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Behavioural factors related to metabolic control in patients with phenylketonuria

M. R. CRONE[1,*], F. J. VAN SPRONSEN[2], K. OUDSHOORN[1], J. BEKHOF[3], G. VAN RIJN[4] and P. H. VERKERK[1]
[1]*TNO Prevention and Health, Leiden;* [2]*Section of Metabolic Diseases, Beatrix Children's Hospital, University Hospital of Groningen;* [3]*Department of Pediatrics, Isala Hospital, Sophia Zwolle;* [4]*Department of Facilities, University Hospital Groningen, The Netherlands*

[*]Correspondence: Department of Child Health, TNO Prevention and Health, PO Box 2215, Leiden, 2301CE, The Netherlands. E-mail: mr.crone@pg.tno.nl

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Summary: Background. The objective of this study was to determine the importance of parental factors possibly related to dietary control in early and continuously treated patients with phenylketonuria (PKU). **Methods**. A questionnaire was disseminated among parents of 238 patients with PKU born after the nationwide introduction of newborn screening for PKU (1 September 1974) until 31 December 1995. The questionnaire was based on a behavioural model measuring people's attitudes, subjective norms, and self-efficacy. Dietary control was defined on the basis of mean phenyl- alanine (Phe) concentration of the PKU patients measured between 1 January 1994 and 31 December 1996. **Results**. Response rate was 71%. *Attitudes*: children of parents who believed that their child adheres well to the diet, even if his or her Phe concentrations are sometimes too high, had lower Phe concentrations than children of parents who disagree with this statement (adjusted difference −103 μmol/L, $p < 0.001$). *Subjective norm*: Phe concentrations were higher when parents answered that their relatives did not approve when their child deviates from the diet ($p = 0.004$). *Self-efficacy*: children of parents who reported difficulties in having their child eat the synthetic protein substitute three times a day had higher Phe concentrations than those of parents who did not have such difficulties (adjusted difference 156 μmol/L, $p = 0.007$). **Conclusion**. More attention should be given to parents having their child eat the synthetic protein substitute at least three times a day and to teaching parents to keep strictly to the diet without being too rigid. These factors were strongly associated to dietary control and may be amenable to change.

Phenylketonuria (PKU) is an autosomal recessive disease caused by a deficiency of the enzyme phenylalanine hydroxylase (Scriver et al 1995). Accordingly, the amino acid phenylalanine (Phe) cannot be converted into tyrosine as usual, resulting in high Phe concentration in blood and tissues and severe brain damage, although the precise mechanisms are still unclear (van Spronsen et al 2001).

Since the introduction of the national screening for PKU in The Netherlands in 1974, about 10 patients are detected every year (Verkerk 1995). Most patients are treated before the age of 3 weeks (Verkerk 1995). The treatment of PKU is based on a Phe-restricted diet. This diet consists of two parts: restriction of natural protein (to lower the Phe intake) and supplementation with amino acids to achieve a normal total 'protein' intake. The synthetic protein substitute contains all amino acids except Phe and it is advised to take it three times a day. This advice, however, is not strictly followed by a significant percentage of the patients (MacDonald et al 1996; Prince et al 1997). Until recently, in The Netherlands PKU patients of all ages were advised to maintain a Phe blood concentration (Phe concentration) between 200 μmol/L and 500 μmol/L (Verkerk 1995). Currently, lower concentrations are advised during the first 12 years of age.

Most guidelines agree that dietary treatment of PKU should be continued throughout adult life (Seashore et al 1999). In The Netherlands also patients are advised to follow the diet all their life and to keep Phe concentrations well within the target range. Many patients, however, do not adhere strictly to the diet (Verkerk et al 1994), resulting in Phe concentrations that are often clearly above the target range. When patients do not follow the diet strictly, both in young and older patients, higher rates of problems related to Phe concentration, prolonged reaction time and a decrease of the prefrontal functions are found (Huijbregts et al 2002; Stemerdink et al 1999). Attempts to find factors associated with dietary compliance of PKU patients, and in particular during childhood and adolescence, are therefore important.

So far, research on the determinants that may play a significant role in the adherence to the diet—and in the intra- and inter-individual variance of the Phe concentrations in treated PKU patients—has been scarce (Bekhof et al 2003). This project aims to study the parental determinants that influence adherence among early and continuously treated PKU patients up to 22 years of age in The Netherlands. These determinants will be used to develop better-tailored information for parents with a child with PKU, aiming to increase the dietary adherence of PKU patients.

METHODS

Parents of PKU patients detected by neonatal screening, born between 1 September 1974 and 31 December 1995, received a questionnaire ($n = 238$). Since the start of the nationwide screening programme (in 1974), all children with a positive screening result are referred to one of the eight university paediatric clinics (Verkerk 1995; Verkerk et al 1994). At that time, patients were diagnosed as having PKU when they had a pre-treatment Phe concentration higher than 500 μmol/L and, at the age of 1 year, a tolerance for dietary PKU of less than or equal to 50 mg/kg (Lanting and Verkerk 2002). The Dutch National PKU Steering Committee and the medical ethical committees of all university hospitals approved the study. All paediatricians in the Dutch university child clinics agreed to participate and to inform the target population about the study and to send them the questionnaire. The questionnaire was sent to the parents in 1997.

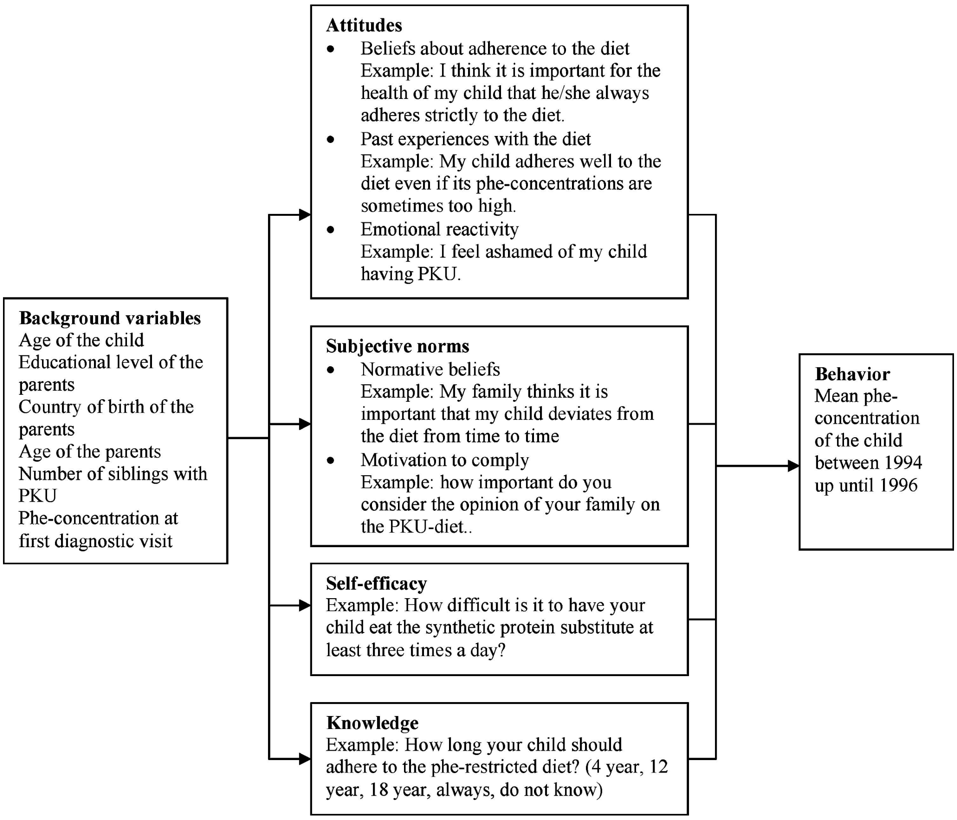

Figure 1 Theoretical framework based on the Theory of Planned Behaviour and Social Cognitive Theory extended with knowledge

Questionnaire and theoretical framework: The questionnaire was based on the Theory of Planned Behaviour and Social Cognitive Theory (Ajzen 1991; Bandura 1986). This model takes into account people's attitudes, subjective norms and self-efficacy as an explanation of their behaviour. The questionnaire was developed according to this integrated model and the results of interviews held with parents of children with PKU prior to the development of the questionnaire. The theoretical framework used in this study is represented schematically in Figure 1. All questions were rated using a 5-point Likert-type scale.

Attitudes of parents consisted of their beliefs about their child's adherence to the diet. The expected-beliefs construct was measured by six belief items such as 'I think it is important for the health of my child that he/she always adheres strictly to the diet'. According to principal component analysis and Cronbach's Alpha, it was not possible to reduce the items by creating well-determined variables. The items were included separately in the analysis and for modelling the answers were re-scored in three categories. The attitude construct also included the past experiences of parents with PKU and the diet, and their emotional reaction to PKU and the diet. All items comprised answers ranging from 'I totally disagree' to ‘I totally agree’. The past-experiences construct was represented by six items. A typical example was ‘My child always adheres well to the diet even if his or her Phe concentrations are sometimes too high’. The items were included separately in the analysis. The emotional reactivity construct was measured by eight items, such as ‘I feel guilty when I eat normal food’. The answers to these items were also re-scored in three categories and the items were included separately in the analysis. Subjective norms relate to a person’s perception that the majority of ‘significant others’ think he or she should adopt a specific behaviour. Subjective-norm constructs consist of normative beliefs and motivation to comply. Normative beliefs were measured by asking how important the respondent thought partners, relatives, or friends considered the adherence of the PKU patient to the diet. The answers were scored from -2 (negative towards the preventive behaviour) to $+2$ (positive towards the preventive behaviour). The motivation to comply was measured by asking how important the opinions of these three groups were to the respondent. The answers ranged from ‘I totally disagree’ (1 point) to ‘I totally agree’ (5 points). In the analysis, for each person rated, the normative-belief variable was multiplied by the motivation of the parents to comply. In this way, the score of the resulting variables ranged from -10 to $+10$. A score of -10 meant that the person rated was considered not to find it important that the respondent adhered to the diet and that the opinion of this person was important to the respondent.

Self-efficacy of parents was measured by 23 items. Self-efficacy means the perceived capacity of the respondent to behave in a certain way. According to a homogeneity analysis, the answer categories of the items could be seen as continuous.

In addition, we measured knowledge of the disease and its treatment. As possible confounders we considered the following variables: the Phe concentrations (μmol/L) at the first diagnostic visit of the child as a measure of the severity of the disease, age of the child (in months), age of the mother and father (in years), number of children in a family (one, two, three or more), number of siblings with PKU, ethnicity of the parents (born in The Netherlands or abroad) and educational level of the parents (low, average, high). A low educational level referred to persons who had not finished secondary education or had received only lower education; the average level referred to persons who had finished average or higher secondary education; and the high level included those with a masters or bachelors degree. One patient had a pre-treatment concentration of 102 μmol/L at first diagnostic visit, which in most circumstances does not lead to the diagnosis of PKU. However, in this patient the blood Phe concentration was collected at day zero because of siblings with PKU; Phe concentration rose in the following days. Three patients had improbably high pre-treatment Phe concentrations; these three patients were omitted from the analyses.

As outcome variable we used the mean Phe concentrations of the child (μmol/L) in the period 1 January 1994 until 31 December 1996. To avoid the effect of *ad hoc* fluctuations in the Phe concentrations (due to illness, etc.) we decided to take the mean concentration over a period of 3 years. The reason for using the period 1994 to 1996 was that it represented the last three years before parents completed the questionnaire. All Phe concentrations were measured quantitatively in plasma using ion-exchange liquid amino acid analysers.

Analysis: When univariate analysis showed significant association between the variables described above and mean Phe concentration, these variables were included in the multivariate analysis. We used multivariate linear regression with stepwise forward selection. A difference was considered to be statistically significant when $p < 0.05$.

RESULTS

A total of 170 parents (71%) completed and returned the questionnaire. Most (53%) questionnaires were completed by mothers (Table 1). Mean age of the PKU-children of the participating parents was 11 years. Frequencies of other demographic variables and mean Phe concentration are presented in Table 1. Mean individual Phe concentration remained relatively constant until 13 years of age (approximately 400 µmol/L), but increased after this age. This relation is quadratic rather than linear (Figure 2). Mean Phe concentration of patients of parents who returned the questionnaire was not significantly different from the mean Phe concentration of patients of parents who did not return the questionnaire.

Table 1 Frequencies and means of demographic variables including Phe concentrations and Phe tolerance

Demographic variables	*Frequencies and means* ($n = 167$)	
Person who completed the questionnaire	Mother	53%
	Father	5%
	Father and mother together	41%
	Other	1%
Educational level of the mother	Low	53%
	Average	31%
	High	16%
Educational level of the father	Low	47%
	Average	30%
	High	22%
Country of birth of the mother	Netherlands	92%
	Foreign country	8%
Country of birth of the father	Netherlands	89%
	Foreign country	11%
Mean age of the mother	38 years (24–64 years)	
Mean age of the father	41 years (25–63 years)	
Mean age of the child	11 years (1–22 years)	
More than one child with PKU in the family	21%	
Number of children	1	17%
	2	58%
	3	15%
	4 or more	9%
Mean Phe concentration between 1994 and 1996	435 µmol/L (150–1140 µmol/L)	
Mean Phe concentration at first diagnostic visit	1685 µmol/L (102–4150 µmol/L)	

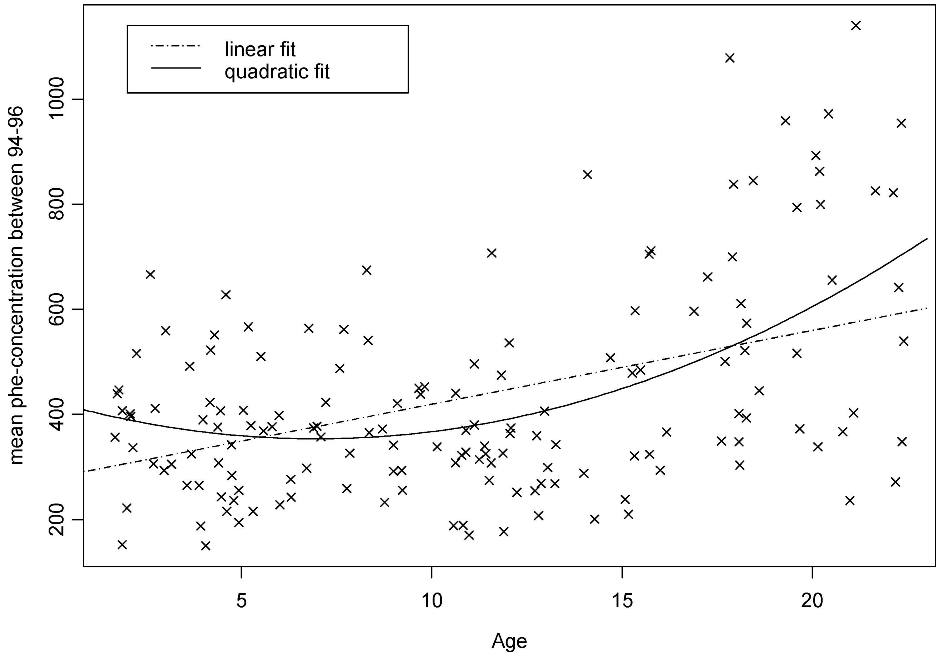

Figure 2 Mean Phe concentrations (μmol/L) between 1994 and 1996 versus age

In total 29% of the patients who participated in the study had a mean Phe concentration above 500 μmol/L and 2% had a mean Phe concentration above 1000 μmol/L.

Twenty per cent of the parents returning the questionnaire had more than one child with PKU. The educational level of the parents was significantly lower than in a representative sample of the population of parents with children in The Netherlands (mothers $\chi^2 = 6.99$, df $= 4$, $p = 0.03$; fathers $\chi^2 = 10.57$, $p = 0.005$) (Brugman et al 2001). Eight per cent of the mothers and 11% of the fathers were born abroad.

Table 2 presents the results of the regression analysis. The most important associations were as follows.

- Mean Phe concentration was lower when parents' past experiences were that their child adhered well to the diet, even if his or her Phe concentration was sometimes too high. Nine per cent of the parents thought that their child did not adhere well to the diet even when his/her Phe concentration was only sometimes too high.
- Mean Phe concentration was higher when parents answered that their relatives did not approve when their child deviated from the diet.
- Mean Phe concentration was lower when parents answered that having their child eat the synthetic protein substitute three times a day was easy. This variable consisted of four categories: very difficult, difficult, neither easy nor difficult, and easy. The difference between the highest and lowest categories was therefore 156 μmol/L (3 × 52 μmol/L). Twenty-four per cent of the parents found it easy to have their child eat the protein substitute three times a day.

Table 2 Predictors of mean Phe concentration

Variables		*Unadjusted coefficient*	*Adjusted coefficient*	*95% CI*	*p*
Age		−21	−15	(−36 to 6)	0.167
Age squared		18	13	(3 to 24)	0.014
Country of birth of the mother	Netherlands (ref.)	0	0		0.018
	Foreign country	129	144	(25 to 264)	
Other children with PKU in family	No (ref.)	0	0		0.102
	Yes	39	57	(−12 to 126)	
Academic hospital	Hospital F (ref.)	0	0		0.142
	Hospital A	−29	−89	(−187 to 10)	
	Hospital B	−46	−15	(−117 to 87)	
	Hospital C	−206	−117	(−219 to −14)	
	Hospital D	−27	−73	(−182 to 37)	
	Hospital E	−4	−13	(−111 to 84)	
Attitudes: Past experiences					
My child adheres well to the diet even if he/she does not always eat the synthetic protein substitute	Agree (ref.)	0	0		0.104
	Do not agree	74	75	(8 to 141)	
	Neutral	176	89	(−15 to 194)	
My child adheres well to the diet even if his/her Phe concentrations are sometimes too high	Do not agree (ref.)	0	0		0.000
	Agree	−103	−121	(−215 to −27)	
	Neutral	67	72	(−58 to 201)	
Within the diet you can make tasteful meals	Agree (ref.)	0	0		0.014
	Do not agree	93	90	(−1 to 181)	
	Neutral	−119	−65	(−185 to 55)	
Subjective norm					
The extent to which relatives do not approve when the child deviates from the diet		10	10	(3 to 17)	0.004
The extent to which the partner finds it a challenge to make the child adhere to the diet		5	6	(1 to 11)	0.021

(*Continued on next page*)

Table 2 (Continued)

Variables	*Unadjusted coefficient*	*Adjusted coefficient*	*95% CI*	*p*
Self-efficacy				
The extent to which it is easy to have the child eat the synthetic protein substitute three times a day	−82	−52	(−89 to −15)	0.007
The extent to which it is easy to refuse when somebody offers the PKU child forbidden food	−44	27	(−10 to 65)	0.150
The extent in which it is easy to raise a child with PKU	−93	−50	(−94 to −6)	0.028

DISCUSSION

We found that parental past experiences with PKU and the diet, subjective norms, self-efficacy and demographic variables were associated with mean Phe concentration of the child (Table 2). The most important finding is the fact that mean Phe concentration is considerably lower when parents stated that (a) having their child eat the synthetic protein substitute three times a day was easy and (b) their child adhered well to diet even if his/her Phe concentration was sometimes too high. These results seem to indicate that a strict use of the synthetic protein substitute is even more important than a very strict handling of the restriction of the natural protein intake. We stress that these findings should be interpreted with caution owing to the limitations of our study design. However, these findings are further supported by the studies on daily variations in the Phe concentrations in PKU patients by MacDonald and colleagues and van Spronsen and colleagues (MacDonald et al 1996, 1998; van Spronsen et al 1993, 1996). These studies showed that dividing the synthetic protein substitute evenly over the day is more important than dividing the natural protein intake evenly over the total day.

Combination of those results with the results of the present study seems to indicate that there may be a delicate balance in the strictness of the treatment and that too strict handling of the dietary Phe restriction is not associated with lower Phe concentrations. At the same time, an even distribution of the daily intake of the prescribed amino acid intake is of great importance. This seems to be in line with the study of Shulman, who stated that—notwithstanding the importance of a strict diet—it is important for families to develop an efficient system to make the child adhere to the diet without being too rigid, allowing some deviation from the diet from time to time. Further studies are necessary to investigate the precise influence of these day-to-day aspects within the treatment strategy that results in adequate Phe concentrations but also results in a diet that is not too much of a burden. It is important to prevent deterioration due to too rigid a system (Shulman et al 1991).

Another implication of the findings of the present study is that not always eating the synthetic protein substitute may tell us more about the adherence to the diet in general. Not using the amino acid supplement adequately may indicate that the diet is not taken seriously and that the importance of the protein substitute is not fully understood, or even that the disease is not 'accepted'. Another explanation for not eating the protein substitute could be that its taste and smell are still not very appetizing (Prince et al 1997).

Mean Phe concentrations were also higher when parents answered that their relatives did not approve when their child deviated from the diet. These perceived subjective norms often represent the way parents themselves deal with the dietary adherence of their child. Therefore, our results seem to support the hypothesis as formulated above that a strict adherence to the diet is important. However, parents and family should not be too rigid by not allowing some deviation from time to time. It is, however, also possible that a higher Phe concentration of the child leads to a stricter attitude of the relatives. This limitation is due to the fact that our study is cross-sectional rather than longitudinal. We cannot, therefore, assess whether a strict attitude of relatives precedes or follows high mean Phe concentrations. The more the partners of the respondent experienced the adherence of the child to the diet as a challenge, the higher was the mean Phe concentration. We had expected to find an opposite relationship. A possible explanation could be that parents who still think that the diet is a challenge have not accepted PKU completely and have not yet integrated the diet into their normal lives. This suggests that respondents perhaps associated the item with a negative rather than a positive meaning of the word challenge.

When parents experience difficulties in raising their child with PKU, the Phe concentrations are higher. This sounds logical: parents who have more difficulties have more problems keeping the child in line and will more often have a child with higher concentrations. Higher Phe concentrations may also influence the behaviour of the child (Smith and Beasley 1989; Smith et al 1988; Stemerdink et al 2000; Weglage et al 1992). Poor adherence may drag a family into a negative vicious circle. Poor adherence causes high Phe concentrations, which leads to behavioural problems in the child or adolescent, and as a consequence to less adherence to the diet, and so on. It is well known that older children with PKU have higher Phe concentrations (Bekhof et al 2005; MacDonald 2000; Shulman et al 1991; Walter and White 2004). Problems with dietary adherence during adolescence are in line with findings in children with chronic diseases such as diabetes (Hoffmann 2002; McQuaid and Nassau 1999). These age-related problems with the diet may be due to the fact that patients, at an age when acceptance of rules and restrictions is at a minimum, are more prone to reject a given regime, especially when it is imposed by their parents and other authority figures. However, increase in problems with dietary adherence could also be due in part to hormonal changes and the decreasing need for protein after the period of increased growth.

The fact that the country of birth of the parents is associated with Phe concentrations has been reported before (Verkerk et al 1994). Apart from problems related to language, cultural eating habits, and different ways of following the instructions of a medical centre, a possible explanation is that there is little specific information available for this group. Giving dietary advice to this group of patients and parents may be more difficult for Dutch healthcare workers, who are likely not to have enough knowledge of the eating habits and ingredients in other cultures.

In conclusion, this survey among parents of PKU children showed some important factors related to mean Phe concentration of the patient. Based on the results of the present study, parents of PKU patients should be advised more strongly and encouraged to have their children eat the synthetic protein substitute at least three times a day, and to instigate strict dietary control without being excessively rigid. In addition, parents as well as patients should be given directions about what really constitutes a deviation from the diet and what deviation is acceptable.

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