Current status and use of resources of Lysosomal Storage Diseases: Analysis of a Spanish claims database

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ABSTRACT

Background: The knowledge of the pathophysiology of Lysosomal Storage Disorders has slowly increased, but information on their incidence is still scarce. The objective of this study was to evaluate the status and use of resources of these disorders in Spain from 1997 to 2015.

Methods: Records from 4,999 patients diagnosed with a Lysosomal Storage Disorder were extracted from a Spanish database containing data from public and private hospitals from 1997 to 2015.

Results: The database registered 2,441 patients with a LSD in Spain during the study period. Leukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease and sulfatide lipidosis represented, as a group, the most common disease cluster in Spain, affecting 26% of total patients. Average age of diagnosis of these disorders was 16.7 years. A sex bias was observed in most groups, with a proportion male/female of 60 to 40%. The direct medical cost of Lysosomal Storage Diseases was €5,686 per patient with an average cost per hospital admission of €4,923. Global costs displayed a growing tendency.

Conclusions: Contrarily to worldwide disease incidence estimations, the group to include Krabbe disease registered the highest occurrence numbers in the study period, which makes evident the need for accurate regional disease incidence and patient demographic studies. Altogether, data suggests the need to improve LSDs diagnostic protocols, and supports the inclusion of these disorders in standard new-born screening programs.

KEYWORDS

Lysosomal storage diseases, inherited metabolic diseases, claims database analysis, economic impact study, Spain, Krabbe disease.

INTRODUCTION

Lysosomal storage diseases (LSDs) are a group of metabolic disorders characterised by lysosomal dysfunction, which leads to the accumulation of macromolecules inside lysosomes. All LSDs are progressive, and in most cases there is a neurodegenerative course. Symptoms in other organ systems are frequent, including bones and joints, eyes, heart, kidneys, lungs, spleen, liver and skin [1]. The onset of most disorders is infantile or juvenile, although in a few cases an adult onset is possible. This description comprises over 70 inherited diseases that altogether affect about one in 5,000 births, although individually the disorders are rare.

LSDs are classified in several groups based on the type of disorder and age of onset of the first symptoms, key to diagnosis. A general disease classification includes glycogen storage diseases or glycogenosis, disorders of carbohydrate transport and metabolism, lipidoses, cerebral lipidoses, mucopolysaccharidoses, and leukodystrophy [2]. Two lipidoses were the first LSDs described, Gaucher disease was the first, in 1882, followed by Fabry disease in 1898 [3-5]. Nonetheless, its recognition as LSDs took place after the 1960s, when the function and importance of lysosomes was characterised [6]. Since its description, the knowledge of LSDs pathophysiology has slowly increased, identifying multiple potential clinical targets. Enzyme replacement therapy (ERT) is the best-known therapeutic approach, widely investigated, and approved for the treatment of several LSDs, including Gaucher, Fabry, and three mucopolysaccharidoses [7].

Contrarily, epidemiological studies are not abundant, and in many countries, as in Spain, there is no information on the incidence of LSDs or individual disorders. Estimations of LSDs prevalence worldwide point at Fabry disease as the most common LSDs, with 1 in 40,000 to 60,000 males, and no data on females. Pompe would affect about 1 in 40,000 people in the United States, and Gaucher disease would occur in 1 in 50,000 to 100,000 people [8].

Other world regions as North East Italy or Illinois have tried to establish the utility of new-born screenings for certain LSDs (Pompe, Gaucher, Fabry, mucopolysaccharidosis type I and Niemann-Pick disease) with potential benefits derived from the screening [9, 10]; however, there is a lack of wider studies that determine disease incidence.

In many occasions, significant disease occurrence differences have been reported among patients with diverse ethnicities and origins. For instance, Type 1 Gaucher disease can occur in 1 in 500 to 1,000 people in people of eastern and central European Jewish heritage [8]. Hence the importance of determining disease occurrence in a certain region in order to establish the utility of new-born standard screenings and optimal health care procedures.

This study was designed to analyse LSDs occurrence in Spain, as well as to determine their economic impact from the National Health Service perspective. Thus, we reviewed patient characteristics, use of resources and hospitalisation costs of LSDs in Spain during 18 years using a national claims database.

METHODS

Records of patients diagnosed with LSD disorders were extracted from the Spanish claims database Minimum Basic Data Set (Conjunto Mínimo Básico de Datos (CMBD) [11], by means of the appropriate International statistical classification of diseases and related

health problems, 9th revision (ICD9) code. The CMBD database contains patient records from 192 private and 313 public hospitals from 1997 to 2015. Prior to extraction, parameters such as health centres and medical history identifiers were re-coded in order to maintain records anonymised, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, and thus, ethics committee approval was not required (Law 14/2007, July 3, on Biomedical Research, Spain).

ICD9 codes utilised to select the data were: 271.0, 271.8, 272.7, 277.5, 330.0 and 330.1, corresponding to glycogenosis, other disorders of carbohydrate transport and metabolism (ODCTM), lipidoses, mucopolysaccharidosis, leukodystrophy and cerebral lipidoses respectively, all corresponding to LSDs disease clusters.

Data analysis

Data presentation and analysis are descriptive. Duplicate data was discarded to obtain information of individual patients, relying on the first record entry as the index event. Such records were employed to obtain single-patient information of disease occurrence (patient characteristics), direct medical cost per patient and financial scheme. Disease comorbidities have also been studied. The complete admission data was used to extract information on the nature of patient hospitalisations, diagnosis-related group (DRG) and cost per DRG. Via DRG, direct medical cost was calculated, which included treatment (examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources.

All available information has been included in the analyses, except for the extraction of direct medical costs, where 1997 and 1998 data was excluded to obtain a more consistent analysis.

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

RESULTS

Characteristics of patients included in the database

LSDs included in the study were determined by ICD9 codes, which claimed 47 disorders, listed in

Table .

Such codes identified 2,441 patients in the database with a LSD diagnosis. The most common disease group included Leukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease and sulfatide lipidosis with a total number of 624 patients diagnosed (

Table). Lipidoses were in the second place, with 510 patients. This group includes diseases as Fabry and Gaucher.

In terms of patients' sex, certain differences were observed. Leukodystrophy, lipidoses, glycogenosis and mucopolysaccharidosis showed a proportion male/female of around 60 to 40%. As for other specified disorders of carbohydrate transport and metabolism and cerebral lipidoses the proportion of male and female patients identified was of 53 to 47% and 54 to 46% respectively, presenting a smaller sex bias. Files with unknown sex and others represented less than 1% in all cases.

Patients' age distribution varied among disease clusters. Patients diagnosed with glycogenosis had an average age of 15.75 years (SD ±19.91). For ODCTM it was of 13.23 years (SD ±17.65). The average was of 26.22 years (SD ±23.58) for lipidoses, 9.31 years (SD ±11.94) for mucopolysaccharidosis, 16.72 years (SD ±20.07) for leukodystrophy, and of 11.94 years (SD ±17.02) for patients with cerebral lipidoses (Figure). On the other hand, the number of diagnoses over time displayed a growing tendency for glycogenosis. These shifts are not likely to be representative of disease prevalence and further conclusions cannot be extracted due to a lack of information. Other clear tendencies were not observed (Figure). LSDs regional distribution analysis showed that the Spanish Autonomous Community with the highest number of patients with glycogenosis, lipidoses, leukodystrophy and cerebral lipidoses was Madrid. Andalusia was the one with the most cases of mucopolysaccharidosis, and Catalonia of ODCTM (data not shown).

Regarding disease comorbidities different symptoms are linked to the distinct disease clusters (Table 1). Mental disorder symptoms appear repeatedly among the mucopolysaccharidosis, leukodystrophy and cerebral lipidoses groups. Another repeated condition is hyperthension, which appears in patients with glycogenosis and lipidoses. In patients with ODCTM chronic renal disease is the most common comorbidity.

Healthcare resources

The analysis of the available admission data revealed information on the nature of patients' hospitalisation. Programmed admissions were predominant for most patients, except in those with a diagnosis of leukodystrophy or cerebral lipidoses (Table). Patients' destination after discharge was predominantly to their residence; transfers to other hospitals or social

care centres, voluntary discharge, death and others represented less than 1% of the cases. Average hospitalisation time was 8 days, and readmission rates were around 6% in patients with lipidoses and mucopolysaccharidosis, and between 0.5 and 2% in patients included in other disease clusters. The service that attended the highest number of patients was paediatrics.

The most common medical procedures registered in admission files were evaluated for each LSD cluster to obtain an approximation to disease management. In patients diagnosed with glycogenosis, lipidosis or a mucopolysaccharidosis the injection of a therapeutic substance, which includes enzyme replacement therapy (ERT), was the most repeated procedure, carried out in 31, 30 and 45% of patients' admissions respectively. In patients with ODCTM, leukodystrophy and cerebral lipidoses the administration of therapeutic substances as ERT was performed only in 14, 4 and 7% of admissions respectively. In all cases, diagnostic techniques as abdomen echographies, radiographies and magnetic resonance of the brain and brain stem were significant. Enteral or parenteral infusion of concentrated nutritional substances took place in between 4 and 14% of admissions, with the highest percentages found in patients with cerebral lipidoses. Mechanical ventilation and oxygen enrichment were performed in around 8% of all admissions, with the higher percentage found too in patients with cerebral lipidoses (12%). Lastly, it is worth noting the relatively elevated presence of haemodialysis in patients with ODCTM (11%).

Finally, the direct medical cost per patient was €5,686 with an average cost of €4,923 per hospital admission, being the costs of treating disorders of carbohydrate transport and metabolism the highest, and the costs associated to lipidoses the lowest (Table). Global

medical costs increased slightly over time (Figure), with an average annual direct medical cost of around €30,600 considering all LSDs. The Spanish social security system financed between 95 and 99% of the patients (Figure). The remaining patients used private financing, mutual health care or other unspecified sources.

DISCUSSION

Information regarding LSDs epidemiology is still scarce in many countries, restricting the application of more specific health protocols, as new-born screening, that could allow a better handling of these diseases. LSDs are currently not included in new-born screening programs in Spain, although a previous study in the north of the country evaluated the viability of including Fabry disease in routine screenings [12]. Recommendations to include this disease in systematic screenings followed the study, but further assessment of the patient population was considered necessary in order to establish appropriate protocols for patients' management. Herein, data provided by the CMBD database allowed a retrospective analysis of LSDs patients' demographic information and disease occurrence in the country. Data revealed possible discrepancies with worldwide prevalence estimations. In Spain the most diagnosed diseases were, as a group, Leukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease and sulfatide lipidosis. Worldwide, Fabry disease is considered the most prevalent [8], whereas, in Europe, previous estimations situated Krabbe at 1 per 100,000 [13]. In terms of sex biases in the population, the fact that this disease cluster includes Pelizaeus-Merzbacher disease, linked to the X chromosome, could explain the sex ratio revealed for this disease group (60 to 40%). The same sex bias found in other groups is consistent with previous findings [1]; although not all existing reports

show such differences. This could be explained by a founder effect in some countries, which also justifies reported differences among distinct ethnic groups; for instance, glycogenosis (GSD II) mutations appear four times more than expected in the Netherlands [14]. This supports the importance of regional evaluations. Herein, as for patients' regional distribution, Spanish Autonomous Communities with the highest number of patients corresponded to the most populated regions.

Most LSDs are typically diagnosed during the first years of life given the severity of its symptoms. Spanish patients' age distribution displayed in the present study suggests a late detection of these diseases, although a certain number of errors in patient records cannot be ruled out. Still, average age of diagnosis per group was between 9 and 26 years, which could be a result of small groups of patients showing the first symptoms during adolescence or early adulthood, together with a rate of misdiagnosis, which can worsen patients' prognosis. Provided that the rate of misdiagnoses and delayed diagnoses caused the increase in this parameter, a major occurrence of preventable complications should be considered, together with the derived increased use of healthcare resources. For instance, listed complications derived from delayed Gaucher diagnosis include serious complications as progressive liver disease, chronic bone pain, growth failure and severe sepsis among others [15]. In parallel, the database allowed an analysis of patients' disease comorbidities, which were repeatedly consistent with LSDs described symptoms. Mental disorders were found, typically present in patients with mucopolysaccharidosis, leukodystrophy and cerebral lipidoses [16-20], and hypertension can be common in patients with glycogenosis and lipidoses [21, 22]. As for patients with disorders of carbohydrate transport and

metabolism (ODCTM), kidney failure and an end-stage renal disease is frequent [23, 24]. Subsequently, an evaluation of current treatment protocols was considered of interest. Currently in Spain, there is a lack of specific clinical guidelines that describe protocols for suspected LSDs, only available for Fabry disease [25], and it is evident that the availability of effective and palliative treatment determines the efficiency of new-born screening programs and their viability. Medical procedures performed on admission were analysed as a rough approximation to disease management. The administration of therapeutic substances as ERT has been approved for the treatment of several LSDs [1] and prevails as the main therapy, especially significant in patients with glycogenosis, lipidosis or a mucopolysaccharidosis. Ventilation and oxygen enrichment were significant in all groups, although augmented in percentage when ERT was not applicable. This could be observed for Krabbe or Tay-Sachs disease, which have no specific treatments available and mostly receive symptomatic and supportive therapy [26]. It is noteworthy the percentage of patients with ODCTM receiving haemodialysis, a clear response to the symptoms of disorders as hyperoxaluria, in which renal damage is the principal outcome [27]. As a whole, disease management data did not reveal any significant discrepancies in Spanish clinical practices.

An estimation of the burden that LSDs represent for the healthcare system is hardly obtainable given the wide number of disorders and their variety of clinical manifestations. Herein, we obtained LSDs direct medical cost via the analysis of the costs associated to each hospitalisation. The annual direct medical cost in Spain was €5,686 per patient between the years 1999 and 2015, with an average cost of €30,600 for all registered patients per year.

Similarly, in the UK it was estimated that the annual cost for LSDs patient care was €3,400-13,700 per adult patient [28]. Moreover, studies that have measured the costs of enzyme replacement therapies have estimated annual costs of around €200,000 per patient [29]. The lack of accurate epidemiologic data however, hardens a realistic study of LSDs total burden, which would take into account indirect costs and their impact on society, although in this study they appear to have an increasing tendency. On the other hand, a previous analysis developed by a regional Spanish Health Department measured the costs that new-born screening for Fabry, Gaucher, Pompe and Niemann-Pick would represent, a total sum of 0.53 million euros annually [30]. In Spain, disorders may be incorporated in standard new-born screenings given the following conditions: severe morbidity or mortality derive from delayed diagnosis, new-born detection is inefficient, effective or palliative treatment is available, incidence is over 1 in 10.000-15.000, procedure is cost-effective, there is a familiar and reproductive benefit derived, and clinical infrastructure is prepared [31]. Altogether, this study remarks the need to improve LSDs diagnosis, and supports their addition in screening programs. Patient descriptive parameters served as an approximation to the population characteristics, yet, in order to implement systematic screening, further research will be needed to determine recurrent genetic variants in the country.

CONCLUSIONS

Data obtained in this study remarks the need to improve LSDs diagnostic protocols, and supports the inclusion of these disorders in standard new-born screening programs. In addition, medical costs per patient, in an increasing tendency, considered together with the presumed indirect costs of the disease, suggest a cost-effective situation. Still, further

research will be required to determine the presence of specific genetic variants in the country that may lead to the selection of more precise screening tests.

LIST OF ABBREVIATIONS

CMBD: Conjunto mínimo básico de datos (Spanish claims database Minimum Basic Data Set).

DRG: Diagnosis related group.

ERT: Enzyme replacement therapy.

ICD9: International statistical classification of diseases and related health problems, 9th revision code.

LSD: Lysosomal storage disease.

MPS: Mucopolysaccharidosis.

ODCTM: Other specified disorders of carbohydrate transport and metabolism.

Ethics Approval and Consent to Participate

Data was anonymised prior to extraction, and thus, ethics committee approval was not required for this study (Law 14/2007, July 3, on Biomedical Research, Spain).

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The data that support the findings of this study is available from the Spanish Ministry of Health with restrictions applied.

Conflict of interest

The authors declare no conflict of interests financial or otherwise.

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JD contributes to the investigation by interpreting the economic current situation of LSDs in Spain, was a major contribution in the intellectual content revision and gave final approval of the version to be published. AM analysed the current occurrence rate of LSDs in Spain, analysed and interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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FIGURES

Figure 1 Patients average age at diagnosis.

Figure 2 Evolution of LSDs over time (1997 to 2015).

Figure 3 Annual costs of LSDs per hospital admission (1999 to 2015).

Figure 4 Percentage of patients that are financed by the Spanish social security system.

TABLES

Table 1 LSDs clusters determined by ICD9.

Table 2 Number and characteristics of patients diagnosed with a LSD.

Table 3 Disease comorbidities in patients diagnosed with a LSD.

Table 4 Admission origin and patients destination after discharge.

Table 5 Costs associated with healthcare of patients with a LSD. Costs per hospital admission and per patient.

FIGURES

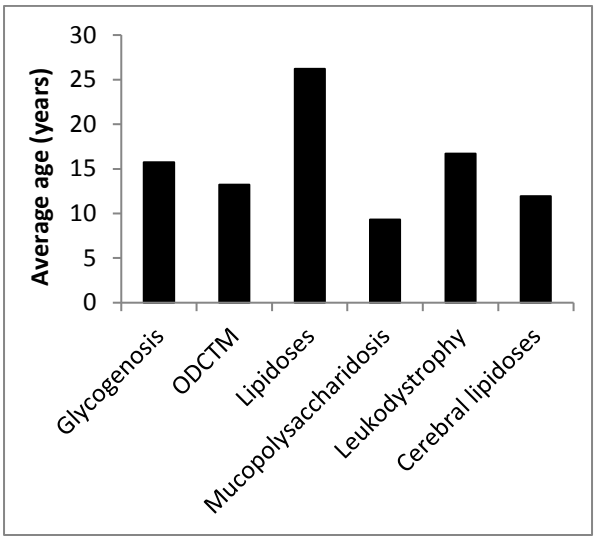

Figure 1

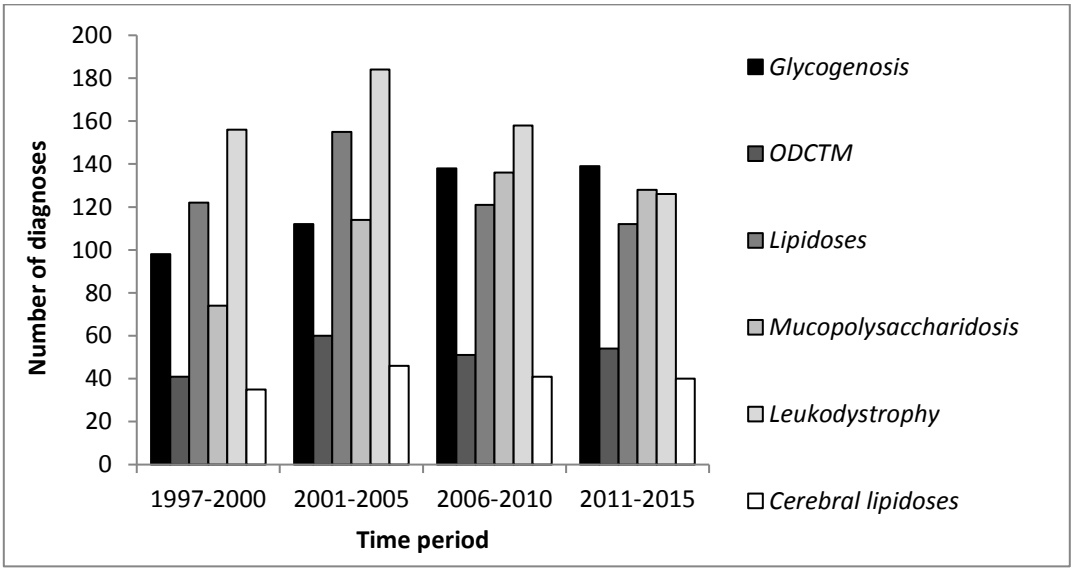

Figure 2

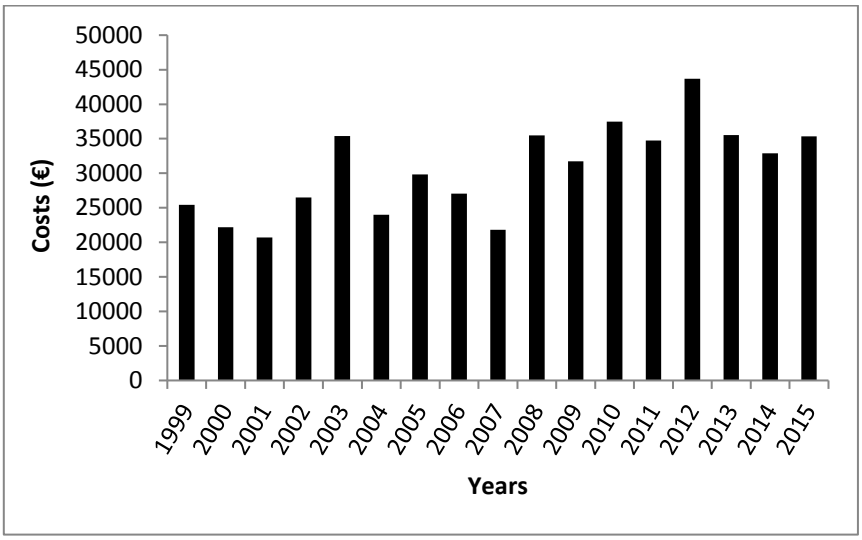

Figure 3

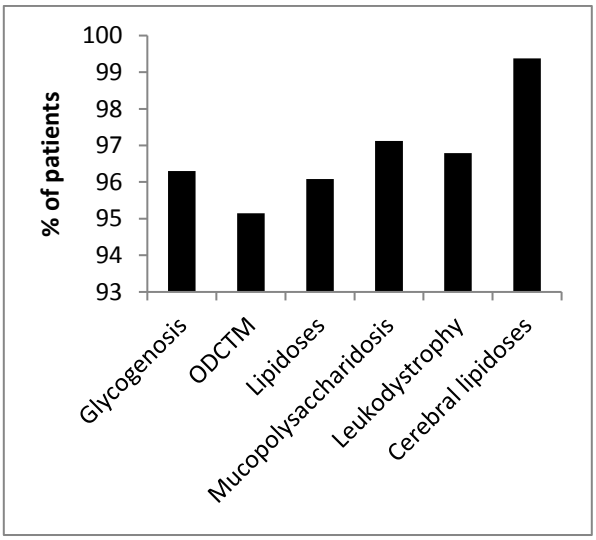

Figure 4

TABLES

Table 1

Glycogenosis	**Other specified disorders of carbohydrate transport and metabolism (ODCTM)**
Amylopectinosis	Glycolic aciduria
Glucose-6-phosphatase deficiency	Fucosidosis
Glycogen storage disease	Primary hyperoxaluria
McArdle's disease	Mannosidosis
Pompe disease	Oxalosis
von Gierke disease	Essential benign pentosuria
	Xylosuria
	Xylulosuria
Lipidoses	**Mucopolysaccharidosis (MPS)**
Chemically induced lipidosis	MPS I
Disease:	MPS II
Anderson	MPS III
Fabry	MPS IV
Gaucher	MPS VI
I cell [mucolipidosis I]	MPS VII
lipoid storage NOS	MPS IX
Niemann-Pick	
pseudo-Hurler or mucolipidosis III	
triglyceride storage, Type I or II	
Wolman's or triglyceride storage, Type III	
Mucolipidosis II	
Primary familial xanthomatosis	
Leukodystrophy	**Cerebral lipidoses**
Krabbe disease	Amaurotic (familial) idiocy
Leukodystrophy:	Disease:
NOS	Batten
globoid cell	Jansky-Bielschowsky
Metachromatic	Kufs'
Sudanophilic	Spielmeyer-Vogt
Pelizaeus-Merzbacher disease	Tay-Sachs
Sulfatide lipidosis	Gangliosidosis

Table 2

Disease cluster	Number of patients	% of total patients	% of male patients	% of female patients	Average patient age
Glycogenosis	487	19.95	62.22	37.78	15.75
ODCTM	206	8.44	46.60	52.91	13.23
Lipidoses	510	20.89	57.45	42.55	26.22
Mucopolysaccharidosis	452	18.52	61.73	38.27	9.31
Leukodystrophy	624	25.56	60.42	39.58	16.72
Cerebral lipidoses	162	6.64	46.30	53.70	11.94

Table 1

Disease cluster	Disease comorbidities	% of patients
Glycogenosis	Patients with a gastrostomy status	6.78
	Unspecified essential hypertension	5.34
ODCTM	Chronic kidney disease	13.59
	End stage renal disease	8.25
Lipidoses	Unspecified essential hypertension	4.51
	Splenomegaly	3.14
Mucopolysaccharidosis	Unspecified special symptoms [a]	5.09
	Acute respiratory failure	3.98
Leukodystrophy	Unspecified special symptoms [a]	4.97
	Corticoadrenal insufficiency	4.65
Cerebral lipidoses	Epilepsy	14.81
	Unspecified special symptoms [a]	6.79

[a] applies to communication disorders, hair plucking, lalling, lisping, masturbation, nail-biting and thumb-sucking.

Table 4

Disease cluster	Origin of admissions (%)		Destination after discharge (%)		
	Urgent	Scheduled	Patients' residence	Transfer	Voluntary discharge
Glycogenosis	6.01	8.60	14.09	0.24	0.04
ODCTM	1.70	2.10	3.59	0.06	0.00
Lipidoses	5.62	8.81	13.69	0.21	0.09
Mucopolysaccharidosis	7.14	8.71	15.29	0.18	0.05
Leukodystrophy	6.73	4.18	9.88	0.31	0.04
Cerebral lipidoses	2.01	0.80	2.36	0.03	0.01

Table 5

	Cost per admission (€)	Cost per patient (€)
Glycogenosis	3,865	5,071
ODCTM	8,362	9,685
Lipidoses	3,066	3,898
Mucopolysaccharidosis	4,301	5,508
Leukodystrophy	4,985	5,071
Cerebral lipidoses	4,959	4,886
Global costs	4,923	5,686