Main causes and risk factors for hospitalisation in patients with primary Sjögren's syndrome

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Abstract

Objective

To identify the causes and risk factors for hospitalisation in primary Sjögren's syndrome (pSS).

Methods

We included 170 pSS patients who regularly attended our Institution (2000-2013) and retrospectively collected demographic, clinical (glandular and extraglandular features) and serological (anti-Ro/SSA, anti-La/SSB, RF, low C3 or C4 and immunoglobulin levels) data. If they were hospitalised, a rheumatologist determined the primary cause. We registered the length of hospitalisation, need for Intensive Care Unit (ICU) admission, number of hospitalisations and death. The Disease Damage Index (SSDDI) (excluding the oral and ocular items) and the Charlson comorbidity Index were assessed. We used a logistic regression analysis and multiple imputation method for missing data.

Results

Fifty-five (32%) patients were hospitalised, representing 111 hospitalisations (28 patients had ≥1 hospital admission). The hospitalisation incidence density rate was 6.49/100 patient / years. The median length of hospital stay was 9 days (IQR 6–15), there were 7 ICU admissions and 6 deaths. The main causes of admissions were disease activity (33.3%) and infection (32.4%). At the multivariate analysis, the variables associated with hospitalisation were hepatic involvement (OR=5.4; 95% CI 1.61–18.15; p=0.006), vasculitis (OR=3.8; 95% CI 1.11–13.09; p=0.03), the SSDDI (OR=1.3; 95% CI 1.01–1.66; p=0.03) and the use of antimalarials (OR=0.08; 95% CI 0.02–0.22; p<0.001).

Conclusion

The major causes for hospitalisation were disease activity and infection. Patients with hepatic involvement, vasculitis and more damage accrual had the highest risk for being hospitalised, while the use of antimalarials was protective.

Key words

primary Sjögren's syndrome, hospitalisation

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Introduction

Primary Sjögren's syndrome (pSS) is a multisystem autoimmune disease with an estimated prevalence from 0.09 to 2.7% that mainly affects women in the middle age (1). The most common manifestations of the disease are related to the sicca complex, however, the spectrum of the disease also encompasses extraglandular manifestations (2).

Patients with pSS have a decreased quality of life (3) compared to subjects without the disease. In addition, they have higher indirect and direct healthcare costs, with a considerable percentage due to hospitalisations (4). Even so, there is scant information on the frequency, main causes and risk factors for hospitalisation in this entity. This data could help to better understand the clinical course of the disease and identify patients with a higher risk of hospitalisation. The aim of this study was to identify the incidence, causes of hospitalisation and the associated variables for this outcome in a cohort of patients with pSS.

Methods

This study was conducted in a tertiary care referral centre. We identified all consecutive adult patients with diagnosis of pSS according to the AECG criteria (5) who regularly attended (at least two visits per year) to our Institution from January 2000 to April 2013.

Patients' clinical records were carefully reviewed according to a pre-established protocol. We retrospectively collected demographics, disease duration defined as the onset of the first symptom attributed to pSS, the presence ever of ocular or oral symptoms and the following extraglandular features previously defined (1): non-erosive arthritis, Raynaud's phenomenon, vasculitis, lung involvement (pneumonitis or fibrosis), kidney involvement (renal tubular acidosis, glomerulonephritis or interstitial nephritis), neurological involvement (polyneuritis or mononeuritis, involvement of cranial nerves or myelitis) hematologic involvement (thrombocytopaenia, leukopenia, neutropenia, lymphopenia), splenomegaly, lymphoma, hepatic involvement (primary biliary cirrhosis or autoimmune hepatitis). We also recorded the rheumatoid factor, antinuclear antibodies, anti-SSA anti-SSB antibodies, cryoglobulins, globulins, C3 and C4 levels closest to hospitalisation during a three-month period, as well as the use of prednisone and immunosuppressors. Comorbid conditions were evaluated using the Charlson's comorbidity score (6). We registered the primary cause of hospitalisation, the length, age at hospital admission or last visit, stay of Intensive Care Unit (ICU) admission, number of hospitalisations and death. We also scored a modified Sjögren's Syndrome Disease Damage Index (SSDDI) excluding the ocular and oral items (7) at the hospitalisation or at the last medical appointment.

Patients who required at least one hospital admission were identified and compared with patients seen during the same time period and who were not admitted to hospital. For patients with multiple hospitalisations, the first one was used for comparison purposes. As it is possible that the same patient had the overlap of two or more causes of hospitalisation, the first one recognised, was used for comparison purposes. We defined disease activity as the presence of any of the manifestations recognised by the ESSDAI (8) domains except for the biological domain where we only registered the item cryoglobulinaemia. In addition we recorded the presence of autoimmune hepatitis, hyperviscosity syndrome and cryofibrinogenaemia (severe phenotype of cryoglobulinaemia). We excluded patients who required hospitalisation for elective procedures.

Statistical analysis

We used descriptive statistics and Pearson's Chi squared or Fisher's exact test and independent sample *t*-test or Mann-Whitney U-test as appropriate according to variable distribution. A probability value less than 0.05 for a two-tailed test was considered significant. A Kaplan-Meier analysis was made to determine the risk of hospitalisation through time. In our study missing information affected approximately 15% of the total cohort with respect to at least one serological data per patient. Thus, to address this issue, we used multiple imputation (9) which is a statistical technique that replaces each

missing value with a value drawn from an appropriate estimated distribution. Five imputed datasets were created for this purpose and analysed using logistic regression analysis. Then the models were analysed combined. All the analyses were performed with SPSS statistics software v.20.0

Results

A total of 170 patients (162 females, 95%) were included, with a median time since diagnosis of 7.7 (IQR 3.5–12.9) years. Fifty-five patients were hospitalised at least once, representing 111 hospitalisations; 28 (51%) of these patients had more than one hospitalisation. On the other hand, 16 out of 28 patients were hospitalised two times, five patients three times, five patients four times, one patient five times and one patient 12 times. The hospitalisation cumulative incidence was of 32.3% and the incidence density rate 6.49/100 person-years. Figure 1 shows the Kaplan-Meier plot for survival free of hospitalisation for the entire cohort.

The median length of hospital stay was 9 (IQR 6–15) days. The causes of hospitalisations were disease activity in 37 patients (33.3%), infections in 36 patients (32.4%), neoplasia in 8 patients (7.2%), cardiovascular disease in 7 patients (6.3%), hepatic disease in 4 patients (3.6%) and miscellaneous causes in 19 patients (17%). Regarding the infectious causes, most of the cases corresponded to bacterial pneumonia (30%), urinary tract infections (16.6%) followed by herpes zoster, cellulitis, gastroenteritis, chickenpox, influenza, tuberculosis and septic shock.

The distribution of cases regarding disease activity according to the ESSDAI was as follows: 8 patients with peripheral nervous system domain (7 sensorymotor polyneurophaties, 1 mononeuritis multiplex), 6 patients with central nervous system domain (2 transverse myelitis, 2 optic neuritis, 1 patient with both transverse myelitis and optic neuritis), 4 patients with lymphadenopathy domain, 4 patients with renal domain (2 patients tubular acidosis and renal failure, 2 patients glomerular involvement and renal failure), 3 patients with haematological domain (2 with neutrophils <500/mm^3, 1 patient with thrombocytopenia), 3 patients with constitutional domain (all with weight loss and one also with fever), 2 patients with pulmonary domain (interstitial lung disease). In addition we identified 3 patients with autoimmune hepatitis, 3 patients with hyperviscosity syndrome and 1 patient with cryofibrinogenaemia.

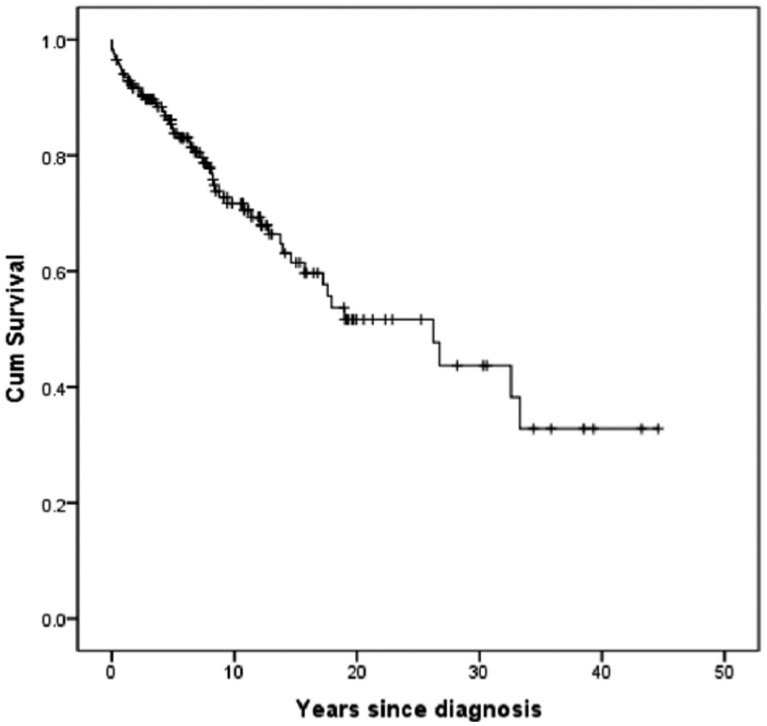

Fig. 1. Kaplan-Meir curve of survival free of hospitalisation.

Six patients had the overlap of two causes of hospitalisation. Two patients had disease activity and during the hospitalisation developed pneumonia. In the other four patients, the coexistence of two infections was documented.

There was no difference among the hospital stay length between the two main causes: activity *versus* infection (median 12, IQR 7-20 *vs*. 8, IQR 6-14 respectively, p=0.10). The age at admission was similar between the activity (48.2±16.8) and infection (52.4±15.9) groups, p=0.27. There was no difference in disease duration between patients admitted due to activity (median 7.4, IQR 4.2–13.8) *versus* those hospitalised for other reasons (median 4.9 years, IQR 1.4–10.9), p=0.38. There were seven ICU admissions and the patients admitted to the ICU had a longer hospital stay (median 26 days, IQR 13–41). The causes of ICU admissions were pneumonitis (n=1), pneumonia (n=2), ischaemic cardiopathy (n=1), hypertensive crisis (n=1) and one patient had two admissions at different hospitalisations for adrenal crisis.

Six patients died while hospitalised, four deaths were attributed to infections and two secondary to hepatic failure; however all the deaths occurred among patients with more than one hospitalisation. Thus the in-hospital case-fatality rate was 5.4% (95% CI 2–11.4%)

Table I shows the demographic, clinical and serological variables among pSS patients who were and were not hospitalised during the study period. The variables associated with hospitalisation at the univariate analysis were shorter disease duration, vasculitis, glomerulonephritis, neurologic manifestations, hepatic involvement and hyperviscosity syndrome. Hospitalised patients also had higher levels of immunoglobulins, low C4 as well as a higher SSDDI modified score and a Charlson comorbidity index ≥2.

At the multivariate analysis the hepatic involvement, the presence of vasculitis, the modified SSDDI score and the use of antimalarials (this last with a protective role) remained as factors associated with hospitalisation (Table II).

Table I. Demographics, clinical and serological data among SS patient with and without hospitalisations.

Variable	Hospitalised SS patients n=55	Non-hospitalised SS patients n=115	*p*-value
Age in years (mean ± SD)	55.97 ± 16.6	56.1 ± 14.2	NS
Median disease duration in years (IQR)	6.3 (1.6-12.1)	8.2 (4.6 14.1)	0.01
Prednisone, n (%)	21 (38)	40 (35)	NS
Azathioprine, n (%)	11 (20)	17 (15)	NS
Cyclophosphamide, n (%)	2 (4)	0 (0)	NS
Methotrexate, n (%)	3 (5)	20 (17)	0.03
Antimalarials, n (%)	5 (9)	65 (56)	<0.001
Ocular symptoms, n (%)	52 (94)	113 (98)	NS
Oral symptoms, n (%)	50 (91)	107 (93)	NS
Salivary flow <0.01 ml/min, n (%)	25/29 (86)	77/100 (77)	NS
Positive fluorescein stain, n (%)	19/30 (63)	57/82 (69)	NS
Splenomegaly, n (%)	6 (11)	4 (3)	0.07
Non-erosive arthritis, n (%)	22 (40)	37 (32)	NS
Raynaud, n (%)	6 (11)	19 (16)	NS
Vasculitis, n (%)	11 (20)	8 (7)	0.01
Lung involvement, n (%)	11 (20)	15 (13)	NS
Glomerulonephritis, n (%)	5 (9)	0 (0)	0.003
Neurological involvement, n (%)	24 (44)	29 (25)	0.01
Haematological involvement, n (%)	22 (40)	38 (33)	NS
Lymphoma, n (%)	2 (4)	3 (3)	NS
Hyperviscosity syndrome, n (%)	3 (5)	1 (0.8)	0.05
Hepatic involvement, n (%)	12 (22)	6 (5)	0.001
Positive antinuclear antibodies (≥1:320), n (%)	38 (69)	74 (64)	NS
Positive anti-SSA antibodies, n (%)	48 (87)	94 (82)	NS
Positive anti-SSB antibodies, n (%)	36 (65)	59/114 (52)	0.09
Positive rheumatoid factor, n (%)	45 (82)	79 (69)	0.06
Positive cryoglobulins, n (%)	5/23 (22)	2/46 (4)	0.03
Median immunoglobulins mg/dl (IQR)	4.2 (3.4-5.7)	3.8 (3.4-4.4)	0.03
Low C3 (<52 mg/dl), n (%)	5/41 (12)	6/87 (7)	NS
Low C4 (<12 mg/dl), n (%)	16/41 (39)	13/86 (15)	0.003
Modified SSDDI (median, IQR)	2 (0-2)	0 (0-2)	0.001
Charlson's comorbidity score ≥2, n (%)	20 (36.4)	18 (15.6)	0.003

Discussion

This is the first study that explores the causes of hospitalisation and their associations in patients with pSS. Herein we found an incidence rate of 6.49 events per 100 patient-years. In a study from Thailand, which analysed 6861 admissions in one-year period among patients with connective tissue diseases, the prevalence of hospitalisations attributable to pSS was only 0.2% unlike systemic lupus erythematosus (SLE) with 75.9% and scleroderma 12.9% (10).

The main causes of hospitalisation in our patients were disease activity (33%) and infections (32%); causes that coincide with those observed in lupus patients (11-15). Regarding other rheumatic diseases, for instance in scleroderma the main indications for hospitalisations are infections (47.9%) followed by pulmonary hypertension (34.3%) (16). Furthermore, in rheumatoid arthritis, psoriatic arthritis and spondyloarthropathy, when comparing the prebiologic and biologic treatment era, a significant decrease in hospitalisations due to exacerbation of rheumatic disease but an increase in infections events were observed in the latter group (17).

Table II. Variables associated with hospitalisation at the multivariate analysis.

Variable	OR (95% CI)	*p*-value
Hepatic involvement	5.4 (1.61-18.15)	0.006
Vasculitis	3.8 (1.11 - 13.09)	0.033
Modified SSDDI score	1.3 (1.01 - 1.66)	0.035
Use of antimalarials	0.08 (0.02 - 0.22)	<0.001

Hospitalised patients had a shorter disease duration compared to patients seen during the same time period and not admitted to hospital. However, we did not find a difference in disease duration when compared hospitalised due to activity *versus* other reasons. In contrast, in lupus patients a shorter disease duration has been observed among patients who were hospitalised due to flares (12). The average length of hospitalisation in our study (9 days) was similar to the reported length in SLE (4-8.5 days) (11-12) and scleroderma (5 days) (16). There was no significant difference among the median length of stay between activity or infections groups. Regarding the ICU stays, we found a prevalence of 6.3% that contrasts to the one reported in SLE (14.3%) (12).

pSS is a systemic autoimmune disease where sicca features primarily affect the quality of life and the presence of extraglandular manifestations are associated with the disease prognosis (18). Herein we found at the multivariate analysis, that the risk factors for hospitalisation were hepatic involvement (either attributed to disease activity or a complication mainly of PBC), vasculitis and a higher modified SSDDI score, whereas the use of antimalarial was protective.

In this sense, the prevalence of clinical liver disease in pSS is about 20% (19-20). Moreover, hepatic involvement has been identified as a marker of a more aggressive disease (21) and a Chinese series recognised it as a risk factor for mortality (22). All our pSS patients with PBC with the exception of two, had also the coexistence of another extraglandular manifestation attributed to SS. In the other two patients, the diagnosis of SS was established several years prior to the PBC diagnosis. Whether or not these two patients correspond to cases of secondary SS is a matter of debate, as PBC and pSS share several clinical, histological, serological features, as well as pathogenetic mechanisms (23). Nevertheless our study highlights that hepatic involvement is a cause of hospitalisation among pSS patients. Moreover PBC is recognised as an item of chronicity according to the SSDI index (24) conversely to the SSDDI score that does

not (7). On the other hand, the presence of autoimmune hepatitis is not recognised by the ESSDAI activity score (8). Similarly, vasculitis has a strong association with mortality in pSS (25) as well as a risk factor for the development of lymphoma (21). On the other hand, a higher SSDDI score (more damage accrual) was also a risk factor for hospitalisation.

Overall, the presence of cryoglobulinaemia, low C3 levels and positivity of anti-Ro/SSA and anti-La/SSB have been linked with systemic involvement (2, 18, 26). Herein we did not find any serological variable associated with the risk of hospitalisation.

Some interesting information has emerged from our study. We identified that the use of antimalarials had a protective role. As this drug is generally used in pSS for mild symptoms (being the main indication arthritis or parotid enlargement in our cohort), this fact would suggest a possible indication bias. Nevertheless, this issue might be attenuated at the multivariate analysis when including the modified SSDDI score. Moreover, in SLE, the use of antimalarials has multiple beneficial effects, including control of disease activity, reduction in cardiovascular events and improvement of survival (27). However, further confirmation of this finding is needed.

Our study is limited by the retrospective nature of the data collection. For instance, we were not able to evaluate disease activity using the ESSDAI score in the control group, however it is evident that the cases with disease activity would have the highest scores. However we considered more appropriate the evaluation of a modified SSDI for damage accrual. Finally, as our Institution is a reference tertiary centre, there is a likelihood of selection bias toward a more severe SS disease phenotype.

In conclusion, in this retrospective cohort, infection and disease activity were the most frequently causes of hospitalisation. Risk factors for hospitalisation were hepatic involvement, vasculitis and a higher SSDDI score whereas the use of antimalarials seemed to be protective.

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