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Dietary treatment in Dutch children with phenylketonuria: An inventory of associated social restrictions and eating problems

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ABSTRACT

Objectives: Dietary treatment in phenylketonuria (PKU) is known to cause eating problems, but knowledge of both prevalence and magnitude, especially for social restrictions, is scarce. Our aim was to evaluate the social restrictions and eating problems that children with PKU and their caregivers experience with dietary treatment.
Methods: A web-based questionnaire, based on the Behavioral Pediatrics Feeding Assessment Scale with additional PKU-specific questions, was developed in close collaboration with and distributed by the Dutch PKU Association, which sent an e-mail to its members containing a link to the questionnaire. The questionnaire was completed by caregivers of children with PKU in the Netherlands and caregivers of age-matched children without PKU. Data were analyzed with the Kruskal-Wallis and Mann-Whitney *U* test using SPSS.
Results: Compared with caregivers of children in the control group (ages 1–16 y; $n = 50$), caregivers of children with PKU (ages 1–16 y; $n = 57$) reported more difficulty in offering food variety, experienced more stress when eating an evening meal outside the home and during vacation, and were stricter about (accidental) spilling of food during dinner by the child ($P < 0.05$). They also reported to being angrier, more frustrated, and more anxious when feeding their child, and they more often felt that their child's eating pattern had a negative influence on the child's general health ($P < 0.05$).
Conclusion: This pilot study provides further evidence that restriction of social activities and eating problems associated with dietary restrictions is more common in children with PKU, and warrants awareness on this topic among professionals working with these children.

Introduction

Phenylketonuria (PKU; OMIM #261600) is an autosomal recessive inborn error of metabolism caused by mutations in the *PAH* gene—which encodes phenylalanine hydroxylase (PAH)—and is present in approximately 1 in 10 000 live births [1]. PAH is a hepatic enzyme that converts phenylalanine (Phe) to tyrosine. Consequently, a deficiency in PAH leads to high blood Phe concentrations that can have disastrous effects on the brain, with severe developmental delays in untreated children [2]. The principal treatment is a lifelong diet of Phe restriction combined with Phe-free protein substitutes and special low-protein foods. Some people have become less dependent on dietary restriction thanks to their tetrahydrobiopterin (BH_4) responsiveness [1].

Apart from the (often very socially demanding) dietary restrictions, the protein substitutes may give rise to several eating problems. These protein substitutes must be taken several times a day, and have strong bitter tastes. They contain additional energy that

Abbreviations: PKU, Phenylketonuria; PAH, Phenylalanine hydroxylase; Phe, Phenylalanine; BH4, Tetrahydrobiopterin; DO, Dietary treatment only; CG, Control group; BPFAS, Behavioral Pediatrics Feeding Assessment Scale

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can result in less optimal intake of other foods [3]. Some children with PKU are also known to have food neophobia [4]. Rejection of new foods may correlate with limited exposure to varied foods in the weaning period, fear of eating unsuitable foods, or unpleasant experiences with protein substitutes [5]. It is hypothesized that this may explain, and also be part of, the general increased anxiety that has been reported in people with PKU [6].

The strict diet may give rise to eating problems in children and influence their social activities [5]. Up to now, literature on this topic is scarce and available only with respect to young children [7–9]. MacDonald et al. [7] reported feeding problems in young children (ages 1–5 y) with PKU using a feeding assessment questionnaire in 1997. The main problems described in that article include poor appetite, a limited variety of foods consumed, and slowness to feed. More recently, MacDonald et al. [8] and Evans et al. [9] reported on the complexity of feeding and social inclusivity of the food environment during the weaning period in young children (<2 y) with PKU. They found that parental anxiety may contribute to early termination of breastfeeding, extended bottle feeding with Phe-free infant protein substitute, prolonged spoon-feeding, and evening meals where food is given at a different time from the rest of the family [8,9].

Eating problems in young children can lead to parental frustration and stress, and may impair the nutritional status of the child [2,10]. The rigid dietary restrictions, in combination with the Phe-free protein substitutes, may also have an impact on their social activities [10]. It is important to be aware of the potential consequences of the dietary treatment on (eating) behavior [7] and possibly also on neuropsychological development, especially executive functioning [11].

Over 20 y have passed since MacDonald et al. published their first article about feeding difficulties in young children with PKU [7]. Over those decades the choices, compositions, and presentations of the protein substitutes have improved. For example, prepackaged and premeasured products improve adherence and accuracy [3]. Despite new developments in the taste, texture, and quality of the content of the protein substitutes, they are still associated with poor palatability and breath odor [3]. In addition, more validated questionnaires have become available to assess eating problems in children [12].

We hypothesize that even though there has been progress in these aspects of the treatment of PKU, there are still social restrictions and eating problems related to the dietary treatment in children. We furthermore hypothesize that the behavioral problems in young children differ from those seen in older children with PKU. To balance the effects of treatment and outcome, and to select the best treatment, clinicians must be aware of the struggle their patients are facing in daily life. The aim of this pilot study was to evaluate the social restrictions and eating problems in children aged 1 to 16 y with PKU, using the Behavioral Pediatric Feedings Assessment Scale (BPFAS) [13] supplemented with PKU-specific questions.

Materials and methods

General information

We performed a pilot survey study using a Web-based questionnaire on social restrictions and eating problems. The CHERRIES checklist (Supplementary Appendix A) for reporting results of the Web-based questionnaire was used to write this manuscript [14]. The Medical Ethics Review Board of Groningen confirmed that for this pilot survey study, the Medical Research Involving Human Subjects Act did not apply. This is a pilot study, so we did not perform a sample-size calculation.

Participants

Inclusion criteria were caregivers of children aged 1–16 y with and without PKU having no other chronic diseases. Following these criteria, three groups were made: a group with children with PKU following dietary restriction only (DO), a group with children with PKU following dietary restriction and BH_4 supplementation (BH_4), and a control group with children without PKU (CG).

All members of the Dutch PKU Association received the e-mail for participation in the questionnaire. In the e-mail it was explained that only parents of children aged 1 to 16 y would be included in the study.

Feeding assessment

Behavioral Pediatrics Feeding Assessment Scale

The BPFAS was used to gather information on mealtime behavior during the evening meal, as this is the main family meal in the Netherlands. This instrument is a validated parent report which focuses on types of behavior the child shows during mealtime and the ways parents handle or feel about these situations [13]. It consists of 35 items: 25 describe the child's behavior (eg, enjoys eating, takes longer than 20 min to finish, spits out food), and 10 describe the parent's feelings around mealtime behavior (eg, I feel confident my child gets enough to eat, I get frustrated and/or anxious when feeding my child). A 5-point Likert scale from never (1) to always (5) was used to rate the frequency of the behaviors, with higher scores meaning more problems during mealtime. Two questions, regarding drinking milk and eating meat/fish, were removed from the section on child behavior, because children with dietary restriction are not allowed to drink milk or eat meat or fish.

PKU-specific questionnaire development

To assess any problems specific to PKU, a set of PKU-specific questions was developed (Supplementary Appendix B) in collaboration with caregivers of children with PKU and adults with PKU at a virtual meeting organized by the Dutch PKU Association. In this virtual meeting, eating problems and social restrictions were discussed. The set of questions developed was returned to the attendees of the meeting. Taking their comments into consideration, a list of 18 questions was finalized to assess PKU-specific social restrictions and eating problems not covered by the BPFAS. A scale of 1 to 5 was used to rate the influence of PKU on eating habits during the evening meal and social events, with 1 being the lowest score and 5 the highest. The scale differed per question, including from never to always and from not stressful to very stressful, with 1 meaning the item is not influenced by PKU and 5 meaning it is very much influenced by PKU. The questions were focused on the influence of PKU-related dietary restriction on social events (eg, going out for dinner, the child's first sleepover, school trips) as experienced by the parents (eg, How stressful do you find going out for dinner? To what degree does PKU influence your choice of vacation location?).

Questionnaire distribution

The questionnaire was anonymously filled out using Qualtrics, a Web-based survey platform. A link to the online questionnaire was distributed through the Dutch PKU Association via e-mail and social media platforms. An invitation letter was added to the e-mail with an explanation of the study, instructions for completing the questionnaire, and privacy regulations. Informed consent was obtained from all participants via the first question in the questionnaire. Participants were asked to send the questionnaire link to a parent with a child of the same age as their child with PKU, thus creating an age-matched control group. Three reminders were sent, after 1, 3, and 6 wk. The questionnaire was available only in Dutch and was open to anyone with the link.

Data analysis

The analysis used data from participants who consented to their answers being used in this research and stored for later research. They were analyzed using descriptive statistics in SPSS version 23. The data were not normally distributed, and so the nonparametric Kruskal–Wallis test was used, with $\alpha < 0.05$ seen as statistically significant. Post hoc between-groups analysis was performed using the Mann–Whitney *U* test. A Bonferroni correction (*P* value times 3, for three subject groups) was done to correct for type I error.

Results

Participants

The questionnaire was completed by 147 respondents; 40 had children over age 16 y or completed only the first question, so those data were excluded. This gave 107 questionnaires at least partly completed by caregivers of children ages 1–16 y, 57 of whom were children with PKU and 50 of whom were children without PKU (CG). Of the 57 children with PKU, 43 were prescribed dietary restriction only (DO) and 14 were prescribed dietary

Table 2
Significantly different scores on the Behavioral Pediatrics Feeding Assessment Scale by group

Question Variable*	DO (n = 43)	BH_4 (n = 14)	CG (n = 50)	DO vs. CG†
Child behavior				
Eats vegetables	1.00 (1–4)	2.00 (1–4)	2.00 (1–4)	0.012
Total score‡	50 (35–76)	45 (31–70)	45 (30–84)	0.027
Parent behavior/feelings				
Frustration during feeding	2.00 (1–5)	1.50 (1–4)	1.00 (1–4)	0.030
Preparation of alternative food when the child dislikes the food served	2.00 (1–5)	2.00 (1–5)	2.00 (1–4)	0.006
Negative influence of eating pattern on general health	2.00 (1–4)	2.00 (1–3)	1.00 (1–3)	0.003
Anger during mealtime	1.00 (1–3)	1.00 (1–2)	1.00 (1–2)	0.012
Confidence in the amount of food my child takes during mealtime	2.00 (1–4)	1.00 (1–4)	1.00 (1–5)	0.018
Total score§	18 (10–34)	17.50 (10–25)	14 (10–29)	0.015

BH_4, group with phenylketonuria with dietary restriction and tetrahydrobiopterin supplementation; CG, control group (without phenylketonuria); DO, group with phenylketonuria with dietary restriction only
Values are given as median (range)
*For all items except "Eats vegetables" and "Confidence in the amount of food my child takes during mealtime," answers are on a scale of 1 (never) to 5 (always); for those two items, the scale is reversed (1 = always, 5 = never).
†P value multiplied by 3, from the post hoc Mann–Whitney U test.
‡Minimum = 23, maximum = 115.
§Minimum = 10, maximum = 50.

restriction and BH_4 supplementation (BH_4). All caregivers stated that their child did not have any other chronic disease. The ages and numbers of children in each group are shown in Table 1.

Behavior Pediatrics Feeding Assessment Scale

The median and range for each group, and the significant differences between the DO and CG groups, are given in Table 2. The first part of the BPFAS comprises questions about the frequency of the child's mealtime behaviors. Caregivers in the DO group reported that their children ate more vegetables than in the CG group ($P < 0.05$). The second part of the BPFAS consists of questions about parental behavior and feelings around mealtime. Caregivers in the DO group were more frustrated and anxious when feeding their child, felt less confident that their child received sufficient food, and more often felt that their child's eating pattern had a negative influence on their general health than in the CG group. They also reported that they more often prepared alternative food if their child did not like what was being served (mean rank: DO = 63.92, CG = 45.24; $P < 0.05$), and they (the caregivers) were more likely to become angry during mealtime (mean rank: DO = 59.97, CG = 48.15; $P < 0.05$).

One significant difference was found between the BH_4 and CG groups. Caregivers in the BH_4 group more often had the feeling that their child's eating pattern might have a negative influence on the child's general health than in the CG group ($P < 0.05$). No statistically significant differences were found between the DO and BH_4 groups.

The PKU group (DO + BH_4) was split into two age groups (1–7 y and 8–16 y) to assess differences between younger (n = 31) and older (n = 26) children with PKU. Caregivers of younger children with PKU indicated that their child ate more vegetables (median = 1; range, 1–3) and overall enjoyed food less (median = 2; range, 1–3) than older children with PKU (respectively: median = 2; range, 1–4; and median = 1; range, 1–4; $P < 0.05$). During mealtime, younger children were reported to get up from the table more often (median = 3; range, 1–5) than older children (median = 1; range, 1–5; $P < 0.05$). They also more often whined or cried (median = 2; range, 1–4) and had tantrums during mealtime (median = 2; range, 1–4) than older children (for both: median = 1; range, 1–3; $P < 0.05$). Caregivers of younger children reported getting more frustrated during mealtime (median = 2; range, 1–4) than caregivers of older children (median = 1; range, 1–5), and more often coaxed their child to get the child to take a bite (younger: median = 3; range, 1–4; older: median = 1.5; range, 1–4; $P < 0.05$).

Table 1
Ages of participants' children with phenylketonuria

Group	n	Age, y (median)	Range, y
PKU with dietary restriction	43	7	1–16
PKU with dietary restriction and BH_4 supplementation	14	7.5	2–16
Control group	50	9	1–16

BH_4, tetrahydrobiopterin; PKU, phenylketonuria

PKU-specific questionnaire

Table 3 shows the median and range, and statistically significant differences, for the PKU-specific questionnaire. Children in the DO group were more likely to eat their evening meal separate from the rest of the family and were less likely to try new foods compared with the CG group ($P > 0.005$). Caregivers in the DO group also found it more difficult to offer a varied diet to their child and experienced more stress when eating an evening meal outside the home and during vacation. They were stricter in their approach to spillage of food during mealtime than the CG group ($P < 0.005$), meaning they were more likely to keep a close eye on the amount of food being spilled during mealtime, or even to measure it.

Comparing the DO and BH_4 groups, caregivers in the BH_4 group indicated that PKU had less influence on their choice of vacation location ($P < 0.05$).

As for BH_4 versus CG, children in the BH_4 group tended to be more likely to eat their evening meal separate from the rest of the family (P > 0.05; not significant after Bonferroni correction).

Discussion

This pilot study assessed both social restrictions and eating problems in children ages 1–16 y with PKU. The studied sample was relatively large in comparison to previous studies assessing eating problems in children with PKU [7–9]. This underlines caregivers' interest and the relevance of this subject. The most important findings are that caregivers whose children with PKU are following dietary treatment only (without BH_4) experienced more stress and frustration around the evening meal and social events than parents of children without PKU. Children with dietary

Table 3
Significantly different scores on the PKU-specific questionnaire

Question Variable*	DO (n = 43)	BH_4 (n = 14)	CG (n = 50†)	DO vs. CG†	DO vs. BH_4‡
Offering varied eating pattern	3.00 (1–5)	2.50 (1–4)	2.00 (1–3)	<0.001	NS
Separation during evening meal	4.00 (1–5)	2.00 (1–5)	1.00 (1–5)	<0.001	NS
Choice of restaurants	2.00 (1–5)	1.00 (1–5)	1.00 (1–5)	<0.001	NS
Stress during dinner outside of the home	2.00 (1–5)	1.50 (1–4)	1.00 (1–4)	<0.001	NS
PKU influence on choice of holiday	2.00 (1–4)	1.00 (1–2)	–	–	0.039
Stress during holiday	2.00 (1–5)	1.50 (1–3)	1.00 (1–3)	<0.001	NS
Difficulty trying new foods	3.00 (1–5)	3.00 (1–5)	2.00 (1–5)	<0.001	NS
Approach to spilling food	2.00 (1–5)	1.50 (1–3)	1.50 (1–5)	0.006	NS
Total score§	39 (23–55)	32 (20–45)	28 (14–44)	<0.001	0.048

BH_4, group with phenylketonuria with dietary restriction and tetrahydrobiopterin supplementation; CG, control group (without phenylketonuria); DO, group with phenylketonuria with dietary restriction only; NS, not significant; PKU, phenylketonuria
Values are given as median (range)
*Answers are on a scale of 1 (not influenced by PKU) to 5 (very much influenced by PKU).
†The first two questions were completed by 50 participants, the remaining questions by 44 participants.
‡P value multiplied by 3, from the post hoc Mann–Whitney U test.
§Minimum = 14, maximum = 70.

restriction only ate more vegetables, had more difficulty trying out new foods, and ate their evening meal separate from the rest of the family more often.

Before discussing the results in more detail, a few methodological issues need to be addressed. First of all, we did not perform a sample-size calculation for this pilot study. This means there is a risk of having too low a power to support clinical importance of our findings. Second, this is the first time our PKU-specific questionnaire was used. The questions were not validated, because of the small size of the PKU population that fully completed the questionnaire. They were, however, developed and reviewed by members of the Dutch PKU Association. Furthermore, the questionnaire was available only in Dutch, possibly excluding families that do not read Dutch fluently. We did not differentiate between families with one or more children with PKU or with or without healthy siblings. Because of the low number of BH_4 participants (in comparison to DO participants), it was not possible to do a subanalysis of age in both the BH_4 and DO groups. Most significant differences were found between the DO and CG groups. This might partly be due to the small number of BH_4 participants in comparison to DO participants; the lack of significant differences between the BH_4 group (n = 14) and the DO group (n = 43) might be explained by the small size of BH_4 group. Although the first question in the questionnaire made it possible to differentiate between BH_4-responsive PKU and non-BH_4-responsive PKU, dietetic data on the severity of protein restriction were not included. The severity of protein restriction might have an effect on the degree of eating problems and social restrictions that children and their caregivers experience.

The BPFAS showed a higher level of anxiety and insecurity among caregivers of children with PKU. This might be explained by the consequences of poor metabolic control in the child with PKU; however, we did not evaluate metabolic control. A subanalysis by age within the PKU group showed that mealtime behaviors like crying and tantrums were more common in younger children with PKU. These types of behavior might be related to younger children in general. Since MacDonald et al. [7] reported eating problems in children ages 1–5 y, we also performed a subanalysis for this age group compared to the CG group (results not reported). In addition to the main problems reported by MacDonald et al. (slowness to feed, poor appetite, dislike of sweet foods, and limited variety of foods consumed), we found that caregivers of children ages 1–5 y with PKU were more likely to get frustrated during mealtime than in the CG group, and more often prepared alternative food when their child did not like what was being served ($P < 0.05$).

Consistent with the report by MacDonald et al. [7] in 1997, children with PKU are still more likely to eat their evening meal separate from the rest of the family. This means that they will not experience their evening meal as a social occasion, which might negatively influence appetite and feeding negatively. Having the evening meal together with the rest of the family has been reported to protect against disordered eating and obesity, and can furthermore affect a child's cognitive development and academic achievement, not forgetting the improved perception of family relationships [15]. Possibly because of the strict routine of feeding and having to take protein substitutes, children with PKU and dietary restriction have more difficulty trying new foods. This in turn may influence the ability of caregivers to offer a varied eating pattern. The rigid dietary restriction, the extra measurements needed for dinner outside of the home and during vacation, and the fear of the child receiving too much protein may explain the higher level of stress among caregivers of children with PKU and dietary restriction.

Comparing children with PKU using dietary restriction only and those using BH_4 supplementation as well, we found that PKU had a lower influence on vacation location and accommodation in families with children using BH_4. This might be related to the fact that children with BH_4 supplementation can tolerate more Phe, and therefore can have less severe dietary restriction and need fewer extra measurements to be taken [2]. In contrast to our results, studies by Demirdas et al. [16] and Ziesch et al. [17] assessing the effect of BH_4 responsiveness on quality of life (QoL) showed no differences between children with PKU that was and was not responsive to BH_4; but these studies did not study eating problems in detail. This can be explained by the use of health-related QoL questionnaire that were not specific to PKU, and by the different focus of these studies, which mainly focused on aspects of QoL that are not that clearly related to eating problems. Recently, PKU QoL questionnaires have been developed and validated [18], and they have subsequently been used to assess QoL in adults with classical and less severe PKU [19]. The difference between QoL in PKU that is and is not responsive to BH_4 has not explicitly been assessed using this PKU QoL questionnaire.

People with adult PKU that is early and continuously treated have a higher risk of problems such as depression and anxiety [20]. Outside of PKU, data suggest that high stress during childhood, such as family problems and situations affecting safety during early years, increase risk of anxiety and mood issues during adulthood [21]. This is supported for people with PKU as well, by Manti et al. [22], who showed that the burden of strict dietary treatment is a psychological stress for children and their families. They found that patients who

continuously followed dietary treatment during their first decade of life more often experienced psychiatric disorders later in life. In another survey study, it was shown that a rigid parental approach to the dietary treatment of their child with PKU was less often correlated with optimal Phe control [23]. This emphasizes the great impact that dietary treatment can have on children and their families, as well as the need for appropriate guidance.

The BPFAS used in our questionnaire was originally designed for use with children ages 1 to 8 y with cystic fibrosis [13]. It has, however, been used in several other chronic diseases and psychiatric disorders to assess eating behaviors, as well as with children over age 8 y [24]. Most of our participants fell in the validated age range of 1 to 8 y, but we aimed to evaluate social restrictions and eating problems for children ages 1 to 16 y. For future studies evaluating ages from 8 to 16 y, it might be necessary to develop questionnaires suited for this age group, since most currently existing questionnaires are designed for younger children only [12].

The results of this pilot study show several aspects of the social restrictions and eating problems that children with PKU and their caregivers experience in daily life, hopefully raising awareness of these problems in PKU. Awareness among PKU health care workers might make it easier to address these problems in daily care and to guide parents through the several hurdles that the dietary treatment brings. It is important for parents to know that the problems they are experiencing are common, and talking about the problems with PKU health care workers might be a first step toward improved quality of the dietary treatment and family life. Furthermore, one can think of education of PKU families to prevent social restrictions. Additional studies, preferably with an international focus to include other eating cultures, might lead to additional insights into the dietary treatment and the social restrictions and eating problems it brings.

Conclusion

The results of this pilot study show a broad picture of the social restrictions and eating problems that children with PKU and their caregivers experience because of dietary restrictions. To further improve the quality of dietary treatment in PKU, more awareness on this topic is necessary, and social restrictions and eating problems consequent to dietary treatment need to be further investigated using questionnaires adapted not only for young childhood but for all other ages.

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Supplementary materials

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