A lifetime with Phenylketonuria

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Chapter 2

Mental health and social functioning in early treated Phenylketonuria: The PKU-COBESO study

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ABSTRACT

This article presents a new Dutch multicentre study ("PKU-COBESO") into cognitive and behavioural sequelae of early and continuously treated Phenylketonuria (PKU) patients. Part of the study sample will consist of young adult PKU patients who have participated in a large neuropsychological study approximately 10 years ago, when they were 7-to-15-year-olds (Huijbregts, de Sonneville, van Spronsen, Licht, & Sergeant, 2002). Their neurocognitive development will be mapped in association with their earlier and continued metabolic history, taking into account possible changes in, for instance, medication.

A second part of the sample will consist of PKU patients between the ages of 7 and approximately 40 years (i.e., born in or after 1974, when neonatal screening was introduced in The Netherlands), who have not participated in the earlier neuropsychological study. Again, their cognitive functioning will be related to their metabolic history. With respect to aspects of cognition, there will be an emphasis on executive functioning. The concept of executive functioning will however be extended with further emphasis on the impact of cognitive deficits on the daily lives of PKU patients, aspects of social cognition, social functioning, and behaviour/ mental health (i.e. COgnition, BEhaviour, SOcial functioning: COBESO).

In addition to a description of the PKU-COBESO study, some preliminary results with respect to mental health and social functioning will be presented in this article. Thirty adult PKU patients (mean age 27.8, SD 6.4) and 23 PKU patients under the age of 18 years (mean age 11.0, SD 3.3) were compared to 14 (mean age 26.9 years, SD 5.9) and 7 matched controls (mean age 10.5, SD 2.6) respectively, with respect to their scores on the Adult Self-Report or Child Behavior Checklist (measuring mental health problems) and the Social Skills Checklist or Social Skills Rating System (measuring social skills).

Whereas there were very few significant group differences (except for mental health problems in the internalizing spectrum for adult PKU patients), possibly due to the small control groups, several significant associations between mental health problems and phenylalanine (Phe) levels were observed for the PKU patients. Childhood Phe levels and internalizing problems for adult PKU patients were related; concurrent Phe was associated with both internalizing and externalizing behavioural problems for those under the age of 18. These preliminary results underline the importance of early dietary adherence.

1. INTRODUCTION

Phenylketonuria (PKU; OMIM 212600) is an inherited metabolic disorder. Due to a deficient phenylalanine hydroxylase enzyme (PAH), phenylalanine (Phe) cannot be converted into tyrosine (Tyr) (Blau, van Spronsen, & Levy, 2010). The result is an accumulation of Phe and a shortage of amino acids such as Tyr and tryptophan, with as potential consequences low concentrations of neurotransmitters such as dopamine and serotonin. Dopamine is an important neurotransmitter for the prefrontal cortex mediated executive functions (Kolb & Whishaw, 2003). Executive functions are the regulatory cognitive abilities underlying behavior, e.g. inhibitory control, flexibility, and planning (Pennington & Ozonoff, 1996). Loss of dopamine is related to executive dysfunction (Christ, Huijbregts, de Sonneville, & White, 2010). A decrease of serotonin activity has also been associated with cognitive problems (especially those mediated by the orbitofrontal cortex) and with mood disorders as well (Kolb & Whishaw, 2003).

Untreated PKU leads to severe mental retardation and neurological disabilities. Keeping Phe below the advised upper target limit of 240 or 360 μmol/l (in most countries) may prevent neurotransmitter shortages and, as such, prevent cognitive and mental health problems in PKU patients (Blau et al., 2010). However, early and continuously treated PKU patients, especially those with high Phe levels, still have problems with executive functioning (Christ et al., 2010; DeRoche & Welsh, 2008; Huijbregts et al., 2002) and appear to have internalizing behavioral problems as well (Anjema et al., 2011; Arnold et al., 1998; DeRoche & Welsh, 2008; Huijbregts et al., 2002; Smith & Knowles, 2000).

Many studies investigated cognitive functioning either in children or adults with PKU (for an overview see Christ et al., 2010), whereas mental health has mainly been assessed in adult PKU patients (Anjema et al., 2011; Smith & Knowles, 2000). Because of a lack of longitudinal studies, it has been difficult to map the development of cognitive and/or mental health problems in association with development of metabolic control (e.g. Phe levels). Most studies focusing on older PKU patients have studied IQ and/or basic executive abilities (e.g. inhibition and cognitive flexibility). Although results have not always been consistent, adults with PKU who have been treated early and at least into early adolescence appear to display some executive function impairments as well (Channon, Mockler, & Lee, 2005; ten Hoedt et al., 2011; White, Nortz, Mandernach, Huntington, & Steiner, 2001). Whereas these results may be very informative, there is a lack of studies investigating more complex executive functions or multiple executive (and non-executive) functions simultaneously. Also, there are no PKU studies focusing on social cognitive abilities. It appears important to focus on more complex executive and social cognitive abilities in adolescent and

adult PKU patients, who often have relaxed diets or have stopped the diet altogether, considering the fact that social demands become more complex when people get older, and the fact that especially for these more complex functions prolonged developmental trajectories have been demonstrated that extend into (early) adulthood (Peters et al., 2013). Thus, there is a need for longitudinal studies as well as a broadening of the scope regarding cognitive abilities in PKU research.

With respect to behavioural problems and social skills in adolescent and adult PKU, even fewer studies have been published compared to those addressing cognitive abilities. There are some findings indicating that PKU patients exhibit internalizing behavioural problems such as depression, anxiety, phobic reactions, poor self-image, and mood swings (Anjema et al., 2011; Arnold et al., 1998; Smith & Knowles, 2000; Weglage et al., 2000). However, results are inconsistent and externalizing problems have not been investigated much, possibly because early results appeared to indicate that PKU patients are less aggressive and disruptive than healthy populations (Smith & Knowles, 2000). Social functioning in PKU has never been examined earlier. As social functioning and mental health are strongly related to executive and social cognitive abilities (Catroppa & Anderson, 2008), it seems reasonable to expect that deficits in these domains influence mental health and social functioning in PKU patients. The translation of cognitive deficits to daily life functioning (as expressed in social functioning, behaviour, or quality of life) is therefore another important outstanding issue in PKU research.

The main objective of this article is to provide information on a new Dutch multicentre study, the PKU-COBESO study, which aims to address all of the outstanding issues described above, i.e. examining more complex executive or COgnitive functions, BEhavioural problems, and SOcial functioning (COBESO) in early and continuously treated PKU patients in relation to their metabolic control. Some preliminary results concerning behavioural problems and social functioning in early and continuously treated PKU patients will also be presented.

2. THE PKU-COBESO STUDY

2.1. Participants

The PKU-COBESO study is a new Dutch multicentre study addressing cognitive, behavioural and social sequelae of early and continuously treated Phenylketonuria patients in relation to (history of) metabolic control. The study sample consists of young adult PKU patients who have participated in a large neuropsychological study 10-15 years ago, when they were 7-to-15-year-olds (De Sonneville et al., 2010; Huijbregts et al., 2002; Huijbregts et al., 2003) and “new” patients, who have not

participated in this earlier neuropsychological study, aged 7 to (approximately) 40 years, i.e. they should have been born in or after 1974, when neonatal screening was introduced in The Netherlands.

PKU patients from six out of seven university medical centres in The Netherlands participate in this study. The aim is to include 120 PKU patients and 120 age- and gender-matched controls. Patients should have been treated early through neonatal screening and continuously at clinical centres. All patients are on treatment: either on diet, on BH_4, or both. Controls are recruited, in part, from the patients' families and friends in order to have maximum proxy control of familial and environmental factors that might also influence cognition and behaviour. Non-family control participants will also be included, since part of the shared genetic make-up between PKU patients and their family members might involve the PAH gene. Family members could also have suboptimal PAH gene functioning resulting in somewhat heightened Phe levels (but not heightened to such an extent that an HPA diagnosis would be made), and in turn, this might lead to suboptimal cognitive and social functioning. Exclusion criteria are presence or history of mood disorders or other forms of psychopathology, and medical conditions associated with cognitive and/or motor problems.

2.2. Instruments

The PKU-COBESO study involves a neuropsychological assessment, questionnaires (see Table 1 for an overview of all instruments), and an examination of PKU patients' metabolic control. The neuropsychological assessment starts with the subtests Block Design and Vocabulary of the Wechsler Intelligence Scale for Children Third Edition (Wechsler, 1991) or Wechsler Adult Intelligence Scale Third Edition (Wechsler, 1997), depending on age of the participant, to calculate an IQ estimate.

The Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 1999) and a number of paper-and-pencil tasks are then utilized to measure 1) executive functions, 2) social cognitive skills, and 3) motor control (see Table 1). The ANT (De Sonneville, 1999), a computerized test battery, is used to assess executive functions, such as inhibitory control, cognitive flexibility, and working memory, and to assess a number of different social cognitive skills, i.e. face recognition and identification of facial emotions. Also, general reaction time and motor control are evaluated with this instrument. Regarding social cognitive skills, there are different age-dependent tasks. For children the Dutch Social Cognitive Skills Test is used (Van Manen, Prins, & Emmelkamp, 2007). Adolescents and adults complete a Faux-Pas test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999) and the Reading the Mind in the Eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The neuropsychological assessment can generally be completed in 2.5-3 hours including breaks.

In addition to neuropsychological tasks, several questionnaires must be filled out by patients and/or their parents. These questionnaires are used to collect 1) general demographic information, 2) executive functioning in daily life settings (Gioia, Isquith, Guy, & Kenworthy, 2000; Roth, Isquith, & Gioia, 2005), 3) social functioning (Baron-Cohen & Wheelwright, 2004; Gresham & Elliot, 1990; Kort, Schittekatte, & Compaan, 2008; Novotni, 2000; Zimet, Dahlem, Zimet, & Farley, 1988), 4) behavioural/mental health problems (Achenbach & Rescorla, 2003; Carver & White, 1994; Luman, van Meel, Oosterlaan, & Geurts, 2012), and 5) quality of life (Verrips, Vogels, den Ouden, Paneth, & Verloove-Vanhorick, 2000) (for details see Table 1). The questionnaires are age-dependent, e.g. the Child Behavior Checklist (CBCL) is given to participants younger than 18 years whereas the Adult Self-Report (ASR) is given to those from 18 years onwards (Achenbach & Rescorla, 2003). Furthermore, the instruments used are the standardized translated versions in Dutch.

Metabolic control of PKU patients is represented by historical blood Phe and Tyr levels, from birth until the day of testing, to calculate Phe trajectories, lifetime Phe and Tyr, Phe fluctuation, and Phe:Tyr ratios. On the day of testing prior to the neuropsychological assessment, blood samples are taken preprandially from the PKU patients to determine concurrent Phe and Tyr levels, other large neutral amino acids (LNAA), serotonin, and metanephrines, noradrenalin and adrenalin metabolites. It is expected that these biochemical measurements are associated with cognition and behaviour. A national approval for this study was given by the Medical Ethics committee of the University Medical Centre Groningen. The study is registered in the CCMO Register (NL38932.042.11). All participants and/or their parents signed an informed consent.

3. PRELIMINARY RESULTS

At present, data collection is being carried out for the PKU-COBESO study. Currently, the sample consists of 53 PKU patients and 21 control participants. For the majority of PKU patients, concurrent Phe and Tyr levels are available, and for a small subset (n = 9) of adult patients (i.e. those who had participated in the earlier neuropsychological study) childhood Phe levels (i.e. Phe levels up to the age of 12) are available. For the preliminary analyses presented here, we focused on possible mental health and social problems of PKU patients and possible associations with childhood and concurrent Phe levels. Patients and controls were divided into an adult group (30 PKU patients and 14 control participants), and a group under the age of 18 (23 PKU patients and 7 control participants) (see Table 2). Independent samples t-tests were used to compare PKU patients and controls with respect to mental

Table 1. Overview of instruments

Neuropsychological tasks	
WISC-III or WAIS-III, Block design and Vocabulary	IQ estimate
ANT: Baseline speed	Overall baseline speed
ANT: Feature identification	EF: Manipulation and monitoring of working memory
ANT: Flanker interference task	EF: Focused attention, inhibition of irrelevant distractors
ANT: Focused attention 4 letters	EF: Focused attention, inhibition of irrelevant distractors
ANT: Memory search 2 dimensions	EF: Divided attention, working memory
ANT: Shifting attentional set visual	EF: Inhibition of prepotent responding and cognitive flexibility
ANT: Sustained attention dots	EF: Sustained attention, inhibition of prepotent responding
ANT: Visuospatial sequencing	EF: Working memory for visuospatial patterns
ANT: Face recognition	Social cognition: recognition of faces
ANT: Identification of facial emotions	Social cognition: identifying emotions
P&P: Social cognitive skills test	Social cognition: social cognitive skills (Theory of Mind)
P&P: Faux Pas test	Social cognition: recognizing violations of social rules
P&P: Reading the mind in the Eyes test	Social cognition: identifying emotions from eyes only
ANT: Tracking	Motor control
ANT: Pursuit	Motor control
Questionnaires	
Demographics questionnaire	Background information: school, work, friends
Behavioral Rating Inventory of Executive Function (-A)	Executive functioning in daily life settings
Pragmatic language questionnaire	Pragmatic language, communication skills
Empathy quotient	Social cognitive skills
Social Skills Rating System or Novotni Social Skills Checklist	Social skills
Multidimensional Scale for Perceived Social Support	Social support
Child Behavior Checklist, Teacher Report Form, Youth Self-Report, or Adult-Self-Report	Behavioural problems
Sensitivity to Punishment and Sensitivity to Reward Questionnaire (-C)	Behavioural Inhibition System and Behavioural Approach System
Behavioral Inhibition System / Behavioral Approach System	Behavioural Inhibition System and Behavioural Approach System
Questionnaire for Children's or Adult Health-Related Quality of life	Quality of life

ANT = Amsterdam Neuropsychological Tasks [20]; P&P = Paper-and-pencil task; EF = executive function

Table 2. Descriptive statistics for PKU and controls under and above 18 years of age

	PKU <18 years	PKU ≥ 18 years	Controls <18 years	Controls ≥ 18 years
	(n = 23)	(n = 30)	(n = 7)	(n = 14)
Gender (male:female)	09:14	12:18	03:04	04:10
Mean age ± SD (range)	11.0 ± 3.3 (7.0-17.5)	27.8 ± 6.4 (18.8-40.0)	10.5 ± 2.6 (7.3-14.8)	26.9 ± 5.9 (19.0-36.0)
Mean Concurrent Phe ± SD (range)	454 ± 283 (158-1280)	693 ± 422 (106-1760)		
Mean Concurrent Tyr ± SD (range)	56 ± 23 (25-107)	52 ± 29 (15-168)		
Mean Childhood Phe ± SD		285 ± 86 (192-452)[1]		

[1] Childhood Phe was available for 9 out of 30 patients

health problems as measured by the ASR for the adults and the CBCL (Achenbach & Rescorla, 2003) for the children/adolescents, and social skills as measured by the Novotni Social Skills Checklist (SSC) (Novotni, 2000) for the adults and the Social Skills Rating System (SSRS) (Gresham & Elliot, 1990) for the children/adolescents. Associations between concurrent Phe, and, when applicable, childhood Phe levels, and the dimensions of the questionnaires were examined using Pearson correlations.

Preliminary results showed that, compared to controls (see Table 3), adult PKU patients tended to differ on the ASR dimension 'Internalizing problems' ($t(38) = -1.92$, $p = .062$). On the DSM dimensions of the ASR patients reported more 'Avoidant personality problems' ($t(37) = -2.47$, $p = .018$). On the SSC, adult PKU patients scored worse on the dimensions 'Relationships' ($t(38) = -2.04$, $p = .048$) and 'Self-care' ($t(38) = -2.33$, $p = .025$). PKU children and adolescents did not significantly differ from controls on behaviour and social skills.

Table 3. Results of independent t-tests and mean scores for adult participants

			Mean PKU	Mean Controls
	t	*p*	(n = 30)	(n = 14)
Adult Self-Report				
Internalizing problems	-1.92	.062	9.3 ± 7.6	5.9 ± 3.8
Avoidant personality problems	-2.47	.018	2.9 ± 2.5	1.4 ± 1.3
Social Skills Checklist - Self-Report				
Relationships	-2.04	.048	2.7 ± 3.0	1.3 ± 1.2
Selfcare	-2.33	.025	2.4 ± 2.9	0.9 ± 1.1

In the adult PKU patients concurrent Phe levels were not significantly related to behavioural problems and social skills. Childhood Phe levels just failed to be significantly related to 'Physical complaints' ($r = .646$, $p = .060$), but were significantly related to 'Thinking problems' ($r = .699$, $p = .036$) and 'Somatic problems' ($r = .708$, $p = .033$). This indicates that adult PKU patients with high blood Phe levels in childhood experienced more physical complaints, thinking problems, and somatic problems in adulthood. Regarding the PKU patients younger than 18 years, concurrent Phe levels were positively and significantly related to mental health problems with correlations ranging from $r = .515$ to $r = .814$ (see Table 4). This indicates that PKU patients under 18 years with high concurrent Phe levels exhibit more behavioural/mental health problems.

Table 4. Pearson Correlations CBCL - Concurrent Phe (n = 17)

Child Behaviour Checklist	*r*	*p*
Withdrawn/depressed	.808	.000
Anxious/depressed	.627	.009
Physical complaints	.711	.002
Social problems	.663	.005
Thinking problems	.814	.000
Attention problems	.515	.041
Aggressive problems	.673	.004
Delinquent behaviour	.790	.000
Internalizing problems	.753	.001
Externalizing problems	.730	.001
Total problems	.813	.000
Affective problems	.773	.000
Anxiety problems	.585	.017
Somatic problems	.676	.004
Attentional Deficit Hyperactivity problems	.627	.009
Oppositional problems	.627	.009
Conduct problems	.623	.010

4. DISCUSSION

The Dutch multicentre PKU-COBESO study has ambitious objectives. We would like to answer several questions that have remained unanswered for many years. One of the most important questions we would like to answer is whether a more lenient Phe restricted diet from adolescence onwards is harmful in light of cognitive and behavioural outcomes, and whether this will reduce the chances for PKU patients to thrive in their adult lives. The possibility remains that good dietary adherence during childhood and early adolescence will protect PKU patients sufficiently so that they can indeed live satisfactory adult lives. In order to be able to investigate this thoroughly, a longitudinal study design is required. For example, groups of patients with good dietary or metabolic control until adolescence must be compared to those with continued good metabolic control. Similarly, certain developmental patterns of Phe levels may turn out to be safe in the long term, rather than specific upper target Phe levels at different ages.

A second important question the PKU-COBESO study tries to answer concerns the extent to which Phe-related cognitive problems express themselves in the daily lives of PKU patients. First, a more complete profile of cognitive functioning in treated PKU must be established: are the well-established executive function deficits central to other potential problems in PKU, such as poorer quality of life or internalizing behavioural problems? Or do other aspects of cognition, which have been related to such problems and to the biochemical abnormalities observed or hypothesized in PKU, play a unique role as well? In this context, it is of particular interest to examine social cognitive abilities such as the Theory of Mind, emotion recognition, and reward and punishment sensitivity in PKU.

In this article, we also presented some preliminary results that may be of interest to the abovementioned core questions. Adult PKU patients presented with more internalizing behavioural problems than adult controls, and they also scored higher on avoidant personality problems. Furthermore, PKU adults reported more problems with relationships and self-care. Children and adolescents with PKU did not differ from controls of the same age regarding mental health and social skills. Also, childhood Phe levels were associated with physical complaints, thinking problems, and somatic problems (all part of the spectrum of internalizing behavioural problems) among the adult PKU patients. In children and adolescents with PKU concurrent Phe levels were significantly related to all behavioural problems.

Previous studies on behaviour in PKU have shown that patients exhibit internalizing problems such as depression and mood swings (Anjema et al., 2011; Cappelletti et al., 2013; Smith & Knowles, 2000). Although depressive problems were not significantly different from those reported by the control group, adult

PKU patients in our study differed from controls regarding internalizing problems, despite strict treatment and monitoring from infancy onwards. Weglage et al. (2000) also found internalizing problems in 42 adolescent PKU patients, including depression, anxiety, and physical complaints by means of the CBCL. Cappelletti et al. (2013) also demonstrated with the CBCL more internalizing problems in their group of 35 children and adolescents with PKU, i.e. on depressive mood, social withdrawal, and on the anxious/depressed scale. Avoidant personality problems are an interesting finding that has not been reported previously. People with avoidant personality problems show a pervasive pattern of social inhibition, feel inadequate, are extremely sensitive to negative evaluation, and avoid social interaction (American Psychiatric Association, 2000). There is an indication that our PKU patients exhibit these difficulties.

Whereas these results should still be considered preliminary (particularly when taking into account the small number of healthy controls and the lack of statistical control for multiple comparisons), they are in line with expectations and emphasize the importance of studying mental health and social functioning in early treated PKU. Future challenges include studying the associations between cognitive functioning and such outcomes in PKU, and thorough investigation of associations between cognitive, behavioural/mental health, and social outcomes on the one hand, and a wider range of biochemical parameters on the other.

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