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Sjögren's Syndrome

Diagnosis and Therapeutics

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To our patients, who have taught us the subtleties and challenges of Sjögren's syndrome, inspired us with their perseverance, and contributed to progress against this condition by participating in research. Along with you, we look forward to a new era of more effective treatments soon

Foreword

We are poised on the verge of major breakthroughs in the understanding and treatment of Sjögren's syndrome (SjS). Though this complex, multi-organ system disorder has been little understood, poorly described, and relatively ignored for decades, successful collaboration on an international scale, careful epidemiologic studies, basic research on the immunological dimensions of this condition, clinical trials, and other investigations have led us to the brink of meaningful advances for patients. As we move forward into an era of individualized medicine for patients with SjS more rational, mechanism-based therapies, it is timely and appropriate to gather collected knowledge from SjS experts around the world on this condition.

This book is divided into four major sections: (I) Scientific Basis; (II) Clinical Manifestations; (III) Diagnosis and Prognosis; and (IV) Therapeutic Aspects. The Scientific Basis chapters address the epidemiology, genetics, proteomics, and immunopathogenesis of SjS. They also discuss the potential roles of viruses in causing SjS, and consider the emerging understanding of the importance of B lymphocytes in the inflammatory symphony of this condition. Within these chapters are themes that promise advances in therapies based upon fundamental understanding of the disease mechanisms of SjS. As the book's editors, we have attempted to carry those themes forward through subsequent sections of the book.

The Clinical Manifestations chapters extend far beyond the sicca symptoms to describe in detail the features of this disorder in virtually every organ system. For example, three separate chapters are devoted to the neurological manifestations of SjS – one each to the central, peripheral, and autonomic nervous system complications of this condition. Similarly, both the vasculitic and non-vasculitic cutaneous features of SjS are given proper attention in separate, well-illustrated chapters. New understandings of pancreatic disease in SjS are elaborated in light of an emerging disease long confused with SjS; namely, autoimmune pancreatitis and IgG4-related disease. Raynaud's phenomenon, the pulmonary complications, and obstetrical/gynecological issues are also given thorough treatments, along with the rest of the organs touched by this protean disorder.

Diagnosis and Prognosis, areas to which the world's SjS have expended much collaborative energy over the past 30 years, are given full consideration with ample reference to consensus documents and evidence-based studies. The lengthy, sometimes contentious, but ultimately fruitful efforts at consensus in the American and

European Classification Criteria are described lucidly. Thorough and practical discussions of the approaches to diagnosis for clinical purposes, an area often confusing for practitioners, are also provided. Aspects of malignancy as they relate to SjS and its prognosis are given appropriate weight in this section, and then considered further in Therapeutic Approaches.

Finally, the growing number of treatment options for SjS are considered in non-overlapping chapters that address the therapy of sicca features; the treatment of B-cell lymphoma; classic immunosuppressive and immunomodulatory drugs for extra-glandular disease; new immunosuppressive and immunomodulatory drugs; B-cell targeted therapies; and experimental treatments.

As co-editors of this book on SjS we would like to thank the 100 contributors who participated as experts in the assembly of this work. You have enabled the creation of a body of knowledge related to SjS not seen on such a scope before. We have learned much from your writing, wisdom, and experience. Our readers will, too.

Finally, two of us – M.R.-C. and J.H.S. – thank the third, H.M.M., for his remarkable contributions to the field of SjS investigation and clinical care that now span more than 30 years. Much of the progress outlined in these pages has stemmed directly from his vision and devotion to fostering new understandings of SjS and to mentoring the next generation of SjS researchers and clinicians. We hope that this book will do the same.

Manel Ramos-Casals
John H. Stone
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Part I
Scientific Basis

Chapter 1
Epidemiology

Yannis Alamanos and Alexandros A. Drosos

Contents

Sjögren's syndrome (SS) is an autoimmune disease characterized by inflammation of exocrine glands, mainly the lacrimal and salivary glands. The disease may occur either independently (primary SS) or in association with other autoimmune diseases such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus (secondary SS) [1, 2]. The association of SS with other autoimmune rheumatic diseases is discussed in details in Chap. 32. In this chapter we present the epidemiology of primary SS.

1.1 Primary Sjögren's Syndrome

Patients with primary SS may have major complaints, including several systemic features. The impact of these symptoms on disability and quality of life of the subjects affected can be substantial [3, 4]. However, the symptoms of primary SS vary widely and the disease may have an insidious onset, a variable course, and a wide

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Table 1.1 Incidence rates (and 95% CIs) of primary SS in studies carried out in adult general populations (cases/100,000)

Study	Population size	Design	Classification criteria	Country	Incidence (95% CI)
Pillemer et al. [15]	~ 100,000 (total population of Olmsted County, Minnesota)	Population-based	Physician diagnosis	USA	3.9 (2.8–4.9)
Plesivcnik et al. [16]	~ 600,000 (total population of Ljubljana region)	Referral center	European (5)	Slovenia	3.9 (1.1–10.2)
Alamanos et al. [14]	~ 500,000 (total population of NW Greece)	Population-based	AECC (12)	Greece	5.3 (4.5–6.1)

spectrum of clinical manifestations. As a consequence, patients with primary SS may be missed or misclassified, or the diagnosis may be delayed. These issues pose several challenges to the study of the epidemiology of primary SS.

1.1.1 Diagnostic Criteria

Diagnostic criteria for primary SS are required in order to provide a rational basis for establishing the diagnosis, assessing prognosis, and guiding therapy. Diagnostic and classification criteria are essential for epidemiologic studies also, because case identification is frequently an important methodological issue in making valid estimations of incidence and prevalence. Several sets of classification criteria for SS have been proposed [5–11], leading to some confusion in the interpretation of some epidemiologic studies. The American–European Consensus criteria (AECC), published in 2002, are the most acceptable for the classification of patients with SS and offer a basis for valid and relatively homogenous epidemiologic studies [12]. The AECC and other sets of classification criteria proposed are reviewed Chap. 29.

The few descriptive epidemiologic studies in primary SS suggest important variations in disease occurrence. These variations may reflect the specific population groups studied, the different classification criteria used, and contrasting methods of case ascertainment [13, 14]. Epidemiologic studies of primary SS in the general population have generally yielded highly heterogeneous results, particularly with regard to disease prevalence. The principal reasons for this stem from differences in diagnostic criteria and study design. As a result, the true prevalence of primary SS in the general population is unclear. In contrast, investigations of the incidence of this condition tend to yield similar results.

1.1.2 Incidence

Table 1.1 summarizes the incidence rates estimated in studies carried out in the general population. The major methodological issues, individual study designs,

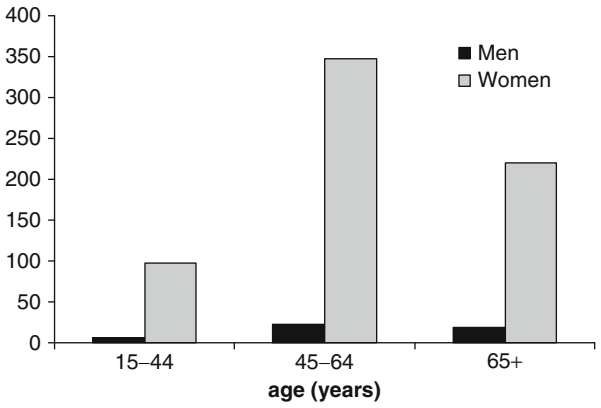

Fig. 1.1 Age- and sex-specific incidence rates of primary SS in NW Greece (cases per 10^5 inhabitants) for the period 1982–2003

and the criteria applied for case identification are also shown. Three incidence studies carried out in Slovenia, Greece, and the USA found an annual incidence of the disease of about 4–5 cases per 100,000 inhabitants. These studies found similar incidence rates even though they used different methods for case ascertainment and case identification. They also found a 10- to 20-fold higher incidence in women than in men, and a peak of age-specific incidence in the age group 50–60.

In a population-based study from Olmsted County, Minnesota, the average annual age- and sex-adjusted incidence of physician-diagnosed Sjögren's syndrome per 100,000 population was estimated to be 3.9 (95% CI = 2.8–4.9), with a significantly higher incidence in women (6.9; 95% CI = 5.0–8.8) than in men (0.5; 95% CI = 0.0–1.2).

In a study carried out in Slovenia the average annual incidence for primary SS in the Ljubljana region was calculated as 3.9 cases per 100,000 inhabitants (95% CI = 1.1–10.2). The incidence in women was tenfold higher than in men.

In a study conducted in a defined area of Greece, the age-adjusted mean annual incidence rate for the adult population was 5.3 (95% = CI 4.6–6.3) cases per 10^5 inhabitants (0.5 for men and 10.1 for women).

The mean (SD) age of newly diagnosed cases in the Olmsted County, Minnesota study was 59 (15.8) years, compared with 51.3 (14.5) years (range 19–78) in the Slovenian study and 55.4 (12.5) years (range 18–81) in the Greek study. Figure 1.1 presents the age and sex distribution of incident cases in the Greek study.

The disease is rare in children. Usually only case reports of SS are reported. In a study presenting 13 pediatric patients of primary SS (11 girls and 2 boys) referred during a 15-year period at a rheumatology clinic, the mean (SD) age at disease onset was 9.4 (2.2) years, ranging from 6 to 14 years. In the same period, only two pediatric SS cases associated with juvenile chronic polyarthritis were diagnosed at the same clinic [17].

In a multicenter study of primary SS survey in the pediatric age, a total of 40 cases were identified (35 girls and 5 boys). The age at disease onset ranged from 9.3 to 12.4 years (mean 10.7 years) [18].

Table 1.2 Prevalence estimate rates (and 95% CIs) of primary SS in studies carried out in adult general populations

Study	Population or sample size	Study design	Criteria applied	Country prevalence (per 100)	
Thomas et al. [19]	1,000 (sample)	Sample survey	European (5)	UK	3.3 (2.2–4.4)
Tomsic et al. [20]	889 (sample)	Sample survey	European (5)	Slovenia	0.6 (0.1–2.2)
Dafni et al. [21]	837 (total community population) (female population)	Sample survey	European (5)	Greece	0.6 (0.2–1.4)
Zhang et al. [22]	2,066 (total community population)	Sample survey	San Diego (8) Copenhagen (10)	China	0.34 0.77 (0.44–1.25)
Miyasaka et al. [23]	120,000,000 (Japanese population)	Population-based	Japanese (8)	Japan	0.02 (0.01–0.03)
Alamanos et al. [14]	500,000 (total district population)	Population-based	AECC (12)	Greece	0.09 (0.08–0.10)
Trontzas et al. [24]	8,740 (sample)	Sample survey	AECC (12)	Greece	0.15 (0.09–0.21)
Birlik et al. [25]	2,835 (sample)	Sample survey	European (5)	Turkey	0.35 (0.17–0.65)
Kabasakal et al. [26]	939 (sample of adult women)	Sample survey	AECC (12) European (5)	Turkey	0.6 (0.24–1.39) 1.4 (0.74–2.37)

1.1.3 Prevalence

The prevalence studies of primary SS carried out in general population present wide variations in their prevalence estimates. Table 1.2 summarizes the prevalence estimates for studies conducted in general populations, as well as their major methodological issues, study designs, and criteria for case identification [14, 19–26].

The prevalence estimates vary between 0.2 cases per 1,000 inhabitants (in a study estimating the prevalence of primary SS in the general Japanese population), and 33 cases per 1,000 inhabitants (in a study carried out in a sample of about 1,000 inhabitants in Manchester, UK). These wide variations may partly reflect methodological differences among studies.

Population-based studies using systematic recording of diagnosed cases tend to present lower prevalence estimates than surveys based on the examination of representative samples of general populations. Studies based on systematic recording of diagnosed cases may underestimate the prevalence of an autoimmune rheumatic disease because they miss some cases, mainly the milder cases. On the other hand, sample surveys may

overestimate the prevalence of autoimmune rheumatic diseases as they often present relatively low response rates, which may be related to selection bias [27].

Another important methodological issue concerns the different diagnostic criteria applied for case identification. As seen in Table 1.2, even surveys carried out in the same samples gave different prevalence estimates when using different classification criteria.

The results of prevalence studies carried out in different populations suggest a possible role of ethnic differences in the role of the disease. A study carried in the general Japanese population gave a prevalence estimate many fold lower than any other study. On the other hand, a study carried out in a sample of the general population in Manchester, UK, gave a prevalence estimate several fold higher than any other study. These extreme variations are not likely to be due only to methodological differences among studies. The influence of genetic and environmental factors, possibly related to these ethnic differences, remains unclear.

SS in elderly people is relatively common, may be subclinical, and is often associated with a benign clinical course. The disease may also present laboratory and histopathological particularities in this age [28]. In studies analyzing the prevalence estimates by age, the peak of age-specific prevalence was in the age group 66–75 for both sexes. When considering a diagnosis of SS in the elderly, it is important to obtain a thorough drug history. The use of tricyclic antidepressants and antipsychotic agents, which can cause symptoms of dry mouth, is more prevalent in this population. In a population-based study of elderly individuals aged between 65 and 84 years, approximately 27% reported dry eyes or dry mouth [29]. A significant proportion of the population (62%) had sicca symptoms potentially caused by medications, which again emphasizes the importance of the drug history. The prevalence of dry mouth symptoms increases with age and is estimated to be 17% in an elderly population [30]. A minor salivary gland biopsy can be very helpful for diagnosing SS. However, lymphocytic infiltration in minor salivary glands is not specific for SS and has been reported in the healthy elderly, in other autoimmune rheumatic diseases, and occasionally in healthy non-elderly volunteers [31, 32]. In a study performed with 62 elderly volunteers, labial salivary gland biopsy revealed fibrosis and/or fatty infiltration in the majority of individuals examined. This appeared to be related to aging. Three subjects were diagnosed as having primary SS. Four other subjects some histopathological or clinical criteria for SS but could not be classified with certainty as having that condition. All these individuals were asymptomatic, but some of them had anti-Ro (SSA) or anti- La (SSB) autoantibodies [28]. Age-related histological changes of acinar atrophy, fibrosis, and ductal dilatation have been described in the elderly up until the ninth decade [33, 34].

In conclusion, the occurrence of SS likely has important variations among countries and areas of the world. However, the relatively small number of studies for most areas of the world, as well as their methodological differences and the lack of incidence studies for the developing countries, limits our understanding of worldwide SS epidemiology.

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Chapter 2
Genetics, Genomics, and Proteomics of Sjögren's Syndrome

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Contents

2.1 Introduction

Dramatic advances in identifying the genetic basis of many human diseases are transforming our fundamental understanding of etiology and pathogenesis. Over the past decade, large global efforts to characterize sequence variation in the human genome have provided the foundation for this extraordinary progress. Success in mapping disease genes has also been fueled by revolutionary advances in our technical capacity for genotyping and analyzing complex genetic datasets. These advances include the technical capacity for genotyping millions of known variants and have ushered in a new era of powerful, large-scale, and highly successful genome screens for many diseases. Scanning the human genome for association of variants with disease is unbiased and not limited by prior selection of a putative candidate gene for testing. As a result, the genes that are associated with disease can be surprising, oftentimes linking previously unsuspected molecular pathways to

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