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REVIEW

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Survey of national guidelines for the treatment of phenylketonuria

Abstract Phenylketonuria treatment policies vary not only between different countries worldwide, but also within one country. Recommendations and guidelines for phenylketonuria should deal with the following subjects:

1. What is the target age to start dietary phenylalanine restriction under newborn-screening conditions?
2. At which plasma phenylalanine concentration should phenylalanine restriction be initiated?
3. Which are the recommended plasma phenylalanine concentrations at different ages?
4. What is the recommended frequency of monitoring phenylalanine in plasma?

Statements from the following countries are presented: Czech Republic, Denmark, France, Germany, Great Britain, Hungary, Ireland, Poland, Slovakia and the United States.

Conclusion Due to the lack of internationally accepted guidelines, management of phenylketonuria still varies between different countries. Our efforts should focus on the formulation of internationally acceptable and accepted recommendations for the treatment of patients with phenylketonuria at different ages.

Key words Phenylketonuria · Dietary treatment · Guidelines · Recommendations

Abbreviations *Phe* phenylalanine · *PKU* phenylketonuria

Introduction

Phenylketonuria (PKU) treatment policies vary not only between different countries worldwide, but also within one country. Concerned patients and parents have urged professionals to review scientific data and medical facts and suggest recommendations for the acceptable management of PKU, regardless of costs and personal convenience. Virginia Schuett from the United States wrote "… guidelines should be based on "outcome" data, and not on subjective opinion of PKU professionals" [16].

Recommendations and guidelines for PKU mainly deal with the following subjects:

1. What is the target age to start dietary phenylalanine (Phe) restriction under newborn-screening conditions?
2. At which plasma Phe concentration should Phe restriction be initiated?
3. Which are the recommended plasma Phe concentrations at different ages?
4. What is the recommended frequency of monitoring Phe in plasma?

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During the 40 years since Bickel's sensational development of low-Phe casein hydrolysates in 1952, the duration and degree of dietary Phe restriction at different ages in patients has varied in different countries. For example, the French group of Saudubray, Rey and coworkers had ceased diet at 5 years of age [14, 15] and now continue until 8 years (Lille) or 10 years (Paris) respectively (Abadie, personal communication), followed by a less restricted diet without Phe-free amino acid mixtures in the majority of patients. The group of Bickel and coworkers in Heidelberg, Germany, initially continued strict diet for at least 8 years. They and others later recommended a life-long diet [6]. Thus, the following slogans have been established during recent years: "Life with PKU" – "Diet for life" – "Life with diet" and they reflect the personal impact of patients and their families in dealing with PKU [16].

Published recommendations

Up to now, two recommendations have been published. In the United Kingdom, the Medical Research Council Working Party on PKU, under the chairmanship of Cockburn, Smith and coworkers, published recommendations in 1993 [12, 13]. In Germany, the "Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen" (Working Group for Inborn Errors of Metabolism) formulated new guidelines in 1997 [3] and published the rationale for these recommendations in 1999 [7]; former guidelines were published in 1990 [18]. Nationwide guidelines for the United States of America and France have still not been established. In the United States, the Committee on Genetics of the American Academy of Pediatrics and the National Institute of Health have attempted to set up guidelines since 1993 [16]. However, we do have precise information of the treatment policies of both countries from publications and reports of, example given, Koch et al. [11], Fisch et al. [10], Azen et al. [1, 2] and Wappner et al. [19] for the United States and Rey et al. [14], Saudubray et al. [15] and Abadie (personal communication) for France. Statements from the following countries are also presented: Denmark (Güttler, personal communication), the Czech Republic [9, 20] and Zeman (personal communication), Ireland (Naughten, personal communication), Hungary [17] and Schuler (personal communication), Poland [8] and Cabalska (personal communication) and Slovakia (Zeman, personal communication). A tetrahydrobiopterin test in order to exclude a tetrahydrobiopterin deficiency is accepted in all the above-mentioned countries.

Start of dietary phenylalanine restriction

Recommendations for the target age to start dietary Phe restriction under newborn-screening conditions actually do not vary significantly between the countries. In the United Kingdom it is recommended to start treatment within 20 days, the German recommendation of 1997 [3] aimed at initiation of diet within the first 8 weeks of life, later "as early as possible after birth" [7]. The first 3 weeks of life are also recommended in the Czech Republic, France, Hungary, Poland and Slovakia and in the United States.

Concerning the plasma Phe concentration at which Phe restriction should be initiated, the British recommendations favour >400–600 μmol/l (>6.6–10.0 mg/dl) for several days under normal protein feeding conditions. The same holds true for the Czech Republic, Hungary, Poland and Slovakia. The German Working Group of Inborn Errors of Metabolism recommends to start dietary Phe restriction at plasma Phe levels >600 μmol/l (>10 mg/dl).

Plasma Phe concentrations during dietary treatment and duration of treatment

The recommended plasma Phe concentrations during dietary treatment and the duration of treatment also differ between the countries:

Czech Republic, Hungary, Slovakia 1998

0–6 years: <360 μmol/l (<6 mg/dl); >6–10 years: <480 μmol/l (<8 mg/dl); >10–15 years: <600 μmol/l (<10 mg/dl); >15 years and life-long (with amino acid mixtures): <900 μmol/l (<15 mg/dl).

Denmark 1995/99

0–8 years: 180–400 μmol/l (3.0–6.7 mg/dl); >8–10 years: <600 μmol/l (<10 mg/dl); >10–12 years: <700 μmol/l (<11.7 mg/dl); >12–18 years: <900 μmol/l (<15 mg/dl), >18 years and life-long (with amino acid tablets): <1500 μmol/l (<25 mg/dl).

France 1997 (Lille)

0–8 years: 300–540 μmol/l (5–9 mg/dl); >8 years (without amino acid mixtures): <1200 μmol/l (<20 mg/dl).

France 1998 (Paris)

0–10 years: 120–420 μmol/l (2–7 mg/dl); >10 years (usually without amino acid mixtures): <1200–1500 μmol/l (<20–25 mg/dl).

Germany 1997/99

0–9 years: 40–240 μmol/l (0.7–4.0 mg/dl); >9 –15 years: 40–900 μmol/l (0.7–15.0 mg/dl); >15 years (with amino acid mixtures): 40–1200 μmol/l (0.7–20 mg/dl).

Great Britain 1993

0–5 years: 120–360 μmol/l (2–6 mg/dl); 6–16 years: 120–480 μmol/l (2–8 mg/dl); >16 years and life-long (with amino acid mixtures): 120–700 μmol/l (2.0–11.7 mg/dl).

Ireland 1987/1996

0–>18 years (with amino acid mixtures): 200–400 μmol/l (3.3–6.6 mg/dl).

Poland 1998

0–5 years: 120–240 μmol/l (2–4 mg/dl); 6–14 years: 120–480 μmol/l (2–8 mg/dl), >14 years through reproduction period in women with amino acid mixtures: <720 μmol/l (<12 mg/dl), >14–18 years in boys: relaxed diet and stop of diet thereafter in male adults (Cabalska, personal communication).

United States 1996

Childhood: 140–480 μmol/l (3–8 mg/dl); adolescence and adulthood (usually with amino acid mixtures) 480–720 μmol/l (8–12 mg/dl) [11].

To demonstrate the differences between the countries concerning duration of dietary treatment J.P. Farriaux from Lille, France, is quoted who wrote in LA DEPECHE, the proceedings of the French handicapped association in 1997: "…et nous ne voyons aucune raison de prescrire à vie un régime avec substituts pauvres en protéines de façon systématique." ("We do not see any reason to prescribe a life-long regimen with low-protein substitutes in a systematic manner.").

Frequency of monitoring of plasma Phe concentrations

There is also variation between the recommended frequency of monitoring of plasma Phe concentrations:

Czech Republic, Slovakia 1998

0–1 year: weekly to fortnightly, >1–6 years: monthly, >6–15 years: every 2–3 months, >15 years: every 3 months.

France 1996/1997

0–2 years: weekly; 3–8 years: fortnightly; 9–13 years: every 3 months; >13 years: yearly.

Great Britain 1993, Hungary 1998

0–4 years: weekly; 5–9 years: fortnightly; >9 years: monthly.

Germany 1997

<1 year: weekly to fortnightly; 1–9 years: fortnightly to monthly; 10–15 years: monthly; >15 years: every 2–3 months.

Poland 1996

0–6 months: weekly, >6–12 months: fortnightly, >1 year: monthly.

Official recommendations of "The European Society for Phenylketonuria and allied Disorders treated as Phenylketonuria" (ESPKU) have not been published up to now (Wachtel, personal communication). The recommendations of Great Britain and Germany were presented and discussed in the journal of the society instead [5].

Conclusion

Due to the lack of internationally accepted guidelines, management of PKU still varies between different countries. Patients and parents desire recommendations for an acceptable management of PKU in all countries, regardless of costs and personal convenience. Recommendations also have to include frequent dietary training and repeated medical and psychological counselling for patients and their families [4, 7]. Our efforts should therefore focus on the formulation of internationally acceptable and accepted recommendations for the treatment of patients with PKU at different ages.

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