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Original Research Article

Daily practices of phenylketonuria in various centres in Turkey "a retrospective, cross-sectional study"

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Abbrevations

PKU: phenlketonuria
HPA: hyperphenylalaninemia
Phe: phenylalanine

There is an large diversity in treatment aims and procedures in phenylketonuria (PKU) through the pediatric nutrition and metabolic disease clinics in different regions of Turkey. A survey among professionals was done to determine goals and daily practice.A questionnaire was sent to professionals of the pediatric nutrition and metabolic disease clinics of different regions of Turkey, addressing diagnostic and treatment procedures, numbers of patients necessary for a PKU centre, quidelines followed, numbers of patients treated and professionals involved in care, target phenylalanine (Phe) concentrations, amount of protein prescribed, frequency of monitoring and clinical visits, need for follow-up of various clinical and biochemical data. The dates of diagnosis, blood Phe levels (last 2-3 years), last anthropometric measurements (body weight, height) were ascertained from medical dossiers and records.Eight clinics of six countries answered the questions of daily practices in PKU. Among the various clinics, differences in daily practice were observed with regards to blood Phe values (mg/dL) accepted for initiation of medical nutrition treatment, target blood Phe concentrations (mg/dL), the recommended protein intake and the dosages of protein substitutes, allocating daily Phe allowance, definition of foods that could be eaten without restriction ("free foods"). Responses show that PKU care varies widely between centres, so it was confirmed that it is necessary to develop a guideline specific for Turkey that covers all practices beginning from the screening of newborns to follow-up.

Key words: Phenylketonuria, quidelines, daily practice, phenylalanine

INTRODUCTİON

PKU is an inherited metabolic disorder caused by deficiency in Phe hydroxylase enzyme (PAH), which converts Phe to tyrosine. If ileft untreated from birth, this results in rapid accumulation of toxic concentrations of Phe in the blood, leading to severe brain damage. The vast majority of cases are now identified via neonatal screening programmes, allowing timely intervention to avoid severe consequences.

A low-Phe diet currently forms the principal strategy to limit Phe accumulation in the blood and, therefore, in tissues such as the brain. The low-Phe diet restricts the intake of high-protein foods, and the remaining nutritional requirements must be obtained from Phe-free amino acid supplements (protein substitute) and special or natural foods that are low in Phe. The treatment goal with dietary restriction is to maintain blood Phe concentrations within defined target limits which may vary from centres (2–6 mg/dL).

Newborns born in maternity hospitals in the metropolitan areas of 27 cities in Turkey have been screened for PKU since 1986. On the other hand, the

Turkish Ministry of Health organized a nationwide neonatal screening programme for PKU and congenital hypothyroidism since 25 December 2006. In 2001 the incidence of persistent HPA was found to be 1/4172 and PKU was 1/5049 in Turkey. In 2007 246, in 2008 217, in 2010 182 of the newborns diagnosis of PKU, indicating the last digit for Turkey was determined as 1/6228. Thus, Turkey seems to have a higher with other countries and has a particularly high consanguinity rate (45.7 %).

Although PKU is seen widely in Turkey, we do not have a national guideline on the treatment of PKU, so we simply do not know what the practices is in various clinics. In 1993 the British and in 1999 the German PKU working groups had published their national guidelines on the treatment of PKU (Burgard et al 1999; MRC 1993a, b). This identifying target Phe concentrations and other concerning PKU care. Therefore in 2011, a study was started to determine daily practices of PKU in the pediatric nutrition and metabolic disease clinics in different regions of Turkey. The present paper shows the results of this study.

METHOD

In 2011, a questionnaire was administered face-to-face during course hours by the researcher to one or more professionals (16 physicians and 15 dieticians) of eight pediatric nutrition and metabolic disease clinics in different regions of Turkey (Ankara (2 clinics), İzmir (2 clinics), Adana (1 clinic), Kayseri (1 clinic), Sivas (1 clinic), Eskişehir (1 clinic). If the survey was answered more than once by the same centre (answered by both a dietician and physician), the survey performed again by the physician was taken into account.

To determine the practices of physicians and dieticians, a multiple-choice questionnaire consisting of the sections entitled “newborn screening and diagnosis (10 question)”, “medical and medical nutritional treatments (60 question)” , “evaluation of growth and nutrition (15 question)”, “dietary compliance (13 question)” and “monitoring (11 question)” was used. The survey was completed in the middle of 2012.

The dates of diagnosis, blood Phe levels, last anthropometric measurements (body weight, height) were ascertained from medical dossiers and records. File records of 61.1 % PKU (1215 PKU children) and 17.7 % (138 HPA children) hyperphenylalaninemia (HPA) patients, total 1383 (50.0 %) have reached.

Total of 8654 blood Phe measurement results were collected. The median blood Phe concentration for the preceding 3-year period was used as an indicator of metabolic control in this study because there was a strong positive correlation between the measured last blood Phe concentration (0.1-29.8 mg/dL) and the median blood Phe concentration (0.2-28.0 mg/dL) for the previous 3-year period ($r = 0.499$, $p<0.05$).

Body Mass Index (BMI) value was calculated, with the formula of body weight (kg) / height (m^2). BMI (kg/m^2) value > 2 standard deviation (SD) per age has been classified as obesity, body height under <-2 SD has been evaluated as short body height (stunding), this evaluations are in accordance with WHO 2006 standards.

Tugba Kucukkasap Comert, Gulden Koksal declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation. Informed consent was obtained from all clinicans (dietitians and doctors) and patients’ family for being included in the study. And this study was approved by the Ethical Committee for Medical, Surgical and Drug Research at Hacettepe University Faculty of Medicine, Ankara, Turkey (LUT 12/83-10).

Statistical analysis

Evaluation of the data, with the SPSS 15.0 statistical software package was used. Answers of the questionaire, descriptive analyses with mean, median and range were performed. The relationship between the median blood Phe values (mg/dL) and age, as well as the relation between the date of diagnosis (days) was determined using the pearson correlation coefficient. All statistical tests were taken as the lowest significance level of 0.05.

RESULTS

Data of the eight pediatric nutrition and metabolic disease clinics in different regions of Turkey could be used. Centres included were from Ankara (2), İzmir (2), Adana (1), Kayseri (1), Sivas (1), Eskişehir (1). It is determined that 15 dieticians, 23 doctors are worked and 1998 PKU, 778 HPA, total 2768 patients are followed. Questionnaires were answered by all dieticians (15) and 16 physicians, 1215 PKU (61.1 %), 138 HFA (17.7), total 1383 (50.0 %) patients have been reached.

Table 1 presents the data on the number of doctor, dietician and patients per pediatric nutrition and metabolic disease clinic in the time of the study.

Table 2 shows the number of patients (PKU/HPA) per doctor and dietician in each pediatric nutrition and metabolic disease clinic in the time of the study. It is indicated that the number of patients per dietician (184) is higher than doctor (173) and is widely changed among clinics.

The age of diagnosis of PKU varied between 1.00-9169.00 days before the screening program of newborns is conducted entire Turkey in 2006. After the years of 2006 it ranged from 1.00-2040.00 days and the median date of diagnosis is less (30.00 days) than the previous (60.00 days).

According to the blood Phe levels definitions of PKU was found same, while moderate PKU, mild PKU and HPA was found to vary between clinics. According to the blood Phe levels (mg/dL) definition of PKU/HPA in different clinics is shown in Table 3.

Table 1. Data on the number of doctor, dietician and patients per pediatric nutrition and metabolic disease clinic in the time of the study (n=8)

Participating centres	Pyhsician	Dietician	PKU patients	HFA patients	TOTAL patients
A(April 2013)	4	6	1350	485	1835
B(November 2010)	6 (2)	1	300	50	350
C(July 2011)	2	1	110	180	290
D(November 2010)	3	1	45	3	48
E(April 2011)	3 (2)	1	56	-	56
F(June 2011)	1	1	70	7	77
G(July 2011)	2 (1)	3	25	5	30
H(October 2012)	2 (1)	1	42	50	92
TOTAL	**23**	**15**	**1988**	**780**	**2768**

*In the paranthesis it is indicated that the number of doctors continuously working

Table 2. Number of patients (PKU/HPA) per doctor and dietician in each pediatric nutrition and metabolic disease clinic in the time of the study (n=8)

Participating centres	Number of patients (PKU/HPA) per doctor and dietician	
	Doctor	Dietician
A	458	305
B	583	350
C	145	290
D	16	48
E	18	56
F	77	77
G	14	28
H	46	92
TOTAL	**173**	**184**

Table 3. According to the blood Phe levels (mg/dL) definition of PKU/HPA in different clinics

CLINICS								
	A	B	C	D	E	F	G	H
Definition	**Blood Phe levels (mg/dL)**							
Classical PKU	>20	>20	>20	>20	>20	>20	>20	>20
Moderate PKU	15-20	15-20	15-20	20	10-20	15-20	15-20	10-20
Mild PKU	10-15	10-15	10-15	10—20	6-10	<15	10-15	<10
HPA	>10	2-10	>10	>6	>6	>10	>10	>10

Blood Phe concentration of PKU patients was found between the range of 0.20-28.00 mg/dL and the median blood Phe concentration 6.15 mg/dL. It was found statistically significant that PKU patient <1 year age had the lowest blood Phe level (5.33 mg/dL) .

In this study there was a large diversity found in the recommendation of blood Phe levels for age by various clinics (Table 4). There was a lack of concensus on what was the target blood Phe level.

In this study a statistically significant relationship was found between the median value of blood Phe levels (mg/dL) and the diagnosis age (day) of PKU patients ($p<0.05$) (Table 5).

In all clinics, recommendation of protein decreased with age due to lower protein requirements for growth. But recommended amount of protein in all ages varied from clinic to clinic (Table 6).

Phe can either be allocated in total daily amounts where all Phe containing foods are counted in the diet, or by Phe exchange systems, where portion sizes of Phe-containing foods are precalculated for a defined amount of Phe in the treatment of PKU.

There were also differences among clinics in the types of higher protein-containing foods permitted, none of the clinics used many higher biological value protein containing foods (meat, fish, cheese) to constitute part of their Phe allowance for all patients with PKU, only one clinic used these for HPA patients (Table 7).

Table 4. Desirable blood Phe levels (mg/dL) by age in patients with PKU in different clinics

CLINICS								
	A	B	C	D	E	F	G	H
Age group	**Blood Phe levels (mg/dL)**							
Newborn	2.0-6.0	2.0-6.0	2.0-6.0	6.0	6.0	2.5-5.0	2.0-6.0	2.0-6.0
Preschool age	2.0-6.0	2.0-6.0	2.0-6.0	6.6	8.0	<5.0	2.0-6.0	2.0-6.0
School age	2.0-10.0	2.0-6.0	2.0-10.0	8.0	10.0	<10.0	2.0-10.0	2.0-6.0
Adolescent	10.0-15.0	2.0-6.0	10.0-15.0	10.0	10.0	10.0-15.0	10.0-15.0	2.0-6.0
MPKU(before pregnancy)	3.0-5.0	2.0-6.0	2.0-4.0	-	10.0	2.5-5.0	2.0-4.0	2.0-6.0
MPKU (after pregnancy)	3.0-5.0	2.0-6.0	2.0-6.0	-	6.0	2.5-5.0	2.0-6.0	2.0-6.0

Table 5. Relationship between the median value of blood Phe levels (mg/dL), diagnosis age (day) and age (year) in PKU ($p<0.05$)

Variable	Median value of blood Phe levels (mg/dL)	
	n	R
Diagnosis age (day)	1245	0.074*
Age (year)	1245	0.163*

*r=spearmen correlation coefficient

Table 6. Recommended amount of protein by age in patients with PKU in different centres

CLINICS								
	A	B	C	D	E	F	G	H
Age group	**Protein (g/kg/day)**							
0-3 months	2.0	2.5-3.5	2.0	3.0-3.5	3 .5	3.0	2.0	2.0
3-6 months	2.0	2.5-3.0	2.0	3.0-3.5	3.0	2.5	2.0	2.0
6 month-1 year	2.0	2.5	2.0	2.5-3.0	3.0	2.4	2.0	2.0
1-3 years	1.5	2.0	2.0	≥30 g/day	3.0	1.9	2.0	2.0
4-10 years	1.2	1.5-2.0	1.5	≥35 g/day	2.5	1.6	1.5	1.5
>10 years	1.0	1.5	2.0	≥40 g/day	2.0	1.5	2.0	2.0

Table 7. Number of clinics permitting use of high protein foods as part of dietary PA allocation

Frequency of allowed food consumption in low-PA diet as part of their PA allocation				
Food	**Never**	**Generally**	**HPA patients only**	**Selected patients**
Meat/meat products	7 (A, B, C, D, F, G, H)	0	1 (E)	0
Fish	8 (A, B, C, D, E, F, G, H)	0	1 (E)	0
Cheese	7 (A, B, C, D, F, G, H)	0	1(E)	0
Yoghurt	2 (B, F)	2 (D, H)	6 (A, B, C, E, G, H)	4 (A, C, G, H)
Milk	1 8F)	5 (A, B, C, G, H)	6 (A, B, C, E, G, H)	6 (A, B, C, D, G, H)
Standard bread	0	2 (F, H)	6 (A, C, E, F, G, H)	7 (A, B, C, D, F, G, H)
Standard rice	0	3 (B, F, H)	6 (A, C, E, F, G, H)	5 (A, C, D, F, G)
Chocolate	7 (A, B, C, D, F, G, H)	0	1 €	0
Ice-cream	3 (D, F, H)	1 (B)	4 (A, C, E, G)	3 (A, C, G)

Clinics were opposed to the incorporation of most higher protein foods to make up Phe allowance because of the potential for patients to become accustomed to the taste, which could lead to a desire for more of it and the consumption of more than the required amount, which would thereby reduce compliance.

The benefits of breastfeeding babies with PKU are relatively well established; breast milk is low in Phe and is one of the best natural sources of BH4, and longer-term outcomes have been shown to be improved among

Table 8. Frequency of biochemical and heamotological measurements by age among clinics

Age Groups							
Measurements	**0-3 months**	**3-6 months**	**6 months-1 year**	**1-5 year**	**6-15 year**	**>15 year**	**MPKU**
Follow-up	1 (A, B, C, D, E, F, G, H)	3 (A, B, C, D, E, F, G, H)	3 (A, B, C, E, F, G, H) 2 (D)	4 (A, B, C, D, G, H) 3 (E, F)	6 (A, C, G, H) 5 (B, D) 4 (E, F)	7 (A, C, G, E, H) 5 (D, F) 6 (B)	1 (A, E)
Measurement of blood Phe levels	1 (A, B, E, D, F, H)	3 (A, B, E, D, F, H)	3 (A, B, E, D, F, H)	4 (A, B, D) 3 (E, F)	6 (A) 5 (B, D) 4 (E, F)	7 (A, E) 5 (D, F) 6 (B)	1 (A) 2 (E)
General healthcare	3 (A, B, C, D, E, F, G, H)	3 (A, B, C, D, E, F, G, H)	4 (A, C, F, G, H) 3 (B, D, E)	4 (A, B, C, F, G, H) 5 (D), 3 (E)	5 (A, B, C, D, F, G, H) 4 (E)	7 (A, C, D, E, F, G, H) 6 (B)	3 (A) 2 (E)
Food frequency questionnaire	3 (A, B, D, E, F)	3 (A, B, D, E, F)	4 (A, D, E, F) 3 (B)	5 (A, B, C, F, G, H) 3 (E), 4 (D)	5 (A, B, C, D, F, G, H) 4 (E)	6 (A, B, C,F, G, H) 5 (D) 7 (E)	3 (A) 2 (E)
Anthropometric measurements	3 (A, B, C, D, E, F, G, H)	3 (A, B, C, D, E, F, G, H)	4 (A, C, D, E, F, G, H) 3 (B)	5 (A, B, C, F, G, H) 3 (E), 4 (D)	5 (A, B, C, D, F, G, H) 4 (E)	6 (A, B, C,F, G, H) 5 (D) 7 (E)	3 (A) 2 (E)
Blood vitamine level	5 (A, F) 6 (D, E)	5 (A, F) 6 (D, E) 7 (B)	5 (A, F) 6 (D, E) 7 (B)	5 (A, C, F, G, H) 6 (D, E) 7 (B)	6 (A, C, D, E, F, G, H) 7 (B)	6 (A, C, D, F, G, H) 7 (B, E)	3 (A) 5 (E)
Complete blood count	6 (A, B, D, E, F) 5 (C, G, H)	6 (A, B, D, E, F) 5 (C, G, H)	6 (A, B, D, E, F) 5 (C, G, H)	6 (A, B, D, F) 3 (E) 5 (C, G, H)	7 (A, F) 3 (E) 6 (B, D) 5 (C, G, H)	7 (A, F) 4 (E) 6 (B, D) 5 (C, G, H)	5 (A) 4 (E)
Neuropsychological tests	-	-	-	7 (A, B, D, E, F)	7 (A, D, E, F)	7 (A, D, E, F)	-
Bone mineral density	-	-	-	7 (A, D, E, F)	7 (A, D, E, F)	7 (A, D, E, F)	-
Illness knowledge of the family members	5 (A, B, D, E, F)	5 (A, B, D, E, F)	5 (A, B, D, E, F)	6 (A, E, F) 4 (B, D)	6 (A, E, F) 5 (D)	7 (A, E, F) 5 (D)	3 (A, E)
Life quality tests	-	-	-	-	-	-	-

breastfed babies compared with those fed with formula. Most clinics (except one) encouraged breastfeeding (in combination with Phe-free infant aminoacid formula) in newly diagnosed infants with PKU.

Biochemical and haematological measurements varied widely among clinics (Table 8). Only general healthcare frequency was found same until 6 months in all clinics. Neuropsychological tests and bone mineral density measurement never done in maternal PKU patients. Anthropometric measeurements was done three times between the 0-3 months and 3-6 months of age in patients in all clinics. And life quality tests never done in all age groups in all clinics. The variation was seen for almost all measures in all age groups.

In this study it was taken care of that short stature was higher between the age of 10-19 years (30.6 %) than age of under five years old (8.8 %) in patients with PKU. In additionally obesity was shown quitely higher between the age of 5-10 years old (11.3 %) than the age of <5 years old.

DİSCUSSİON

The most important finding of the present study was the large diversity in treatment aims and procedures in the treatment of PKU all over Turkey. The second important finding was that the therapeutic targets of the PKU clinics were not comparable. Therefore, definition of good or poor compliance of patients at various clinics is quite difficult. At the same time, the diversity was still large with the recommendation amount of protein intake, desirable blood Phe levels (mg/dL) and permittion use of high protein foods as part of dietary Phe allocation in PKU patients.

Diagnosis age is as important as treatment in PKU. In developed countries, target age of diagnosis for PKU is 7-10 days, according to our country the first target of the diagnosis age is 15 days. In this study, after the screening program of newborns is conducted entire country in 2006, it is found that diagnosis of PKU <15 days rate is 21.2 % and is below the our national target. In Turkey, screening procedures of PKU should be evaluated, missing should be obstructed.

In this study a statistically significant relationship between the median value of blood Phe levels (mg/dL) and the diagnosis age (day) of PKU patients was shown ($p<0.05$) (Table 5). It is confirmed with our data that adherence of treatment in PKU is being diffucult within the increasing age, as a result of developing social life. In additionally development of brain damage result of the late diagnosis age, bringing together adherence to medical nutrition therapy difficulties may cause high blood Phe levels was confirmed with our data.

In this study it is determined that 15 dieticians, 23 doctors are worked and 1998 PKU, 778 HPA, total 2768 patients are followed in pediatric nutrition and metabolic disease clinics.

Number of patients that were followed was learnt by verbal estimate, consequently determination of the actual number of patients was unable.

All the dietitians who were responsible for the treatment

of PKU, was determined that their only responsibility was not metabolic disease, PKU, it was only one part of their work. It was clearly demonstrated that there wasn't a specialized dietitian in any of pediatric nutrition and metabolic disease clinics. Also child development, social worker and a psychologist was not a part of pediatric nutrition and metabolic disease team in any of centres, they received support from other departments, only nurse was worked as a part of metabolic team.

Dietitians have unequal training, status and responsibilities throughout Turkey. Degree courses in dietetics are not of equivalent standard, and dietitians may have different skills and competencies. There is no standardised qualification or international association for those responsible for managing diet in patients with PKU. Accordingly, in practice, dietitians often gain their knowledge through practical experience, research, private study and study meetings. Medical doctors prescribe the diet, whereas dietitians prepare the dietary information for families, and support them in its application.

In this study there was a large diversity in the recommendation of blood Phe levels for age by various clinics was determined (Table 4). In this case, our country has revealed clear differences in dietary treatment practice with PKU patients.

Generally, the recommended amount of protein varied from clinic to clinic and in all of the clinics recommended amount of protein was decreased with age (Table 6). It was noticed that this situation effect growth - development and metabolic control of PKU patient efficiently.

Insufficient amount of Phe free amino acid mixture is associated with short stature in PKU. Phe free amino acid mixture is the most important part of effective medical nutrition therapy in PKU, especially for older individuals tablets, liquid forms, special aromas to provide flavor changes have been developed in the growing food industry instead of the powder form. So it is suggested that PKU patients compliance with these new Phe free amino acid products will increase and short stature is disappeared.

As a result of dietary restriction, PKU patients generally consume a diet enriched in foods containing carbohydrates ("Phe free foods") that could potentially increase their risk for overweight and obesity. Findings from this study are confirmed these data, obesity was shown quitely higher between the age of 5-10 years (11.3 %) than the age of <5 years old.

Sharing education tools and improving communication within and between families and treatment clinics remains a key challenge to all health professionals, particularly when patients are spread over a large geographical area with limited numbers of healthcare professionals to support them. Consensus on acceptable blood Phe concentrations would be helpful. The introduction of a universal self-monitoring kit with patient/carers having immediate access to blood results may provide an effective monitoring tool and ultimately improve blood Phe control.

Regardless of geographical area, all patients and their caregivers should be supported to optimise their treatment within the confines of overall dietary management, by being taught how to make their diets palatable and interesting. Further research into the relative benefits and burdens of dietary approaches would allow treatment centres to take an evidence-based approach when caring for their patients, enhancing the ease of administration and the effectiveness of the diet. Consensus on acceptable goals for blood Phe concentrations would also facilitate patient management. There is also a clear need for more shared education and communication about PKU across Turkey with respect to all elements of management based on broad consensus guidelines. Increased interchange of knowledge would facilitate better treatment for patients within the resources available. The provision of accessible resources applicable to all patients, if agreed and endorsed by professionals working in PKU across Turkey would be invaluable. If these tools were then available via an accepted PKU website, this may reduce some of the conflicting information given to families.

Initially, studies are needed to compare different treatment methodologies with the aim of identifying best practice approaches to optimise Phe control and adherence to dietary management. The differences in treatment methodologies identified in this study attest to the need for a broad consensus in the management of PKU

The guidelines to be developed in inherited metabolic diseases, PKU:

- reduce the difference between clinics and clinical practice,
- include recommendations about dietary treatment and other treatments that will lead clinicians to success,
- include definition of treatment in case of patients' metabolic and genetic changes,
- develop recommendations for lifetime effective target blood Phe levels for age,
- in addition to provision of target blood Phe levels, to be comprised of malnutrition, overweight or obesity prevention issues,
- targeting the increasing the individual's quality of life and should contain clear recommendations on the reduction of medical, educational and social costs.

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