All-cause hospitalizations in multiple sclerosis patients

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Introduction. There is poor knowledge on current hospitalizations in the multiple sclerosis (MS) population. The purpose of this study was to determine hospitalization causes and outcomes in a MS hospital-based cohort.

Patients and methods. A retrospective chart review was performed on all patients admitted at our centre between August, 2009 and July, 2015, excluding those with no previous established diagnosis.

Results. 308 hospitalizations were included, representing a total of 155 patients (female, 67.5%). Median age at hospitalizations was 47 years, with median disease duration of 12 years. The most common overall reason for hospitalization was infectious diseases (22.1%), followed by MS relapses (12.7%) and neurogenic bladder (11%). The median length of hospitalization for all patients was 5 days and the progressive subtype of MS had longer lengths of hospitalization than the relapsing-remitting MS. Intensive care unit admission occurred in 23 cases (7.5%) and were associated with increased mortality and length of hospitalization. Of the 308 hospitalizations, 9 (2.9%) resulted in death.

Conclusion. Infections are the most common cause of hospitalizations in our study, although MS relapses or complications related to MS continue to be significant causes of morbidity. Almost 8% of all MS hospitalizations required intensive care unit admission and these were related to longer admission lengths and higher death rates.

Key words. Hospitalization. Infection. Intensive care. Length of stay. Mortality. Multiple sclerosis.

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Introduction

Multiple sclerosis (MS) is a complex chronic neurological disorder that typically begins in young adults, placing a high burden on patients, families and the healthcare system [1,2]. Substantial changes in MS care have occurred over the last 20 years, including the update of diagnostic criteria and the licensing of disease-modifying therapies [3].

Health care utilization is high in the MS population, with up to 25.8% of the MS population being hospitalized annually, exceeding the rate of hospitalizations in the general population [4]. The hospitalizations undergone by patients with MS are frequently assumed by researchers to be a surrogate for worsening disease, for health related quality of life, and for demands on direct health service resources [5-7].

Despite this, little information is available regarding hospital admission patterns in MS. In a large European study, addressing costs and quality of life of patients with MS, the rate of hospitalizations was found to vary considerably across countries [7] and in one American study, describing hospitalizations in the MS population over the period 1984-2011, the MS-related hospitalizations rates appeared to have declined over the last decades [3]. However, until now, few others have investigated hospital admissions in MS and some important factors, such as disability or comorbidity, are not evaluated.

In this study we describe the hospitalization causes and outcomes in a contemporary MS cohort, composed by all patients with the prior diagnosis of MS admitted at Centro Hospitalar São João, over six years, aiming to analyse the burden of disease in this population, be aware of possible preventable conditions and thus, contribute to improve the patient's management and the health care planning for future needs.

Patients and methods

Study design

A retrospective chart review was conducted of all patients with MS admitted at Centro Hospitalar São João between August 1, 2009 and July 31, 2015. It is a reference and university teaching centre that serves a large region of the north of Portugal with a reference population of 330 000 people, following

about 500 patients with MS. The study protocol was reviewed and approved by the local ethics committee. No written consent was needed due to the retrospective study design. To protect confidentiality data, linkage was performed via scrambled personal health identification number using anonymized versions of the databases.

Study population

Patients were identified by the discharge diagnosis code 340, which refers to MS as per the International Statistical Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Then, we excluded those with no previous established diagnosis, according to McDonald criteria [8]. Patients without mention of MS in their electronic record, because of errors in the attribution of ICD-9-CM, were also excluded.

Outcomes

Patient demographics –age, gender and treatment– and disease history –type of the disease, Expanded Disability Status Scale (EDSS), disease duration and annualized relapse rate before and after admission– were obtained from hospitalization and clinic visit notes in the electronic patient record. For each patient we retrospectively calculated the Charlson's comorbidity index (CCI) as a measure of comorbidity. We evaluated in-hospital mortality and morbidity, being the latter determined by the inpatient length of stay and intensive care unit (ICU) requirement. The primary cause for hospitalization was determined by a physician based on review of hospitalization records and taking into account the ICD-9-CM chapters.

Statistical analysis

Statistical analyses were done using SPSS v. 22.0 software. For continuous variables, normal distribution was confirmed using the Lilliefors corrected Kolmogorov-Smirnov test. As all quantitative variables were non-normal distributed, the analysis was based on non-parametric tests.

Descriptive statistics are presented as absolute (*n*) and relative (%) frequencies for categorical data or medians and interquartile range (IQR) for quantitative data. Mann-Whitney test was performed to compare mean ranks of two independent samples. Chi square test and Fisher's exact test, when one or more of our cells had an expected frequency of five or less, were used to determine whether there is a significant association between two categorical variables; $p < 0.05$ values were considered to be statistically significant.

Results

We found 429 hospitalizations of patients with MS admitted at our hospital from August 2009 to July 2015, 308 of which met study inclusion criteria, representing a total of 155 patients (female, 67.5%). Median age at hospitalizations was 47 years (IQR: 39-59), with median disease duration of 12 years (IQR: 7-15). Other demographic and clinical characteristics of patients are summarized in table I. Patients with progressive subtype of MS compared to relapsing-remitting MS patients had older age (57 years; IQR: 45.3-62; $p < 0.001$), higher CCI (4; IQR: 2-5.75; $p < 0.001$) and higher EDSS score (6.5; IQR: 5-7.5; $p < 0.001$). The temporal trends in MS admissions over this 6-year interval are illustrated in the figure.

The median number of hospitalizations per patient was 1 (IQR: 1-2). During these six years of study, 88 patients (56.8%) only needed to be hospitalized once, 32 (20.6%) twice, and 6 (3.8%) required hospital admission more than five times, essentially due to infectious diseases (44.6%) and diseases of the nervous system and sense organs (28.6%).

The most common overall reason for hospitalization was infectious diseases (22.1%), particularly urinary tract infection. Diseases of the nervous system and sense organs were the next most common causes (21.4%), the majority (59%) corresponding to hospitalizations due to MS relapses. Diseases of the genitourinary system were also an important reason for patient hospital admissions (13.6%), 81% of these related to a common complication of MS (neurogenic bladder). Almost 10% of the hospitalizations were attributed to diseases of the circulatory system, especially ischemic heart disease and cerebrovascular disease. Neoplasms were responsible for 6.8% of admissions and 95% of them were malignant (Table II).

From the 308 hospitalizations events, 39 (12.7%) could be attributed to a MS relapse. Patients hospitalized for this reason compared to other causes were younger (40 years; IQR: 28-44; $p < 0.001$), had more frequent relapses two years before (21; 63.6%; $p < 0.001$) and after admission (31; 96.9%; $p < 0.001$) and had a lower CCI (2; IQR: 0-2; $p = 0.002$). There were no significant differences in gender, subtype of MS, EDSS and disease duration at observation between these two groups.

Figure. Temporal trends in multiple sclerosis admissions from August 2009 to July 2015.

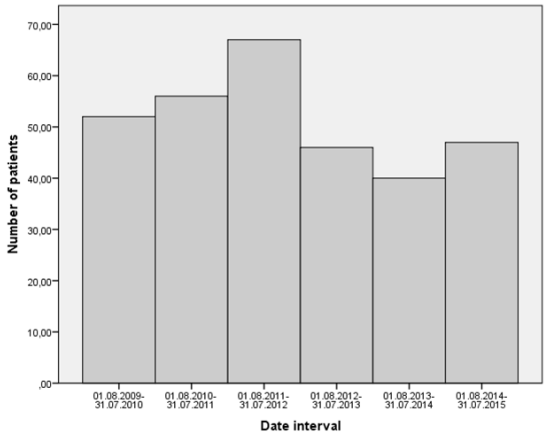

Table I. Demographic and clinical characteristics of patients in overall cohort (n = 308).

Age [a]		47 (39-59) years
Female sex		208 (67.5%)
Charlson comorbidity index [a]		2 (0-4)
Subtype of multiple sclerosis	Relapsing-remitting	145 (51.1%)
	Progressive	139 (48.9%)
	Not available	24
Expanded Disability Status Scale [a,b]		4.5 (1.5-6.5)
Relapses, two years before admission [c]		74 (33.2%)
Relapses, two years after admission [d]		66 (35.5%)
Disease duration at observation [a]		12 (7-15) years
Current disease-modifying therapy	None	95 (31.7%)
	Interferon β-1a	70 (23.4%)
	Interferon β-1b	52 (17.3%)
	Glatiramer acetate	16 (5.3%)
	Natalizumab	39 (13.0%)
	Fingolimod	14 (4.7%)
	Others	14 (4.7%)
	Not available	8
Length of stay [a]		5 (2-10) days
Intensive Care Unit admission		23 (7.5%)
Deaths during hospitalization		9 (2.9%)

[a] Median (interquartile range); [b] Only with the information of 208 patients because of the missing values in the clinical records; [c] Only with the information of 223 patients because of the missing values in the clinical records; [d] Only with the information of 186 patients because of the missing values in the clinical records.

The median inpatient length of stay for all patients from 2009 through 2015 was 5 days (IQR: 2-10). It decreased from 6.5 days in the first year of study (from August 2009 to July 2010) to 4 days in the next year, after which it remained near 5.0, excluding the interval of time between 2013 and 2014 in which the median length of stay was 6 days. The progressive subtype of MS had longer lengths of stay (7 days; IQR: 4-12) than the relapsing-remitting MS (4 days; IQR: 2-7; $p < 0.001$). There was no significant difference in length of hospitalization between patients admitted with MS relapse (5 days; IQR: 4-11) and those admitted for others reasons (5 days; IQR: 2-10).

Twenty-three hospitalizations (7.5%) resulted in ICU admission (Table III). The length of stay (12 days; IQR: 5-32; $p = 0.001$) and death rate (4; 17.4%; $p < 0.001$) were higher in patients requiring ICU care than those who did not. None of the hospitalizations requiring ICU stay were due to a MS relapse and just two were due to a possible MS related cause, both resulted from elective procedures (trigeminal neuralgia and deep brain stimulation to treat tremor). There were no significant differences in age, gender, MS disease duration, subtype of MS, CCI or EDSS in those needing ICU care compared with those who did not.

Nine hospitalizations (2.9%) resulted in death. None of these patients had been hospitalized due to a MS relapse; four patients required ICU stay (44%) (Table III). Increased CCI was statistically related to fatality (4; IQR: 2.5-8; $p = 0.01$). The average age was 53.8 years (10.2%) and 6 (66.7%) were female. The most frequent causes were intracerebral hemorrhage (2; 22.2%), upper urinary tract infection (2; 22.2%) and neoplasms (2; 22.2%), including one metastatic breast carcinoma and one non-Hodgkin lymphoma. The other causes were acute myocardial infarction, haemophagocytic syndrome and acute respiratory failure.

Table II. Causes of hospitalization.

Infection and parasitic diseases (*n* = 68) Upper urinary tract infection (*n* = 18) Lower urinary tract infection (*n* = 16) Lower pulmonary tract infection (*n* = 18) Skin and soft tissues infection (*n* = 4) Gastrointestinal tract infection (*n* = 2) Peritonitis (*n* = 1) Baclofen pump infection (*n* = 1) Central nervous system infection (*n* = 3) Others (*n* = 5)	22.1%
Diseases of the nervous system and sense organs (*n* = 66) [a] Relapses (*n* = 39) Other symptoms secondary to multiple sclerosis (*n* = 19) Others (*n* = 8)	21.4%
Diseases of the genitourinary system (*n* = 42) [a] Neurogenic bladder (*n* = 34) Others (*n* = 8)	13.6%
Diseases of the circulatory system (*n* = 30) Ischemic heart disease (*n* = 10) Cerebrovascular disease (*n* = 11) Others diseases of the arteries and veins (*n* = 9)	9.7%
Others (*n* = 25)	8.1%
Complications of pregnancy, childbirth and puerperium (*n* = 23)	7.5%
Neoplasms (*n* = 21) Malignant (*n* = 20): breast (*n* = 4), bladder (*n* = 2), thyroid (*n* = 3), cerebellum (*n* = 4), blood related (*n* = 7) Benign (*n* = 1)	6.8%
Diseases of the digestive system (*n* = 18) [a]	5.8%
Diseases of the respiratory system (*n* = 7) [a]	2.3%
Diseases of the skin and subcutaneous tissue (*n* = 5) [a]	1.6%
Mental disorders (*n* = 2)	0.6%
Diseases of the blood and blood-forming organs (*n* = 1)	0.3%

[a] Excluding infectious causes, already represented in the first group.

Discussion

In this study we describe new data about the hospitalizations patterns and outcomes in the Portuguese MS population. As a whole, we found that infections were the leading cause of hospitalization, relapses or MS related procedures also represented a significant part, few patients required ICU admission and the mortality rate was low.

Regarding infections, our findings are consistent with others studies, suggesting that infectious disease constitute the most frequent cause for hospitalizations [3,9]. According to a Swedish study [9], MS patients are at a noticeably raised risk of serious infections leading to hospital admissions and infection-related mortality, even at younger ages. Similarly to what is reported in the literature, we found that urinary tract and respiratory infections are the most common infectious diseases requiring hospitalization in MS patients. The risk of urinary tract infection may be raised by the vesicourethral and bladder dysfunctions experienced by MS patients [10,11], while a reduced muscle strength, bulbar dysfunction, and ineffective clearance of secretions, can lead to lower lung volumes and reduced respiratory function, increasing therefore the risk for respiratory tract infections [12].

Diseases of the genitourinary system were one of the three most common causes of inpatient care in our study. The frequency that we found of these kind of complication is in accordance with a Canadian study [3], being the majority related to neurogenic bladder, a common complication of MS. Neurogenic bladder is characterized by detrusor and sphincter related dysfunction and is usually not preventable in the evolution of MS with a prevalence ranging 32% to 96.8% and often requiring hospitalization [10]. However, it would be important to ascertain if some of those hospitalizations verified in our series could be avoided by improving self-care or by using alternative sites of care, such as outpatient settings for neurogenic bladder management.

Circulatory diseases were, also, an important cause for hospitalization in our study. Recent studies [13-15] suggest an increased risk of ischemic heart disease, congestive heart failure, ischemic stroke, and peripheral vascular disease in the MS population as compared to the general population, which can be explained by several factors. Firstly, MS patients have a higher frequency of adverse health behaviors, such as smoking [16]. Secondly, some evidence indicates that MS population is substantially less physically active than the general population and this may increase the risk of secondary conditions such as subclinical atherosclerosis [17]. Finally, as in other immune-mediated conditions the risk of vascular disease may be not entirely explained by traditional risk factors (such as smoking, hypertension, diabetes), which suggests that inflammatory processes related to the conditions themselves may independently increase this disease risk [16].

The frequency of admissions for neoplasms in our study fits that reported in a Canadian study [3]. Some studies state that the overall risk is lower in

MS patients than in the general population although these findings are somewhat inconsistent, since other works addressing this issue suggest that there is a possibility of increased breast, bladder and brain neoplasms in MS patients [18]. Knowing that the incidence of neoplasm increases substantially with age and MS patients are living longer [19], it would be important to understand the reasons for the differences observed in cancer risk, and possibly how to reduce it.

Patients admitted due to MS relapse were younger, with lower CCI and had more relapses two years before and after admission. The age of these patients is consistent with the literature that suggests that relapses incidence decreases by age [20]. The lower CCI observed in patients admitted for MS relapse may be associated with the lower age of this patients. This is consistent with what is known about the progressive nature of the disease and increasing disability in older MS patients [1]. In our hospital, the treatment of relapses with corticosteroids is usually at the ambulatory care setting. So, the patients that need hospital admission may have a more aggressive disease, with more frequent relapses, that difficult the adequate relapse management at the usual outpatient setting. Previous studies concerning this matter suggested that high relapses activity may indicate a refractory form of MS that requires a more complex management, including more hospitalizations [21,22].

According to our hospital statistic data [23,24], the average length of stay for neurological diseases is decreasing (from 10.5 days in 2009 to 7.41 days in 2014). However, findings about hospital length of stay in the MS population are inconsistent [1,3] and in our study we found no uniform trend in the last years. The median length of hospitalization in our study (5 days) is slightly higher than the national median reported in other Portuguese study (4 days) [25], suggesting that hospitalized MS patients in our hospital have higher in-hospital morbidity compared with the general hospitalized MS patients nationwide. However, our results reflect the median length of hospitalization over the six years whereas the other mentioned study only analyzed hospitalized patients with MS during one year (2013). Unfortunately, we could not find any other study that assessed median length of hospitalization during longer periods. The progressive subtype of MS had longer lengths of stay, contrasting with findings from British Columbia that did not find any association between disease course and extended hospital stay. [2] However, our results may be associated with the older age and higher CCI and EDSS score observed in patients with progressive subtype of MS in our study.

Table III. Reason for ICU admission and ICU survival.

		Death during admission
Infection and parasitic disease (*n* = 10)	Urinary tract infection (*n* = 4)	Yes (*n* = 1)
	Pulmonary tract infection (*n* = 3)	No
	Central nervous system infection (*n* = 1)	No
	Peritonitis (*n* = 1)	No
	Skin and soft tissue tract infection (*n* = 1)	No
Disease of the circulatory system (*n* = 8)	Ischemic heart disease (*n* = 3)	Yes (*n* = 1)
	Cerebrovascular disease (*n* = 4)	Yes (*n* = 1)
	Aortic stenosis (*n* = 1)	No
Diseases of the nervous system and sense organs (*n* = 3)	Tremor (*n* = 1)	No
	Trigeminal neuralgia (*n* = 1)	No
	Seizures (*n* = 1)	No
Diseases of the blood and blood forming organs (*n* = 1)		Yes (*n* = 1)
Diseases of the respiratory system (*n* = 1)		No

In our series, 7.5% of the hospitalizations had ICU stays, translating into a significant increase in the length of stay and death rate. Prior work regarding the frequency of ICU admission is limited, yet our findings are consistent with recent studies, suggesting that infections and circulatory diseases are the most common cause for ICU admissions in MS [26,27].

Previous studies have indicated that while overall ICU mortality is quite high, it is even higher in MS patients [26,27]. In our study, the MS patients admitted to the ICU were higher mortality compared with the literature, which ranged from 7% to 11.7% [26,27]. These results may be due to our small sample size; another explanation may rely on the fact that our hospital, as a reference and university center, receives more severe cases, which may influence the mortality rate.

Limitations of this study should be considered. As a retrospective cohort study, only based on clinical records, some important clinical features may have been under-documented, such as EDSS and frequency of relapses. The smallest number of patients with this information available may limit the generalization of our findings. Also, we do not know

whether all patients with MS were effectively captured in the database, for instance untreated or remotely diagnosed MS patients could miss. Underdiagnosis for these reasons would be more likely to occur in older than in younger patients. Moreover, we cannot control for repeated admissions of individuals patients, which may bias data. We also did not evaluate the impact of specific comorbidities due to challenges in consistently identifying comorbidities over the entire study period. Although that could be an important issue, it would require a different study design.

Hospital-based data derived from a single center, and the relatively small sample size, on the other hand, might carry a potential bias and may limit the generalization of our findings. However, our center is unique in its nature, serving a large region of the north of Portugal. Strengths of this study include use of validated methods to identify study population, evaluation of multiple aspects of health care utilization and consideration of multiple confounding factors. In order to avoid errors in the classification of the hospitalization cause, we took into account not only the primary diagnosis of the hospitalization but also what was mentioned in the hospitalization records.

Despite the fact that patients with MS are relatively high users of the healthcare system, surprisingly few details are known about hospitalizations. In this contemporary cohort, infectious disease and MS relapses or complication related to MS continue to be significant causes of morbidity. Increased patient and health care provider education regarding the risks of infections in MS may encourage patients to seek attention earlier and allow for lower thresholds for suspicious of infections and initiation of appropriate treatment. Given the observed reasons for ICU admission, prevention of infection and management of comorbidities, including cardiovascular disease, may be important avenues for reducing ICU admissions in the MS population that should be pursued in future studies. To summarize, our findings provide further epidemiological data on MS in Portugal, healthcare resource use in these patients, and impetus to investigate other efforts to reduce hospitalizations in this population.

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Causas de hospitalización en pacientes con esclerosis múltiple

Introducción. Existe un escaso conocimiento actual sobre las hospitalizaciones en la población con esclerosis múltiple (EM). El propósito de este estudio fue determinar las causas y resultados de la hospitalización en una cohorte hospitalaria de pacientes con EM.

Pacientes y métodos. Se realizó un estudio retrospectivo de los registros clínicos de todos los pacientes ingresados en nuestro centro entre agosto de 2009 y julio de 2015, excluyendo a los que no tenían un diagnóstico previo establecido.

Resultados. Se incluyeron 308 hospitalizaciones, lo que representa un total de 155 pacientes (mujeres, 67,5%). La mediana de edad en las hospitalizaciones fue de 47 años, con una duración media de la enfermedad de 12 años. La principal razón para la hospitalización fueron las enfermedades infecciosas (22,1%), seguidas de los brotes (12,7%) y la vejiga neurógena (11%). La duración media de la hospitalización para todos los pacientes fue de cinco días, y el subtipo progresivo de la EM tuvo una mayor duración de la hospitalización que la EM remitente recurrente. El ingreso en la unidad de cuidados intensivos ocurrió en 23 casos (7,5%), que se asociaron con mayor mortalidad y duración de la hospitalización. Del total de hospitalizaciones, nueve (2,9%) acabaron en muerte.

Conclusiones. Las infecciones son la causa más frecuente de hospitalización, aunque las recaídas de la EM o las complicaciones relacionadas siguen siendo causas importantes de morbilidad. Casi el 8% de todas las hospitalizaciones por EM requirió ingreso en la unidad de cuidados intensivos, lo que se relacionó con una mayor duración de la estancia y mayores tasas de mortalidad.

Palabras clave. Cuidados intensivos. Duración de la estancia. Esclerosis múltiple. Hospitalización. Infección. Mortalidad.