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PKU—What is daily practice in various centres in Europe?

Data from a questionnaire by the scientific advisory committee of the European Society of Phenylketonuria and Allied Disorders

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Summary
Background: Since the start of the European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU) in 1987, an increasing number of parental organizations of member countries have joined. Treatment varies widely within Europe. A survey among professionals was done to determine goals and practice.
Method: In 2005, a questionnaire was sent to professionals of member countries, addressing diagnostic and treatment procedures, numbers of patients necessary for a PKU centre, guidelines followed, numbers of patients treated and professionals involved in care, target phenylalanine concentrations, amount of protein prescribed, frequency of monitoring and clinical visits, need for follow-up of various clinical and biochemical data, the importance of various abnormalities, and definition of (non)compliance.
Results: Seventeen centres of 12 countries answered. Professionals of 13 countries could not be reached or did not respond. Differences in care were observed in many issues of care including target phenylalanine concentrations. Only few issues had general consensus.
Conclusion: Not all countries were really active at ESPKU level. In the active countries, a professional could not always be contacted. Responses show that PKU care varies largely between European countries. Notwithstanding the large diversity on many issues of day-to-day care and therapeutic targets, results showed increasing consensus on some issues. The most important outcome of this questionnaire might be that the Scientific Advisory Committee of the ESPKU initiated meetings for professionals of different backgrounds taking care of PKU patients besides the already existing programme for parents, patients and delegates. Discussion among these professionals may improve quality of care.

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Abbreviations

ESPKU	European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
Phe	phenylalanine
PKU	phenylketonuria

Introduction

The European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU) is an umbrella organization of national societies of patients with phenylketonuria (PKU) and other diseases treated in a comparable way. Since the start of ESPKU in 1987, an increasing number of countries have joined. Every year a meeting is organized by one of the member countries or the ESPKU board. Among these meetings, every second year there is a small meeting for delegates of the parental national societies of PKU; in the years in between there is a large meeting with delegates from each country and families, especially of the organizing national society. From the start, professionals were asked to give lectures, both overview and research papers. These lectures are organized by the scientific advisory committee of the ESPKU. Since the time that the scientific advisory committee was chaired by Professor Baerlocher (2001–2006), it became practice to exchange ideas between professionals on day-to-day care and research projects in the centres present at the meeting.

In 1993 the British, and in 1999 the German PKU working groups published their national guidelines on the treatment of PKU (Burgard et al 1999; MRC 1993a, b).

The paper of Burgard and colleagues (1997) clearly showed different treatment perspectives in France and Germany. There have been some initiatives towards an international guideline, especially regarding target phenylalanine (Phe) concentrations (Schweitzer-Krantz and Burgard 2000). The truth is, however, that we simply do not know what the practice is in all countries. This applies to target Phe concentrations and other concerning PKU care. In 2005, a survey was done to determine what the treatment strategies of PKU were in various centres of the European countries. The present paper shows the results of this questionnaire.

Method

A questionnaire was sent by e-mail to one or more professionals (physicians, nutritionists and dieticians, and psychologists) of 33 centres known to work in the member countries of ESPKU. The centres were asked to return the questionnaire before a tight deadline to enable presentation of the data at the 2006 ESPKU meeting. The questionnaire addressed issues about the following main topics (1) treatment procedures/organization; (2) diagnostic procedures; (3) specific guidelines followed; (4) care for patients under the age of 16 years; (5) care for patients over the age of 16 years; (6) care for women with PKU aiming to bear children; (7) problems observed in adult patients; (8) the importance of test results. If the survey was answered more than once by the same centre (answered by both a dietician and physician), the survey returned by the physician was taken into account.

In the questions concerning care for patients, the questionnaire focused on the target Phe concentrations, the amount of protein prescribed, the frequency of monitoring and clinical visits, and the necessity for follow-up of various clinical and biochemical data and the way this was performed in the various centres. Participants were asked to judge measures in adulthood that could be regarded as important by centres (e.g. decreased bone density, too high Phe concentrations), on a scale from 1 ‘not important’ to 5 ‘very important’.

Statistical analysis

Owing to the nature of the study, only descriptive analyses with ‘most observed value or number’, mean, and range were performed. With regard to the importance of specific measures of follow up, means with range were calculated.

Results

Of the 25 countries participating in the ESPKU in 2005, data from 12 countries (17 centres) could be used. Centres included were from Belgium, Denmark, Germany (2), Italy, Latvia, Lithuania, Norway, Poland (2), Slovenia, Swiss, The Netherlands (3), United Kingdom (2). Questionnaires were mainly answered by physicians, but also by dieticians (2). Three centres responded by sending responses of both physician and dietician.

Results of the questionnaire on issues concerning treatment procedures/organization showed that the PKU team always consisted of a physician and a clinical dietician. In most paediatric centres the physician was a paediatrician specialized in metabolic diseases, but in four centres the physician was a paediatric neurologist, a clinical geneticist, or a general paediatrician. The nutritionist/dietician in most centres also took care of patients with other metabolic diseases. Three centres cared for adult PKU patients only. Two of these centres had a physician specialized in metabolic diseases in adults, one centre had a

Table 1 Demographic characteristics of participating centres

Centre	<16 years (% lost to follow-up)	>16 years (when not specified)	>16 years (male) (% lost to follow-up)	>16 years (female) (% lost to follow-up)	Number of pregnancies in previous 2 years	Longest distance to PKU clinic	Number of children/ adults considered necessary for a PKU centre
A	97 (6)		32 (31)	34 (15)	3	100	
B	54 (9)		29 (10)	25 (12)	1	300	<20
C	0		146 (?)	191 (?)	30	200	20–50
D	57 (0)		17 (?)	23 (?)	3	300	<20
E	54 (?)	0				300	<20
F	71 (0)		38 (?)	52 (?)	9	500	20–50
G	408 (18)	368 (5)					
H	92 (0)		54 (33)	47 (21)	2	500	
I	145 (27)	60 (?)			6	200	20–50
J	0		23 (0)	27 (0)	7		
K	496 (2)		153 (7)	185 (9)	3	100	80–100
L	133 (5)		82 (4)	98 (10)	10	300	
M	126 (1)		77 (40)	92 (21)	20	100	20–50
N	0		30 (100)	50 (60)	2		
O	65 (2)		54 (32)	75 (44)	4	100	20–50
P	83 (1)		22 (14)	20 (5)	2	400	20–50
Q	38 (?)		14 (?)	18 (?)	2	100	20–50
Mean/*most reported	137 (?)		45 (?)	55 (?)	7	205	*20–50
Range	38–496 (0–27%)		17–153 (0–100)	18–191 (0–60)	0–30	100–500	1–100

Table 2 Data on diagnostics procedures and first treatment aims

Participating centres	Day at which screening was performed	Phenylalanine cut-off concentration (μmol/L)	Phenylalanine conc. at which treatment is started (μmol/L)	Target phenylalanine concentration at start of treatment (μmol/L)
A	3–4	168	480	120–360
B	2	120	360	120–360
C	5–7	250	360	
D	3–5	120	400	<360
E	4–5	150	360	120–240
F	3	170	400	120–400
G	4	120	360	<360
H	5	172	420	120–300
I	3–4	130	400	100–350
J	4–7	240	360	
K	3–4	168	480	120–360
L	3	123	600	60–240
M	6	240	360	
N	3	123	600	
O	4	150	490	<360
P	4–7	240	360	120–360
Q	4–7	240	360	<240
Mean/*most reported	4.2	211	421	*120–360
Range	2–7	120–250	360–600	60–400

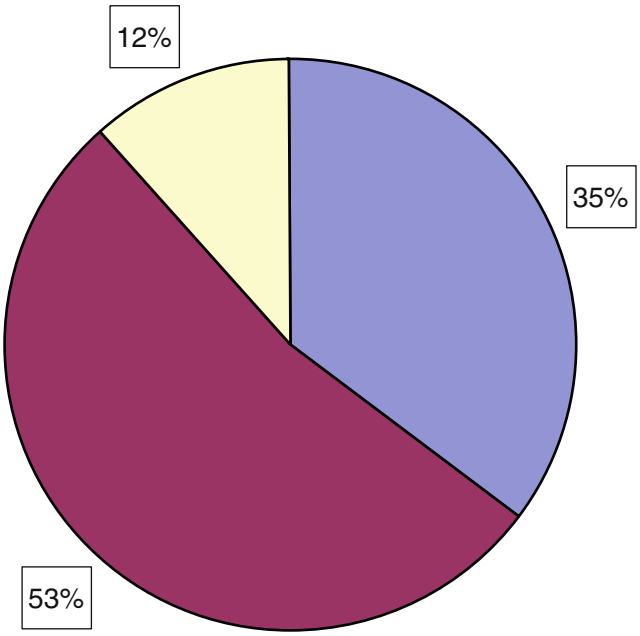

Fig. 1 Use of PKU guidelines by the 17 answering centres in Europe. Blue: Centres' own guidelines; Red: national guidelines; Yellow: non-British centres following British guidelines

paediatrician specialized in metabolic diseases. Ten centres had a psychologist, eight centres a specialized nurse, five centres a social worker, two centres a clinical geneticist, while one centre had a diet cook and one centre a neurologist as part of the PKU team.

Table 1 presents data on numbers of patients ≤16 and >16 years of age with percentage loss of patients, recent experience with maternal PKU, maximum distance to the clinic, and numbers of patients considered necessary to function as a PKU centre for children and/or adults. There is a clear variation in demographic characteristics of centres. Three centres treat only adults; most of the reporting centres treat both children and adults with PKU. The questionnaire showed some high numbers of patients lost to follow-up. One centre reported losing more children than adults, but that may refer to the fact that many of these children had very mild hyperphenylalaninaemia.

Concerning diagnostic procedures, national newborn screening programmes had become available in all of the responding countries between 1964 and 1994 (Table 2). In 2005, tetrahydrobiopterin loading tests were performed in 50% of the participating centres, and DNA analysis was routinely performed in nine centres. Figure 1 shows that most centres follow national guidelines. When international guidelines were followed, the (non-British) centres indicated that they followed the British guidelines rather than the German guidelines. Breastfeeding was encouraged in all centres directly after diagnosis (although the method of prescribing human milk may vary). When establishing the Phe intake, nine centres also took the low-Phe food into account.

Table 3 shows the most frequently observed answers with ranges for target Phe concentrations for various ages, amount of prescribed protein, frequency of clinical evaluation, Phe control and complete amino acid analysis. Variation in frequency of blood sampling for analysis of Phe concentrations, amino acid concentrations, and clinical visits was largest during treatment

Table 3 Data on targets of treatment in PKU care

	Age (years)							Issue
	0–1	1–4	4–10	10–12	12–16	>16		Pregnancy (intention)
						Male	Female	
Frequency blood Phe/month[a]	4 (1–6)	3 (1–4)	1.5 (1–3)	1 (1–2)	1 (0.5 –2)	1 (.33 –2)	1 (.33 –2)	8 (1.5 –12)
Frequency blood amino acid measurements/year[a]	2 (0–4)	1 (0–4)	0 (0–2)	1 (0–1)	1 (0–1)	1 (0–2)	1 (0–2)	3 (0–10)
Frequency of clinical evaluation/year[a]	9 (2–12)	4 (1–6)	3 (1–4)	2 (1–4)	1 (1–3)	1 (1–2)	1 (1–2)	9 (3–18)
Advised total protein intake/kg body weight[a]	2.5 (1.9–3.2)	2.5 (1.6–3.0)	2 (1.4–2.5)	1.5 (1.2–2.5)	1.5 (1.2–2.5)	1 (0.8–2.0)	1 (0.8–2.0)	1.2 (1–2)
Target Phe range (μmol/L)[a]	120–360 (0-400)	120–360 (0-400)	120–400 (0–480)	120–360 (0–900)	120–600 (0–900)	120–700 (0–900)	120–700 (0–900)	120–240 (60–360)

[a] Most frequent observed number or value with range.

Table 4 Summary of measurements of follow-up in PKU patients of various age groups

Measurements	Age (years)								
	0–10[a]			10–16[a]			>16[b]		
	Never	When indicated	Routine	Never	When indicated	Routine	Never	When indicated	Routine
Clinical neurological studies	0	0	14	0	0	14	0	0	17
MRI brain	13	1	0	9	1	4	12	1	4
Bone density	11	1	2	7	2	5	7	3	7
Calcium	5	0	9	4	1	9	4	1	12
Trace elements	5	1	8	6	1	7	8	1	8
Vitamin B_{12}	7	0	7	5	1	7	5	1	11
MRS brain	14	0	0	11	1	2	13	2	1
(Neuro) Psychological studies	3	3	8	2	2	10	5	2	10
Essential fatty acids	9	1	4	8	1	5	11	1	5

[a] Data apply to 14 centres taking care of children with PKU.
[b] Data apply to 17 centres taking care of adults with PKU.

during pregnancy or the intention of pregnancy. There was variation in total protein intake throughout the total period of care. There was no difference in targets of control and Phe concentrations between male and female patients, but the target Phe concentration in particular differed between centres after the first decade of life.

Table 4 presents the data on follow-up measurements in patients 0–10 years of age, 10–16 years of age and >16 years of age. Follow-up until 10 years of age always included clinical evaluation of neurological function, usually included measurement of calcium concentrations in blood and/or urine, vitamin B_{12} concentrations, trace elements, and (neuro)psychological evaluation, but never included MRI and MRS. Although many centres performed (neuro)psychological studies routinely, the frequency varied from once up to five times during the first decade. Bone density was analysed once by one centre during the first decade. Within the periods 10–16 years of age and >16 years of age, the frequency of these measures increased or remained comparable. The variation was seen for almost all measures in all age periods. The measures that are relatively constantly performed in some centres are clinical neurological examination and (neuro)psychological studies.

Fifteen out of the 17 centres answered the questions related to the care for maternal PKU (Table 1). The numbers of pregnancies treated within the previous two years varied between 1 and 30. In the total of 111 pregnancies reported for the previous two years, blood Phe concentrations were within target range in 78 patients at conception. When the Phe concentrations were within target range, they usually remained so.

Table 5 shows the importance of specific issues in adulthood. The responding professionals did not consider a normal fatty acid profile or having all phenylalanine concentrations within target range in adults to be of relatively high importance. In contrast, issues such as fewer than 50% of the Phe concentrations in range, inadequate intake of amino acid supplement (and vitamins and minerals), and abnormal neuropsychological outcome were considered of high importance by most of the professionals.

Table 5 Average grade of importance of specific issues of care in adults. Issues were graded from 1 to 5, where 5 is the maximum score

Phenylalanine concentrations in range in 100%	2.3
Abnormal fatty acid profile	2.8
Brisk reflexes	2.9
Abnormal MRI	3.1
Low tyrosine concentrations	3.3
Phenylalanine concentrations in range in 75%	3.9
Suboptimal sociopsychological well being	3.9
Neurological problems (apart from brisk reflexes)	4.1
Decreased bone density	4.2
Abnormal neuropsychological results/IQ measures	4.3
Inadequate intake of amino acid supplement	4.3
Inadequaate intake of vitamins/minerals	4.3
Phenylalanine concentrations in range in 50%	4.3

Discussion

The most important finding of the present study was the large diversity in treatment aims and procedures all over Europe. Even within countries with a national guideline, the diversity can be large. The second important finding was that the therapeutic targets of the PKU centres were not always comparable, especially for adolescent and adult PKU patients. Therefore, definition of good or poor compliance of the patients at an international level is quite difficult.

Before discussing the results of the questionnaire more closely, some drawbacks of the present study should be acknowledged. Professionals of 13 countries did not answer or did not even receive the questionnaire. There was a lack of knowledge of contact professionals in some European countries. The ESPKU did not have actual details of each member organization at that time, and even less data on contact addresses of professionals, as there was no real structure of ESPKU professionals. Thus, some colleagues were addressed based on personal contacts rather than activities within the ESPKU. Because distribution of the questionnaire among countries was poor, we had to opt for descriptive rather than full analytic statistics. The present study showed that there was quite some diversity between centres in many aspects of care of patients with PKU. Some of the centres may be regarded as small, especially those with fewer than 20 patients to care for. It is disputable whether these centres provide optimal care (Camfield et al 2004). However, when the next centre is either >300 km away or abroad, there may still may be a real need for that centre.

The present data show an increase in uniformity in guidelines on some of the issues addressed by Schweitzer-Krantz and Burgard (2000), and uniformity with issues such as breast feeding. At the same time, the diversity was still very large with respect to the recommended plasma Phe concentrations during dietary treatment. The diversity was even larger for issues not addressed by Schweitzer-Krantz and Burgard (2000). For example, professionals of centres/countries were rather diverse in the follow up, both clinical and biochemical, the importance of specific findings in clinical and biochemical follow-up, and their definition of good compliance. Differences in frequency of amino acid measurement were the most obvious during the first year of life and in maternal PKU. Some countries did not perform amino acid analyses at all.

In this survey, we asked professionals to indicate how often specific measures were performed, including blood and urine measures, bone density, MRI, neuropsychological outcome, and to present their view on the importance of the outcome of these measures in adulthood. There seems to be some consensus on these issues. At the same time, even though MRI, neuropsychological outcome measures and bone density were considered important, they were not studied on a routine basis within all centres. This survey did not ask specifically about the importance of vitamin B_{12} deficiency. However, most centres took vitamin B_{12} into account in their follow-up programme. Vitamin B_{12} deficiency is probably the most important risk of deficient intake of amino acid mixtures (Hanley et al 1993), but the prevalence of this issue needs to be investigated in future studies.

In the past, Walter et al (2002) showed that a high number of adult PKU patients have too high plasma Phe concentrations. The present study substantiates this finding, showing that—as an average—some 60% of the adult patients had Phe concentrations above target range.

Guidelines clearly were not evidence based. Many professionals made their own guidelines, especially based on daily practice. This could be due to a lack of time, lack of supportive team members, and—even more important—lack of available data with which synthesize an evidence-based guideline. Large-scale (European) studies may provide the data necessary for international guidelines. These guidelines may help to define common targets not only of Phe concentrations but also of other variables of outcome and compliance. This study clearly shows that the road to consenus is long. Apart from this, guidelines do not tell the whole truth of day-to-day care (van Spronsen and Burgard 2008). Even using the same guidelines for Phe targets may result in different Phe concentrations (Walter et al 2002).

One of the most important 'results' of this survey might be that after 2005 the scientific advisory committee started to organize meetings for professionals at the ESPKU. Therefore, this questionnaire should be seen as a start to enable further discussion rather than an end-result of discussion. Since 2006, the meeting has been divided into two parts. On the first day, patients/parents/delegates and professionals have their own programmes. During the sessions for professionals only, discussions are with dieticians, physicians, biochemists and psychologists in a very informal atmosphere, so that experience and research details can be discussed quite extensively. In this way, the ESPKU meetings for professionals aim to be a platform of all professionals taking care of PKU patients, and to improve the quality of our care for these patients. On the second/third day, patients/parents/delegates and professionals have a common

programme, professionals presenting papers and conclusions from their discussions the day before, with a forum discussion.

In conclusion, this survey among European centres taking care of PKU patients shows that treatment organizations, strategies and procedures varied widely between the individual member countries of ESPKU, clearly necessitating a more structured discussion of the targets of treatment centres, aiming for an international guideline that not only addresses the target plasma Phe concentrations but also advises on other issues of PKU care both for children and adults.

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