Increased Susceptibility to Pneumococcal Disease in Sjögren Syndrome Patients

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Abstract

Susceptibility to pneumococcal infections in Sjögren syndrome (SS)—an autoimmune inflammatory disease—patients is not well known, although these patients frequently develop respiratory diseases. The relative risk of developing pneumococcal disease in SS patients versus diabetes mellitus type 2 (DM-2) patients, matched by age, gender, and length of enrolment was studied. From January 1998 to September 2013 the records of Donostia University Hospital were analyzed, which among other patient's data includes: number and type of hospital admissions and number and type of laboratory determinations. *Streptococcus pneumoniae* isolates of the same serotype causing recurrent infections were characterized by PFGE. The study comprised 127 patients in the SS group (69 primary and 58 secondary) and 127 in the DM-2 group as control. In 12 SS patients, (9.4%) 22 pneumococcal disease episodes were detected. Two patients (1.6%) with a single episode each one were observed among DM-2 patients, $p = 0.01$, RR for SS patients 6 (95% CI 1.4 to 26.3). No differences could be demonstrated between the two groups of patients in infections caused by *Staphylococcus aureus* or *Streptococcus agalactiae*. Most pneumococcal serotypes in SS patients belonged to the 13-valent (50%) and 23-valent (75%) anti-pneumococcal vaccine. SS patients are associated with and increased risk of suffering from pneumococcal disease. Vaccination should be considered in this group of patients.

Keywords

Sjögren Syndrome, Diabetes Mellitus Type 2, Pneumococcal Vaccine, *Streptococcus pneumoniae*

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Sjögren syndrome (SS) is one of the most prevalent chronic autoimmune inflammatory diseases characterized by a disorder of exocrine glands, mainly salivary and lachrymal, causing xerostomia (dry mouth) and keratoconjunctivitis sicca. This disease can give rise to other clinical manifestations, such as arthritis, neuropathies, and others dysfunctions. The syndrome can present in a primary form or associated with an underlying connective tissue disease, most commonly rheumatoid arthritis or systemic lupus erythematous (secondary SS). It mainly affects middle-aged women with a female to male ratio ≥ 9:1 [1] [2]. A large number of articles refer to the role of several infections in the pathogenesis of SS and the influence of these infections as a trigger for SS symptoms [3] [4]. However, few of these articles mention the susceptibility of these patients to new infections other than intraoral or ocular infections. Patients with SS have defects in their immune system, such as acquired or inherited complement deficiencies [4] [5], and frequently use immunomodulatory drugs, all of which predispose to bacterial infections. Infections caused by encapsulated organisms or tuberculosis may be those posing a higher risk for SS patients [3] [5] [6]. Because SS patients need frequent health care attention, the control group chosen was diabetic type 2 (DM-2) patients. DM-2 patients need regular medical services, have a greater number of community-acquired infection episodes [7] [8] and are significantly more susceptible to pneumococcal infections than healthy individuals of the same age [9]-[11]. In Spain, as in most other regions, DM-2 patients are considered a risk group for pneumococcal infections and are recommended to undergo pneumococcal vaccination. Nevertheless, the percentage of DM-2 patients vaccinated against pneumococci in our region is very low, which also favoured the selection of this control group. The aim of this study was to establish whether the risk of having a pneumococcal disease was similar or higher in people with SS than in DM-2 patients.

All potential cases of SS were identified by a computerized search of the University Donostia Hospital electronic database. However, only patients that met four or more criteria for SS, as suggested by the American-European Consensus Group in 2002 [12] and whose clinical data were available for a minimum of 3.5 years, were included in the study. Each SS case was matched to a DM-2 patient by age, gender and the length of enrolment in the Donostia University Hospital database. All SS patients with diabetes mellitus (type 1 or 2) were excluded from the study. The medical records of all patients (SS and DM-2) included in the study were followed-up from January 1st 1998 to September 30th 2013 or up to the date of death. No minor or self-managed infections were recorded and only infections that required a microbiological diagnosis and targeted treatments were included in the study. All confirmed episodes of pneumococcal infection (positive culture and/or positive pneumococcal urinary antigen) were included. Pneumococcal isolates were serotyped by the Quellung reaction, an antibody-based microarray serotyping technique (Pneumoarray, Abyntek, Spain) and/or multiplex polymerase chain reaction (PCR). Isolates of the same serotype causing recurrent infections were characterized by pulsed-field gel electrophoresis (PFGE). The relative risk for infections in each group of patients and differences in infection rates were assessed with Fisher's exact test or the chi-squared test, as appropriate (SPSS Statistics, version 20). The SS cohort initially included 157 patients. However, after the cases were reviewed, 27 of these 157 patients were excluded because they had diabetes mellitus and another 3 were excluded because the clinical follow-up was very short (less than 3.5 years). Sex, age and other relevant data of SS patients and diabetic patients used as controls are shown in **Table 1**. The mean follow-up time was slightly longer in the DM-2 group (5361 days) than in the SS group (5115 days) due to the higher mortality rate among SS patients: 25.9% vs. 19.7% ($P = 0.23$). SS patients had a significantly higher prevalence of malignancy than the control group. It is known that SS patients are more prone to premature death from cardiovascular diseases and to non-Hodgkin lymphomas [13] [14]. The number of laboratory tests requested, both biochemical and microbiological, was higher among SS than among DM-2 patients, probably due to the greater severity of SS, highlighting the increased number of respiratory and invasive samples requested from SS patients. Regarding comorbidities, heart diseases, including hypertension and obesity, were significantly higher among the DM-2 group. The other underlying diseases were similar in both groups (**Table 1**). Overall, 12 SS patients received medical care for pneumococcal disease. These 12 SS patients were female with ages ranging from 52 to 83 years. Five had primary SS (4 with chronic obstructive pulmonary disease [COPD] or bronchiectasis and 1 with heart disease) and 7 had secondary SS (4 associated with rheumatoid arthritis, 1 with scleroderma and COPD and 1 with multinodular goiter and hypertension). Four patients with pneumococcal infection (33.3%) had two or more pneumococcal episodes of infection. Overall, there were 22 episodes of *S. pneumoniae* infection: 10 pneumonias in 5 patients, 7 other lower respiratory tract infections (acute infection in bronchiectasis patients), 2 recurrent keratoconjunctivitis episodes, 1 septic-shock episode, 1 case of meningitis and 1 infection of an abdominal surgical wound. Three SS patients received the 23-valent pneumococcal vaccine and one received the 13-valent pneumococcal conjugated vaccine. One SS

Table 1. Characteristics of 127 patients with Sjögren disease and 127 patients with diabetes mellitus type 2 included in the study.

	Sjögren syndrome	Diabetes mellitus type 2	*P*
Patients number	127	127	
Women	120 (94.5%)	120 (94.5%)	
Median age and interquartile range	60 years (47 - 71)	62 years (52 - 71)	
Underlying diseases[1]			
• Cirrhosis	3 (2.4%)	3 (2.4%)	NS
• Pulmonary disease (COPD, bronchiectasis or fibrosis)	15 (11.8%)	9 (7.1%)	NS
• Heart disease (including hypertension)	43 (33.9%)	81 (63.8%)	$P < 0.001$
• Cancer (non-lymphomas)	16 (12.6%)	4 (3.1%)	$P = 0.009$
• Chronic renal disease (stage > 3)	4 (3.1%)	4 (3.1%)	NS
• Obesity	3 (2.4%)	12 (9.4%)	$P = 0.030$
Deaths during the study period	33 (25.9%)	25 (19.7%)	NS
Follow-up time in days[2]: mean and median	5114.9 (SD ± 1349.4); 5751 (IQ 5751-5751)	5360.9 (SD ± 977.9) 5751 (IQ 5751-5751)	NS
Number of laboratory requests[3] per patient: mean and median	73.7 (SD ± 60); 60 (IQ 36-98)	40.3 (SD ± 48.8); 28 (IQ 14-48)	$P < 0.001$
Number of microbiological cultures requested per patient: mean and median	13.9 (SD ± 16.8); 9 (IQ 4-17)	5.9 (SD ± 12); 2 (IQ 1-7)	$P < 0.001$
Respiratory samples and/or sterile samples cultured: mean and median	3.7(SD ± 6.4); 2 (IQ 0-4)	1.2(SD ± 4); 0 (IQ 0-1)	$P < 0.001$
23-valent pneumococcal vaccine	4 (3.1%)	3 (2.4%)	NS
Patients with pneumococcal diseases	12 (9.4%)	2 (1.6%)	$P = 0.011$; RR 6 (95% CI 1.4 to 26.3)
Respiratory and/or invasive pneumococcal episodes	19 (15%)	2 (1.6%)	$P < 0.001$; RR 9.5 (95% CI 2.3 to 40)
Patients with *Staphylococcus aureus* infections	20 (15.7%)	10 (7.9%)	NS ($P = 0.08$)
Patients with *Streptococcus agalactiae* infections	10 (7.9%)	4 (3.1%)	NS

[1]Non-Hodking lymphomas or arthritis not included; [2]From 01-01-1998 to 09-30-2013 or until the date of death; [3]One request includes multiple biochemical laboratory tests; NS: not significant; SD: standard deviation; IQ: interquartile range; COPD: chronic obstructive pulmonary disease.

woman with rheumatoid arthritis and bronchiectasis was hospitalized 4 times for pneumococcal disease (2 episodes of pneumonia) before receiving the pneumococcal 23-valent vaccine. After vaccination, this patient was hospitalized again for a fifth episode, a pneumococcal bronchial infection without pneumonia. The pneumococcal isolates of 2 prevaccination pneumonias were included in the 23-valent vaccine. The remaining 3 vaccinated patients had no pneumococcal diseases. Two patients (1.6%) with a single episode of pneumococcal infection each were observed among DM-2 patients. The frequency of *S. pneumoniae* infections was significantly higher in patients with SS than in those with DM-2 (**Table 1**). No significant differences were observed in the rate of pneumococcal diseases between patients with primary (5/69, 7.2%) and secondary (7/58, 12.1%) SS ($P = 0.8$). In the SS group, the RR of having pneumococcal disease was 6 (1.4 to 26.3). Eleven different serotypes were identified in the 22 episodes of pneumococcal infection, the most frequent being serotype 19F with 5 isolates. Other serotypes found were: 3 (n = 3); 10A (n = 2); 12F (n = 2); 19A (n = 2) and 1 single isolate per serotypes 4, 9N, 15A, 16F, 23A and 31. Two isolates were non typeable. Six of 22 isolates (27.3%) were resistant to 1 or more antimicrobials: 8.2% were non-susceptible to tetracycline, erythromycin, and clindamycin, 4.5% were re-

sistant to penicillin and erythromycin and 4.5% were penicillin non-susceptible. Among 4 recurrent pneumococcal episodes of infection, only 2 were caused by the same clone (same PFGE pattern in the original and recurrent isolates): one 89-year-old woman with recurrent keratoconjunctivitis episodes 1 month apart due to the same serotype 19F isolate and a 60-year-old woman with bronchiectasis and pneumonia caused by the same serotype 10A pneumococcal isolate that had caused another pneumonic episode 48 months previously. The remaining 2 recurrent episodes caused by isolates of the same serotype but with different PFGE pattern (similitude < 80%) were 2 pneumonias: 1 in a 68-year-old woman with 2 different serotype 19A pneumococci isolated 9 months apart and the other in a 65-year-old woman with 2 serotype 19F pneumococci isolated 10 months apart. The 2 episodes of *S. pneumoniae* infection in the DM-2 patient were pneumonia and a COPD exacerbation. The aetiology of this pneumonia was only diagnosed by a urinary antigen test and the episode of COPD exacerbation was diagnosed by culture of an *S. pneumoniae* serotype 10A isolated simultaneously with a non-encapsulated *Haemophilus influenzae*. The higher frequency of pneumococcal infection in SS patients than in DM-2 controls might be related to the SS disease itself, because of immune function disorders and other factors such as a reduction of mucous secretion of the glands of the upper and lower respiratory tracts. No significant differences were found for *Staphylococcus aureus* or *Streptococcus agalactiae* infections between SS and DM-2 patients, although the percentage of *S. aureus* infections was almost double in SS patients. Neither *Neisseria meningitis* infections nor tuberculosis infections were detected in SS or DM-2 patients during the study period. Most of the pneumococcal serotypes isolated in SS patients belonged to the 13-valent and 23-valent vaccine (10/20, 50% and 15/20, 75%, respectively). The pneumococcal polysaccharide vaccine is recommended to adult patients with several chronic illnesses, including diabetic mellitus requiring insulin or oral hypoglycaemic drugs, but specific mention of SS in recommendations has been very scarce or totally absent [15] [16]. Three decades ago, a 14-valent polysaccharide vaccine was suggested for SS patients [17] and a recent article on people admitted to hospital with immune-mediated diseases showed an increased risk for SS patients of 3.2 (2.9 to 3.5) compared with that in patients admitted to the hospital for surgery or non-immune-mediated diseases [18]. One limitation of our study is that it included only patients seeking medical attention. Nevertheless, our findings highlight an increased susceptibility of SS patients to pneumococcal infections and underscore the need to consider SS as an indication for pneumococcal vaccination.

Conflict of Interest

None to declare.

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