fact, their attention related functions may be disrupted with time. Another interesting finding was the similarity of working memory index scores between the HPA patients and healthy controls while other index scores were significantly lower in HPA patients, since working memory is an important domain of executive functions. It is known that executive functions (EF) are also categorized as Hot EF and Cool EF.[32] Hot EF is reported to be related with emotion regulation, attention problems and overactive behaviors whereas Cool EF is linked with poor cognitive flexibility, working memory, inhibitory control and academic performance.[32] As there is no significant difference between groups –in other words as both groups have similar performance on working memory- while controls have better performances on other indexes, one can suggest that HPA patients in this study can keep information in mind and manipulate it (which are functions of working memory); however, they may have difficulty in other Cool EF skills such as cognitive flexibility functions (e.g., switching their attention, perspective taking, changing their way of thinking) and in inhibitory control functions (e.g., inhibiting their attention and their responses).

The results related to psychological difficulties of children with HPA are consistent with their cognitive assessments. Children in the "Phe 240-360 μmol/L group" had higher peer relation problems compared to healthy controls. This result is congruent with expectations for two reasons. First, emotion regulation, which is related to peer relations, is a function of Hot EF. As the results related to attention skills, which is also a Hot EF function, showed that children with HPA have lower performance on most of the attention related tasks, it may be suggested that lower emotion regulation in children with HPA is consistent with expectations based on other results of the study. Secondly, blood Phe levels are known to be damaging to the prefrontal cortex.[33,34] As both cognitive functions and emotional or behavioral self-regulation are related to similar brain regions such as the prefrontal lobe and limbic system,[35,36] it can be suggested that increased Phe levels may cause defects on cognitive functioning, and in turn, impair psychological functioning.

There are some limitations of the study. First of all, maternal education level can be associated with the parenting styles of the mothers and, in turn, higher maternal education level in healthy controls may have affected the results. And secondly, even though the sample size of the present study is bigger than many previous studies, a larger sample could give more accurate and informative results. Future studies may increase the sample size, include more patients with lower phenylalanine levels and they may be conducted prospectively. In addition to these, adding a fourth group consisting of treated PKU patients can give further information.

Despite these limitations, implications of this study are important because it had a pure untreated HPA sample, multiple comparisons were performed between healthy controls and two groups of children with different lifetime Phe levels, and statistically significant results were obtained.

The results demonstrated that children with untreated Phe levels above 240 μmol/L are at higher risk for cognitive deficits and attention-related problems. The significance of these findings can potentially influence decision-making processes for determining optimal Phe levels that necessitate treatment and for conducting treatment plans. Specifically, the evidence of cognitive impairment associated with Phe levels between 240-360 μmol/L may require revision of current treatment guidelines, where treatment is recommended for Phe levels above 360 μmol/L. In order to maintain blood Phe levels as close to normal levels as possible, we propose that it would be better to lower the "safe" upper limit.

Sources of Financial Assistance

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