Molecular Genetics and Metabolism 110 (2013) S57–S61

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

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

Rianne Jahja [a,*], Stephan C.J. Huijbregts [b], Leo M.J. de Sonneville [b], Jaap J. van der Meere [c], Annet M. Bosch [d], Carla E.M. Hollak [d], M. Estela Rubio-Gozalbo [e], Martijn C.G.J. Brouwers [e], Floris C. Hofstede [f], Maaike C. de Vries [g], Mirian C.H. Janssen [g], Ans T. van der Ploeg [h], Janneke G. Langendonk [h], Francjan J. van Spronsen [a]

[a] Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[b] Department of Clinical Child and Adolescent Studies, Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
[c] Department of Developmental and Clinical Neuropsychology, University of Groningen, Groningen, The Netherlands
[d] Academic Medical Center, Amsterdam, The Netherlands
[e] Academic Hospital Maastricht, Maastricht, The Netherlands
[f] Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands
[g] Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[h] Erasmus Medical Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 16 October 2013
Accepted 16 October 2013
Available online 22 October 2013

Keywords:
PKU-COBESO
Phenylketonuria
Childhood phenylalanine
Mental health
Social functioning

ABSTRACT

This article presents a new Dutch multicenter study ("PKU-COBESO") into cognitive and behavioral 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 et al., 2002 [1]). 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 behavior/mental health (i.e., COgnition, BEhavior, 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 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 behavioral 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) [2]. The result is an accumulation of Phe and a shortage of amino acids such as Tyr and tryptophan, with potential

Abbreviations: ANT, Amsterdam Neuropsychological Tasks; ASR, Adult Self-Report; CBCL, Child Behavior Checklist; LNAA, large neutral amino acids; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, Phenylketonuria; PKU-COBESO, Phenylketonuria cognition, behavior, social functioning study; SSC, Social Skills Checklist; SSRS, Social Skills Rating System; Tyr, tyrosine.

* Corresponding author at: University Medical Center Groningen, Beatrix Children's Hospital, Division of Metabolic Diseases CA33, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail address: jahjar@umcg.nl (R. Jahja).

1096-7192/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.10.011

consequences of low concentrations of neurotransmitters such as dopamine and serotonin. Dopamine is an important neurotransmitter for the prefrontal cortex mediated executive functions [3]. Executive functions are the regulatory cognitive abilities underlying behavior, e.g. inhibitory control, flexibility, and planning [4]. Loss of dopamine is related to executive dysfunction [5]. 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 [3].

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 [2]. However, early and continuously treated PKU patients, especially those with high Phe levels, still have problems with executive functioning [1,5,6] and appear to have internalizing behavioral problems as well [1,6–9].

Many studies investigated cognitive functioning either in children or adults with PKU (for an overview see Christ et al. [5]), whereas mental health has mainly been assessed in adult PKU patients [8,9]. 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 [10–12]. Whereas these results may be very informative, there is 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 [13]. 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 behavioral 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 behavioral problems such as depression, anxiety, phobic reactions, poor self image, and mood swings [7–9,14]. 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 [8]. Social functioning in PKU has never been examined earlier. As social functioning and mental health are strongly related to executive and social cognitive abilities [15], 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, behavior, 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 multicenter 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, behavioral problems, and social functioning (COBESO) in early and continuously treated PKU patients in relation to their metabolic control. Some preliminary results concerning behavioral 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 multicenter study addressing cognitive, behavioral 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 [1,16,17] 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 centers 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 centers. 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 behavior. 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 [18] or Wechsler Adult Intelligence Scale Third Edition [19], depending on age of the participant, to calculate an IQ-estimate.

The Amsterdam Neuropsychological Tasks (ANT) [20] 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 [20], 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 [21]. Adolescents and adults complete a Faux-Pas Test [22] and the Reading the Mind in the Eyes Test [23]. The neuropsychological assessment can generally be completed in 2.5–3 h 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 [24,25], 3) social functioning [26–30], 4) behavioral/mental health problems [31–33], and 5) quality of life [34] (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 [31]. 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.