

**Characteristics, comorbidities and use of healthcare resources of patients
with phenylketonuria: a population-based study**

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ABSTRACT

Background: Phenylketonuria is a well-known disease, yet the characteristics of the affected population and their use of healthcare resources have not been comprehensively evaluated. Patient characteristics and use of resources are subjects of interest for most governments, especially for a disease included in new born screening programs.

Objective: The aim of this study was to determine characteristics and use of healthcare resources of patients with phenylketonuria in the region of Catalonia.

Methods: Records of 289 patients admitted with phenylketonuria between 2007 and 2017 were extracted from the PADRIS database that includes admission data from primary care centers, hospitals (inpatient and outpatient care), extended care facilities and mental health centers.

Results: Patient population was composed by 140 males and 149 females, and 102 patients were registered via newborn screening during the study period. Patients were admitted on average 2.19 times per year, mostly into primary care centers which concentrated the biggest portion of direct medical expenses. Similar percentages of urgent and scheduled admissions were registered both in primary care and hospitals. Annual direct medical cost of treating patients with PKU was €667 per patient. Finally, 66.80% of the patients suffered from chronic conditions affecting 2 or more systems, likely to correspond to a wide variety of conditions.

Conclusions: Altogether, phenylketonuria patient demographics and direct medical costs in Catalonia have been revised. Patients diagnosed with phenylketonuria appeared 1.3 times more likely to suffer from chronic conditions in distinct organ systems, which is expected to have an effect on their use of healthcare resources. These results support the need to adapt and improve the health care system taking multimorbidity into consideration in an effort to control the medical expenses derived.

KEYWORDS

Phenylketonuria; Epidemiology; Population-based study; Direct medical costs; Spain.

SHORT TITLE

Characteristics, comorbidities and use of healthcare resources of patients with phenylketonuria

INTRODUCTION

Phenylketonuria (PKU) is a genetic condition in which the enzyme that processes phenylalanine, phenylalanine hydroxylase (PAH), is deficient or absent. As a consequence, phenylalanine accumulates in the blood, causing a series of symptoms that vary in accordance with age of diagnosis and underlying genetic heterogeneity. Once hyperphenylalaninemia (HPA) is detected, the patient is tested for PAH deficiency and to exclude a non-phenylketonuric HPA caused by the deficiency of its cofactor, tetrahydrobiopterin (BH4) [1]. When PKU is properly diagnosed the first days of life, patients benefit from nutritional, clinical and biochemical follow-up, and few symptoms are observed; contrarily, when undiagnosed, symptoms include eczema, seizures, autism, behavioral issues, and eventually, severe intellectual disability [2]. Disease prevalence varies among geographical regions. In Europe, it affects one per 10,000 live births [3], although in Turkey it increases to one in 4,000 [4]. On the contrary, in Finland, prevalence is as low as one per 100,000 live births [5]. In Spain, the geographical distribution of the underlying mutations causing PKU has been analyzed, revealing differences between Mediterranean descendants and originals from the north-west of the country [6].

PKU is currently diagnosed the first days of life due to the well-established new born blood screening. Such screenings were established in Spain in 1978 (Real Decreto 2176/1978, 25th of August) and were soon implemented in the whole country [7]. Their benefits have been evident, with practically all symptoms of the disease being reduced only by dietary restriction [8]. Phenylalanine-restricted diets are still the primary treatment for PKU, often in combination with sapropterin, which reduces blood phenylalanine, or enzyme substitution therapy [9]. In general terms, PKU is a well-known disease, yet the characteristics of the affected population and possible regional discrepancies have not been comprehensively

evaluated. Similarly, patients' use of healthcare resources in a certain region is a subject of interest for most governments, especially for diseases part of new born screening programs. In such cases, neonatal screenings are justified based on the reduction of costs associated with treating patients later on [10]. A previous study analyzed the costs associated to PKU in Spain, together with its epidemiology [11]; however, in Spanish regions as Catalonia (7.5 million inhabitants) the regional government is in charge of the health care system, hence the interest of regional evaluations. In order to facilitate the management and examination of patient data, the local government has developed a specialized program that recruits patient information: the data analysis for research and innovation in health program (PADRIS) [12]. With this in mind this study was designed to evaluate the current status of PKU in the region of Catalonia, focusing on analyzing patient characteristics, revising disease management and calculating the direct medical costs of the disease.

MATERIALS AND METHODS

Records of all registered patients with a diagnosis of PKU in the region of Catalonia (7.5 million inhabitants) between 2007 and 2017 were analyzed. Data was obtained from project PADRIS via the approval from the University of Barcelona's Bioethics Commission. Parameters such as health centers and medical history identifiers were re-coded prior to extraction to maintain records anonymized in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

The database includes detailed information on patients' use of healthcare resources, comprising primary care centers, hospitals (inpatient and outpatient care), emergency rooms (ER), extended care facilities and mental health centers. Records in the database are validated automatically via the evaluation of data consistency. Patient diagnoses and procedures were determined by means of the 9th revision of the International Statistical Classification of

Diseases and Related Health Problems (ICD-9). When necessary, the extraction of single-patient information was carried out by eliminating repeated records corresponding to separated admissions, relying on the first admission registered during the study period as the index event.

The classification assigns patients an adjusted morbidity group (GMA), according to the number of systems they have affected by chronic diseases, and into 5 levels of complexity or risk. As it increases, GMA level correlates with a higher number of healthcare admissions of these patients and major pharmaceutical costs [13]. Direct medical costs associated with the use of healthcare resources were calculated based on the mean costs of medical procedures determined by the Catalan government for the year 2013 [14, 15].

Data presentation is mainly descriptive. Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The study evaluated records of 289 patients diagnosed with PKU in the region of Catalonia between 2007 and 2017 (Table 1). Not significant differences were observed in the percentage of male and female patients, 48.44% vs. 51.56%. Surprisingly, patients' mean age at first admission was 14.90 years (SD=18.07), although age median was of 8 years. In total, 102 patients included in the study were registered after diagnosis via newborn screening.

A total number of 15,018 healthcare admissions were analyzed, corresponding to primary health centers, hospitals, ER, extended care facilities and mental health consultations. Data was gathered between the years 2007 and 2017, averaging 2.19 annual admissions per patient. Significantly, 8.78 admissions were registered annually in primary care centers and only 0.23 annual admissions per patient were into hospitals.

All available information was used to determine the origin of admissions in primary care and hospitals, and the nature of emergency admissions (Figure 1). A similar proportion of scheduled and urgent visits were observed both in hospitals and primary care, while admissions into ER were mainly due to minor conditions with no vital risk associated.

Mean hospitalization time was 4.57 days, while the mean time patients spent in extended care facilities was 9.8 days. Generally, admissions into ER required stays of less than a day. After hospital discharge, 95.03% of the patients returned to their residence, a percentage slightly lower, 89.73%, in ER admissions (Table 2).

Patient admission files include a principal diagnosis (hospitalization motive), which was PKU in all cases, and a series of secondary diagnoses registered during the hospitalization. Secondary conditions diagnosed in more than 1.5% of admissions were acute nasopharyngitis (4.40%), unspecified essential hypertension (4.06%), asthma (3.41%), diabetes mellitus type II (2.59%), diabetes mellitus type I (1.94%) and acute tonsillitis (1.58%) (Table 3).

The Catalan institute of health (ICS) assigns patients a value according to the number of systems they have affected by chronic conditions. The year 2016 (last available data), 49.80% of patients with PKU had 2 or 3 systems affected by a chronic condition, and 17.00% of patients had 4 or more systems affected (Figure 2). A 5.13% and 2.66% increase was observed in each of these two categories since 2014. Two distinct approaches have been used to approximate the costs that PKU patients represent for the health care system. In terms of disease complexity or risk associated with patients' condition, in 2016 there were 7 times more patients in this group at very high risk, and 67% of patients displayed a certain level of risk versus the 50% in the general population (Figure 3). This data suggests that increased medical costs will derive from the treatment of patients with PKU in comparison with the general population.

On the other hand, an approximation to the direct medical costs of treating patients with PKU was made based on the mean costs of medical procedures established by the regional government (Table 4). Resources destined to primary healthcare were estimated based on the mean cost per admission according to its urgency. Thus, primary attention costs were the most relevant, summing €641,134. ER costs were calculated equally. Hospitalization costs were estimated per admission in outpatient consultations, and based on the average days of stay (1 day or more) and the cost per day. Finally, resources associated to stays in extended care facilities were determined by the cost per admission. Altogether, the annual direct medical cost per patient equaled €667, a total amount that reflects the cost to treat a patient with PKU

Finally, patients' contribution to pharmaceutical expenses was considered of significance to infer medical costs. Patients are assigned a co-payment percentage according to income, age and disease. The majority of patients, 54.21%, contributed to 40% of pharmaceutical expenses (Table 5). 8.30% of patients were exempted from contribution due to age or long term unemployment.

DISCUSSION

The present study revised all admission records of patients registered with PKU between 2007 and 2017 in the region of Catalonia. Altogether, results showed a predominance of admissions into primary care centers versus secondary care, with an annual cost per patient of €667. A significant frequency of multimorbidities was also measured among these patients.

The analysis revealed few differences to previous evaluations in the whole country. Patients' age at first admission, 14.90 years, was relatively elevated in comparison with the 4.5 years determined in Spain [11]. However, patients' diagnoses are registered in the database solely

after 2007, and diagnoses made before that year are not included. Thus, patients born and diagnosed before the study period elevate this parameter preventing a correlation with PKU's first diagnosis age.

Patients were admitted on average 2.19 times per year into a healthcare center, mostly into primary care centers. The Spanish healthcare system, as many others, promotes the use of primary care as a method to increase prevention and maximize healthcare resources [16]. In addition, the characteristics of PKU and its relatively simple control through diet, determine a need for general attention received in primary care facilities, and a minority need for urgent attention [2], consistent with the results of this study.

In terms of secondary diagnoses and comorbidities, no clear tendencies have been identified. A number of patients suffer from chronic conditions as diabetes type I and II, hypertension or asthma, but GMA indicators reflect much higher percentages; 66.8% of the patients had chronic conditions affecting 2 or more systems in 2016, while in the general population this percentage was 51.7 the same year [17]. The low percentages obtained in the analysis of secondary diagnoses in admission data suggest that patients' comorbid conditions correspond to a great variety of diseases. This data supports the findings of previous studies that described an elevated presence of multimorbidities in PKU patients affecting various organ systems, including conditions as allergic and chronic rhinitis, esophageal disorders, overweight, anemia, gastroesophageal reflux disease, dermatitis and eczema, all significantly higher than matched non-PKU controls [18]. Therein, it is speculated that HPA could have consequences beyond neurologic, neurocognitive and neuropsychiatric conditions, but further research is required to evaluate that option. Equally, the restrictive diet necessary to control PKU could have consequences in other organ systems as differences in parameters as fat oxidation have been confirmed [19].

On the other hand, the typical neurologic manifestations of an untreated PKU [20] were not detected in this study; the low prevalence of these conditions indicated that the elevated age of first admission does not reflect age of diagnosis in the region

In general terms, multimorbidity groups have been associated with an increased complexity of disease management and, subsequently, increased medical costs [21]. Additionally, in Catalonia, the ICS has determined a correlation between the presence of multimorbidities and an increased risk and subsequent use of healthcare resources [13]. Health systems are rarely prepared to handle multimorbidity [22], hence the interest of governments in evaluating disease costs and their relation with multimorbid patients.

The direct medical costs of PKU patients summed €1,348,364 between 2007 and 2017, with a mean annual cost per patient of €667. This cost is presumed higher than in the general population as a consequence of the major use of healthcare resources that derives from the higher portion of patients with chronic comorbid conditions. In Spain cost estimations situated annual costs of PKU at around €4,239 in 2015, however, therein, calculation methods were based on patients' diagnoses and are not entirely comparable [11]. Currently, the majority of costs associated with the disease are indirect costs, covered by families and patients, due to the extended use of a dietary treatment [23, 24], although prospective treatments facing all disease outcomes might increase medical costs [25], dramatically rising as well by the presence of comorbid conditions.

Finally, a number of limitations could have influenced the results of this study. Data recording in the distinct healthcare sources did not begin uniformly in 2007, and no previous information is available for patients born before that year. Moreover, patients with PKU may not need medical attention in relation with the illness for several years, and a number of patients can remain unregistered in the database.

CONCLUSIONS

The characteristics and use of healthcare resources of patients with PKU in the region of Catalonia have been revised. The increased presence of multimorbid conditions affecting distinct organ systems supports the need to evaluate the weight of secondary symptoms derived from this illness. Further research will be required to determine the importance of multimorbid conditions in healthcare use patterns, which will be essential in order to adapt and improve health care systems.

TRANSPARENCY

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Authors' contributions

Not applicable.

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Not applicable.

Competing interests

The author declares no competing interests.

Ethics approval and consent to participate

Project approved by the University of Barcelona's Bioethics Commission. Patient consent was not required for this study.

Data sharing statement

Deidentified individual participant data will not be made available due to legal stipulations from the Catalan Health Department.

LIST OF ABBREVIATIONS

BH4: Tetrahydrobiopterin.

ER: Emergency Room.

GMA: Adjusted Morbidity Groups.

HPA: Hyperphenylalaninemia.

ICD9: 9th revision of the International Statistical Classification of Diseases and Related Health Problems.

ICS: Catalan Institute of health (Institut Català de la Salut).

PADRI: Program of data analysis for research and innovation in health (Programa d'Analítica de Dades per a la Recerca i la Innovació en Salut).

PAH: Phenylalanine hydroxylase.

PKU: Phenylketonuria.

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TABLES

Table 1 Description of the studied population based on index event (first admission).

SD=standard deviation.

Number of patients	289
<i>% of male patients</i>	48.44
<i>% of female patients</i>	51.56
Patients' age (years)	
<i>Mean ± SD</i>	14.90 ± 18.07
<i>Median</i>	8
<i>Age range</i>	0 to 86

Table 2 Patients' destination after discharge from hospitals and ER (=Emergency Room).

	<i>Hospitals</i>	<i>ER</i>
Patients' residence	95.03%	89.73%
Admission for inpatient care	-	5.50%
Discharge, external care	1.86%	0.00%
Transfer to a extended care facility	0.93%	4.78%
Death	2.17%	0.00%

Table 3 Secondary conditions diagnosed in more than 1.5% of admissions of patients with phenylketonuria.

<i>Diagnoses</i>	<i>% of cases</i>
Acute nasopharyngitis; Coryza	4.40
Unspecified essential hypertension	4.06
Asthma	3.41
Diabetes Mellitus type II	2.59
Diabetes Mellitus type I	1.94
Acute tonsillitis	1.58

Table 4 Direct medical costs (2007-2017) based on mean costs of medical procedures established by the regional government. ER=Emergency Room.

Admissions						Total cost
		<i>Scheduled</i>	<i>Cost</i>	<i>Urgent</i>	<i>Cost</i>	
Primary care	13,768	6,100	€ 41	6,307	€ 62	€ 641,134
Hospitals Inpatient	276	<i>Mean days of stay</i>	<i>Cost per day</i>	<i>Cost per admission</i>		€ 583,826
		5.41	€ 391	€ 2,115		
Hospitals Outpatient	75	<i>Cost per admission</i>				€ 7,800
		€ 104				
Extended care	14	<i>Cost per admission</i>				€ 944
		€ 67				
ER	882	<i>Cost per admission</i>				€ 114,660
		€ 130				
Total						€ 1,348,364

Table 5 Patients' contribution to pharmaceutical costs.

<i>Patients' contribution</i>	<i>% of patients</i>
10% contribution (monthly limit at € 8.23)	11.07
10% contribution (monthly limit at € 18.52)	0.35
40% contribution	51.21
50% contribution	27.34
60% contribution	0.35
60% contribution (monthly limit at €61.75)	0.35
Exempted	8.30
Excluded/Unspecified	1.04

FIGURES

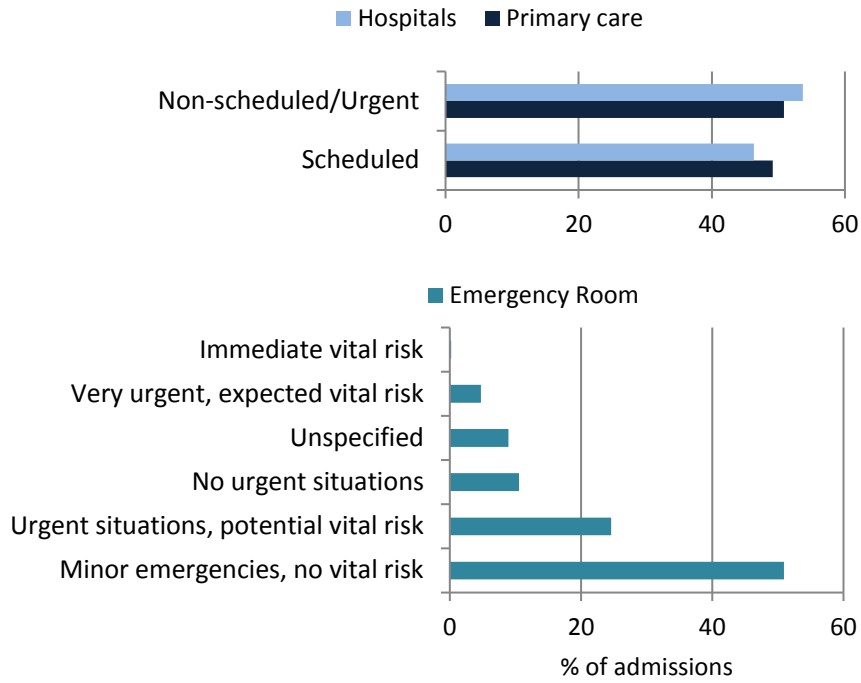


Figure 1

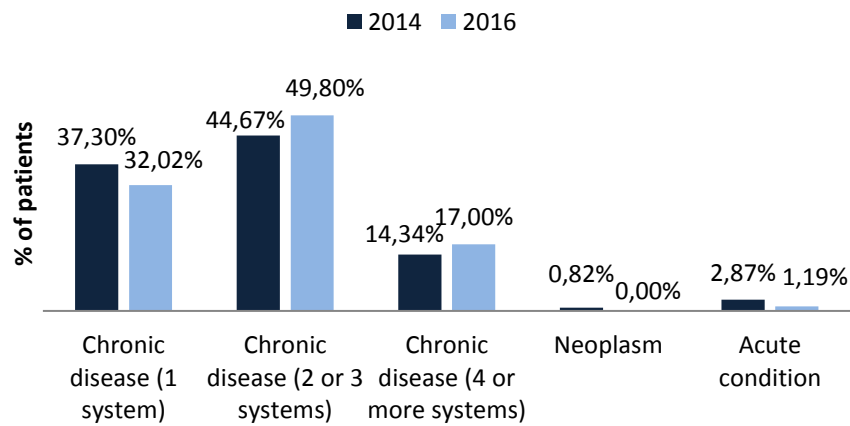


Figure 2

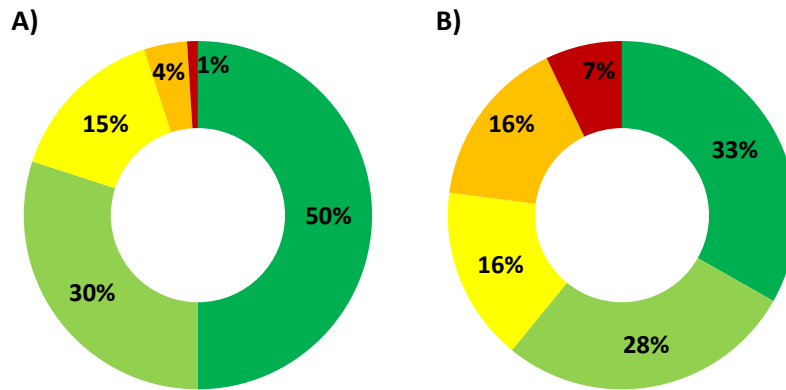


Figure 3

Figure 1 Origin of admissions of phenylketonuria patients.

Figure 2 Comorbidities in patients with phenylketonuria.

Figure 3 Disease complexity levels associated to risk (1 -green- low risk to 5 -red- very high risk) in A) general population [13] and B) patients with phenylketonuria in 2016.