Executive dysfunction in treated phenylketonuric patients

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Abstract *Objectives* Executive function deficits have been described in early and continuously treated patients with phenylketonuria (PKU). The aim of this study was to examine performance on executive function tasks of treated patients with PKU diagnosed by 2 years of age. *Patients and methods* Ten patients with PKU and normal intelligence score who were diagnosed before the age of 2 years and subsequently treated continuously, were compared with 15 typically developing control children on a battery of neuropsychological tests, including the tower of London (TOL), continuous performance test (CPT), and Stroop test. *Results* PKU cases showed significantly poorer performance on the TOL task compared to the control group with the difference being significant in the first three levels of the test. With the CPT, PKU cases had significantly more omission errors than control subjects. On the Stroop test there was no statistically significant difference between the groups. No significant correlation was found between the concurrent serum phenylalanine (Phe) level and results of the executive tests in PKU patients. *Conclusion* This study identified executive dysfunction in early-treated PKU patients with normal IQ, particularly in the planning and attention domains. Further studies are required to compare the results with those from other neurodevelopmental disorders such as ADHD and autism, to establish whether the pattern of findings is specific to PKU.

Key words early-treated phenylketonuria – executive function – neuropsychology – serum phenylalanine

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Introduction

Phenylketonuria (PKU) is the most frequent inborn error of aminoacid metabolism, which was first described by the Norwegian physician Dr. Asbørn Følling in 1934 [9]. It is estimated to affect 1 in 10,000 to 12,000 live births in different populations [21]. Early diagnosis and treatment has made classical PKU phenotype a matter of historical rather than current interest [25]. However, a study performed in the institutions for the developmentally delayed in Tehran, Iran, revealed the prevalence of hyper-phenylalaninemia (HPA) to be 2.75% [26]; and the incidence of PKU in Iran is estimated to be one in 3,672 [14]. Despite the relatively high levels of PKU in Iran, which are the highest reported rates in the literature, screening programs have yet to be widely instituted in Iran. Consequently, diagnosis is delayed in the majority of affected individuals and the low-phenylalanine regimen is often not introduced in time to prevent development of the clinical disorder. There are therefore only a few patients in Iran with early and continuously treated PKU within the normal range of intelligence, as measured by IQ. Untreated PKU is the most common biochemical cause of mental retardation, with excessive amounts of aminoacid phenylalanine (Phe) in the brain leading to severe learning disabilities, neurological impairments and behavioral problems including hyperactivity, inattention, aggressiveness and autistic features [24].

From a different perspective, the range of deficits associated with PKU suggests that the disorder may represent an excellent model for the study of cognitive processes during early development. Even in infants and young children with early treated PKU, subtle yet specific cognitive deficits occur which are not typically detected using traditional IQ measures, giving rise to a Prefrontal Dysfunction Hypothesis [5]. Previous studies find evidence of deficits in working memory and other high-level reasoning skills even in the presence of normal IQ [5, 31]. The theoretical basis for the presence of a prefrontal dysfunction syndrome in PKU is that the metabolic disorder leads to a deficiency in monoaminergic neurotransmitters, causing dopamine depletion in the prefrontal cortex, which in turn results in impaired executive functions [6, 20]. Executive functions encompass the ability to maintain a problem-solving set that is appropriate for goal acquisition, including formulation, strategic planning, self-monitoring, mental flexibility, and the ability to change strategies in response to new information. In fact, EF can be viewed as an umbrella term for a set of cognitive functions critically supported by the pre-frontal cortex including regulation of attention, inhibition of inappropriate responses, coordination of information in working memory and cognitive flexibility [7, 16]. Impairments in EF have been found in patients with a wide range of neurodevelopmental disorders including autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) [11] and the fragile-X syndrome [12].

Assessment of the impact of elevated Phe concentrations on the prefrontal cortex in patients with early-treated PKU has produced diverse conclusions about the presence or specificity of executive function deficits [10, 29]. Mazzocco found no evidence of prefrontal dysfunction while studying PKU patients aged 6–13 years, suggesting that the cognitive deficits observed in younger children (preschool children) represent an early developmental delay rather than persistent developmental deficit [17]. In another study, Feldmann compared 42 adolescent patients with PKU to diabetic patients on a variety of measures of executive function (Wisconsin Card Sorting Test, Stroop Task and Test d-2) and did not find specific frontal deficits in the patient group [8].

In contrast to Mazzocco's findings, White and colleagues in a study on 20 PKU subjects aged 6–17 years demonstrated that PKU related deficits in working memory were prominent later in childhood. Thus, they suggest a *developmental deficit* rather than a *developmental delay* in working memory for children with PKU [34]. In another study, Ris and colleagues compared the neuropsychological performance of adults affected by PKU with that of their unaffected siblings and found that the PKU patients were relatively impaired on measures of attention, visual-constructional ability, and cognitive flexibility [22]. Leuzzi and colleagues [15] showed that young subjects with early-treated PKU performed worse in comparison to age and IQ matched controls on various tasks including tower of London (TOL), Visual Search Test, Rey-Osterreith Complex Figure Test, Weigl's Sorting Test, and Motor Learning Test indicating problems with planning and problem solving, set shifting, selective and sustained attention and sorting of categories.

In healthy individuals, the activity of the enzyme phenylalanine hydroxylase (PAH) ensures that Phe levels are kept in balance. For people with PKU, dietary treatment is expected to keep Phe levels within a safe range, usually between 180 and 480 μmol/l. While these levels are considerably lower than those seen in untreated PKU subjects (around 1,200 μmol/l), they are still three to eight times higher than that found in people who do not have PKU (around 60 μmol/l: [24, 28]. As Phe, tyrosine (Tyr), tryptophan and other large neutral aminoacids compete for limited quantities of the same transporter proteins to cross the blood–brain barrier, the elevated levels of Phe that arise from the metabolic dysfunction in PKU leads to inhibited transport and thereby a deficit of tyrosine,

tryptophan and other neutral aminoacids in the brain [18, 19]. When Phe levels are only moderately elevated, as found in patients with early and continuously treated PKU, the decrease in the amount of Tyr and other neutral aminoacids reaching the brain will be relatively small; however even small decreases in brain Tyr may affect dopamine metabolism in the PFC while leaving most areas of the brain unaffected or much less affected [4].

In a longitudinal study, Diamond and colleagues [5, 6] found that children with PKU who had been on dietary treatment since the first month of life and had blood Phe levels that were approximately 3–5 times the normal range, displayed impairments on tasks that required working memory and inhibitory control. They assessed dorsolateral prefrontal cortical function using tests of executive function and found that when both working memory and inhibitory control were required, children with Phe levels of 360–600 mol/l performed worse than subjects with Phe levels below 360 mmol/l, unaffected siblings and age and gender matched controls. This group showed no impairment on any of the battery of control tasks, most of which required the functions of the medial temporal or posterior parietal cortices. Furthermore, the concurrent Phe level correlated highly with performance on the tasks, not only within the PKU group but also within individual children with repeat measures over time. These findings support the hypothesis that performance is related to current blood Phe levels at the time of evaluation, as opposed to mean Phe levels over a wide age range or during the first month or year of life.

A recent meta-analysis by DeRoche and Welsh [7] that aimed to identify whether a consistent profile of deficits in PKU has emerged from data published over the last 25 years, found moderate effect sizes for working memory and planning; and larger effect sizes for measures of inhibition and cognitive flexibility. The meta-analysis therefore provides some evidence for specificity of the EF deficits in individuals with early-treated PKU, with particular weakneses in the abilities to inhibit and flexibly shift responses.

In this study, we were interested to evaluate the specific cognitive processes that contribute to clinically significant individual differences in a group of early- and continuously treated PKU patients from Iran. In particular we wished to test the predictions from the meta-analysis suggesting the presence of EF deficits.

Methods

Subjects

The sample included 10 children and young adults (8 girls and 2 boys) with early-treated PKU and a group of 15 age, sex, and IQ matched controls (12 girls and 3 boys). The PKU group were recruited from the database of the PKU Society in Asma Center, Tehran, Iran and ranged from 6 to 20 years of age (Mean = 13 years and 3 months). Inclusion criteria for the study were a diagnosis of PKU, treatment started before the age of 2 years, an initial Phenylalanine level greater than 1,000 μmol/l (16 mg/dl) and an IQ of at least 80 on the Raven test. The PKU group was compared with a group of unrelated, normally developing children and adolescents from a similar socio-economic background. Individuals in the control group ranged from 7 to 18 years of age (mean = 10 years and 9 months). Ethical approval was obtained from Deputy of Research, Tehran University of Medical Sciences and informed consent was obtained from all participants.

Measures

The child and adult versions of the Raven progressive matrices were used to estimate IQ in the 6–9 year old and >9 year old subjects respectively. Since autism and ADHD are also associated with EF deficits and both behavioural syndromes are relatively common in PKU [1, 2], the childhood autism rating scale (CARS) and Conner's Parent Rating Scale were used to exclude the two disorders in addition to clinical observation by an experienced child psychiatrist. The following set of neuropsychological measures were used to assess the cognitive profile of patients in the field of executive functions:

Tower of London (TOL)

In this task participants have to plan and implement an organized sequence of moves to transform an initial configuration of disks into a goal state. This test evaluates the ability to inhibit irrelevant responses, as well as the ability to generate sub-goals in working memory. In this study the computerized version was used. The average number of moves to complete each set, planning time (time between presenting the discs and making the first move) and subsequent thinking time (time spent on executing the plan) were measured [27].

Continuous performance test (CPT)

CPT is used to measure processes related to vigilance, response inhibition, signal detection, and sustained attention. Various CPT tasks all have in common a series of letter or number/figure presentations in which the participant is required to make a discrimination between target and non-target stimuli and to

respond accordingly. The computer-based version used in this study involves the rapid presentation of stimuli (a number and a figure, e.g. '3♠', on each page) for up to 5 min. Total number of stimuli was 120, including 15 targets. Subjects were instructed to respond *only* to the 'target' stimulus by pressing space bar key on the computer if both the number and the figure were repeated on the presentation, and to refrain from responding to 'non-target' stimuli (the repeat of either of the number or the figure). CPT performance measures include correct responses, omission errors (when the participant fails to respond to the target stimulus), commission errors (when the participant responds to a non-target stimulus) and reaction time (RT). The number of successfully recognized matches by the subject was recorded at the end of each experiment.

Stroop test

We used the classic single-task Stroop test and not the intermixed ink-color/word-reading trials, which more exactly assesses the set-shifting paradigm. The colour-word-interference-task (CWIT) according to Stroop, is a classical experimental paradigm used in behavioral neuroscience to assess attention, set-shifting, inhibitory control and cognitive flexibility. It consists of three parts: reading the colour of dots (Dots Card); colour naming (Words Card); and the interference task (Colours Card). Subjects note the strong interference of word reading with the third card which is called the Stroop interference effect. The number of errors and the time required for reading each card were recorded for each subject. The difference between the time of reading the third and the first card was used as a variable, called 'Difference Index' [30].

Procedure

All participants were examined in the neuropsychology laboratory of the Institute for Cognitive Science Studies in Tehran. In each session, after completing a demographic questionnaire for the participant, the Raven Intelligence Scale was performed. A battery of TOL, CPT, and Stroop was then applied. In patients with PKU, the concurrent blood Phe and Tyr levels were also determined by obtaining a 2 ml venous blood sample on the day of neuropsychological testing.

Statistical analyses

Data were analyzed using SPSS 11.5. The independent sample *t* test was applied to determine statistically significant group differences on demographic variables and IQ. Cognitive task variables were compared between the two groups using the non-parametric Mann–Whitney *U* test because of the small sample size. Spearman's rank correlation coefficient was applied to the neuropsychological variables as well as to the IQ and biochemical measures.

Results

Characteristics of participants in terms of age and IQ are listed in Tables 1 and 2. Mean age at diagnosis in the PKU group was 6.8 months (range 0.5–24 months; SD = 7.78). Mean age at initiation of treatment (i.e. low-Phe dietary control) was 7.20 months (range 0.5–24 months; SD = 7.75). Nine out of ten parents in the PKU group had consanguineous marriage; five were first cousins and four were 2nd or 3rd cousins. Family history of PKU was positive in seven of the ten families. Results of the CARS and Conner's questionnaires did not fall above threshold for either autism or ADHD in any of the participants and was consistent with clinical observation. There were no statistically significant group differences for any of the demographic variables (Table 1). The mean IQ score was however lower in the PKU group compared to the control group with a trend towards significance ($P = 0.06$).

Group differences in cognitive measures

TOL

Results of TOL task are shown in Table 3. No significant difference was found between the two groups in

Table 1 Descriptive characteristics of the participants

Variables	Group						*P*-value
	PKU ($n = 10$)			Control ($n = 15$)			
	Mean	Range	SD	Mean	Range	SD	
Age (months)	159.30	79–238	49.61	129.33	94–205	28.68	0.06
Full scale IQ	108.40	90–128	12.44	115.33	106–126	4.95	0.06

Table 2 Detailed characteristics of the patients

	Age (month)	Gender	IQ	Current Phe (μmol/l)	Age at Diagnosis (month)	Onset of low-Phe regimen (month)
Case 1	92	M	91	704	0.5	1
Case 2	79	F	128	1,418	9	9
Case 3	205	F	112	1,402	1.5	1.5
Case 4	145	M	120	1,207	1.5	1.5
Case 5	204	F	115	2,025	0.5	0.5
Case 6	138	F	109	1,600	24	24
Case 7	174	F	110	704	5	7
Case 8	156	F	113	1,487	1.5	1.5
Case 9	238	F	90	1,400	15	15
Case 10	162	F	96	1,691	10	11

Table 3 TOL task performance

	PKU group		Control group		*P*-value
	Mean	SD	Mean	SD	
Average number of moves to complete					
2-move problems	2.3	0.51	2.3	0.83	0.76
3-move problems	4.12	1.12	3.96	1.27	0.68
4-move problems	8.85	3.38	6.88	2.10	0.09
5-move problems	10.47	4.24	9.11	3.55	0.42
Planning times (s)					
2-move problems	7.14	3.43	3.80	1.13	0.004
3-move problems	10.84	8.19	6.04	1.92	0.01
4-move problems	9.45	8.78	4.90	1.04	0.03
5-move problems	8.38	4.29	6.09	2.12	0.16
Subsequent thinking times (s)					
2-move problems	17.16	8.03	11.16	11.25	0.005
3-move problems	32.11	19.66	20.06	11.21	0.10
4-move problems	60.69	27.46	30.88	12.36	0.01
5-move problems	71.68	31.18	45.70	26.23	0.09

terms of the number of moves. With regard to planning and executing time, there were significant differences between the two groups at the movement levels of 2, 3, and 4 ($P < 0.05$).

CPT

The number of commission errors was *not* significantly higher in PKU patients; however subjects with PKU showed significant impairment in terms of the number of omission errors ($P = 0.005$). With regard to mean reaction time, there was no significant difference between the two groups. Finally, the number of successfully recognized matches was greater in the control group ($P = 0.005$) (Table 4).

Stroop task

In the single-task Stroop test there was no significant difference between the two groups regarding the time taken to read the Dots Card and Words Card. Mean time spent to name the Colours Card was higher in

Table 4 CPT task performance

	PKU group		Control group		*P*-value
	Mean	SD	Mean	SD	
Commission errors (number)	5.50	3.59	3.93	2.31	0.33
Omission errors (number)	4.80	2.97	1.73	1.83	0.005
Mean reaction time (s)	0.79	0.22	0.73	0.10	0.72
Successfully recognized matches (number)	67.7	19.90	88.2	12.26	0.005

Table 5 Stroop Test Performance (Single-task)

	PKU group		Control group		*P*-value
	Mean	SD	Mean	SD	
Time in dots card (s)	19.32	7.79	15.68	4.81	0.28
Errors in dots card (number)	0.11	0.33	0.13	0.35	0.95
Time in word card (s)	31.33	18.45	23.82	7.21	0.48
Errors in word card (number)	0.11	0.33	0.07	0.25	0.86
Time in color card (s)	41.77	15.73	30.09	10.89	0.07
Errors in color card (number)	0.33	0.70	0.27	0.59	0.90
Difference index	22.78	11.87	14.41	8.46	0.31

PKU subjects but this was not significant ($P = 0.07$). The number of errors in the interference task was not noticeably higher in the PKU group. Finally the difference Index was greater in the PKU group that was not significant ($P = 0.31$) (Table 5).

Relationship between biochemical indices, IQ, and cognitive functions

To control for the potential effect of IQ on executive functioning, the analyses were controlled for IQ. No significant correlation was found between IQ and EF scores in any of these analyses. In addition, there was no significant correlation between IQ and concurrent serum Phe level ($r = 0.20$). To examine the association between performance on the cognitive tasks and the metabolic measures in the PKU group, we calculated Spearman correlations between the variables and concurrent Phe levels as well as Phe to Tyr ratio (Phe/Tyr). We found that none of the pairwise comparisons showed significant correlations (Table 6).

Table 6 Association between executive function variables and biochemical indices

	Phe level	Phe/Tyr ratio
TOL		
Average number of moves to complete		
2-move problems	0.17	−0.2
3-move problems	−0.14	−0.32
4-move problems	0.06	0.36
5-move problems	0.23	0.00
Planning times (s)		
2-move problems	−0.09	−0.2
3-move problems	0.08	−0.42
4-move problems	0.17	−0.41
5-move problems	−0.01	−0.43
Subsequent thinking times (s)		
2-move problems	0.07	−0.35
3-move problems	0.03	−0.43
4-move problems	0.3	0.09
5-move problems	0.4	−0.09
CPT		
Commission errors (number)	0.27	0.08
Omission errors (number)	0.15	−0.49
Mean reaction time (s)	−0.03	0.07
Successfully recognized matches (number)	−0.15	0.49
Stroop task		
Time in dots card (s)	0.02	−0.51
Errors in dots card (number)	0.27	−0.41
Time in word card (s)	0.03	−0.33
Errors in word card (number)	−0.27	0.13
Time in color card (s)	0.2	0.02
Errors in color card (number)	0.43	0.27
Difference index	0.41	0.41

Discussion

Executive dysfunction is the most commonly reported deficit in children with early-treated PKU [5, 28], although some conflicting findings exist [8, 17]. We examined whether a group of early-treated children and adolescents with PKU who remained on dietary treatment showed any evidence of deficits on selected tests of executive functions. PKU participants in this study had lower IQ compared to controls, albeit within the normal range; a finding that is in accordance with previous reports [5, 32]. For example, results from the longitudinal PKU Collaborative Study indicated that early dietary treatment is related to intellectual levels in the normal range, however, children with PKU often do not achieve IQ levels predicted from the scores of unaffected parents and siblings [33].

In this study, using the TOL task we demonstrated various levels of impairment in the PKU group. In particular, planning time and subsequent thinking time were one to four times higher than that seen in the comparison control group. Prolonged planning time at the first three levels of the TOL task indicate that the PKU patients spent more time figuring out or deciding which movements to make, which led to poorer overall results, lower number of moves and subsequently reduced thinking times. Prolonged subsequent thinking time might be related to an impairment in proper planning and number of movements; therefore subjects require online plan-

ning for problem solving. Improper planning and movement prediction therefore calls for additional moves to solve the problem. Our findings reproduced part of the study by Welsh and colleagues that showed impairment of executive functions in 11 pre-school early-treated PKU children compared to age- and IQ-matched unaffected peers using EF measures such as Tower of Hanoi, Motor Planning and Visual Search. They did not find any group differences in non-executive function tasks such as recognition memory. It was shown that performance on executive function tests was inversely related to concurrent Phe level and more weakly it was related to mean lifetime Phe levels [31].

Our study showed that PKU subjects performed more poorly than controls on CPT. Comission errors (the index of impulsivity) were not significantly different between two groups, however the number of successfully recognized matches was significantly lower and omission errors (the index of attention or working memory) was significantly greater in PKU patients compared to controls.

We did not find any significant differences between two groups on the single-task Stroop test which might be a result of not having a task-switching block; there may have been differences if an intermixed ink-color/word-reading trial in the same block was available. What seems really difficult in overcoming one's inertial tendency to continue in the same mindset, is switching between one mental set and another, proposed by some researchers to replace the classic single-task Stroop test [3].

There are many discrepancies in the findings regarding phenylalanine levels across previous studies, although the reasons for this remain unclear. This could be due to differences in the cognitive domains evaluated, task specific factors, the age of participants, phenylalanine level or the quality of strict dietary control [34]. In this study, we did not find any evidence of a relationship between cognitive performance and biochemical measures (i.e. Phe level and Phe/Tyr ratio) as all correlations were non-significant. This might be attributable to the fact that blood Phe levels are poor indicators of brain Phe levels [13]. Low statistical power of the sample studied may also have limited the capacity to detect significant correlations.

Luciana and colleagues assessed EF and non-EF functions in 18 PKU-affected adolescents with normal IQ, in comparison to unaffected peers and chronically ill controls. Although the overall performance of the PKU group did not differ from that of the other two groups, the proficiency of the PKU group in a number of tests of executive and non-executive functions was associated with the concentrations of Phe and Tyr and most strongly with Phe to Tyr ratios measured at several points in development. Luciana introduced the ratio (Phe/Tyr) as one of the best indicators of dopamine availability in PKU [16]. However, in the study by White and colleagues in the field of working memory, no significant correlation between concurrent Phe levels and cognitive performance was reported [34].

Most studies of executive function in early and continuously treated PKU have focused on a limited age group (infants, preschoolers, adolescents or adults). Unfortunately, as the PKU screening program has not been widely instituted in Iran, there are not many treated PKU patients with normal IQ and we had to accept a wide age range. Moreover, due to poor follow-up of PKU patients by their clinics, some clinically relevant data (such as the mean level of Phe throughout their dietary control) was lacking. This sample could therefore be heterogeneous in this regard (Table 2). The study subjects were not randomly selected, and the sample was quite heterogeneous in terms of Phe levels and patients' treatment history (i.e. the age at which their dietary treatment was implemented; duration of treatment; and quality of Phe control). Given the range of treatment histories and the small sample size it is difficult to control for these potentially confounding variables by applying a multivariate analysis. These considerations increase the chance that our sample lacked power because of small sample size and that some of the correlations, while not reaching statistically significant levels, could still reflect positive rather than negative findings.

Clinical and research implications

Overall, our findings based on a sample from Iran, a very different population from that used in previous studies, are consistent with previous reports regarding the magnitude and pattern of neuropsychologic impairments in patients with early treated PKU. These findings contribute to the emerging literature that indicates the need to continue Phe-free diets for longer periods. Our PKU subjects performed worse in comparison to age-, sex- and IQ-matched controls on various tasks reflecting executive function procesess such as planning, problem solving, and attention. These results do not however imply a selective impairment of executive functions since other non-executive functions were not investigated in our sample. Previous research suggests that the observed deficits in executive functions are not absolutely irreversible, even in adults who have been off the dietary treatment for some time [23].

One limitation of this study is that we did not evaluate the association between mental state changes and the Phe-free diet, which might be important in ruling out comorbid psychiatric disorders that could

also lead to EF impairments. The results of studies in this area also indicate that future studies could usefully investigate detailed aspects of both EF and non EF deficits in PKU. Future longitudinal investigation with a larger sample size is required for a better understanding of the etiology of these deficits, and their relationship to treatment history. Designing a study to examine whether executive dysfunction is developmentally stable over time in a more homogenous group of early and continuously treated PKU will help us to see if the pattern of dysfunction is a developmental delay or deficit. Moreover, large-scale studies are needed, in comparison to other neurodevelopmental disorders like ADHD and autism, before further elaborating on these findings as being specific to PKU. Results of such studies can hence help to determine cut-off points for the dietary recommendations and for optimal Phe levels even at different age groups.

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