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The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK

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ABSTRACT

Introduction: Management of phenylketonuria (PKU) is mainly achieved through strict dietary control that aims to limit the intake of phenylalanine (Phe). Adherence to this diet is burdensome due to the need for specially prepared low-Phe meals and regular monitoring of Phe concentrations. A UK cross-sectional study was conducted to identify the personal time and monetary burden associated with aspects of the PKU lifestyle for caregivers of children (aged <18 years) living with PKU.

Methods: Caregivers of pediatric patients with PKU attending one of four specialist metabolic centers in the UK were invited to participate in a questionnaire-based survey that evaluated different aspects of PKU management that could potentially present out-of-pocket costs (OOPCs) or time burden. Medical clinicians/dieticians provided patient information on PKU severity and an assessment of blood Phe control.

Results: The survey was completed by 114 caregivers of 106 children having mild or moderate (n = 45; 39%) or classical (n = 60; 53%) PKU (severity data missing for n = 1), among whom 8 (8%) and 87 (82%) reported poorly controlled and controlled blood Phe status, respectively; Phe control data were missing for 11 children. Dietary management of PKU incurred a median time burden of >19 h per week. OOPCs were incurred via attendance at PKU events, PKU-related equipment, and extra holiday expenditure. 21% of caregivers reduced their working hours (median 18.5 h/week) to care for their child, with a further 24% leaving their paid jobs completely.

Discussion and conclusions: Dietary management of PKU is associated with a considerable time burden for caregivers of pediatric patients with PKU. A personal financial burden also arises from OOPCs and lost earnings.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder characterized by accumulation of phenylalanine (Phe) in blood and body fluids that is caused by defective Phe hydroxylase activity (PAH, EC 1.14.16.1) [1]. PAH deficiency is classified as classical PKU (Phe > 1200 μmol/L), mild PKU (Phe 600–≤1200 μmol/L) or mild hyperphenylalaninaemia (Phe < 600 μmol/L) [2]. The incidence of PKU varies according to ethnic background. In the UK, PKU affects about 1 in every 10,000 newborns of white European ancestry [3] with around 70 babies born with PKU annually, suggesting that over 6000 people in the UK have PKU.

If left untreated, the prolonged high Phe concentrations in the blood and tissue that can occur in classical PKU can result in severe cognitive impairment, seizures, behavioral problems and features of autism [4]. Such irreversible complications can be avoided through early treatment with a low-Phe diet from the first few weeks after diagnosis [5,6] and throughout life [4,7–9]. Pharmacological treatments are also available and currently include the synthetic formulation of tetrahydrobiopterin (BH_4), sapropterin dihydrochloride [10], and medical food or amino acid supplements, including formulations of large neutral amino acids such as tryptophan and tyrosine [11].

Dietary treatment of PKU is achieved via a low-Phe diet that severely restricts the intake of natural protein in order to achieve control of blood Phe concentrations [12,13]. The low-Phe diet includes food that is naturally low in protein, such as fruit, some vegetables, fats and oils, as well as specially formulated low-protein products, such as low-protein flour, pastas and bread. All patients on dietary treatment require Phe-free L-amino acids, usually supplemented with additional carbohydrate, with or without fat, vitamins and minerals [14]. Adherence to dietary treatment is essential, thus careful planning, dietary supervision and monitoring are required. Adherence to this treatment regimen is considered demanding [7] and includes sourcing and purchasing speciality foods, supervising the intake of Phe-free L-amino acid supplements,

Abbreviations: ACBS, Advisory Committee on Borderline Substances; DLA, Disability Living Allowance; NHS, National Health Service; NRES, NHS Research Ethics Committees; OOPC, out-of-pocket cost; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

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planning daily Phe consumption, preparing low-Phe meals (often involving additional cooking), monitoring Phe intake, and attending clinic visits [15]. Blood tests are conducted by parents at home usually with the following frequency: weekly for children aged ≤5 years and between twice monthly and monthly for children ≥6 years [15]. Thus, the many aspects of PKU management appear time-consuming for caregivers who manage the PKU lifestyle on top of regular childcare. PKU has already been shown to impact a caregiver's life and even their ability to continue regular work responsibilities [16], with 11% of parental caregivers in one survey reporting they had to stop paid work and 20% reporting that they had to change jobs [17].

The cost of PKU to the National Health Service (NHS) is well documented; retrospective database analyses estimated that Phe-free L-amino acids and low-protein foods are responsible for around 60% and 10%, respectively, of the total NHS costs for managing a patient with PKU [5]. Appropriate reimbursement of special PKU dietary products and L-amino acids via subsidized Advisory Committee on Borderline Substances (ACBS) prescriptions and financial help schemes, such as the Disability Living Allowance (DLA), Carers Allowance and Family Fund, are important in helping to reduce the financial burden on caregivers. Fortunately, in the UK, many products are available on prescription (free for under 16 s) and the DLA is considered an essential income source for many families with a child with PKU [18].

Given that living with PKU impacts caregivers' lives and that the time-consuming nature of PKU remains unknown in a UK population, we conducted a cross-sectional study to quantify the personal time and monetary burden for caregivers of children (aged <18 years) living with PKU in the UK.

2. Methods

2.1. Study participants

This cross-sectional study was designed to assess the personal time burden and out-of-pocket-costs (OOPCs) for caregivers (usually parents) of children living with PKU. The study was conducted through four NHS metabolic care clinics in the UK. National ethics approval was obtained via the NHS Research Ethics Committees (NRES) and hospital research and development departments. One hundred and ninety-five caregivers were included via four NHS specialist metabolic dieticians from Birmingham Children's Hospital, the Bristol Royal Hospital for Children, St Luke's Hospital in Bradford, and Evelina Children's Hospital in London, between September 2012 and March 2013. Caregivers of early and continuously treated pediatric patients were invited to participate in this study, and informed parental consent was obtained. Children gave assent when their age and understanding was appropriate. Confidentiality was maintained by assigning numerical codes to individual patient data sets. Caregivers were asked to complete a questionnaire, and on its return a voucher worth £15 was sent.

2.2. Questionnaire items

The data were collected via a caregiver-reported questionnaire evaluating the different aspects of the PKU lifestyle that could potentially present an OOPC or a time burden to caregivers of pediatric PKU patients. The questionnaire was developed for use in two studies, one in The Netherlands, published in 2013 [19] and the current study in the UK population. In brief, the questionnaire was based on: a) the published literature on aspects of PKU management that may pose a financial or time burden on patients or caregivers; b) the insights from interviews with six PKU specialists, to ensure that all relevant items were captured regarding the lifestyle aspects related to the time and cost burden of PKU [19]. The resulting questionnaire was piloted with four caregivers who provided additional feedback. The questionnaire collected background information on the child or children with PKU. Caregivers were asked about their time and costs spent on 'Social Life', 'Health and Work' and 'The PKU Diet'. The 'Health and Work' section included the Short Form Health & Labour Questionnaire [20], a prevalidated questionnaire that investigates the impact of a disorder on a respondent's employment. Respondents provided answers using weekly and monthly recall periods. In addition to the respondent's questionnaire, consent was asked for the child's dietician or treating specialist to report in an addendum on the disorder severity and control status of the child with PKU. Disease status was recorded as 'Mild', 'Moderate' or 'Classical' (determined by diagnostic blood Phe concentration [i.e. Mild < 600 μmol/L, Moderate > 600–1200 μmol/L, Classical > 1200 μmol/L] and Phe tolerance and stability of blood Phe control) and control status recorded as 'Controlled' or 'Uncontrolled' (determined by blood Phe concentrations based on the previous 3 months Phe concentrations). Blood Phe within the controlled Phe range for ≥70% of the time was considered good control. If the respondents did not permit access to the child's blood Phe concentration data, the expert opinion of the child's dietician's was used for disease and control status.

2.3. Data analysis

The time burden and OOPCs for caregivers of pediatric patients with PKU were assessed in: a) the overall study population; b) subgroups related to PKU severity and Phe concentration control status. Patients with mild or moderate PKU were grouped together and compared with those with classical PKU, and patients who successfully controlled their Phe concentrations were compared with those who were 'uncontrolled'. Analyses were performed on the available data; therefore, the sample number for each analysis varies depending on the outcome of interest. Outcomes were continuous variables (time and OOPCs) and were described in terms of medians and ranges.

3. Results

3.1. Study population characteristics

From November 2012 to March 2013, 195 caregivers of children diagnosed with PKU were invited to take part in the study. Of these, 114 surveys were completed and returned, with each survey representative of one pediatric patient. All patients were under the age of 18 years, the majority had classical PKU, and >90% of those for whom control status was known were considered to have controlled PKU (Table 1). Of the patients, >90% were treated with a low-Phe diet (n = 106) and special

Table 1
Characteristics of PKU patients.

Caregivers invited to participate, n	195
Survey completed and returned, n	114
Median age of PKU patients, years (range)	7 (1–17)
Patients treated with low-Phe diet, n (%)	106 (93.0)
Patients treated with low-protein foods, n (%)	108 (94.7)
Patients taking Phe-free L-amino acid supplements, n (%)	87 (76.3)
PKU severity, n (%)[a]	
Mild (<600 μmol/L)	8 (7.5)
Moderate (Phe 600– ≤ 1200 μmol/L)	37 (34.9)
Classical (>1200 μmol/L)	60 (56.6)
Unknown	1 (<1)
Control status of PKU, n (%)[a]	
Controlled uncontrolled	87 (82.1)
Unknown[b]	8 (7.5)
	11 (10.4)

Phe, phenylalanine; PKU, phenylketonuria.

[a] Analysis based on all patients treated with a low-Phe diet (n = 106); control status determined from the previous 3 months Phe concentrations.

[b] Respondents answered 'don't know' to the question 'Do you know what your PKU child's maximum **daily** recommended number of 'exchanges' is (their level of protein intake), as recommended by their doctor or dietician that they should try not to exceed?'