European Journal of Clinical Nutrition (2011) 65, 275–278

0954-3007/11
www.nature.com/ejcn

ORIGINAL ARTICLE

Blood phenylalanine control in phenylketonuria: a survey of 10 European centres

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Background: Only limited data are available on the blood phenylalanine (Phe) concentrations achieved in European patients with phenylketonuria (PKU) on a low-Phe diet.
Objective: A survey was conducted to compare blood Phe control achieved in diet-treated patients with PKU of different age groups in 10 European centres.
Methods: Centres experienced in the management of PKU from Belgium, Denmark, Germany, Italy, The Netherlands, Norway, Poland, Spain, Turkey and the United Kingdom provided retrospective audit data of all patients with PKU treated by diet over a 1-year period. Standard questions were used to collect median data on blood Phe concentrations, percentage of blood Phe concentrations below upper target reference ranges and frequency of blood Phe sampling.
Results: Data from 1921 patients on dietary management were included. Blood Phe concentrations were well controlled and comparable across centres in the early years of life. The percentages of blood Phe concentrations meeting each centre's local and national target ranges were 88% in children aged up to 1 year, 74% for 1–10 years, 89% for 11–16 years and 65% for adults (>16 years). The frequency of home blood sampling, compared with local and national recommendations for monitoring Phe concentrations, appeared to decline with age (from approximately 100% in infancy to 83% in teenagers and 55% in adults).
Conclusions: Although blood Phe control generally deteriorated with age, some improvement was observed in adolescent years across the 10 European centres. The blood Phe control achieved seemed comparable in many of the European centres irrespective of different dietary treatments or national policies.
European Journal of Clinical Nutrition (2011) **65,** 275–278; doi:10.1038/ejcn.2010.258; published online 1 December 2010

Keywords: phenylketonuria; blood phenylalanine; diet; nutrition; compliance

Introduction

Phenylketonuria (PKU) arises from mutations of the gene coding for the enzyme phenylalanine (Phe) hydroxylase (PAH), resulting in its deficiency. PAH is the major enzyme responsible for the hydroxylation of Phe to tyrosine. Untreated PKU leads to profound and irreversible mental retardation, but treatment from birth with a Phe-restricted diet prevents most of the adverse neuropsychological sequelae of the disorder (Meli and Bianca, 2002). However, the dietary management of PKU varies widely throughout Europe (Ahring *et al.*, 2009) and only limited data are available comparing blood Phe control achieved among diet-treated patients with PKU in different centres across Europe. We compared retrospectively the blood Phe control achieved in diet-treated patients with PKU of all age groups in 10 European centres.

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Received 28 October 2009; revised 30 August 2010; accepted 20 September 2010; published online 1 December 2010

Methods

Retrospective clinical audit data on blood Phe concentrations were obtained using a predefined set of questions for all patients with PKU treated with a diet who were regularly reviewed at clinical centres experienced in the management of PKU in Belgium, Denmark, Germany, Italy, The Netherlands, Norway, Poland, Spain, Turkey and the United Kingdom. The survey included patients treated with a diet for at least 12 months beginning 1 July 2007 up to 1 July 2008 (in Turkey, because of a large patient population and difficulties in assessment of data, results were based on 1 month of treatment of patients attending clinics).

Centres followed local or national age-defined recommendations regarding target blood Phe concentrations (Supplementary Table 1) and frequency of blood sampling (data not shown). Centres in Belgium and Spain recommended that blood samples be collected at the same (unspecified) time of day, whereas other centres recommended sampling in the morning after an overnight fast. Each centre used its routine methodology for measuring blood Phe.

Eligible patients had PKU, were on dietary treatment, with or without BH4 (tetrahydrobiopterin, sapropterin dihydrochloride, Kuvan) therapy and with or without large neutral amino-acid (LNAA) supplements. Key exclusions were patients not on dietary treatment; following preconception diet; pregnant; non-return of blood Phe samples; or lost to follow-up. Ethical approval was required (and obtained) only for the Turkish centre.

Data on each parameter (see Results) were initially reported by each centre in the form of medians (with ranges for median blood Phe concentrations (μmol/l) achieved; Supplementary Tables 2–4). The medians of these medians were then calculated and their interquartile ranges were used as a measure of variability. No statistical analyses were performed to compare results between groups; thus, comparative results reported are solely observational in nature.

Results

Patients

Overall, 1921 patients on dietary treatment met the inclusion criteria; 115 patients in three centres received LNAA and 17 patients from Spain also received BH4 (Supplementary Table 5). Principal reasons for exclusion were return to a normal diet ($n=188$); preconception or pregnancy ($n=40$); loss to follow-up; or failure to return blood Phe samples ($n=143$).

Blood Phe concentrations achieved

Blood Phe appeared to be well controlled up to 16 years of age, as they were within each centres' national or local target ranges (Supplementary Tables 1 and 2). Annual median blood Phe concentrations (Supplementary Table 3) were similar between centres, except for Spain, where median blood Phe concentrations were <100 μmol/l for age <1 year, and Turkey, where median blood Phe was above the goal for 4–10 years. Overall, blood Phe concentrations appeared to increase with age (Table 1). As suggested by the increasing magnitudes of interquartile ranges, the variability of blood Phe concentrations appeared to generally increase with increasing age, except for the 1- to 3-year age group (Table 1).

Table 1 Parameters related to the management of blood Phe concentrations within 12 months in patients with PKU managed using dietary intervention at 10 European centres

Age (years)	*Median blood Phe (μmol/l)*	*Median % blood samples with Phe within or below guideline goals*	*Median % blood samples returned according to guidelines* [a,b]
<1	175 (137–195)	88 (82–96)	102 (100–112)
1–3	230 (206–246)	74 (67–86)	100 (92–121)
4–10	287 (254–327)	74 (58–85)	92 (90–117)
11–16	465 (347–527)	89 (64–95)	83 (66–87)
Adult (>16)	777 (604–855)	65 (44–88)	55 (51–75)

Data shown are medians (interquartile ranges) calculated from median values for each parameter supplied by each centre over a period of 12 months (2007–2008). Median blood Phe concentrations achieved for individual centres are shown in Supplementary Tables 2–4.

[a]The median percent of blood samples for home Phe sampling returned to nine centres (excluding Turkey, which does not employ a home monitoring system) during the study period. These data are expressed as a percentage of the number of samples required by national guidelines.

[b]Percentages >100% resulted when patients returned samples more frequently than required by guidelines.

In the three centres prescribing LNAA, annual median blood Phe concentrations were 1297 μmol/l (Denmark), 876 μmol/l (Italy) and 1274 μmol/l (Norway) (Supplementary Table 3). All these patients were adults, with median ages of 33 (range 19–49), 31 (range 18–42) and 39 years (range 27–48), respectively.

Proportions of blood samples meeting guideline targets

The proportions of blood Phe samples that met target Phe concentration ranges set by local or national PKU guidelines (Table 1, Supplementary Table 3) appeared to decline for age ranges up to 10 years, to improve during adolescence (11–16 years) (89%) and to decline again in adulthood (>16 years). In patients prescribed LNAA, the median percentage of blood samples with Phe concentrations within treatment guidelines was reported to be 72% for Denmark and 100% for Norway (data unavailable for Italy).

Frequency of returning blood Phe samples

Patients used a home blood Phe sampling system, except for those treated at the Turkish centre, where home blood samples were collected in the short term by a small number of families if blood Phe control was unacceptable. Overall,

the proportion of blood samples returned according to guidelines was close to 100% for ages up to 3 years, but then declined with increasing age (Table 1, Supplementary Table 4), with little evidence of variability between centres, as suggested by interquartile ranges (12–29%). The median percentage of blood Phe samples returned according to guidelines was low for patients on LNAA: 35% (Denmark), 3% (Italy) and 27% (Norway).

Discussion

Our data showed that despite the heterogeneity of local and national PKU guidelines across European PKU centres, blood Phe concentrations in patients with PKU appeared to be generally comparable during the early years of life for most of these 10 European PKU centres. Blood Phe concentrations increased with age, consistent with other reports (Mundy *et al*., 2002; Walter *et al*., 2002). Control in adults was similar to that reported elsewhere, although blood Phe control (according to local or national guidelines) appeared better for adolescents than reported previously (Meli and Bianca, 2002; Mundy *et al*., 2002; Walter *et al*., 2002; Walter and White, 2004). Increased availability of relatively palatable liquid protein substitutes (MacDonald *et al*., 2006), an increased range of low protein special food and better patient education may have improved control in teenagers.

Blood Phe control, and the rate of returning of samples, deteriorated markedly (and became more variable between centres) by adulthood, despite the upper limit of target ranges for blood Phe usually being higher than for younger age groups. The apparent suboptimal blood Phe control for most age groups at the Turkish centre was consistent with previous findings (Gokmen Ozel *et al*., 2008). Moreover, given our exclusion criteria, the blood Phe results reported are likely to be from the most adherent and motivated patients in this age group, who attended clinics and returned blood samples.

Our survey was subject to limitations. Centres followed different guidelines for the management of PKU. In addition, we collected no data on dietary intake or adherence with protein substitute (suboptimal dietary compliance known to limit blood Phe control (Walter *et al*., 2002)), missed clinic visits, social backgrounds, educational achievement, PKU centres' education policies or economic factors. Furthermore, this short-term, retrospective analysis could provide only a snapshot of the quality of control of PKU at a given time point. Finally, our exclusion of non-diet-managed patients would favour the inclusion of younger patients, who are more likely to be following the Phe-restricted diet.

It is important to document the degree of blood Phe control achieved across different European centres, as the management of PKU is constantly changing. In the future, for example, the wider availability of the pharmaceutical formulation of BH4 (sapropterin dihydrochloride, Kuvan), when used in combination with a low-Phe diet, may facilitate better blood Phe control in patients with the BH4-sensitive phenotype of PKU. Nevertheless, the management of adult patients remains challenging.

Conflict of interest

Kirsten Ahring has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Amaya Bélanger-Quintana has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU and the Scientific Advisory Board on PKU.

Katharina Dokoupil has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Hulya Gokmen-Ozel has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Anna Maria Lammardo has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Anita MacDonald has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU and as a member of the Scientific Advisory Board on PKU. She has received honoraria for consulting or lecturing from SHS International, Nutricia and Merck Serono. She has received research grant funding from Vitaflo International, Nutricia and SHS International.

Kristina Motzfeldt has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU. She has received honoraria for consulting or lecturing from SHS International and Vitaflo Scandinavia.

Maria Nowacka has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Martine Robert has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU.

Margreet van Rijn has received compensation from Merck Serono as a member of the European Nutritionist Expert Panel in PKU. She has received honoraria for consulting or lecturing from Milupa, Nutricia and Orphan Europe. She has received research grant funding from SHS International, Milupa, Metakids and Vitaflo International.

Acknowledgements

We thank all members of the PKU treatment teams at their centres. We are also grateful to Dr Regina Ensenauer (Department of Metabolism and Nutrition, Dr von Hauner Children's Hospital, University of Munich, Germany) for a critical review of this manuscript. We acknowledge the contributions of physicians from the following countries: Belgium: Dr Philippe Goyens and Dr Corinne De Laet;

Denmark: Dr Jytte Bieber Nielsen; Italy: Dr.ssa Elisabetta Salvatici; Norway: Dr Jens V Jorgensen and Dr Per Mathisen; The Netherlands: Dr Francjan. J van Spronsen; and Turkey: Professor Dr Turgay Co°kun. Data were used with permission of the responsible physicians. This study was sponsored by an unrestricted educational grant from Merck Serono SA—Geneva, Switzerland. We acknowledge editorial assistance provided by Dr Mike Gwilt (GT Communications, supported by Merck Serono SA—Geneva, Switzerland) and Dr Christina Herden (Physicians World Europe GmbH, supported by Merck Serono SA—Geneva, Switzerland).

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Supplementary Information accompanies the paper on European Journal of Clinical Nutrition website (http://www.nature.com/ejcn)