Admissions and Cost of Hospitalisation of Phenylketonuria: Spanish Claims Database Analysis

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Abstract

Background Phenylketonuria is a well-known rare disease included in the neonatal screening of many countries. Therefore, there are few published data on the admissions and costs of phenylketonuria in Spain.

Objective The objective of this study was to assess the number of admissions and the economic burden of phenylketonuria in Spain.

Methods Patients with phenylketonuria were identified from a Spanish database containing data from public and private healthcare centres from 1997 to 2015. The parameters obtained were characteristics of the patients, type of admissions, readmissions, discharges, length of stay, medical service, annual number of visits, annual number of patients, visit-associated costs and patient-associated costs.

Results Five hundred and ninety-four patients with phenylketonuria were identified: 48.32% were male with a mean (standard deviation) age of 4.50 (10.23) years. The hospital admissions were divided into emergency visits (55.94%) and scheduled visits (43.92%). The majority of patients were discharged home (98.86%). The mean (standard deviation) duration of stay was 4.04 (4.98) days. The number of admissions per year ranged between 13 and 88, with an average of 1.18 admissions per patient per year. Finally, the mean cost per visit increased from €1064.91 to €3709.40, and the mean cost per patient increased from €1818.90 to €4239.32 from 1999 to 2015.

Conclusions The access to economic and social data on phenylketonuria in Spain has been updated. The number of admissions and healthcare costs between 1997 and 2015 were calculated. There were 24 admissions as a result of a phenylketonuria diagnosis in 2015 and the mean healthcare cost per patient was €4239.32. This information can help to adapt and improve each healthcare system to take into consideration rare diseases.

Key Points

The available data for economic burden and number of admissions of phenylketonuria are updated in Spain.
The number of admissions and the number of patients increased from 1997 to 2004 and then started to decrease until 2015.
The mean cost per patient increased from €1818.90 in 1999 to €4239.32 in 2015.

1 Introduction

Phenylketonuria (PKU) is a rare and autosomal recessive inborn error of phenylalanine (Phe) metabolism caused by variants in the gene encoding phenylalanine hydroxylase [1]. It causes a deficiency of phenylalanine hydroxylase, which is the enzyme that catalyses the hydroxylation of Phe to tyrosine [2]. An accumulation of Phe in blood causes neurotoxic effects that can lead to irreversible intellectual disability, microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms [1].

A worldwide prevalence rate of 0.04–0.1‰ [3] has been estimated, which varies depending on the geographical region (high rates in Ireland (0.22‰) and Turkey (0.38‰) and a very low rate in Finland (0.005‰) [1]) and the ethnic group (PKU is more common in Chinese people (0.06‰) than in African individuals (0.01‰) [2, 4]). The main risks

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factors associated with PKU are the consanguinity among parents because it is an autosomal recessive disease [5]. Thus, the consanguinity together with the fact that PKU is a rare disease and that an incorrect diagnosis can lead to a significant change in the prevalence rate leads to a variable prevalence rate among populations.

Phenylketonuria is one of the universal diseases included in neonatal screening that meets all the screening criteria and justifies all the associated costs [6]. In Spain, it was the first disease included in national neonatal screening in 1968 [7]. The early detection of this disease and treatment at birth prevent neurocognitive damage. The primary treatment consists of a Phe-reduced diet and/or the use of sapropterin (also called BH4) [8], a co-factor that reduces the Phe blood levels.

However, different parameters and factors regarding this disease are still to be studied. To include a disease in neonatal screening, and from an economic point of view, it must be demonstrated that the costs associated with diagnosing all newborns are less than the costs associated with diagnosing and treating affected individuals in the future [9]. Furthermore, the treatment for PKU is prompt, accessible and effective [10]. Nevertheless, there are few studies on the economic burden of PKU. Thus, there is an obvious need to determine the economic impact of PKU from the National Health Service perspective.

We studied the number of PKU admissions and costs associated with the treatment of patients with PKU in Spain during 18 years. All the necessary information was obtained from a national claims database containing data from private and public hospitals from 1997 to 2015.

2 Methods

2.1 Data Source

This retrospective study was based on a sample extracted from the Spanish claims database Minimum Basic Data Set [Conjunto Mínimo Básico de Datos (CMBD)] [11]. The CMBD contains data from 1997 to 2015 and includes registers of 313 public hospitals and 192 private hospitals (data from 2004). The database contains patient characteristics (age, sex, region of residence, type of reimbursement), hospitalisation diagnosis, comorbidities and complications, therapeutic and diagnostic procedures, length of stay, type of admission and discharge, diagnosis-related group (DRG) for each episode and cost per DRG. Both diagnostics and procedures are codified by the International Classification of Diseases, Ninth Revision, used also to assign the DRG associated with the hospital stay.

2.2 Study Population

The study included all the patients for whom a hospitalisation for PKU (International Classification of Diseases, Ninth Revision code 270.1 documented as a primary diagnosis) was identified in the CMBD database between 1 January, 1997 and 31 December, 2015. This hospitalisation was considered to be the index event. For patients hospitalised for PKU more than once over the study period, the earliest event was considered as the index event. For each eligible patient, information was extracted on demographics (sex and age at the time of the index hospitalisation), hospitalisation for PKU (admission, duration, discharge, readmission and medical service), comorbidities, procedures and cost per hospitalisation.

2.3 Data Analysis

Data presentation is mainly descriptive, and no specific hypothesis was tested. Categorical data are presented as frequency counts and percentages and continuous data are presented as mean values plus standard deviation (SD).

The analysable population consisted of all patients presenting with a PKU diagnosis during the study period. Study variables were described in the total patient population. All PKU diagnoses occurring during the study period were considered for the estimation of incidence. The annual number of patients and visits and the visit- and patient-associated costs were also estimated.

Patient characteristics and the most common comorbidities were also studied. All statistical analyses were performed using Microsoft Excel Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

2.4 Ethical Considerations

As this was a study of an anonymised database and had no influence on patient care, ethics committee approval was not required.

3 Results

3.1 Characteristics of Patients Identified in the Database

During the study period 1997–2015, 699 PKU-related visits were identified in the CMBD database, which corresponded to a total of 594 patients with PKU. Around half of the identified patients were male ($n = 287; 48.32\%$) with an average age of 4.76 (SD = 12.22) years. The identified
female patients \( n = 307 \); 51.68\%) had an average age of 4.25 (SD = 7.91) years (Table 1).

The most frequent comorbidities, which affect more than 1% of identified patients with PKU, were *Escherichia coli* infection (1.43%), epilepsy (1.29%), obesity (1.14%) and urinary tract infection (1.00%) (Table 2).

The hospitalisation admissions for patients with PKU were divided into emergency visits (55.94%) and scheduled visits (43.92%). Only 4.43\% of the patients with PKU were readmitted before 30 days after discharge. The mean (SD) length of hospital stay was 4.04 (4.98) days. Finally, the majority of patients were discharged home (98.86%). More than half of the identified patients were attended by the paediatrics service (69.45\%) (Table 3).

### 3.2 Healthcare Resources

The number of admissions, number of patients and costs were assessed over the study period.

The number of admissions per year ranged between 13 and 88 while the number of patients per year varied from 11 to 78. Both the number of admissions and the number of patients increased from 1997 to 2004 and then started to decrease until 2015 (Fig. 1). Thus, the number of admissions per patient per year ranged between 1.09 and 1.44, with a mean of 1.18 admissions per patient annually.

Finally, the mean cost per visit increased from €1064.91 in 1999 to €3709.40 in 2015. The mean cost per patient increased from €1818.90 to €4239.32 in the same period (Table 4).

### 4 Discussion

#### 4.1 Characteristics of Patients Identified in the Database

In this study, characteristics of the identified patients were studied. In comparison with other studies on patients with PKU previously performed [12, 13], we can determine that there is no difference in PKU prevalence between male and female patients. The early diagnosis of this disease, which has been stated to be a mean age of 4.50 years by the paediatrics service, is mainly owing to the inclusion of PKU in neonatal screening in Spain.

The primary treatment for PKU is the dietary restriction of the amino acid [14]. With this treatment PKU is usually totally controlled and no further PKU-related medical problems have been identified.

#### 4.2 Admissions

In this study, the number of admissions was assessed over the study period. The number of admissions per year ranged between 13 and 88 while the number of admissions per patient per year ranged between 1.09 and 1.44, with a mean of 1.18 admissions per patient annually. A
published study [15] assessed the costs and consequences of managing PKU over the first 36 years of life. This study has estimated the healthcare resource use over 36 years. According to the results, patients had a mean 12 general practitioner visits per year and one hospital outpatient visit annually. The results obtained in our study regarding hospital outpatient visits are similar to those obtained in the previously published study.

### 4.3 Healthcare Costs

A published study [16] analysed the household financial burden associated with PKU in China in 2014. It was based on a questionnaire given to the parents and caregivers at the China-Japan Friendship Hospital. The mean (SD) of medical costs, including medical examination and medical rehabilitation, was $1612.4 ($6383.2) per year and the mean (SD) of non-medical costs, including Phe-free food and accommodation and transport for medical treatment, was $4221.2 ($2135.5) per year. An analysis performed in the UK in 2013 [15] quantified the associated costs of managing a patient with PKU for 36 years. It was based on a computer model derived from a national database. The mean medical cost for a patient who followed the Phe-diet was £149,374, taking into account amino acid supplements, foods and drugs, medical visits, hospital admissions, laboratory tests and diagnostic procedures, which corresponds to £4149.28 per year. For the patients who did not follow the diet, the mean medical cost was £21,367, which corresponds to £593.53 per year. Patients who discontinued the diet and patients who discontinued and then restarted the diet were also studied.

To our knowledge, other economic and social analyses of patients with PKU have been performed: one in the UK [17] and one in the Netherlands [18], which were also based on questionnaires that did not calculate medical costs. One study performed in seven European countries [19] was based on databases that reflect the quality of life of these patients.

### Table 4 Visits and patients per year and costs related to phenylketonuria disease

| Year | Total costs (£) | Mean cost per visit (£) | Mean cost per patient (£) |
|------|-----------------|-------------------------|---------------------------|
| 1999 | 27,283.54       | 1064.91                 | 1818.90                   |
| 2000 | 47,736.13       | 1646.07                 | 2075.48                   |
| 2001 | 36,599.01       | 1742.81                 | 2033.28                   |
| 2002 | 53,718.20       | 2066.08                 | 2984.34                   |
| 2003 | 150,394.84      | 2387.16                 | 2592.95                   |
| 2004 | 206,737.16      | 2349.29                 | 2650.47                   |
| 2005 | 126,742.30      | 2437.35                 | 2880.51                   |
| 2006 | 117,847.58      | 2223.54                 | 2507.40                   |
| 2007 | 94,249.84       | 2772.05                 | 3769.99                   |
| 2008 | 107,079.35      | 2611.69                 | 3059.41                   |
| 2009 | 89,098.22       | 2474.95                 | 2699.95                   |
| 2010 | 114,139.53      | 3170.54                 | 3681.92                   |
| 2011 | 135,785.29      | 3311.84                 | 3993.69                   |
| 2012 | 115,194.12      | 3031.42                 | 3715.94                   |
| 2013 | 128,039.76      | 3879.99                 | 5121.59                   |
| 2014 | 103,545.63      | 3340.18                 | 3835.02                   |
| 2015 | 89,025.65       | 3709.40                 | 4239.32                   |
In our study, the economic results obtained refer to the healthcare costs per year and were associated with the DRG assigned to each hospitalisation. Therefore, it is not possible to establish a relationship between the obtained results in China and the results of this study because the methodologies used to obtain the costs cannot be compared. In addition, the medical policies and healthcare system of China are very different to the healthcare system in Spain. Regarding the results for the UK, it is also not possible to make a direct comparison of the results because the methodologies employed in the studies are completely different. Nevertheless, the results obtained in all the cases, except for the patients in the UK who did not follow the diet (i.e. patients who are not attending hospitals or healthcare centres, thus their medical expenditures are low), are similar, which gives sense to our results.

This study has some limitations. The first limitation is related to the source of the information: all the calculations performed assumed that all the patients with PKU in Spain were included in the database. The second limitation is related to costs. The only costs considered in this study were the healthcare or direct costs because the costs were calculated using the DRG associated with the main diagnosis. This cost is the representation of the mean cost of being hospitalised in Spain with a principal diagnosis of PKU, thus it is a generalisation of a specific situation. Moreover, this DRG does not take into account secondary diagnoses, the age of the patient or the length of stay, which can completely modify the cost. Finally, the last limitation is related to currency fluctuations. Even though this is considered in the DRG-associated costs (the same DRGs have different costs depending on the year), the currency fluctuations between 1997 and 2015 were not considered. Therefore, it is not totally realistic to compare the costs of the different years.

5 Conclusions

The number of admissions in Spain between 1997 and 2015 and the healthcare costs between 1999 and 2015 were calculated. There were 24 admissions related to PKU in 2015, with an admission per-patient per-year rate of 1.14. Finally, the mean healthcare cost per patient was €4239.32.

Understanding the economic and social impact of rare diseases highlights the importance of developing this type of study in every country. This information can help to adapt and improve each healthcare system to take into account rare diseases.

Compliance with Ethical Standards

Funding No sources of funding were received for the conduct of this study or the preparation of this article.

Conflict of interest Josep Darbà and Meritxell Ascanio have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval All procedures in this study were in accordance with the 1964 Helsinki Declaration and its amendments. As this was a study of an anonymised database and had no influence on patient care, ethics committee approval was not required.

Consent to participate As this was a study of an anonymised database and had no influence on patient care, no informed consent was required.

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