Chronic inflammatory demyelinating polyneuropathy in Spain: a retrospective analysis of hospital incidence and medical costs.

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Author contributions

JD contributed to the investigation by analyzing and interpreting the burden associated to CIDP in Spain and was a major contribution in the intellectual content revision. AM analyzed the current situation of CIDP in Spain, 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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Abstract

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disorder that usually involves long-term impairment. Despite the chronic healthcare needs that are often associated, research evaluating the economic burden of this disorder is still scarce. This study aimed to assess the characteristics of patients admitted with CIDP in Spanish hospitals and to determine the associated medical costs.

Methods: A retrospective multicenter study was designed analyzing records of hospital and ambulatory visits of patients with CIDP in Spanish hospitals between 2004 and 2018. Medical costs registered in hospital facilities were evaluated.

Results: Admission files corresponding to 2805 patients diagnosed with CIDP were extracted from the database: 64.7% of patients were males and median age was 60 years. Patients presented comorbidities that included essential hypertension, hypercholesterolemia and diabetes mellitus. The raw number of admissions for CIDP increased significantly over the study period, similarly to mean admission costs for all age groups. Consequently, total hospital medical costs associated to CIDP increased over the study period. Mean medical cost per admission was €3953.

Conclusions: The increasing number of hospital cases of CIDP is associated to rising medical costs. Further research will be required to fully evaluate the medical and societal burden of this disorder.

Keywords: Chronic inflammatory demyelinating polyneuropathy; hospital incidence; medical costs; Spain.

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disorder affecting the peripheral nerves and nerve roots, causing symptoms that include weakness, paralysis and the impairment of motor function [1]. CIDP is thought to be immune-mediated, with genetic and environmental factors associated, although the pathogenesis and etiology of CIDP are not fully understood [2,3]. Recent studies suggest the involvement of two distinct mechanisms, namely paranodal dissection and macrophage-induced demyelination [4,5]; the pathophysiology of CIDP is considered of relevance in selecting an adequate therapeutic strategy [6]. The main characteristic of a typical CIDP is a chronically progressive, monophasic or recurrent symmetric proximal and distal sensorimotor deficit with demyelination, whereas atypical cases include distal acquired demyelinating symmetric neuropathy (DADS), multifocal distributed symptoms with persistent conduction block (Lewis-Sumner Syndrome), pure motor or pure sensory cases [7,8]. The heterogeneous symptomatology and frequent relapses and recurrences may complicate diagnosis, which is usually confirmed by MRI evidence of enlarged nerve roots, evidence spinal fluid albuminocytologic dissociation, or response to immune treatments [9].

The total incidence of CIDP in Spain has not been evaluated; nonetheless, a recent meta-analysis provided a crude global incidence rate of 0.33 per 100,000 person-years, with a higher incidence of this disorder in males [1,10,11]. Despite its low incidence, CIDP is assumed to represent a significant burden for healthcare systems, considering

the long-term impairment that is associated to it [12]. Medical costs have not been evaluated in Spain, however, a 2020 literature review pointed out hospitalization and treatment costs as the main cost drivers in CIDP in several European countries and the United States [13].

The aim of this study was to evaluate the main characteristics of patients admitted with CIDP in Spain at the hospital level and to determine the associated medical costs.

2. Methods

2.1. Study design

Ambulatory and inpatient admissions registered in Spanish hospitals between 1 Jan 2004 and 31 Dec 2018 were analyzed in a retrospective multicenter study. Files were obtained from a Spanish National discharge database, which covers 90% of hospitals in Spain with data from all Spanish regions. Data within the database is codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) after the year 2016 [14,15]. Centers are responsible for data codification, evaluation and confidentiality. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated.

2.2. Data extraction

Records of ambulatory visits and hospital admissions in which CIDP was listed as the admission motive were claimed using the corresponding ICD-9 and ICD-10 codes: 357.81 and G61.81, respectively. Admission records did not contain any parameters identifying healthcare centers or medical history that were previously re-coded to maintain records anonymized, in accordance with the principles of Good Clinical

Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [16].

2.3. Study variables

The variables analyzed were: patients' age, date of admission, type of admission, date of discharge, type of discharge, readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), primary diagnosis, up to 20 secondary diagnoses registered during the admission, medical procedures and total admission medical cost. Costs were not available for the year 2018 at the time of the study.

2.4. Data analysis

The primary diagnosis was used to identify patients with CIDP. Patients' were grouped considering the median, the 25^{th} and 75^{th} percentiles and the pediatric population into: < 18 years of age, ≥ 18 < 47 years of age, ≥ 47 < 60 years of age, ≥ 60 < 72 years of age and ≥ 72 years of age. Patient characteristics were examined in the first admission registered per patient, whereas admission details and medical costs were analyzed using all admission files.

Hospitalization rate was measured as the annual number of patients admitted with CIDP within the total number of admission files in the database. Medical costs of specialized healthcare were extracted from the database, where they are assigned according to the standardized average expenses of admissions and medical procedures determined by the Spanish Ministry of Health (include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel,

medical equipment and resources). Medical costs were adjusted for inflation to 2017 values.

Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean or median and 95% confidence interval (CI) were calculated for continuous variables. Two-tailed non-parametric independent t-test (Mann-Whitney U test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate, with a $p<0.05$ considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2016 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

The code for CIDP claimed 6900 admission files from the database, which corresponded to 2805 individual patients (Table 1). The majority of patients were males (64.7%), and median patient age was 60 years (95%CI, 59-61). Patients were diagnosed with numerous secondary conditions; the most common were essential hypertension (24.0%), hypercholesterolemia (17.5%) and diabetes mellitus (16.6%), associated with patients' age (Table 1). Only 3.9% of files registered autoimmune conditions (excluding diabetes mellitus), which were possibly registered within other categories. Several symptoms of CIDP were also registered, including disturbances in the sensation of smell or taste and unspecified paralytic syndromes.

The hospitalization rate of CIDP in the database was 12.1 per 100,000 patients in 2018; this rate increased significantly between 2004 and 2015 ($p<0.0001$), and decreased between 2015 and 2016 coinciding with the implementation of the new ICD

codification system (Figure 1A). The raw admission number analyzed per age groups revealed an increase in the number of admissions over time in patients over 47 years of age ($p<0.0001$) (Figure 1B).

Most of the obtained files corresponded to inpatient admissions (99.4%). Mean length of stay increased significantly with patients' age ($p<0.0001$) (Table 2). No significant trends were found in the length of hospital stay over time. Urgent admissions represented 36.0% of all admissions, although this portion was significantly larger in patients under 18 years of age ($p<0.0001$); the same phenomenon was observed in the readmission rate. The hospital department registered at discharge was neurology in 80.3% of the files and internal medicine in 11.1%, ER was only registered in 0.1% of files.

A heterogeneous group of medical procedures were registered in admission files. The injection or infusion of therapeutic substance was registered in 86.9% of admissions, primarily specified as subcutaneous immunoglobulin (59.2%) and steroid injection (6.3%) (Table 2). Various diagnostic imaging procedures were registered, as well as diagnostic and therapeutic physical therapy. No significant trends were identified in the registry of therapeutic medical procedures over time.

Medical costs registered in hospital facilities were evaluated, adjusted to 2017 values. Mean medical cost per admission increased significantly over the study period for all age groups ($p<0.0001$) (Figure 2A). Consequently, total medical costs of CIDP at the hospital level increased over the study period ($p<0.0001$), however, this increase was not significant in patients under 18 years of age, presumably due to the small patient number (Figure 2B).

Mean medical cost per admission increased significantly with patients' age ($p<0.0001$). Inpatient admissions represented greater costs than outpatient visits, a cost that increased significantly with length of hospital stay ($p<0.0001$) (Table 3).

4. Discussion

The epidemiology of CIDP in Spain has not been thoroughly evaluated, and few data is available on the medical costs associated to this disorder. The present study evaluated 6900 admission files obtained from a hospital based database, providing admission data of 2805 individual patients diagnosed with CIDP and admitted in a Spanish hospital between 2004 and 2018.

The patient description was comparable to that obtained in previous evaluations in other populations [10,17]. Patients presented a high incidence of hypertension, hypercholesterolemia and diabetes mellitus, which were associated with patients' age. The relation between diabetes and CIDP has been explored in multiple occasions with uncertain results; while several studies did not find a relation, more recent works describe an association between the two disorders [18-20]. Only 3.9% of admissions registered an autoimmune condition (excluding diabetes mellitus), while this figure reached the 15% in an Italian cohort in 2020 [21].

The incidence of CIDP registered at the hospital level (hospitalization rate) in this study was 12.1 per 100,000 patients. This rate is significantly higher to that calculated in the general population; a systematic review published in 2019, including 11 studies, estimated a pooled incidence rate of 0.33/100,000 at the population level [1]. However, the hospitalization rate measured in this database cannot be extrapolated to the general population. The medical needs of patients with a chronic condition as CIDP

may justify this elevated number of hospital admissions. Similarly, the increasing trend observed in the hospitalization rate over the study period could respond to the improved diagnosis of the disorder.

This study was hospital based, and the majority of admissions analyzed were inpatient hospital admissions. The treatment for CIDP is complex, and usually involves corticosteroids, intravenous immunoglobulin, plasma exchange and immunomodulatory agents [9,22]. This is reflected in the database with the general code 'Injection or infusion of therapeutic substance', registered in 86.9% of admissions. Unfortunately, the lack of a more specific coding system hampers the analysis of disease management at the hospital level, however, medical costs are assigned independently in the database. Over 20% of admissions registered physical therapy and exercises, and a variety of diagnostic imaging procedures were listed.

The current treatment options for CIDP require chronic hospital care, often with hospitalization [23]. Patient age was identified in this study as a determinant factor in length of hospital stay, which averaged 8.1 days.

The hospital admissions registered in the database were associated to a mean medical cost of €3953. The increase registered in the hospitalization rate and the raw number of admissions due to CIDP correlates with an increasing total medical cost of this disorder. A recent systematic review found that few studies have aimed to describe the economic burden of CIDP, generally with small sample sizes [13]. Total cost of illness was between €25,574 (2007) and €47,823 (2017) annually per patient, in the UK and France, respectively [13], and hospital care was estimated to account for between 18 and 35% of total costs [13]. Further research will be required to evaluate the total economic burden of CIDP in Spain.

This study was subjected to a series of limitations. This study is based in the hospital population, hence, it excludes patients not seeking hospital care; the results obtained in this study are applicable to the hospitalized population and cannot be generalized to the entire population with CIDP. In addition, the lack of individual codes for the each one of the possible treatment possibilities for CIDP limited the analysis of disease management, however, costs of treatment are included in medical cost calculations. The hospital discharge database appeared to under register autoimmune conditions. In addition, the fluctuations observed in the admission number coinciding with the update of ICD coding system must be considered when interpreting the epidemiological data.

5. Conclusions

The medical costs associated to CIDP are expected to raise as the number of hospital cases of the disorder continue to increase. The substantial medical costs associated to CIDP should be considered in future disease management and resource allocation decisions, although further evaluations will be required to quantify primary care costs and indirect costs associated to the disorder. Finally, medical data codification at the hospital level can be improved to better reflect the characteristics of CIDP.

6. Transparency section

6.1. Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

6.2. Data availability statement

Data sharing is restricted due to legal stipulations, yet the data that support the findings of this study is fully available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at: https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm.

6.3. Declaration of funding

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6.4. Declaration of financial and other interest

The authors declare that they have no competing interests.

7. References

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8. Figures

Figure 1 A) Hospitalization rate per 100,000 admissions over the study period. B) Admission number registered per age group over the study period (2004-2018).

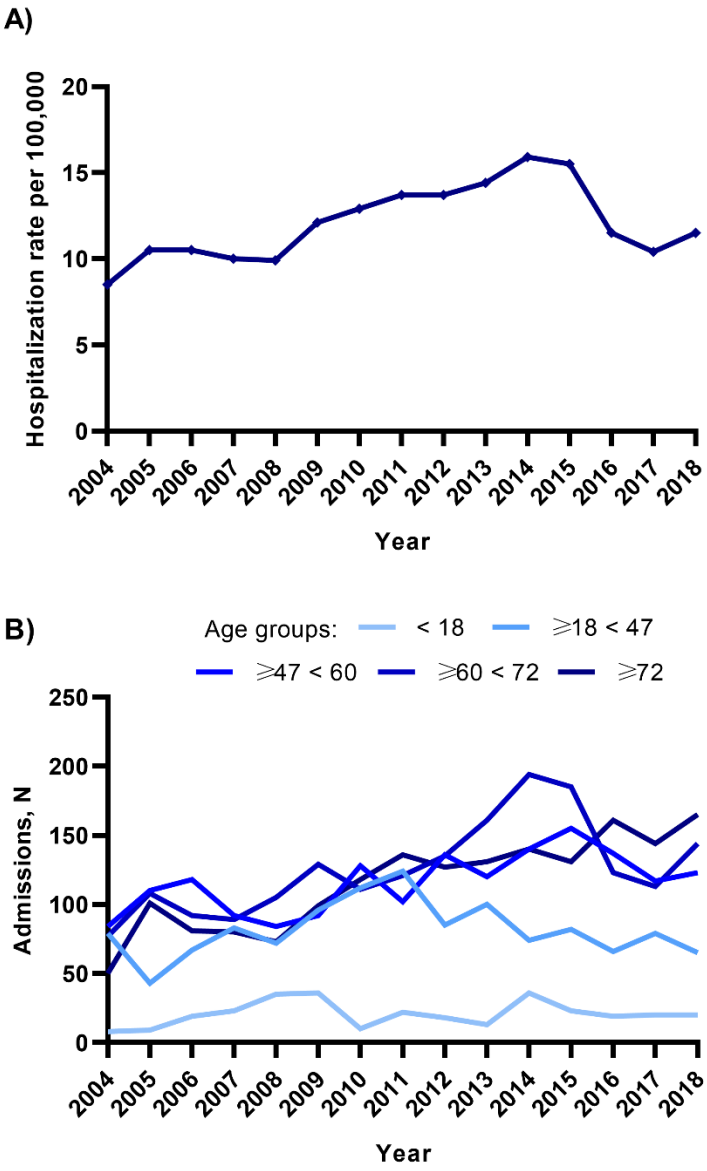
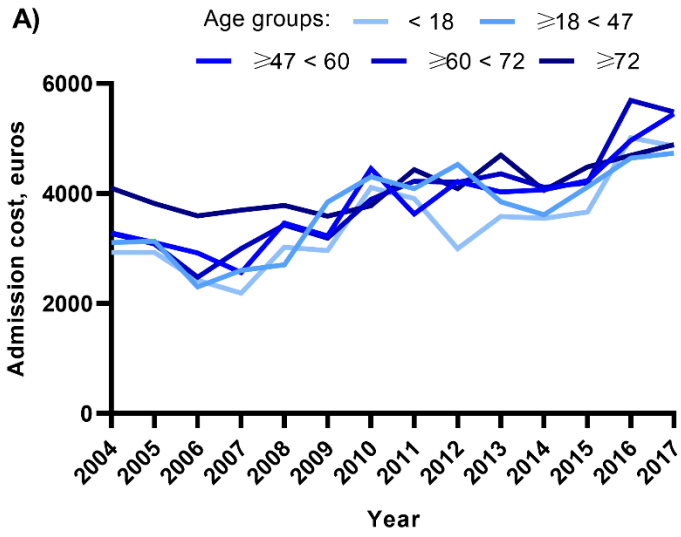
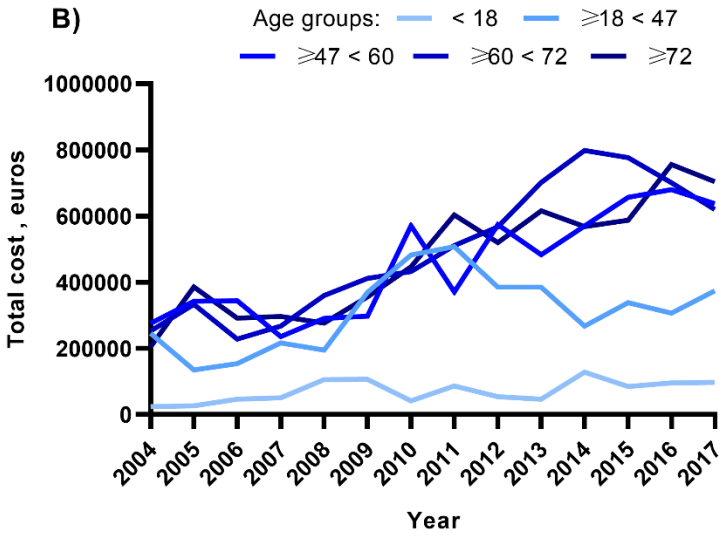


Figure 2 A) Mean medical cost per admission by age groups (2004-2017). B) Total medical hospital cost by age groups (2004-2017) (€ 2017).





9. Tables

Table 1 Patient number and characteristics by age.

	Total	< 18 years	≥ 18 < 47 years	≥ 47 < 60 years	≥ 60 < 72 years	≥ 72 years
Patients, N	2805	107	586	666	714	732
Admissions, N	6900	311	1227	1738	1887	1737
Males, %	64.7	48.6	57.7	64.1	68.9	69.0
Secondary diagnoses, %	-	-	-	-	-	-
Essential hypertension	24.0	1.0	10.7	16.9	33.0	35.1
Hypercholesterolemia and other hyperlipidemia	17.5	0.0	7.9	18.8	23.7	19.5
Diabetes mellitus	16.6	0.0	12.6	15.0	20.3	19.8
Monoclonal paraproteinemia	10.4	0.0	4.7	12.1	12.0	13.0
Thyroid disorders	7.3	1.0	4.6	6.6	10.8	7.3
Chronic obstructive pulmonary disease	7.0	0.6	1.6	6.0	7.0	13.0
Anxiety and depressive disorders	6.1	0.0	5.3	9.4	5.2	5.2
Nephritis or nephrotic syndrome	5.1	0.6	3.7	1.7	3.1	12.5
Spondylitis and other inflammatory spondylopathies	4.9	0.0	5.0	2.8	5.2	7.5
Intervertebral disc disorders	4.3	0.0	8.6	2.9	4.4	3.2
Overweight and obesity	4.1	0.0	2.9	3.7	5.1	5.2
Neoplasms	3.9	0.3	5.2	2.2	4.2	5.1
Autoimmune diseases, elsewhere specified	3.9	1.9	6.9	4.2	3.3	2.6
Anemia	3.6	1.3	2.4	4.0	4.1	4.1
Chronic liver disease and cirrhosis	3.3	0.0	3.7	5.1	3.6	1.3
Cardiac dysrhythmias	3.1	0.0	0.5	0.8	3.2	7.8

Table 2 Admission nature, length of hospital stay (LOHS) and medical procedures registered during the admission.

	Total	< 18	≥ 18 <	≥ 47 <	≥ 60 <	≥ 72

		years	47 years	60 years	72 years	years
Admissions, N	6900	311	1227	1738	1887	1737
Mean LOHS, days (95%CI)	8.1 (7.7-8.5)	4.2 (3.6-4.7)	7.7 (6.8-8.6)	7.5 (6.8-8.1)	8.8 (8.0-9.7)	9.0 (8.4-9.6)
Median LOHS, days (95%CI)	4 (4-4)	3 (2-3)	4 (4-4)	4 (4-4)	4 (4-4)	5 (4-5)
Urgent admissions, %	36.0	48.6	40.4	28.1	35.0	39.6
Readmission rate, %	19.8	37.7	20.0	21.5	19.1	15.0
Medical procedures, %	-	-	-	-	-	-
Injection or infusion of therapeutic substance	86.9	107.9	73.5	84.0	88.7	94.6
Computerized axial tomography of head, thorax, abdomen	22.5	4.0	18.0	20.1	23.8	30.6
Magnetic resonance imaging	19.6	18.3	27.4	17.8	16.1	19.7
Spinal tab	16.0	16.7	21.1	15.7	14.3	14.2
Microscopic examination of specimen	12.4	21.0	15.5	11.2	10.6	11.7
Diagnostic ultrasound	8.3	4.0	4.9	7.2	9.0	12.3
Biopsies	4.8	4.4	4.1	5.1	5.0	5.1
Electrocardiogram	4.5	2.8	4.1	3.8	4.3	6.2
Electroencephalogram and other neurologic function tests	3.4	5.2	4.0	3.7	2.9	2.9
X-ray	3.0	1.2	2.4	3.4	2.5	3.9
Interview, evaluation or neurologic examination	5.1	9.5	2.7	3.5	5.0	8.2
Diagnostic physical therapy	18.6	16.7	20.2	17.1	16.9	21.5
Physical therapy exercises and other therapeutic procedures	3.5	3.2	2.6	3.7	3.7	3.7

CI: Confidence interval.

Table 3 Admission costs by age and type of admission (€ 2017).

	Total	< 18	≥ 18 <	≥ 47 <	≥ 60 <	≥ 72

		years	47 years	60 years	72 years	years
Mean admission cost	3953	3404	3750	3916	3990	4203
Total annual cost	1802439	70745	311231	451778	496803	471883
Outpatient	4111	3610	3355	4677	3883	3618
Inpatient	3953	3402	3751	3912	3991	4203
Inpatient ≤ 4 days	3433	3194	3202	3406	3441	3726
Inpatient > 4 days	4594	4052	4435	4653	4651	4638