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Executive function impairment in early-treated PKU subjects with normal mental development

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Summary: Executive functions were studied in 14 early and continuously treated PKU subjects (age 10.8 years, range 8–13) in comparison with controls matched for IQ, sex, age and socioeconomic status. Brain MRI examination was normal in all PKU patients. Neuropsychological evaluation included Wisconsin Card Sorting Test, Rey–Osterreith Complex Figure Test, Elithorn's Perceptual Maze Test, Weigl's Sorting Test, Tower of London, Visual Search and Motor Motor Learning Test. Whatever the IQ, PKU subjects performed worse than controls in tests exploring executive functions. Subgrouping the PKU subjects according to the quality of dietary control for the entire follow-up period (using 400 μmol/L as cut-off value for blood phenylalanine (Phe) concentration) showed that patients with worse dietary control performed more poorly than both the PKU group with the best dietary control and the control group. However, a mild impairment of executive functions was still found in PKU patients with a good dietary control (Phe < 400 μmol/L) compared to controls. Concerning the PKU group as a whole, no linear correlation was found between neuropsychological performance and historical and concurrent biochemical parameters. We conclude that (a) PKU patients, even when treated early, rigorously and continuously, show an impairment of frontal lobe functions; (b) a protracted exposure to moderately high levels of Phe can affect frontal lobe functions independently of the possible effect of the same exposure on IQ; (c) in order to reduce the risk of frontal lobe dysfunction, the target of dietary therapy should be to maintain blood Phe concentration below 400 μmol/L.

Dietary therapy has dramatically modified the prognosis of PKU patients (Smith and Wolff, 1974; Smith et al 1990). Since the introduction of the treatment, the

determinants of quantity and quality of mental development in PKU subjects have been the topic of a number of studies. Initially, investigators found a small but significant deficit in the IQ of PKU children, even if early treated, compared to unaffected siblings (Dobson et al 1976; Koch et al 1984) or other family members (Hudson et al 1970; O'Flynn and Hsia 1968). Subsequent studies suggested that the intellectual deficit was related to the quality of dietary control. With good dietary control during the first years of life, PKU children seemed to have comparable IQs to their siblings (Berry et al 1979; Burgard et al 1996; Dobson et al 1976; Koch et al 1984). However, despite generally normal intellectual performance, PKU subjects are less competent in academic skills, performing worse than controls of the same age in arithmetic and language achievement (Fishler et al 1987), visual perception and visual-motor skills (Fishler et al 1987, 1989). Many have entertained the notion that dietary treatment might not completely prevent the deleterious effect of PKU (Diamond et al 1997; Fisch et al 1995, Waisbren et al 1994). Recent studies have also reported problems in attention span, concentration and problem solving (Brunner et al 1983; Faust et al 1986; Welsh et al 1990). Diamond and colleagues (1997) proposed a prefrontal dopamine depletion mechanism to explain some of these difficulties.

Our aim was to study executive functions in early and continuously treated PKU patients in comparison with normal controls matched for sex, age, IQ and socioeconomic status.

METHODS

Patients and controls: In total, 28 subjects were tested: 14 PKU (mean age 10.8 years, range 8–13) and 14 controls (mean age 10.9 years, range 8–13). The PKU sample consisted of 12 girls and 2 boys, who had been diagnosed as having classical PKU at birth and were still on diet when the study was performed. The diagnosis was confirmed by genetic analysis in each subject (data not shown). They had started the diet at the mean age of 33.1 days (range 15–61). The mean of the indices of dietary control (median value of IDC of blood Phe) for the entire follow-up period was 491 μmol/L (SD 149.2; range 241–784). For the present work, the following biochemical parameters were computed: IDC of blood Phe and Tyr concentrations for the entire follow-up period; the IDC of Phe and Tyr concentrations from the beginning of the diet to the age of 4 years; the IDC of Phe and Tyr concentrations during the 6-month period before neuropsychological assessment; and blood Phe and Tyr concentrations at the day of the examination. All PKU subjects had a normal brain MRI examination performed during the 12-month period before the test. Mental development and learning achievements of PKU subjects were normal during the entire follow-up. At the time of the study, school performance was considered compatible for each subject with the average level or their own class.

Each subject with PKU was matched with a normal control based on age, sex, socioeconomic status and full-scale IQ as determined by the Wechsler Intelligence Scale for Children Revised (WISC-R). All were of normal intelligence (PKU IQ 102.14 ± 10.21, range 87–121; control IQ 108.8 ± 12.7, range 88–134). All control

subjects had had normal mental development and scholastic careers as far as could be ascertained by parents', teachers' and subjects' own reports.

A signed informed consent was obtained from parents of all the participants enrolled in the study.

Neuropsychological assessment: The following tests were administered in each subject to probe executive functions (1)

Wisconsin Card Sorting Test (WCST) (Milner 1963): This test assesses the ability to form abstract concepts and to shift cognitive set following changes in conceptual rules. The participant is given a pack of cards to be placed, one by one, under one of the four stimulus cards on the table according to colour, form or number of objects printed on the cards. The participant must deduce the sorting or classification criterion from the examiner's responses after each trial. Each time the participant places 10 consecutive cards correctly according to a given criterion, the examiner switches to another criterion. The number of correct and incorrect responses given without shifting to the new criterion indicates potential problems in concept formation, conceptual flexibility, and capacity to make use of cues.

Elithorn's Perceptual Maze Test (Elithorn et al 1955, quoted in Spinnler and Tognoni 1987): This is a test for spatial planning in which visual-spatial and sustained-attention skills can also be evaluated. The subject is asked to connect black dots arranged randomly on grids and to respect several rules (e.g. to draw a line following only the grids without retracing). There are eight subtests in the short version (used for this study). The score is given by the number of mazes completed correctly, the time employed to finish each item and the number of points identified (2 points for each item completed correctly in 1 minute; 1 point for each item carried out correctly in 2 minutes; 0 points for each wrong item).

Visual Search Test (Spinnler and Tognoni 1987): This tests the recognition of visual stimuli (digits) arranged randomly on a matrix made up of 13 rows and 10 digits for each row. There are three different subtests, each with a number of stimuli to be recognized. This test evaluates selective visual attention and control of impulsiveness towards recognizing the wrong stimulus. The score is given by the number of correct answers (range 0–60) and omissions (range 0–60).

Rey–Osterreith Complex Figure Test (Osterreith 1994): This calls into play sustained attention and concentration, planning and visual organization of complex data, as well as visual memory (Lezak 1983). The test is twofold. In the first part, the participant must copy a very complex geometric figure; in the second, the participant must recall the figure and reproduce it from memory, once immediately after copying it and again several minutes later. Late recall was not used in this study. The sums of the accuracy scores for the copying and immediate recall were computed for the present study.

Motor Motor Learning Test (Luria 1966, described in Spinnler and Tognoni 1987) : The subject is shown one of two gestures, a fist or a finger, in random sequence, 40 times. The subject is required to respond each time with the opposite

gesture to the one shown by the tester. The number of correct responses (range 0–40) determines the score. This test makes it possible to measure attention and, mainly, the capacity to inhibit the reproduction of a single gesture.

Weigl's Sorting Test (Goldstein et al. 1982, described in Spinnler and Tognoni 1987) : This is a test of classification of objects that differ in form, colour, symbol, size and thickness. The child is asked to recognize these characteristics by himself/herself (first item) or, in case of a wrong answer, with the help of the tester (second item). In the first attempt, the child must explain the criterion he or she is able to recognize and use spontaneously. If the child does not recognize one or more categories, he or she is asked to explain the criterion of classification used by the tester, thus indicating a category he or she can recognize but still does not use spontaneously. The total score is determined by the sum of the first score (3 points are given for each category identified spontaneously) and the second score (1 point is given for each category made by the tester that the child is able to recognize).

Tower of London (Shallice 1982): This requires subjects to reproduce an arrangement of discs on a board in the minimum number of moves possible. It is deemed a measure of planning (Borys et al 1982) and evaluates the management of goal conflict when alternative moves benefit one subgoal at the expense of another.

Statistical analysis: The score obtained on each executive function (EF) test was used either to compare the performance of PKU and controls (*t*-test) or to investigate the linkage between neuropsychological performance and biochemical parameters in the PKU group (correlation analysis). Moreover, to reduce the number of statistical comparisons for some statistical analyses, the results on EF of each subject were condensed into two scores. The first (EF1) resulted from the sum of the scores on Elithorn's Perceptual Maze Test, Visual Search Test, Rey–Osterreith Complex Figure Test, Motor Motor Learning Test, Weigl's Sorting Test and Tower of London. The second (EF2), reflecting the performances on WSCT, was computed as the algebraic sum of the differential score—on each WSCT subtest—with reference to the score corresponding to the 50th centile of normative data.

Differences between groups for EF scores and biochemical parameters were analysed using one-way analysis of variance (ANOVA) and of covariance (ANCOVA). In the latter case, IQ was considered as covariate. Association among variables has been evaluated using linear correlation and partial correlation coefficients.

RESULTS

The PKU subjects performed less well than controls on virtually all of the executive function tests, although the difference was statistically significant only for three—the Tower of London Test, Elithorn's Perceptual Maze Test and Rey–Osterreith Complex Figure Test with copy (Table 1). On WCST (Table 2) the subjects with PKU were significantly impaired as regards the total number of errors, the number of perseverative responses and errors, the percentage of conceptual level responses

Table 1 Executive function scores in PKU subjects vs controls

Test	*PKU*[a]	*Controls*[a]	*Significance* (p[b])
Tower of London	23.21 (5.22)	29.07 (2.92)	<0.01
Visual Search	54.21 (5.10)	56.38 (2.72)	NS
Elithorn's Maze Test	9.57 (3.33)	15.19 (2.37)	<0.001
Weigl's Sorting Test	10.14 (2.28)	11.07 (1.25)	NS
Motor Motor Learning	37.85 (1.95)	37.46 (1.45)	NS
Rey Figure Test with copy	28.53 (5.17)	34.23 (1.96)	<0.001
Rey Figure Test from memory	19.50 (6.93)	24.88 (6.85)	NS
EF1[c]	183.2 (20.42)	209.5 (9.67)	p < 0.001
Wisconsin Card Sorting Test			
Trials	108.14 (20.47)	93.69 (19.37)	NS
Correct	76.42 (10.63)	76.53 (14.87)	NS
Errors	31.71(19.29)	17.15 (6.64)	<0.05
Perseverative responses	20.92 (14.22)	9.30 (3.42)	<0.01
Perseverative errors	17.71 (11.68)	7.61 (3.17)	<0.01
Nonperseverative errors	14.00 (11.74)	9.46 (5.91)	NS
Percentage of conceptual level responses	64.35 (16.81)	76.30 (7.11)	<0.05
Categories	5.07 (1.32)	6.00 (0.00)	<0.05
Trials 1° category	16.71 (9.72)	11.38 (2.10)	NS
Failure to maintain set	1.50 (1.87)	0.61 (1.04)	NS
Learning to learn	−3.46 (20.12)	−2.99 (13.57)	NS
EF2[d]	52.8 (6.52)	57.9 (2.67)	<0.05

[a] Score and (SD)
[b] NS: $p > 0.05$
[c] EF1, cumulative EF1 score (see text for details)
[d] EF2, cumulative EF2 score (see text for details)

and the number of categories completed. The difference between the PKU subjects and controls was also confirmed when the cumulative scores EF1 and EF2 were considered (Tables 1 and 2, respectively). Since there was a 7-point difference between PKU patients and controls (in favour of the latter), in order to rule out a possible effect of IQ on executive function performance, IQ was correlated with EF1 and EF2 scores in the PKU subjects, in controls and in all subjects (PKU plus controls): no significant correlation was found between IQ and EF scores in any of these analyses. This result was confirmed by the ANCOVA, which showed significant differences between PKU subjects and controls for EF1 and EF2 scores when covarying for IQ ($p < 0.001$ and $p < 0.05$, respectively).

Subgrouping the PKU sample according to the quality of dietary control for the entire follow-up period (IDC $\leqslant$ 400 μmol/L vs IDC > 400 μmol/L) disclosed a more severe impairment, not affecting the IQ level, in the patients (9) with worse dietary control compared to both the PKU patients (5 subjects) with IDC < 400 μmol/L and the control group. The patients with IDC > 400 μmol/L performed worse than the subjects with IDC < 400 μmol/L in all tests, but significantly worse on the Visual Search Test ($p < 0.05$) and Rey–Osterreith Complex Figure Test with copy ($p < 0.05$). The PKU sample with IDC > 400 μmol/L performed worse than the control group

Table 2 Executive function in PKU with IDC > 400 µmol/L and IDC < 400 µmol/L (entire follow-up) vs controls

	IDC > 400 µmol/L			*IDC < 400* µmol/L		
Test	*PKU* (9)[a]	*Controls*[a]	(*p*)[b]	*PKU* (5)[a]	*Controls*[a]	(*p*)[b]
Tower of London	21.12 (5.52)	28.37 (1.84)	<0.01	26.00 (3.46)	30.20 (4.14)	NS
Visual Search	51.75 (5.47)	55.62 (2.82)	NS	57.50 (1.76)	57.60 (2.30)	NS
Elithorn's Maze test	9 (4.16)	14.5 (2.73)	<0.01	10.33 (1.86)	16.3 (1.15)	<0.001
Weigl's Sorting Test	9.87 (1.55)	10.87 (1.24)	NS	10.33 (3.14)	11.40 (1.34)	NS
Motor Motor Learning	37.25 (2.12)	37.87 (1.64)	NS	37.86 (1.96)	37.47(1.46)	NS
Rey Figure Test with copy	26.18 (5.42)	34.75 (1.83)	<0.001	31.66 (2.80)	33.40 (2.07)	NS
Rey Figure Test from memory	17.37 (6.56)	27.31 (6.49)	<0.01	22.33 (6.91)	21.00 (6.04)	NS
WCST Trials	112.12(19.25)	99.00 (22.70)	NS	102.83(22.62)	85.20 (8.78)	NS
WCST Correct	77.62 (11.80)	80.00 (18.33)	NS	74.83 (9.68)	71.00 (3.60)	NS
WCST Errors	34.50 (19.66)	19.00 (6.80)	<0.05	28.00 (13.02)	14.20 (5.44)	NS
WCST Perseverative responses	21.75 (14.38)	9.87 (4.22)	<0.05	19.83 (15.27)	8.40 (1.51)	NS
WCST Perseverative errors	18.12 (11.72)	8.00 (3.85)	<0.05	17.16 (12.71)	7.00 (1.87)	NS
WCST Nonperseverative errors	16.37 (12.85)	10.87 (6.26)	NS	10.83 (10.32)	7.20 (5.06)	NS
WCST Percentage of conceptual level responses	61.50 (17.31)	74.87 (6.28)	NS	68.16 (16.89)	78.60 (8.47)	NS
WCST Categories completed	4.75 (1.58)	6.00	<0.05	5.50 (0.83)	6.00 (0.00)	NS
WCST Trials 1° category	16.50 (8.26)	11.75 (2.54)	NS	17.00 (12.24)	10.80 (1.09)	NS
Failure to maintain set	1.62 (2.38)	0.62 (1.18)	NS	1.33 (1.03)	0.60 (0.89)	NS
Learning to learn	−8.60 (19.11)	−3.72 (14.57)	NS	3.38 (21.03)	− 1.82 (13.34)	NS

[a] Score and (SD)
[b] NS: $p > 0.05$

(Table 2) on the Tower of London Test, Elithorn's Perceptual Maze Test and Rey–Osterreith Complex Figure Test with copy and with memory. In comparison to controls, PKU subjects with IDC > 400 μmol/L performed worse on WCST with regard to the number of perseverative responses, the number of perseverative errors (which contribute to the totality of WCST errors) and the number of categories completed (Table 2). PKU patients with a good dietary control and controls performed comparably in all tests except on Elithorn's Perceptual Maze Test (Table 2).

Taking into consideration the PKU group as a whole, no correlations were found between neuropsychological performance, historical and concurrent biochemical parameters, and the age of diet onset. Moreover, IQ levels do not seem to mediate the influence of biochemical parameters on EF scores since no significant partial correlations were found between biochemical parameters and EF scores, taking into account IQ levels.

DISCUSSION

Our results show that young subjects with early-treated PKU performed worse in comparison to age- and IQ-matched controls on various tasks exploring executive functions such as planning and problem solving, set shifting, selective and sustained attention and sorting category. All of these functions depend on the representation of goals and rules in the form of patterns of activity in the prefrontal cortex. The prefrontal cortex consists of different regions (which probably emphasize different types of information) and configures processing in other parts of the brain (Miller and Cohen 2001). The influence of the prefrontal cortex on the sensory (Banich et al 2000) and the motor (Diamond 1988) systems may be responsible for response selection and inhibitory control. Furthermore, prefrontal signals to intermediate systems may support short-term (or working) memory (Goldman-Rakic 1987) and guide retrieval from long-term memory (Gershberg and Shimamura 1995). While mild impairment in planning and sustained attention is common to all PKU subjects, in our study selective attention, behavioural inhibition, working memory and rule-based or goal-directed behaviour seemed to be more evident in PKU patients with worse dietary control during the entire follow-up. Finally, a disorder of short-term memory was found only in PKU with higher Phe values. Thus, all the different regions of the prefrontal context seem to be involved in the PKU subjects with worse dietary control, whereas a more selective frontal disorder is found in subjects with a stricter dietary control. Several authors have studied neuropsychological executive functions in preschool and early-school treated children with PKU.

Welsh and colleagues (1990) found impairment of executive functions in 11 pre-school early-treated PKU children in comparison to age- and IQ-matched unaffected peers, while no group differences were found in a nonexecutive function task such as recognition memory. Moreover, the performance on executive function tests was inversely related to concurrent Phe level and more weakly to mean lifetime Phe level. These authors proposed a prefrontal dopamine depletion mechanism to explain the specificity of neuropsychological alterations. In older patients, Mazzocco

and colleagues (1994) failed to demonstrate executive function alterations in school-aged (between 6 and 13 years) early-treated PKU children, while Schmidt and colleagues (1994) found that early-treated adult PKU patients (range 17–24 years) had significantly slower reaction times on a sustained-attention tasks than unaffected control subjects. Reaction time improved when Phe levels were lowered in the PKU group, but the performance never attained the level of the control group.

Diamond (Diamond et al 1997) has pursued this line of enquiry by studying cognitive-executive functions, involving the dorsolateral prefrontal cortex, in 148 early and rigorously treated PKU subjects aged 6 months to 7 years, grouped according to three age groups, each examined longitudinally with an appropriate battery of cognitive neuropsychological measures. They found that when both working memory and inhibitor control were required, children with Phe levels of 360–600 μmol/L performed worse than subjects with Phe levels below 360 μmol/L, unaffected siblings, and age- and sex-matched controls. Furthermore, the concurrent Phe levels were strongly and consistently related to performance on the tasks not only inside the PKU group but also in the same child over time. Finally, there was little evidence of any narrowing of the gap between higher-Phe PKU children and their same-age peers, at least from 6 months to 6 years of age.

In a previous paper, Diamond and Herzberg (1996) had shown that PKU children had impaired contrast sensitivity, a dopamine-mediated retinal function (Bodis-Wollner et al 1987; Domenici et al 1985), despite early and continuous dietary therapy and Phe concentrations in the optimal therapeutic range.

More recently, Luciana and colleagues (2001) assessed executive and nonexecutive functions in 18 PKU-affected adolescents with normal IQ, whose functioning was compared with 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 subtests belonging to executive and nonexecutive functions was associated with the concentrations of Phe and Tyr and Phe/Tyr ratios measured at several points in development. Finally, Feldmann and colleagues (2002) did not confirm frontal lobe dysfunctions (as assessed by WCST, Stroop Task and Test d-2) in 42 adolescent PKU patients in comparison to diabetic subjects matched for sex, age and socioeconomic status. They found PKU subjects to have poorer results than diabetic patients because of a reduced performance speed rather than as a result of deficits in specific frontal lobe functions. Contrary to some neuropsychological results reported above, we did not find any correlation between neuropsychological performances and historical or concurrent values of plasma Phe concentration, even though PKU subjects with IDC less than 400 μmol/L for the whole follow-up period performed better than PKU subjects with higher Phe levels. Our data suggest that the relationship between Phe concentration and the neuropsychological functions we have assessed might be nonlinear—at least for the ages we studied and/or in the range of Phe concentrations exhibited by our patients. This recalls what we have already found assessing VEP alterations in PKU patients (Leuzzi et al 1998).

Our work confirms frontal lobe dysfunctions in a small group of early-treated PKU patients with normal IQ. However, the dysfunctions we found cannot be regarded as a

selective result of the disease, since other nonexecutive functions have not been probed in our sample. For the same reason, our data only partially contribute to the debate on the hypothesis of dopaminergic involvement in PKU patients (Welsh et al 1990).

In our study, IQ (as assessed by WISC-R) was not correlated with the degree of executive function derangement, supporting two complementary assumptions: the disorder of executive functions is not necessarily expressed by IQ (Riva et al 2002) and the traditional intelligence tests do not appropriately explore executive functions (Ardila et al 2000). Accordingly, the clinical follow-up of early-treated PKU subjects, starting from late childhood, should include a large spectrum of neuropsychological tests, specifically analysing different cerebral functions as early as they may be tested. Although disorders of executive functions have been reported in developmental learning disorders (Brosnan et al 2002; Swanson et al 1993), none of our patients showed any failure throughout their entire school careers. We speculate that the alterations we found can be compatible with normal performance during this age period, taking into account that, in the intricate interplay of brain functions facing complex requests from the environment, some degree of compensation can occur.

A number of questions are still open about the origins and the final prognosis of neuropsychological alterations in PKU. First, whether they are the result of a transient maturational lag or of a permanent derangement of some nervous circuitry; second, whether they are the inevitable consequence of the incomplete correction of Phe metabolism, however strict the diet might be; and finally, how these disorders affect the adaptive behaviour of the patients and, in a more subtle manner, how they can bias their professional career choices in adult life.

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SOCIETY FOR THE STUDY OF INBORN ERRORS OF METABOLISM

The SSIEM was founded in 1963 by a small group in the North of England but now has more than 70% of its members outside the UK. The aim of the Society is to promote the exchange of ideas between professional workers in different disciplines who are interested in inherited metabolic disorders. This aim is pursued in scientific meetings and publications.

The Society holds an annual symposium concentrating on different topics each year with facilities for poster presentations. There is always a clinical aspect as well as a laboratory component. The meeting is organized so that there is ample time for informal discussion; this feature has allowed the formation of a network of contacts throughout the world. The international and multidisciplinary approach is also reflected in the *Journal of Inherited Metabolic Disease*.

If you are interested in joining the SSIEM then contact the Treasurer: Dr. Graham Shortland, Department of Child Health, University Hospital of Wales, Heath Park, Cardiff, South Glamorgan, UK. The subscription includes the 8 issues of the *Journal of Inherited Metabolic Disease* as well as the regular circulation of a newsletter.

The SSIEM web site is on http://www.ssiem.org.uk