ADMISSIONS AND COST OF HOSPITALIZATION OF PHENYLKETONURIA: SPANISH CLAIMS DATABASE ANALYSIS

Authors: Josep Darbà[1], Meritxell Ascanio[2]

[1]Universitat de Barcelona, Barcelona, Spain; [2]BCN Health Economics & Outcomes Research S.L., Barcelona, Spain.

Short title: admissions and cost of hospitalization of phenylketonuria in Spain

Author for correspondence: Josep Darbà

Department of Economics. Universitat de Barcelona, Diagonal 690, 08034 Barcelona, Spain.
E-mail: darba@ub.edu

Key words: Phenylketonuria, hospitalization cost, admissions, rare disease, healthcare resources

ACKNOWLEDGEMENT

Not applicable.

CONFLICTS OF INTEREST

Not applicable.

FUNDING

Not applicable.

Abstract

Background: Phenylketonuria (PKU) is a well-known rare disease which is included in the neonatal screening of many countries. Therefore there are few published data on the admissions and cost in Spain.

Objective: To assess the number of admissions and economic burden of PKU in Spain.

Methods: PKU patients 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, discharge, length of stay, medical service, annual number of visits, annual number of patients, visit associated costs and patient associated costs.

Results: 594 PKU patients were identified: 48.32% were males with a mean (SD) age of 4.50 (10.23) years. The hospital admissions were divided into emergency visits (55.94%) and scheduled visits (43.92%). Most of the discharges were at home (98.86%). The mean (SD) duration of stay was 4.04(4.98) days. The prevalence rate decreased from 0.27‰ to 0.10‰ from 2007 to 2015. Finally, the mean cost per visit increased from € 1,600 to € 3,700, and the mean cost per patient from € 1,800 to € 4,200 from 2007 to 2015.

Conclusions: The access to economic and social data about PKU in Spain has been updated. The number of admissions in Spain between 2007 and 2015 and healthcare costs between 1997 and 2015 was calculated. There were 24 admissions due to PKU diagnostic in 2015 and the mean healthcare cost per patient was € 4,239.32. This information can help to adapt and improve the healthcare system to the actual situation.

Key points: The available data for economic burden and number of admissions of PKU is updated in Spain.

INTRODUCTION

Phenylketonuria (PKU) is a rare and autosomal recessive inborn error of Phenylalanine (Phe) metabolism caused by variants in the gene encoding Phenylalanine Hydroxylase (PAH) [1]. It causes a deficiency of PAH, 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 geographic region (high rate in Ireland (0.22‰) or Turkey (0.38‰) and very low rate in Finland (0.005‰) [1]) and the ethnic groups (PKU is more common in Chinese people (0.06‰) than in the Africans (0.01‰) [2,4]). The main risks factors associated to PKU are the consanguinity among parents since it is an autosomal recessive disease [5]. Thus, the consanguinity along with the fact that PKU is a rare disease and a wrong detection can lead to a great change in the prevalence rate, leads to a variable prevalence rate among populations.

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

However, there are different parameters and factors regarding this disease that have not been studied yet. In order to include a disease in the neonatal screening, and from the 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 those affected later on [9]. Other clinical criteria that PKU fulfil is a promptly and accessible effectiveness treatment [10]. Nevertheless,

there are few studies on economic burden of PKU. So, there is an obvious need to determine the economic impact of PKU from the National Health Service perspective.

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

METHODS

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, gender, region of residence, type of reimbursement), hospitalization 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 (ICD-9) used also to assign the DRG associated with the hospital stay.

S*tudy population*

The study included all the patients for whom a hospitalization for PKU (ICD-9 code 270.1 documented as a primary diagnosis) was identified in the CMBD database between 1st January 1997, and 31st 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 (gender and age at the time of index hospitalisation), hospitalisation for PKU (admission, duration, discharge, readmission and medical service), comorbidities, procedures and cost per hospitalization.

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 as mean values plus standard deviation (SD).

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

Patient characteristics and most common comorbidities have also been studied.

All statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

Ethical considerations

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

RESULTS

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 males (N=287; 48.32%) with an average age of 4.76 (SD=12.22) years. The identified females (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 in PKU patients were: Escherichia Coli infection (1.43%), epilepsy (1.29%), obesity (1.14%) and urinary tract infection (1.00%) (Table 2).

The hospitalization admissions for PKU patients were divided into emergency visits (55.94%) and scheduled visits (43.92%). Only 4.43% of the PKU patients 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).

Healthcare resources

The number of admissions, number of patients and costs were assessed over the study period. The number of admissions per year ranges between 13 and 88 while the number of patients per year varies from 11 to 78. Both, number of admissions and patients, increased from 1997 to 2004 and then started to decrease until 2015 (Figure 1). Thus, the number of admissions per patient per year ranges between 1.09 and 1.44, with a mean of 1.18 admissions per patient annually.

Finally, the mean cost per visit increased from € 1,064.91 in 1999 to € 3,709.40 in 2015. The mean cost per patient increased from € 1,818.90 to € 4,239.32 in the same period (Table 4).

DISCUSSION

Characteristics of patients identified in the database

In this study, characteristics of the identified patients have been studied. In comparison with other studies about PKU patients carried out previously [12,13], we can determine that there is no difference in PKU prevalence between males and females. The early diagnose of this disease, which has been stated to be diagnose at a mean age of 4.5 years by the paediatrics service, is mainly due to the inclusion of PKU in the neonatal screening in Spain.

Primary PKU treatment is the dietary restriction of the amino acid phenylalanine [14], thus most of the controls and medical problems take place during childhood. With this treatment PKU is usually totally controlled and no further PKU-related medical problems have been identified.

Admissions

In this study, the number of admissions has been assessed over the study period. The number of admissions per year ranges between 13 and 88 while the number of admissions per patient per year ranges 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 the 36 years. According with 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.

Healthcare costs

A published study [16] analysed the household financial burden associated to PKU in China in 2014. It was based on a questionnaire conducted 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 cost, including Phe-free food and accommodation and transport for medical treatment, was $4221.2 ($2135.5) per year. An analysis performed in United Kingdom (UK) in 2013 [15] quantified the associated costs of managing during 36 years a PKU patient. 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 acids supplements, foods and drugs, medical visits, hospital admissions, laboratory tests and diagnostic procedures, which corresponds to £4,149.28 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. Other cases were studied as patients who discontinued the diet and patients who discontinued and then restarted it.

As far as authors know, some other economic and social analyses on PKU patients have been performed: one performed in UK [17] and one in the Netherlands [18], that were also based on questionnaires that do not calculate medical costs, and one performed in seven European countries [19], based on databases that reflects the quality of life of these patients.

In our study, the economic results obtained refer to the healthcare costs per year and were associated to the DRG assigned to each hospitalization. Therefore, it is not possible to establish a relationship between the obtained results in China and the ones of this study since the methodology used to obtain the costs cannot be compared. In addition, the medical policies and healthcare system of China have nothing to do with the healthcare system in Spain. Regarding the results for UK, it is also not possible to make a direct comparison of the results because the methodology employed in both studies is completely different. Nevertheless, the results obtained in all the cases, except for the patients in the UK that did not follow the diet (they are patients that are not attending hospitals or healthcare centres so their medical expenditures are low), are similar, which gives sense to our results.

This study presents also some limitations. The first limitation is related with the source of information: all the calculations were performed assuming that all the PKU patients in Spain were included in the database. The second limitation is related with costs. The only costs considered in this study were the healthcare or direct costs because the costs were calculated by using the DRG associated to the main diagnosis. This cost is the representation of the mean cost of being hospitalized in Spain with a principal diagnosis of PKU so it is a generalization 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 with the price of money fluctuations. Even though, this is considered in the DRG associated costs (the same DRG have different cost depending on the year), the money fluctuations between 1997 and 2015 were not considered. Therefore, it is not totally realistic to compare the costs of the different years.

CONCLUSIONS

In conclusion, the number of admissions in Spain between 2007 and 2015 and healthcare costs between 1997 and 2015 was calculated. There were 24 admissions related to PKU in 2015, with

admission per patient per year rate of 1.14. Finally, the mean healthcare cost per patient was € 4,239.32.

Knowing the economic and social impact of rare diseases highlights the importance to develop this type of studies in every country. This would help to adapt and improve each healthcare system to take into consideration rare diseases.

COMPLIANCE WITH ETHICAL STANDARDS

Funding

No source of funding.

Conflicts of interest

JD has no conflicts of interest to declare. MA has no conflicts of interest to declare.

Ethics Approval

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

Informed Consent

Since this was a study of an anonymised database and had no influence on patient care no informed consent was required.

Table 1: Phenylketonuria patient's characteristics

	All patients	Male	Female
Number of patients (%)	594 (100%)	287 (48.32%)	307 (51.68%)
Age			
Mean	4.50 years	4.76 years	4.25 years
SD	10.23 years	12.22 years	7.91 years
Maximum	111 years	111 years	40 years
Minimum	0 years	0 years	0 years

Table 2: Main comorbidities of phenylketonuria disease

IDC-9 code	Description	Visits
041.4	Escherichia Coli infection	10 (1.43%)
345.90	Epilepsy	9 (1.29%)
278.00	Obesity	8 (1.14%)
599.00	Urinary tract infection	7 (1.00%)

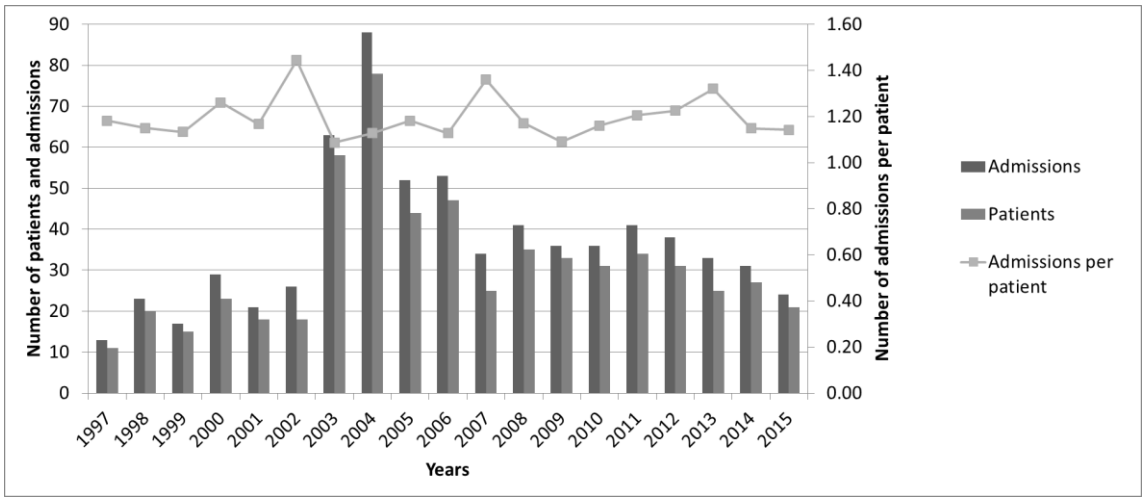
Table 3: Type of admissions, readmissions and discharged of phenylketonuria patients

	Visits	%
Admissions		
Emergency	391	55.94%
Scheduled	307	43.92%
Others	1	0.14%
Readmissions		
New episode	668	95.57%
Readmission	31	4.43%
Discharge		
Home	691	98.85%
Other hospitals	5	0.72%
Voluntary	2	0.29%
Others	1	0.14%
Medical service		
Paediatrics	291	69.45%
Digestive	45	10.74%
Neonatology	36	8.59%
Others	327	46.78%

Table 4: Visits and patients per year and cost related to phenylketonuria disease

	Total costs (€)	Mean cost per visit (€)	Mean cost per patient (€)
1999	€ 27,283.54	€ 1,064.91	€ 1,818.90
2000	€ 47,736.13	€ 1,646.07	€ 2,075.48
2001	€ 36,599.01	€ 1,742.81	€ 2,033.28
2002	€ 53,718.20	€ 2,066.08	€ 2,984.34
2003	€ 150,394.84	€ 2,387.16	€ 2,592.95
2004	€ 206,737.16	€ 2,349.29	€ 2,650.47
2005	€ 126,742.30	€ 2,437.35	€ 2,880.51
2006	€ 117,847.58	€ 2,223.54	€ 2,507.40
2007	€ 94,249.84	€ 2,772.05	€ 3,769.99
2008	€ 107,079.35	€ 2,611.69	€ 3,059.41
2009	€ 89,098.22	€ 2,474.95	€ 2,699.95
2010	€ 114,139.53	€ 3,170.54	€ 3,681.92
2011	€ 135,785.29	€ 3,311.84	€ 3,993.69
2012	€ 115,194.12	€ 3,031.42	€ 3,715.94
2013	€ 128,039.76	€ 3,879.99	€ 5,121.59
2014	€ 103,545.63	€ 3,340.18	€ 3,835.02
2015	€ 89,025.65	€ 3,709.40	€ 4,239.32

Figure 1: Number of admissions and patients evolution from 1997 to 2015



REFERENCES

1. van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12(1):162.
2. El-Metwally A, Yousef Al-Ahaidib L, Ayman Sunqurah A, Al-Surimi K, Househ M, Alshehri A, Da'ar OB, Abdul Razzak H, AlOdaib AN. The Prevalence of Phenylketonuria in Arab Countries, Turkey, and Iran: A Systematic Review. Biomed Res Int. 2018:7697210. doi: 10.1155/2018/7697210.
3. Wasim M, Awan FR, Khan HN, Tawab A, Iqbal M, Ayesha H.Aminoacidopathies: Prevalence, Etiology, Screening, and Treatment Options. Biochem Genet. 2018;56(1-2):7-21. doi: 10.1007/s10528-017-9825-6.
4. Zschocke J, Haverkamp T, Møller LB. Clinical utility gene card for: Phenylketonuria. Eur J Hum Genet. 2012;20(2). doi: 10.1038/ejhg.2011.172.
5. Shawky RA, Elsayed SM, Zaki ME, Nour El-Din SM, Kamal FM. Consanguinity and its relevance to clinical genetics. Egypt J Med Hum Gen. 2013;14:157-164.
6. Berry SA, Brown C, Grant M, Greene CL, Jurecki E, Koch J, Moseley K, Suter R, van Calcar SC, Wiles J, Cederbaum S. Newborn screening 50 years later: access issues faced by adults with PKU. Genet Med. 2013;15(8):591-9. doi: 10.1038/gim.2013.10.
7. Vicente E, Casas L, Ardanaz E. Origin of newborn screening programs and their beginnings in Spain. [Origen de los programas de cribado neonatal y sus inicios en España]. Anales del Sistema Sanitario de Navarra. 2017;40(1):131-140
8. Sanford M, Keating GM. Sapropterin. A Review of its Use in the Treatment of Primary Hyperphenylalaninaemia. Drugs. 2009;69(4):461-76. doi: 10.2165/00003495-200969040-00006.

9. Brosco JP, Sanders LM, Seider MI, Dunn AC. Adverse Medical Outcomes of Early Newborn Screening Programs for Phenylketonuria. Pediatrics. 2008;122(1):192-7. doi: 10.1542/peds.2007-3027.
10. Pitt JJ. Newborn Screening. Clin Biochem Rev. 2010; 31(2):57-68.
11. Registro de Altas de los Hospitales Generales del Sistema Nacional de Salud. Conjunto Mínimo de Bases de Datos (CMBD). Norma Estatal de Años Anteriores. Available at: https://www.mscbs.gob.es/estadEstudios/estadisticas/cmbdAnteriores.htm (Accessed 19th of October 2018).
12. Hsia DY, Dobson J, Koch R, Woolf L. Sex ratio in phenylketonuria. The Lancet. 1970;296(7663):96. doi:10.1016/s0140-6736(70)92661-9.
13. Thiele AG, Gausche R, Lindenberg C, Beger C, Arelin M, Rohde C, Mütze U, Weigel JF, Mohnike K, Baerwald C, Scholz M, Kiess W, Pfäffle R, Beblo S. Growth and Final Height Among Children With Phenylketonuria. Pediatrics. 2017;140(5). doi: 10.1542/peds.2017-0015.
14. Santos LL, Magalhães Mde C, Januário JN, Aguiar MJ, Carvalho MR. The time has come: a new scene for PKU treatment. Genet Mol Res. 2006;5(1):33-44.
15. Guest JF, Bai JJ, Taylor RR, Sladkevicius E, Lee PJ, Lachmann RH. Costs and outcomes over 36 years of patients with phenylketonuria who do and do not remain on a phenylalanine-restricted diet. J Intellect Disabil Res. 2013;57(6):567-79. doi: 10.1111/j.1365-2788.2012.01568.x.
16. Wang L, Zou H, Ye F, Wang K, Li X, Chen Z, Chen J, Han B, Yu W, He C, Shen M. Household financial burden of phenylketonuria and its impact on treatment in China: a cross-sectional study. J Inherit Metab Dis. 2017;40(3):369-376. doi: 10.1007/s10545-016-9995-0.

17. MacDonald A, Smith TA, de Silva S, Alam V, van Loon JM. The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK. Mol Genet Metab Rep. 2016;9:1-5. doi: 10.1016/j.ymgmr.2016.08.008.
18. Eijgelshoven I, Demirdas S, Smith TA, van Loon JM, Latour S, Bosch AM. The time consuming nature of phenylketonuria: A cross-sectional study investigating time burden and costs of phenylketonuria in the Netherlands. Mol Genet Metab. 2013;109(3):237-42. doi: 10.1016/j.ymgme.2013.05.003.
19. Bosch AM, Burlina A, Cunningham A, Bettiol E, Moreau-Stucker F, Koledova E, Benmedjahed K, Regnault A. Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries. Orphanet J Rare Dis. 2015;10:80. doi: 10.1186/s13023-015-0294-x.