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Management of phenylketonuria in Europe: Survey results from 19 countries

Nenad Blau [a,*], Amaya Bélanger-Quintana [b], Mübeccel Demirkol [c], François Feillet [d], Marcello Giovannini [e], Anita MacDonald [f], Friedrich K. Trefz [g], Francjan van Spronsen [h], contributing European PKU centers [1]

[a] University Children's Hospital, Zürich, Switzerland
[b] Unidad Enfermendades Metabolices, Servicio de Pediatria, Hospital Ramon y Cajal, Madrid, Spain
[c] Istanbul University Istanbul Faculty of Medicine, Children's Hospital, Istanbul, Turkey
[d] Centre de Référence des Maladies Héréditaires du Métabolisme, INSERM U954, Hôpital d'Enfants, Nancy, France
[e] Clinica Pediatrica, Ospedale San Paolo, Università degli Studi di Milano, Milan, Italy
[f] The Children's Hospital, Birmingham, UK
[g] Klinik für Kinder und Jugendmedizin, School of Medicine University of Tübingen, Reutlingen, Germany
[h] Beatrix Children's Hospital, University Medical Center of Groningen, Groningen, The Netherlands

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ABSTRACT

To gain better insight in the most current diagnosis and treatment practices for phenylketonuria (PKU) from a broad group of experts, a European PKU survey was performed. The questionnaire, consisting of 33 questions, was sent to 243 PKU professionals in 165 PKU centers in 23 European countries. The responses were compiled and descriptive analyses were performed. One hundred and one questionnaires were returned by 93/165 centers (56%) from 19/23 European countries (83%). The majority of respondents (77%) managed patients of all age groups and more than 90% of PKU teams included physicians or dieticians/nutritionists. The greatest variability existed especially in the definition of PKU phenotypes, therapeutic blood phenylalanine (Phe) target concentrations, and follow-up practices for PKU patients. The tetrahydrobiopterin (BH4; sapropterin) loading test was performed by 54% of respondents, of which 61% applied a single dose test (20 mg/kg over 24 h). BH4 was reported as a treatment option by 34%. This survey documents differences in diagnostic and treatment practices for PKU patients in European centers. In particular, recommendations for the treatment decision varied greatly between different European countries. There is an urgent need to pool long-term data in PKU registries in order to generate an evidence-based international guideline.

Introduction

Phenylketonuria (PKU) is an inherited disorder in phenylalanine (Phe) metabolism with an overall incidence in Europe and the USA of 1:10,000–20,000 live births [1]. The implementation of newborn screening to detect PKU has facilitated the early use of dietary treatment, resulting in near normalization of outcomes of individuals with PKU [2]. However, dietary treatment is very restrictive, may be associated with a risk of nutritional deficiencies, compliance is often poor among adolescent and adult patients with PKU [3], and two thirds of pregnant women in the United States do not follow the diet before becoming pregnant [4]. Thus, long-term patient outcome is not always optimal, and published guidelines for PKU management show considerable variation between PKU centers [5–10]. Recent developments including tetrahydrobiopterin (BH4; sapropterin) treatment [11], large neutral amino acid (LNAA) supplementation [12], phenylalanine ammonia lyase (PAL) enzyme replacement [13], and gene therapy [14] may help to improve the outcome of PKU in the future.

National guidelines for the management of PKU published by several European countries agree that treatment should start as early as possible after birth, and that monitoring of Phe concentrations and clinical parameters should continue throughout life [5–7]. However, these guidelines vary not only between countries worldwide, but also within countries, particularly with respect to recommended plasma Phe concentrations during dietary treatment, the duration of treatment, and the recommended frequency of monitoring blood Phe levels [8,9]. In an effort to gain a greater picture of the most current diagnostic and treatment practices for PKU from a broad group of experts in treatment centers across Europe, a European PKU survey was initiated.

* Corresponding author. Address: Division of Clinical Chemistry and Biochemistry, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland. Fax: +41 44 266 7169.
E-mail address: nenad.blau@kispi.uzh.ch (N. Blau).
[1] Appendix.

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Methods

Participants

Questionnaires were sent to 243 professionals working in the field of PKU in 165 PKU centers in 23 European countries (Austria, Belgium, Bosnia and Herzegovina, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Serbia, Spain, Sweden, Switzerland, Turkey, and UK). The survey was performed between May and October, 2008.

The questionnaire consisted of a total of 33 closed (answer choices provided) and open (no answer choices provided) questions concerning (a) general information (e.g. number of patients, definition of hyperphenylalaninemia [HPA]/PKU); (b) screening practices (e.g. BH4 loading test); treatment practices and follow-up (e.g. target blood Phe levels); and (c) existing guidelines and protocols.

Data analysis

The responses were compiled in a spreadsheet, open questions were grouped or categorized according to responses received, and tabulated. Due to the nature of the study, only descriptive analyses were performed in the form of sums (reported as percent of total responses) and medians. For analysis purposes, each questionnaire was treated as a single response, even when it was completed by a group of professionals or when centers returned more than one questionnaire completed by different professionals. Thus, the term "response" (or "respondent") refers to the answers from an individual questionnaire.

For the overall objective of the paper, most attention was focused on questions concerning screening and treatment practices and the use of guidelines and protocols; less attention was given to questions pertaining to general background information. Some questions could not be included as the variation between responses was so great or too few responses were received such that no meaningful grouping and interpretation of results could be made.

Results

Of the 165 centers in 23 European countries that were contacted, 93 (56%) centers from 19 countries responded (number of responses received): Austria (1), Bosnia and Herzegovina (1), Croatia (1), Denmark (1), Finland (1), Greece (1), Poland (1), Czech Republic (2), Serbia (2), Switzerland (2), Norway (3), Sweden (3), Netherlands (4), UK (8), Italy (11), Spain (12), Turkey (13), France (16) and Germany (18). Six centers returned more than one questionnaire so that the total number of questionnaires (responses) received was 101. Sixteen questionnaires were answered by 2–5 professionals from the same center. For the full list of centers that contributed to the survey, see the Appendix. No responses were received from professionals at PKU centers in Belgium, Hungary, Ireland, or Portugal.

Table 1 contains data on PKU patients and the professionals contributing to PKU teams. The majority of respondents diagnosed less than five new patients per year and were involved in the care of a wide age span of patients (including newborns, children and adults). Regarding the respondent's profession, metabolic pediatrician was the most frequently reported (76%). Four percent of respondents reported that the PKU team at their center did not include a physician; 6% reported that their team did not include a dietician or nutritionist. Only 12% reported a full team consisting of physicians, dieticians/nutritionists, specialty nurses, psychologists and clinical biochemists.

The total number of PKU patients followed up per year in the 93 centers was 12,409 (the median number was 71). The total number of PKU patients reported in these centers was 14,837. Thus, 84% of PKU patients in these centers were followed up at least yearly.

Table 2 presents data on diagnostic testing and treatment practices. Genotype analysis was performed as part of routine diagnostic testing by almost half of the respondents, and the BH4 loading test was performed by more than half of the respondents. The majority of those who performed the test used one single dosage over a 24 h time period. Of those who specified the dose, all reported using a dose of 20 mg/kg/day. BH4 responsiveness was defined most frequently as a 30% reduction in blood Phe levels after 24 h. The majority of respondents indicated that they performed a BH4 loading test in infants, and less frequently in older age groups. Approximately one third of respondents reported that they used BH4 in their patient management. Treatment was started at different blood Phe concentrations. Possible answer choices for blood Phe levels at which treatment with a low Phe diet was initiated were: (a) >200 μmol/L, (b) >400 μmol/L, (c) >600 μmol/L, and (d) other, with levels of <600 μmol/L (>200 and >400 μmol/L) being the most reported (42%). The most common "other" responses included PKU levels of 300, >360, and >400–600 μmol/L (depending on age of patient). Concerning Phe concentrations during treatment, Phe blood testing was most commonly performed at clinical laboratories without the use of home blood collection (with samples then sent to a clinical laboratory).

Regarding the definition of severities of phenylalanine hydroxylase (PAH) deficiency, more than 70% of respondents classified classical PKU as an untreated Phe concentration >1200 μmol/L

Table 1
Summary of PKU patients and medical team profile.

How many PKU patients in your center are newly diagnosed each year?					
0–5	6–10	11–15	16–20	>21	No answer
69.3%	16.8%	5.9%	2.0%	5.0%	1.0%
With which group(s) of PKU patients are you involved?					
Only adults	Only newborns and children		All		No answer
3.0%	18.8%		77.2%		1.0%
Your function[a]					
Metabolic Paediatrician	Adult physician	Dietician	Adult and child metabolic physician	Other	No answer
76.2%	1.9%	7.9%	14.9%	9.9%	1.9%
The PKU team at your center includes which of the following?[a]					
Physicians	Dieticians/nutritionists	Specialty nurses	Psychologists	Clinical biochemists	Other
96.0%	94.1%	34.7%	65.3%	66.3%	24.8%

[a] As more than one answer was given by respondents, the total exceeds 100%.