Molecular Genetics and Metabolism 120 (2017) 190–197

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Adherence to clinic recommendations among patients with phenylketonuria in the United States

E.R. Jurecki [a,*], S. Cederbaum [b,c], J. Kopesky [d,e], K. Perry [f], F. Rohr [g], A. Sanchez-Valle [h], K.S. Viau [i], M.Y. Sheinin [f], J.L. Cohen-Pfeffer [a]

[a] Medical Affairs, BioMarin Pharmaceutical, Inc., Novato, CA, United States
[b] Department of Psychiatry, University of California, Los Angeles, CA, United States
[c] Department of Pediatrics, and Human Genetics, University of California, Los Angeles, CA, United States
[d] Department of Clinical Nutrition, Children's Hospital of Wisconsin, Milwaukee, WI, United States
[e] Department of Genetics, Children's Hospital of Wisconsin, Milwaukee, WI, United States
[f] Trinity Partners, Waltham, MA, United States
[g] Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, United States
[h] Division of Genetics and Metabolism, University of South Florida, Florida, United States
[i] Department of Pediatrics, Division of Medical Genetics, University of Utah, Salt Lake City, UT, United States

ARTICLE INFO

Article history:
Received 3 January 2017
Accepted 4 January 2017
Available online 6 January 2017

Keywords:
Phenylketonuria
Adherence
Blood phenylalanine
ACMG guidelines
Adults

ABSTRACT

Objective: Assess current management practices of phenylketonuria (PKU) clinics across the United States (US) based on the key treatment metrics of blood phenylalanine (Phe) concentrations and blood Phe testing frequency, as well as patient adherence to their clinic's management practice recommendations.
Methods: An online survey was conducted with medical professionals from PKU clinics across the US from July to September 2015. Forty-four clinics participated in the survey and account for approximately half of PKU patients currently followed in clinics in the US (Berry et al., 2013).
Results: The majority of PKU clinics recommended target blood Phe concentrations to be between 120 and 360 μM for all patients; the upper threshold was relaxed by some clinics for adult patients (from 360 to 600 μM) and tightened for patients who are pregnant/planning to become pregnant (to 240 μM). Patient adherence to these recommendations (percentage of patients with blood Phe below the upper recommended threshold) was age-dependent, decreasing from 88% in the 0–4 years age group to 33% in adults 30+ years. Patient adherence to recommendations for blood testing frequency followed a similar trend. Higher staffing intensity (specialists per 100 PKU patients) was associated with better patient adherence to clinics' blood Phe concentrations recommendations.
Conclusion: Clinic recommendations of target blood Phe concentrations in the US are now stricter compared to prior years, and largely reflect recent guidelines by the American College of Medical Genetics and Genomics (Vockley et al., 2014). Adherence to recommended Phe concentrations remains suboptimal, especially in older patients. However, despite remaining above the guidelines, actual blood Phe concentrations in adolescents and adults are lower than those reported in the past (Walter et al., 2002; Freehauf et al., 2013). Continued education and support for PKU patients by healthcare professionals, including adequate clinic staffing, are needed to improve adherence. Future research is needed to understand how to improve adherence to reduce the number of patients lost to follow-up, as the findings of this and similar surveys do not address how to keep patients in clinic.

1. Introduction

Phenylalanine hydroxylase (PAH) deficiency, commonly known as phenylketonuria (PKU), is one of the most prevalent inherited metabolic disorders [1]. PAH deficiency results in elevated concentrations of Phe in the blood and brain, which, if untreated in the newborn period, can cause a range of complications, most notably severe neurocognitive and neuromotor impairments, including attention deficit symptoms, impaired mental processing, and severe intellectual disability [2–4]. The goal of PKU treatment is to lower and maintain the blood Phe concentration within the target range, preferably starting within the first 2 weeks of life. PKU patients undergo regular monitoring to ensure that Phe concentrations are controlled, nutritional

Abbreviations: PKU, phenylketonuria; Phe, phenylalanine; PAH, phenylalanine hydroxylase; ACMG, American College of Medical Genetics and Genomics; US, United States; BH4, tetrahydrobiopterin; GMDI, Genetic Metabolic Dietitians International.

* Corresponding author.
E-mail address: ejurecki@bmrn.com (E.R. Jurecki).

http://dx.doi.org/10.1016/j.ymgme.2017.01.001

requirements are met, and patients are growing and developing appropriately [2].

PKU guideline recommendations for the appropriate target blood Phe concentrations and treatment duration have evolved over the years as the understanding of the disease has improved. Early guidelines published in the 1990s advised stricter target blood Phe concentrations for infants and young children (typically 120–360 μM), but more relaxed targets for adolescents and adults (typically up to 600–900 μM) [1,5]. In some cases dietary treatment was terminated in patients after childhood [4,6]. The National Institutes of Health issued guidelines for life-long treatment in 2000 after controlled clinical studies provided evidence that diet treatment discontinuation resulted in inferior outcomes (e.g., loss of intellectual function, higher rate of depression, neurological symptoms) [7,8]. Additional evidence [9] regarding neurotoxicities associated with elevated Phe concentrations prompted the American College of Medical Genetics and Genomics (ACMG) to update the guidelines in 2014 [2]. These guidelines recommended all patients to maintain blood Phe concentrations of 120–360 μM for life and lifetime treatment and monitoring for all patients to promote optimal outcomes [2].

Patient adherence to treatment recommendations has long been a source of concern to clinicians. Poor adherence may manifest in multiple ways, such as patient-initiated relaxation of dietary restrictions; failure to take medical food, special low protein foods, and/or prescribed medications; not attending regular clinic appointments; and lack of blood Phe monitoring. While no universal quantitative definition of adherence in PKU exists, it is thought that assessment of blood Phe concentrations provides arguably the best measure of a patient's adherence to treatment [9], as blood Phe has been shown to be closely related to patient outcomes [10].

Over the last decade, PKU management in the US has evolved, both in terms of management guidelines and treatment options [2,11], though significant reimbursement issues with medical food and special low protein food exist, especially in adults [4]. However, there is a lack of data as to how these changes are impacting PKU patient adherence. Previous research on patient adherence is limited to publications preceding ACMG guidelines [5,12] or studies performed outside of the US [1,13–15]. Additionally, prior studies in the US were not national level surveys of clinics. Results of these earlier studies showed significant levels of non-adherence to clinic target Phe concentrations [1,12–15]; it is not known whether adherence has improved, declined, or remained unchanged.

In addition to blood Phe concentrations, an important component of PKU management is the frequency of blood testing, which has also been revised in the ACMG guidelines, recommending biweekly to monthly testing [2]. This aspect of adherence has been explored to an even smaller degree as compared to the blood Phe concentrations.

Given the complexity of PKU management, the presence of several specialists (e.g., dietitians, psychologists, social workers, geneticists) on the metabolic multidisciplinary care team may be beneficial to the management of PKU patients. Although several surveys have documented staffing of PKU centers in Europe [13,14,16,17], similar information for the US is lacking. Additionally, there is limited data on the association between staffing and patient outcomes, such as blood Phe control and treatment adherence.

Our study was designed to assess current PKU clinic management practices regarding target blood Phe concentrations and blood Phe testing frequency, and patient adherence to their clinic's recommendations, as well as the impact of clinic staffing on patient adherence in US clinics.

2. Methods

2.1. Survey

The survey was conducted from July through September 2015 and contained 21 questions. Data collected included the respondent's clinic characteristics (location, number of PKU patients, number of full-time staff that treat PKU), PKU treatment recommendations (target blood Phe, target blood testing frequency), and patient adherence to clinic recommendations. Treatment recommendations and adherence were asked for specific patient groups (ages 0–4, 5–12, 13–17, 18–29, 30+ years, and pregnant or planning on becoming pregnant within 12 months). Respondents were asked to define patient adherence to target blood Phe recommendations based on the average Phe concentrations obtained over the past year. Respondents were encouraged to refer to their clinic's patient database, patient medical charts, and clinic members in order to provide accurate answers. The full text of the survey can be accessed online (Supplementary Survey Text).

This study received Institutional Review Board exemption status given minimal risk to participants and de-identified healthcare professional and patient data.

2.2. Study recruitment

A double-blinded recruitment strategy was utilized: participants were recruited by an independent third-party and were in turn blinded to the sponsor of the study. The questionnaire was sent to a total of 212 healthcare professionals from 182 PKU clinics identified by the study sponsor. Respondents from 73 unique clinics replied to the survey (40% response rate) and respondents from 44 unique clinics qualified and completed the survey. Only the first respondent per clinic was allowed to complete the full survey.

Only respondents from clinics with at least 15 actively managed PKU patients, defined as patients that have been seen in clinic within the past 3 years, qualified to complete the survey. This cut-off was selected as a compromise to ensure the representativeness of the sample while eliminating very small clinics or clinics with limited experience in treating PKU patients that could have skewed the results. The clinics meeting inclusion criteria should be the ones more knowledgeable about PKU management across broader types of patients. Respondents from 6 unique clinics were disqualified based on this criterion.

2.3. Data analysis

Initial descriptive analyses were performed by summarizing the data in Microsoft Excel. Depending on the type of variable, each analysis was performed either on a clinic level (each clinic carried a weight of 1), or on a patient level (each clinic was weighted based on the number of PKU patients).

SPSS v22 (SPSS, Inc., Chicago, IL) was used to further explore relationships among variables. Bivariate Pearson correlation was used to analyze associations between continuous variables and one-way ANOVA was used for nominal variables. A two-sided P-value <0.05 was considered significant.

3. Results

3.1. Clinic and patient demographics

The 44 clinics that participated in the survey represented all geographic regions of the US (see Supplementary Text for definitions), with the majority of clinics located in the North Central region (39%) and in the South (30%), followed by the West (20%), and the Northeast (11%). The primary practice setting was academic, either a hospital practice (59%) or specialty/multi-specialty office (32%). The majority of respondents were dietitians (45%), followed by geneticists/genetic counselors (27%), and metabolic specialists (14%). Clinics have been managing PKU patients for an average of about 22 years (range 3–50 years). The median number of actively managed patients per clinic was 78 (range 15–275 patients; note that only clinics with ≥15 patients with PKU were qualified to participate). In total, respondents reported on their clinics' 3772 actively managed PKU patients, 41% of which were adults (Table 1). This represents about half of all actively managed PKU patients in the US (estimated at 7180 in 2012 [4]). The total