Phenylketonuria: impact and implications

ten Hoedt, A.E.

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SUMMARY

Phenylketonuria (PKU; MIM 261600) is an autosomal recessive inborn error of metabolism caused by a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH; EC 1.14.16.1). As a result, the conversion of the essential amino acid phenylalanine (Phe) into the amino acid tyrosine (Tyr) is deficient. Phe, which is neurotoxic at high concentrations, subsequently accumulates in the body. The exact pathophysiologic mechanism of the neurocognitive damage is still not fully resolved. The severe intellectual impairments which ensue if PKU is left untreated, can be prevented by detection through newborn screening followed by initiation of a protein restricted diet, severely limiting the Phe intake from natural protein, in combination with supplementation of all other amino acids. Adherence to the diet is arduous and socially difficult and maintaining Phe levels within the advised ranges is therefore highly demanding. Although there is a general consensus amongst treating physicians and dieters that a Phe restricted diet should best be maintained throughout life, there is discussion on the stringency of this diet during adulthood and consensus guidelines on the dietary treatment of adults with PKU are lacking. In addition, studies have shown that, despite early initiation of treatment, patients with PKU may suffer from subtle intellectual, cognitive and psychological sequelae during adulthood. It is not clear if this is caused by irreversible damage which occurred during childhood or if this is due to easing of dietary control during adulthood.

In chapter 2, a concise review of the literature is provided, addressing the psychosocial aspects in patients with early-treated PKU. The neurocognitive deficits, social difficulties and emotional problems in early treated children and adults are described. The cumulative impact of these hidden disabilities puts this group of early-treated patients with PKU at risk for psychosocial problems later on, such as difficulties with forming relationships, achieving autonomy and acquiring a healthy emotional development.

Chapter 3 presents the results of a cross-sectional study on the health-related quality of life (HRQoL) of parents of children with PKU or galactosemia. A total of 116 parents of children with PKU and 69 parents of children with galactosemia aged 1 to 19 years completed a HRQoL questionnaire and provided information on socio-demographic, medical and psychosocial variables. Parents of children with PKU or
galactosemia reported a HRQoL comparable to parents of healthy children and a better HRQoL than parents of children with other metabolic disorders as reported in previous studies. There were no differences in HRQoL between parents of children with PKU and parents of children with galactosemia. Important predictors for parental mental HRQoL were the psychosocial factors emotional support and loss of friendship. Since parental mental functioning influences the development and adjustment of their children, it is important that treating physicians pay attention to the wellbeing of the parents. The insight that emotional support and loss of friendship influence the HRQoL of parents, enables treating physicians to provide adequate support for these parents.

In chapter 4, the results of a placebo-controlled crossover trial on the effects of high Phe levels on neuropsychological functioning and mood, are presented. Nine adults with PKU, all detected by newborn screening and continuously treated ever since, underwent two 4-week supplementation periods: one with Phe, mimicking a normal dietary Phe intake, and one with placebo. Neuropsychological tests were done at the end of each study period. Furthermore, patients, and for each patient a close friend or relative, completed weekly questionnaires evaluating the patients’ mood. Neuropsychological tests demonstrated impairment in sustained attention at the time of the high Phe values, during Phe supplementation. Both patients and their friend or relative reported lower scores on the mood questionnaires, during Phe supplementation, demonstrating a negative influence of high Phe levels on mood. We conclude that high plasma Phe levels have a direct and negative effect on both sustained attention and on mood in adult patients with PKU. A Phe restricted “diet for life” may therefore be an advisable option for many, if not all, patients.

Chapter 5 focuses on the effects of elevated Phe levels on brain activity. Magnetoencephalograms (MEG) were performed in the nine patients participating in the previous placebo-controlled crossover Phe-loading study in early and continuously treated adults with PKU, at the end of each study period (chapter 4). Phe-loading did not result in a difference in the power of the 5 frequency bands, compared to placebo. In addition there was no difference in the relative power analyzed for the 10 different cortical areas between the Phe-loading study period and the placebo study period. We hypothesize that MEG recordings in PKU patients did not show any alterations on high Phe levels because increased Phe levels might only affect functional interactions between brain regions and do not affect power.
Therefore additional studies, analyzing the functional connectivity in the MEG recordings of these patients, are warranted.

The aim of the study presented in chapter 6, was to evaluate whether increased self-management of PKU patients and/or their parents, by providing direct online access to blood Phe values without immediate professional guidance, is feasible and safe. Thirty-eight patients aged ≥1 year participated in a 10 months trial and were randomized into a study group or a control group. The control group continued the usual procedure: Phe values were provided to them by the dietician. Patients/parents in the study group were provided with a personal “My PKU” web page on which their recent and previous Phe values, extra information on PKU and a message-box through which questions could be send to the dietician, were presented. During the study period, there were no significant differences between the two groups in mean Phe values, percentage of values above the recommended range or in frequency of blood spot sampling for Phe determination. All patients and/or parents expressed a high level of satisfaction with the new way of disease management. We conclude that increased self-management in PKU, by providing patients and/or parents their Phe values without immediate professional guidance, is feasible and safe and is highly appreciated.

In chapter 7, a comparative study on the different methods of analysis available to measure Phe levels, is reported. Three different methods of Phe determination were compared: 1) in plasma by amino acid analyzer; 2) in blood spots directly prepared from the venous blood sample by tandem mass spectrometry, and 3) in capillary blood spots prepared at the time of the venous blood sampling and measured by tandem mass spectrometry. Fifteen adult patients with PKU participated, of whom five were studied twice. The mean Phe concentration in blood spots obtained from capillary blood and from venous blood were 40 µmol/L and 97 µmol/L lower respectively, than the mean Phe concentration measured in plasma. The observed significant differences in Phe levels due to different sampling techniques, warrant caution, and the use of one and the same method during follow-up of individual PKU patients is advised.