

Epidemiology of Sjögren's syndrome

Alan J Silman, Brian K Rooney

Arthritis Research Campaign Epidemiology Unit, University of Manchester, United Kingdom

Introduction

This paper provides an overview of the current knowledge on the epidemiology of Sjögren's syndrome. Included is a discussion of the occurrence of Sjögren's syndrome with respect to age, sex, geographic and ethnic factors, together with an overview of specific risk factors and the relationship with other co-morbidities. Genetic and immuno-genetic factors are discussed elsewhere.

Criteria

The epidemiology of Sjögren's syndrome requires prior consideration of the criteria that are used to define cases. Five criteria sets are currently in general use. These are the San Diego (1), Copenhagen (2), European Community (3), Greek (4) and Japanese criteria (5). It is of note that 1986 was an important year for the publication of criteria!

All of the criteria sets rely upon ascertaining both subjective and objective evidence of dryness of the mouth and eyes. The criteria differ in their emphasis on the presence of objectively verifiable signs as opposed to subjective symptoms and the number of each required for both ocular and oral dryness. The San Diego, Greek and Japanese criteria permit classification as possible Sjögren's syndrome and the Copenhagen and Greek criteria distinguish between Primary and Secondary Sjögren's syndrome. The criteria sets should be considered as tools to assist research by differentiation of one defined population, i.e. Sjögren's syndrome sufferers from another defined group, i.e. the general population, patients with sicca symptoms, or, patient with other autoimmune disease. The necessity for evidence of systemic autoimmune abnormalities in the San Diego criteria may make them more useful in clinical trials but less efficient at distinguishing primary Sjögren's syndrome from other rheumatic diseases with an autoimmune pathogenesis. The EC Criteria, which do not require formal evidence of autoimmune abnormalities, may be more inclusive and representative of the diverse nature of the condition in populations. Fox (6) has suggested that "the frequency of patients fulfilling the European criteria is fivefold to tenfold greater than those fulfilling the San Diego criteria". In the clinical setting, clinical judgement, rather than diagnostic criteria is the final arbiter. The main conclusion is that the criteria set used to ascertain cases should be clearly stated.

Occurrence

The prevalence of Sjögren's syndrome determined from epidemiological studies depends in part upon the stringency of case definition as well as the true occurrence. Seven recent studies (papers since 1990) have reported on the occurrence of Sjögren's syndrome in the general population.

1. Tomić and colleagues (7) have estimated the prevalence of Sjögren's syndrome in Slovenia to be 6 per 1000, using the EC criteria. This study, based on a population sample of 889 residents of Ljubljana, the Capital of Slovenia, was subject to some methodological difficulties. The participation rate was poor, only 37% of the sample participated and no attempt was made to ascertain any details from non-responders. Furthermore, the demographic profile of the study sample differed from that of Slovenia as a whole.
2. In a community based cross-sectional study of adults aged 18-75 years, using the European Community criteria, Thomas and colleagues (8) estimated the prevalence of Sjögren's syndrome in the UK to be 33 per 1000 (95% CI 22 to 44).
3. In a similar American study of community dwelling elderly people, Hochberg et al (9) found that 17% of their sample of 2520 elderly people living in the community in Maryland, USA

had symptoms of dryness of the mouth. Earlier studies among elderly people living in nursing homes and geriatric clinics suggest a prevalence of Sjögren's syndrome between 2 and 5% (10).

4. The estimated prevalence in Greece based on a population of women living in a rural community suggests a prevalence of 6 per 1000 women (95% CI 2 to 14) using the EC criteria (11). Women with other autoimmune rheumatic diseases were excluded.
5. The prevalence of Sjögren's syndrome in a Danish study (12) was found to be 6 per 1000 using the European criteria and 2 per 1000 using the Copenhagen criteria. The study used a random sample from the Copenhagen City Heart study and only included persons aged between 30 and 60 who were living in a central district of Copenhagen in 1976. People with rheumatoid arthritis were excluded. The study was based on a small sample, 504 people. Only a few cases with early stages of Sjögren's syndrome were observed and the author suggested that it was uncertain how representative the sample was of Copenhagen or Denmark as a whole. Furthermore, it is probable a greater prevalence would have been found had older age groups been included, though this was not done for practical reasons.
6. A Chinese community-based study by Zhang *et al* (13) found a prevalence of Sjögren's syndrome of 8 per 1000 using the Copenhagen criteria but only 3 per 1000 using a modified form of the San Diego criteria.
7. Data from Japanese patients seen clinically suggest an estimated crude prevalence of 2 per 100 000 men and 26 per 100 000 women (14) using the Japanese criteria.

Age and Gender

Sjögren's syndrome is considered rare in young people. Most of the population studies were not large enough to provide robust estimates of age specific prevalence rates. Age at onset tends to be between the ages of 40 to 60 years. Younger age at onset has been reported (15) and onset in childhood has also been described (16, 17). The youngest case reported to date is in a three-year-old child (18). In a study of the occurrence of Rheumatic diseases among Japanese children, the crude annual incidence of Sjögren's syndrome was estimated to be 0.04 per 100 000 children in 1994 (19).

The occurrence in women is typically about nine times that in men (18). Wakai *et al* (14) report a female to male rate of 14:1. Thomas *et al* (8), however, found a lower female to male rate of 2:1.

Geography

The epidemiological data on the worldwide distribution, outside Europe and North America, of Sjögren's syndrome is sparse. In a study of 24 500 rheumatology patients in India only three patients had primary Sjögren's syndrome. The occurrence of secondary Sjögren's syndrome, associated with RA or SLE is, however, less rare (20).

The paucity of epidemiological data and the use of different criteria and study designs make international comparisons problematic. Furthermore, while the sparse literature on Sjögren's syndrome in the developing countries may reflect differing medical and research priorities, as Zhang and colleagues (13) suggest for the case of China, lack of awareness of the disease and misdiagnosis may play a role.

There would appear to be no reports of temporal or spatial clustering of Sjögren's syndrome, though the nature of presentation, clinical course and prognosis may vary in different populations.

Risk Factors

Two major exposures have been investigated using epidemiological methods. The first being the role of viruses and the second being exposure to silicone.

Viruses. A number of sero-epidemiological studies have been undertaken. Associations between both Hepatitis B and Hepatitis C viruses and Sjögren's syndrome have been discussed in the

literature. In a study of 90 consecutive primary Sjögren's syndrome patients, 14% had antibodies to Hepatitis C virus and in all of these patients liver involvement was observed (21). It remains unclear however whether this is chance association or if a causal relationship exists (21,22).

A growing area of research is the association between retrovirus and Sjögren's syndrome. Research by Eguchi and colleagues (23) suggests that for a subgroup of Sjögren's syndrome patients, HTLV-1 is an etiological factor in an endemic area of Japan. The use of blood donor controls, for comparisons of positive HTLV-1 reactions may be questionable as those likely to be positive may be discouraged from giving blood. A Greek group has addressed the association by assessing the presence of signs and symptoms of Sjögren's syndrome in a cohort of male and female HIV (+) patients (24). They found that 8% of the cohort showed signs of Sjögren's syndrome, three times that seen in the Greek adult female population.

Silicone Implants. It has been suggested that Sjögren's syndrome might arise subsequent to breast implant surgery. Many of the symptoms reported by patients who have had Silicone breast implants are of a local nature or are non-specific. Freundlich *et al* (25), report that about half of the 50 women in their study complained of dryness of the eyes and mouth and other signs of Sjögren's syndrome. Debate continues as to whether the sequelae to such breast augmentation constitutes, a new syndrome, distinct in nature to other diseases, some form of recognised connective tissue disease or the subsequent chance occurrence of connective tissue disease.

Epidemiological proof is lacking. Numerous studies of a putative association between silicone breast implants and connective tissue disease have been undertaken. In the nurses health cohort study (26), a prospective study, a relative risk of 0.6 (95% confidence interval 0.2 - 2) was observed for the association of breast implant and validated connective tissue disease. In a larger study, The Women's Health Cohort (27) a relative risk of 1.25 (95% confidence interval 1.08 -1.41) was observed. The latter study is unusual in that it is the only study to date with reasonably large numbers of participants to show a positive association. However, it relied upon self reports of breast implants and occurred when considerable media interest surrounded the subject, possibly introducing bias into the study as women who had undergone breast augmentation surgery would be more likely to report symptoms of connective tissue disease and seek medical attention. There is no scientific consensus and only a limited theoretical basis for the nature of a molecular model that would explain a causal association.

Familial Clustering. Familial clustering in Sjögren's syndrome, though rare, has been presented in the literature in the form of case series (28,29). There are, however, no formal epidemiological studies of familial aggregation. The genetic basis for Sjögren's syndrome is discussed elsewhere in this volume.

Co-Morbidity

Associations between Sjögren's syndrome and other diseases have been reported. These can be separated into co-morbidities with non-specific diseases and with other autoimmune diseases.

Associations with Non-Specific Diseases. Dry eyes and dry mouth are considered features of a number of non-specific syndromes. Thus, Bonafede *et al* (30) have reported an association between fibromyalgia and features of Sjögren's syndrome and Calabrese *et al* (31) have reported an association between chronic fatigue syndrome and symptoms of Sjögren's syndrome. It is unlikely that these represent associations between different disease entities.

Associations with other Autoimmune Diseases. The symptoms of primary Sjögren's syndrome overlap with those of other conditions. Patient with primary Sjögren's syndrome can present with similar symptoms to those of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Signs and symptoms of Sjögren's syndrome subsequent to onset of SLE or RA are

thought to indicate secondary Sjögren's syndrome. Debate continues as to the nature of the relationship between these three conditions.

Features of Sjögren's syndrome have also been found in about a quarter of patients in a series diagnosed as having autoimmune thyroid disease (AITD) (32). In a French study, however, the prevalence of other autoimmune disease among AITD patients was only 14% with systemic lupus erythematosus and Sjögren's syndrome being the most frequent autoimmune diseases. Earlier literature reports an association between Sjögren's syndrome and postpartum thyroiditis (33) and more recently associations between Sjögren's syndrome and Non-Hodgkin's lymphoma have also been reported (34).

A case control study conducted with patients with coeliac disease and controls consisting of patients with other gastro-intestinal illnesses found the coeliac patient group had a tenfold risk of Sjögren's syndrome compared to the controls (35).

References

1. Fox R, Robinson A, Curd J et al. Sjögren's syndrome: proposed criteria for classification. *Arthritis Rheum* 1986; 29: 5: 577-585.
2. Manthorpe R, Oxholm P, Prause J, Schiødt M. The Copenhagen criteria for Sjögren's syndrome. *Scand J Rheumatol* 1986; Suppl 61: 52.
3. Vitali C, Bombardieri S, Moutsopoulos H et al. Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36:3: 340-347.
4. Skopouli F, Drosos A, Papaioannou T, Moutsopoulos H. Preliminary diagnostic criteria for Sjögren's syndrome. *Scand J Rheumatol* 1986; Suppl. 61: 22-25.
5. Homma M, Tojo T, Akizuki M, Yamagata H. Criteria for Sjögren's syndrome in Japan. *Scand J Rheumatol* 1986; Suppl. 61: 26-27.
6. Fox R. Epidemiology, pathogenesis, animal models and treatment of Sjögren's syndrome. *Current opinion in Rheumatology* 1994; 6: 501-508.
7. Tomić M, Grmek M, Perković T, Kveder T. Prevalence of Sjögren's syndrome in Slovenia *Rheumatology* 1999; 38: 164-170.
8. Thomas E, Hay E, Hajeer A, Silman A. Sjögren's syndrome: a community-based study of prevalence and impact. *Br J Rheumatol* 1998; 37: 1069-1076.
9. Hochberg M, Tielsch J, Munoz B et al. Prevalence of symptoms of dry mouth and their relationship to saliva production in community dwelling elderly: The SEE project. *J Rheumatol* 1998; 25:3; 486-491.
10. Jacobsson L, Manthorpe R. Epidemiology of Sjögren's syndrome. *Rheumatology in Europe* 1995; 25:2: 46-47.
11. Dafni U, Tzioufas A, Staikos P et al. Prevalence of Sjögren's syndrome in a closed rural community. *Ann Rheum Dis* 1997; 56: 521-525.
12. Bjerrum K. Keratoconjunctivitis sicca and primary Sjögren's syndrome in a Danish population aged 30-60 years. *Acta Ophthal Scand* 1997; 75:3: 281-286.
13. Zhang N, Shi C, Yao Q et al. Prevalence of primary Sjögren's Syndrome in China. *J Rheumatol* 1995; 22:4: 659-661.
14. Wakai K, Tamakoshi A, Ohno Y et al. Estimated prevalence of Sjögren's syndrome in Japan: findings from a nationwide epidemiological survey. *J Epidemiol* 1995; 5:3: 125-129.
15. Ramos-Casals M, Cervera R, Font J et al. Young onset of primary Sjögren's syndrome: Clinical and immunological characteristics. *Lupus* 1998; 7:3: 202-206.
16. Ostuni P, Ianniello A, Sfriso P. Juvenile onset of primary Sjögren's syndrome: a report of ten cases. *Clin Exp Rheumatol* 1996; 14:6: 689-693.
17. Tomiita M, Saito K, Kohno Y et al. The clinical features of Sjögren's syndrome in Japanese children. *Acta Paediatrica Japonica* 1997; 9:2: 268-272.
18. Tzioufas A, Moutsopoulos H. Sjögren's syndrome. In: *Rheumatology 2nd Edition*. Klippel S and Dieppe P (eds) London, Mosby International, 1998.
19. Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. *Acta Paediatrica Japonica* 1997; 39:2: 242-244.
20. Chandrasekaran A, Radhadrsekaran B. Rheumatoid arthritis and connective tissue disorders: India and South-East Asia. In: *Tropical Rheumatology, Baillière's Clinical Rheumatology: International Practice and Research*. McGill P and Adebajo A (Guest Editors) 1995; 9:1: 45-57.
21. Garcia-Carrasco M, Ramos M, Cervera R. Hepatitis C virus infection in primary 'Sjögren's syndrome': prevalence and clinical significance in a series of 90 patients. *Ann Rheum Dis* 1997; 56:3: 173-175.

22. Wattiaux M. Sjögren's syndrome and hepatitis C virus. [Syndrome de Gougerot Sjogren et virus de L'Hepatitis C] not in English. *Presse Medicale* 1997; 26:14: 652-655.
23. Eguchi K, Mizokami A, Katamine S. [HTLV-1 infection in primary Sjögren's syndrome - epidemiological, clinical and virological studies] not in English. *Nippon Rinsho Japanese Journal of Clinical Medicine* 1995; 53:10: 2467-2472.
24. Kordossis T, Paikos S, Aroni K et al. Prevalence of Sjögren's - like syndrome in a cohort of HIV-1 positive patients: descriptive pathology and immunology. *Br J Rheumatol* 1998; 37:6: 691-695.
25. Freundlich B, Altman C, Sandorfi N. A profile of symptomatic patients with silicone breast implants: A Sjogrens-like syndrome. *Seminars in Arthritis and Rheum* 1994; Suppl. 24:1: 44-53.
26. Sanchez-Guerrero J, Colditz G, Karlson E. Silicone breast implants and the risk of connective tissue disease and symptoms. *N Eng J Med* 1995; 332: 1666-1670.
27. Hennekens C, Lee I, Cook N. Self-reported breast implants and connective tissue disease in female health professionals: a retrospective study. *J Am Med Assoc* 1996; 275: 616-621.
28. Foster H, Walker D, Charles P. Associations of DR3 with susceptibility to and severity of primary Sjögren's syndrome in a family study. *Br J Rheumatol* 1992; 31: 309-314.
29. Lichtenfeld J, Kirschner R, Wiernik P. Familial Sjögren's syndrome with associated primary salivary gland lymphoma. *Am J Med* 1976; 60:2: 286-292.
30. Bonafede R, Downey D, Bennett R. An association of fibromyalgia with primary Sjögren's syndrome: a prospective study of 72 patients. *J Rheumatol* 1995; 22:1: 133-136.
31. Calabrese L, Davis M, Wilke W. Chronic fatigue syndrome and a disorder resembling Sjögren's syndrome. *Clin Infect Dis* 1994; 18 Suppl. 1: S28-31.
32. Coll J, Anglada J, Tomas S et al. High prevalence of Sjögren's syndrome features in patients with autoimmune thyroid disease. *J Rheumatol* 1997; 24:9: 1719-1724.
33. Gudbjörnsson B, Karlsson-Parra, Karlsson E et al. Clinical and laboratory features of Sjögren's syndrome in young women with previous postpartum thyroiditis. *J Rheumatol* 1994; 21: 215-219.
34. Andonopoulos A, Tiniakou M, Melachrinou M et al. Sjögren's syndrome in patients with newly diagnosed untreated non-Hodgkin's lymphoma. *Rev de Rhumatisme, Eng Ed* 1997; 64:5: 287-292.
35. Collin P, Reunala T, Pukkala E et al. Coeliac disease - associated disorders and survival. *Gut* 1994; 35:9: 1215-1218.