Impact of gender and age at onset on Sjögren’s syndrome presentation and outcome: state of the art

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ABSTRACT

Sjögren’s syndrome (SS) is a complex and heterogeneous disease that typically affects middle-aged women. However, while it is rare, the disease may occur in male patients and in females during their childhood/adolescence or in the elderly. Contrasting data have been reported on these three subgroups clinical features and long-term outcomes. Notably, recent studies have pinpointed the severity of the disease in male patients and in both the early and the late-onset subgroups. The aim of this review is, therefore, to summarise the available evidence from the recent literature on these phenotypes. The focus will be on the clinical and laboratory features, and on the lymphoma risk observed in the three subgroups distinct phenotypes: of male patients as well as young-onset SS and elderly-onset SS. Ultimately, an accurate phenotypic stratification may represent the first step towards individualised medical approaches.

Introduction

Sjögren’s syndrome (SS) is an autoimmune epithelitis typically characterised by a chronic lymphocytic infiltration of lachrymal and salivary glands resulting in the classical symptoms of dry mouth and dry eyes. SS is indeed a systemic disease potentially leading to inflammation and fibrosis of any extra-glandular organ and system, with progressive accrual of damage and possible lymphoproliferative complications (1, 2).

Finally, SS frequently overlaps with both organ-specific autoimmune conditions and other autoimmune systemic diseases, often influencing their clinical phenotype and outcome (3). As a result, SS cannot be regarded as a single entity, but rather encompasses a wide and complex spectrum of phenotypes exhibiting high heterogeneity in terms of clinical and serologic manifestations, patients reported outcomes (PROs), risk of MALT non-Hodgkin lymphoma and outcomes (4-6).

The accurate stratification of SS patients into homogenous groups is therefore crucial to provide tailored follow-up and therapeutic strategies. Indeed, recent advances led to the identification of new serologic and proteomic biomarkers characterising different subsets of patients with a phenotype- and endotype-based approach (7-13). Interestingly, however, in a clinical setting, valuable information on clinical manifestations and potential outcomes of the disease may be inferred by simple epidemiologic data. Indeed, a very large number of clinical studies have highlighted the association of gender and age at onset with different clinical phenotypes of SS (14-16).

Aim of this review is therefore to summarise available evidence from recent literature on this topic, focusing particularly on the distinct phenotypes of male patients as well as young-onset and elderly-onset SS.

Definition of juvenile Sjögren’s syndrome and elderly-onset Sjögren’s syndrome

It is well known that age at disease onset influences the clinical presentation of a wide range of rheumatic conditions, probably as a result of dynamic changes occurring with ageing in the immune system, as well as in other organs and systems. SS sub-phenotyping based on the age at the diagnosis of the disease has been a point of ongoing debate in the medical literature. Unlike conditions such as systemic lupus erythematosus (SLE),…

Competing interests: C. Baldini is the principal investigator in RCT by GSK, Novartis, Amgen (Horizon), and has received financial support for educational events/advisory boards from GSK, Amgen, Aurinia and Sanofi. The other authors have declared no competing interests.
where paediatric and elderly forms have been extensively studied and better defined, SS is still lacking a universally accepted diagnostic criteria for childhood, juvenile or elderly patients (17). In some studies, the term juvenile Sjögren’s syndrome “ (jSS) is applied to patients under 35 years, including paediatric patients (18). In other studies, a distinction is made between childhood-onset patients (cSS, those under 18 years) and juvenile-onset patients (jSS, those from 18 to 35) (19-23). This approach is the most followed, aligns better with the traditional paediatric classifications and allows for a more precise classification of the disease onset. Additionally, it is important to note that also the definition of elderly-onset (Eo) Sjögren’s syndrome (Eo-SS) varies across studies and clinical guidelines. Depending on the source, the age at onset for this subset of SS patients is variously set at greater than 60, 65, or 70 years (16, 24). Indeed, similarly to what happens in jSS, this lack of uniformity in defining Eo-SS contributes to the challenges in comparing data across studies.

**Elderly-onset Sjögren’s syndrome**

The reported proportion of patients with Eo-SS ranges from 6 to 36% in the largest cohorts (15, 25). However, studies specifically investigating clinical presentation and outcome of patients with an Eo are scarce and relatively heterogeneous compared to those describing the young/paediatric onset phenotype. There are many factors potentially accounting for this heterogeneity. First, most of the studies have been conducted in a very large timespan. As a result, different sets of criteria have been employed for the enrolment, leading to very diverse groups of patients. As an example, the proportion of elderly patients showing a positivity for anti-Ro SSA and/or anti-La SSB antibodies ranges from 21% in the older series to 68% in the most recent works (15, 25). Moreover, the SS control group adopted in these studies is usually represented by the remaining SS population, while only some studies specifically compared older SS patients with those with a typical middle-aged onset. Finally, compared to young patients, tracing back the disease onset to the first appearance of SS symptoms may be very challenging in older people, who often report a very long history of dryness at diagnosis.

Despite these considerations, plenty of evidence supports the concept of an Eo-SS phenotype presenting peculiar clinical-serological features and lymphoma risk compared to younger age groups, probably because of different underlying pathobiological mechanisms. Table I summarises the largest available studies specifically aimed at investigating differences in the expression of SS based on the age of onset.

**Immunologic profile**

Biomarkers reflecting B cell hyperactivation and organization of the immune response in secondary lymphoid structure, including hypergammaglobulinemia as well as the production of rheumatoid factor (RF), cryoglobulins and the specific autoantibodies anti-Ro60/52 and anti-La SSB, are the serological hallmark of SS and have been associated to systemic disease activity, lymphoma risk and outcome (26).

Since early reports, Eo patients have been shown to exhibit a lower prevalence of autoantibodies (27). These differential characteristics may be at least partly driven by the presence in the control groups of young/childhood onset patients, which on the contrary present serum B-cell hyperactivity biomarkers in a very high percentage of cases (28). However, it is noteworthy that in the recent work from Goules et al., Eo patients from Greece and Italy were specifically compared to middle-aged onset SS patients and were proved to present a significantly lower prevalence of both anti-Ro SSA (67.9% vs. 79.3%) and hypergammaglobulinaemia (43.6% vs. 62.1%) (15). The B-cell compartment of Eo patients is indeed thought to be less prone to hyperactivation probably because of physiological immunosenescence.

**Glandular and extra-glandular manifestations**

Sicca symptoms are the clinical hallmark of SS, and together with objective oral and ocular tests are included in almost all sets of classification criteria. Notably, most studies failed to highlight differences in subjective dryness, as well as in the prevalence of positive objective oral and ocular tests between Eo pSS patients and younger patients. However, in the two largest studies on this topic, Eo pSS patients presented more frequently xerostomia and positive oral tests, respectively (15, 29). Regarding the assessment of major salivary gland by ultrasound (SGUS), Lee et al. reported a minor prevalence of positive SGUS in Eo patients (30). These findings are not in contrast with those reporting lower rates of serological biomarkers of disease activity and severity in Eo patients. Indeed, it is well known that subjective dryness in SS patients is not correlated to neither disease activity, immunologic markers of B cell hyperactivation, severity of lymphocytic infiltration on MSGB, nor outcome. Similarly, severe changes on SGUS examination have been correlated both with systemic disease activity and anti-Ro SSA and anti-La SSB positivity, but not with subjective dryness (31). Sicca symptoms tend to be more common in older people, both because of ageing of the salivary glands and comorbidities such as diabetes mellitus, leading to fibrotic changes in the glandular parenchyma and because of the wide use of anti-depressants and psychotropic drugs in elderly people, often causing anticholinergic side effects (32).

Finally, Eo-SS patients seem to present a similar rate of positive MSGB compared to young and middle-aged onset patients (25, 27, 33). However, most studies comparing Eo and younger onset SS patients defined MSGB findings as a categorical variable, whereas data regarding the severity of the lymphocytic infiltration of salivary glands parenchyma in terms of medium Focus Score and presence of germinal-centre (GC)-like structures in Eo-SS patients are lacking.

Regarding extra-glandular manifestations, Eo-SS patients have been shown to present less frequently inflammatory arthralgia and arthritis and a higher prevalence of lung involvement in the form of Interstitial Lung Disease (ILD).
### Table I. Elderly-onset Sjögren’s syndrome.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>n° of Eo pts</th>
<th>Age</th>
<th>Comparison group (yrs)</th>
<th>Classification criteria</th>
<th>Glandular manifestations</th>
<th>EGM</th>
<th>Serology</th>
<th>Outcome and lymphoma risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haga, Jonsson et al. 1999</td>
<td>24/67 (36%)</td>
<td>&gt;60</td>
<td>≤60</td>
<td>Preliminary European, 1992</td>
<td>No differences in prevalence of positive oral tests and MSGB</td>
<td>No differences in prevalence of EGM</td>
<td>Lower prevalence of anti-SSA/SSB (21%), RF (21%), hypergammaglobulinemia (29%)</td>
<td>/</td>
</tr>
<tr>
<td>Tishler et al. 2001</td>
<td>17/85 (20%)</td>
<td>&gt;65</td>
<td>≤65</td>
<td>San Diego, 1994</td>
<td>No differences in prevalence of subjective dryness and PGE</td>
<td>No differences in prevalence of EGM</td>
<td>Lower prevalence of anti-SSA (11%) and RF (12%)</td>
<td>/</td>
</tr>
<tr>
<td>García-Carrasco et al. 2002</td>
<td>43/400 (11%)</td>
<td>&gt;70</td>
<td>≤70</td>
<td>European community study group, 1993</td>
<td>No differences in prevalence of positive oral tests, ocular tests and MSGB</td>
<td>No differences in prevalence of EGM</td>
<td>No differences in prevalence of ANA, anti-SSA, anti-SSB, RF, hypergammaglobulinemia</td>
<td>/</td>
</tr>
<tr>
<td>Botios et al. 2011</td>
<td>21/336 (6%)</td>
<td>&gt;65</td>
<td>41-65 and ≤40</td>
<td>American-European, 2002</td>
<td>No differences in prevalence of positive oral tests, ocular tests and MSGB</td>
<td>No differences in prevalence of EGM</td>
<td>No differences in prevalence of ANA, anti-SSA, anti-SSB, RF, hypergammaglobulinemia</td>
<td>/</td>
</tr>
<tr>
<td>Retamozo et al. 2017</td>
<td>79/303 (2%)</td>
<td>&gt;70</td>
<td>≤70</td>
<td>American-European, 2002</td>
<td>Higher prevalence of positive oral tests (82%)</td>
<td>/</td>
<td>Lower prevalence of anti-SSA/SSB (62%) and low C3 (9%)</td>
<td>/</td>
</tr>
<tr>
<td>Goules et al. 2020</td>
<td>293/1997 (15%)</td>
<td>≥65</td>
<td>36-64</td>
<td>EULAR/ACR, 2016</td>
<td>Higher prevalence of xerostomia (97%)</td>
<td>Higher prevalence of ILD (8%) Lower prevalence of arthritis (10%)</td>
<td>Lower prevalence of anti-SSA (68%) and hypergammaglobulinemia (44%)</td>
<td>Higher prevalence of lymphoma (7%)</td>
</tr>
<tr>
<td>Lee et al. 2021</td>
<td>43/221 (19%)</td>
<td>≥65</td>
<td>&lt;65</td>
<td>EULAR/ACR, 2016</td>
<td>No differences in subjective dryness, ESSPRI and prevalence of positive oral and ocular tests; Lower prevalence of positive SGUS</td>
<td>Higher prevalence of ILD (51%) Lower prevalence of arthritis (7%)</td>
<td>Lower prevalence of anti-SSA (51%) and anti-SSB (7%) Lower levels of IgG, RF and C4</td>
<td>Higher SSDDI No differences in lymphoma prevalence</td>
</tr>
<tr>
<td>Luo et al. 2022</td>
<td>104/742 (14%)</td>
<td>&gt;65</td>
<td>35-65</td>
<td>American-European, 2002 or EULAR/ACR, 2016</td>
<td>No differences in subjective dryness, prevalence of positive oral tests and PGE</td>
<td>Lower prevalence of arthritis (29%)</td>
<td>Lower prevalence of RF (29%)</td>
<td>Lower prevalence of dental caries (24%)</td>
</tr>
</tbody>
</table>

Eo: elderly-onset; EGM: extra-glandular manifestations; MSGB: minor salivary glands biopsy; RF: rheumatoid factor; SGUS: salivary glands ultra-sound; PGE: parotid glands enlargement; ILD: interstitial lung disease; SSDDI: Sjögren’s Syndrome Disease Damage Index.

(15, 30). Indeed, older age at onset of SS has been associated with the presence of ILD and development of ILD as the first manifestation of SS (34, 35). Moreover, it is a well-known risk factor for progression of ILD, representing an adverse prognostic factor (36). No other differences, in terms of extra-glandular manifestations, have been detected to date between Eo and younger SS patients. Interestingly, a recent study, specifically investigating the characteristic features of SS patients with neurologic manifestations, correlated older age at disease onset with the risk of SS-related neurologic involvement (37). However, the reported median age at SS onset in patients with neurologic involvement was 55 (IQ 43.5–64.5) and therefore was not representative of an Eo-SS subset. These findings were also confirmed by a recent systematic literature review (38).

**Outcome and lymphoma risk**

Very few studies have investigated the impact of Eo on SS outcome, in terms of mortality, damage accrual and risk of lymphoproliferative complications. Of note, Goules *et al.* highlighted a higher prevalence of lymphoma in Eo patients. Interestingly, the time from SS onset to lymphoma development was not different compared to matched middle aged SS lymphoma patients, with 80% of Eo patients developing lymphoma within 6 years of disease onset (15).

**Juvenile Sjögren’s syndrome**

Paediatric diseases usually are distinct entities since children are not “miniature adults” but have different metabolic rates, organ functions and enzyme levels. The immune system is not fully matured, and their organs are still growing and developing, consequently, signs and symptoms of diseases can manifest differently in children than in adults. In the most extensive collections of data, jSS accounts for all SS cases between 11% and 19%. Instead, the proportion of childhood patients (under 18 years) ranges from 1% to 6% of all cases (17, 22, 39-41). Nonetheless, SS in children often presents with unique characteristics, making it difficult to meet diagnostic criteria originally designed for adults (18, 42, 43). Although efforts have been made to establish paediatric-specific criteria, as of now, there are no validated criteria. The result is a fluctuating prevalence of the condition across the studies, due to methods of patient selection: based on expert clinical judgment, paediatric criteria, or adult criteria such as the American-European 2002 or ACR/EULAR 2016 classification criteria. The criteria employed may select diverse categories of...
### Table II. Juvenile Sjögren’s syndrome.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>n° of jSS pts</th>
<th>Age cut-off (yrs)</th>
<th>Comparison group (yrs)</th>
<th>Classification criteria</th>
<th>Glandular manifestations</th>
<th>EGM</th>
<th>Serology</th>
<th>Outcome and lymphoma risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokogawa et al. 2016</td>
<td>26/439 (6%)</td>
<td>&lt;18</td>
<td>≥18</td>
<td>Expert Opinion</td>
<td>Higher prevalence of PGE (61.5%), lower prevalence of dry mouth (65.4%) and dry eyes (61.5%)</td>
<td>Higher prevalence of CNS involvement (25.1%), renal involvement (19.2%), fever (23.1%) and lymphadenopathy (46.2%)</td>
<td>Higher prevalence of ANA (96.2%), anti-SSA and anti-SSB (84.6%), RF (72.7%)</td>
<td>No differences in SSDDI</td>
</tr>
<tr>
<td>Anquetil et al. 2018</td>
<td>55/393 (14%)</td>
<td>18-35</td>
<td>&gt;35</td>
<td>EULAR/ACR, 2016</td>
<td>Higher prevalence of PGE (47.2%)</td>
<td>Higher prevalence of lymphadenopathy (25.5%), cutaneous vasculitis (23.6%) and renal involvement (16.4%)</td>
<td>Higher prevalence of anti-SSA (84.6%), anti-SSB (57.8%), RF (41.5%), low C3 (18.9%), low C4 (54.7%), hypergammaglobulinemia (60.8%)</td>
<td>No differences in lymphoma prevalence</td>
</tr>
<tr>
<td>Yayla et al. 2020</td>
<td>40/352 (11%)</td>
<td>≤35</td>
<td>&gt;35</td>
<td>EULAR/ACR, 2016</td>
<td>No differences in dry eye and dry mouth</td>
<td>Higher prevalence of renal involvement (10%) and cutaneous involvement (22.5%)</td>
<td>Higher prevalence of anti-SSA (91.2%), anti-Ro52 (88.9%), anti-SSB (50%), anti-RNP (27.8%), RF (74.3%), low C4 (41.7%), hypergammaglobulinemia (79.3%)</td>
<td>No differences in death</td>
</tr>
<tr>
<td>Goules et al. 2020</td>
<td>379/1997 (19%)</td>
<td>≤35</td>
<td>35-65</td>
<td>EULAR/ACR, 2016</td>
<td>Higher prevalence of PGE (39.1%); lower prevalence of dry mouth (86.5%) and dry eyes (89%); no differences in MSGB positivity</td>
<td>Higher prevalence of lymphadenopathy (20.6%), Raynaud’s phenomenon (36.6%); Lower prevalence of PNS involvement (1.1%) and ILD (1.1%)</td>
<td>Higher prevalence of ANA (91.2%), anti-SSB (91.7%), RF (71%), low C4 (38.5%), hypergammaglobulinemia (71%); Lower levels of CD16/CD56+ NK cells and CD4+ T-cell</td>
<td>Higher prevalence of lymphoma (10.3%) with two incidence peaks of lymphoma within 3 years of onset and after 10 years</td>
</tr>
<tr>
<td>Wei et al. 2021</td>
<td>36/333 (11%)</td>
<td>≤35</td>
<td>&gt;35</td>
<td>American-European, 2002</td>
<td>No differences in dry eye and dry mouth</td>
<td>Higher prevalence of haematological involvement (80.6%), renal involvement (19.5%) and mucocutaneous involvement (50%)</td>
<td>Higher prevalence of Anti-SSA (91.7%), Anti-Ro52 (88.9%), anti-SSB (50%), anti-RNP (27.8%), RF (74.3%), low C4 (41.7%), low C4 (27.8%), hypergammaglobulinemia (79.3%); Lower probability of developing SLE (4.7%)</td>
<td>Higher prevalence of lymphoma (11%)</td>
</tr>
<tr>
<td>Legger et al. 2021</td>
<td>23/56 (41%)</td>
<td>≤16</td>
<td>&gt;16</td>
<td>Expert Opinion</td>
<td>Higher prevalence of PGE (91%); lower prevalence of dry mouth (52.2%), dry eye (26.1%) and stimulated whole salivary flow rate (26.1%)</td>
<td>Higher prevalence of fever (30.4%); cutaneous involvement (26.1%) and biological domain (47.8%); Lower prevalence of haematological domain (8.3%); No differences in laboratory tests</td>
<td>Higher prevalence of lymphoma (11%)</td>
<td>Only a patient with lymphoma</td>
</tr>
<tr>
<td>Ramos-Casals et al. 2021</td>
<td>158/12083 (1%)</td>
<td>≤18</td>
<td>19-36, 37-54, 55-72, ≥73</td>
<td>American-European, 2002 or EULAR/ACR, 2016</td>
<td>Higher Glandular manifestations (47.1%); positive salivary gland biopsy (96.7%); abnormal oral test (81.6%); Lower prevalence of dry eye (70.3%), dry mouth (79.7%) and abnormal ocular test (57.6%)</td>
<td>Higher prevalence of constitutional symptoms (21.9%); lymphadenopathy (25.2%); cutaneous involvement (12.3%) and haematological involvement (28.4%); No differences in laboratory tests</td>
<td>Higher prevalence of ANA (90.3%), anti-SSA (82.7%), anti-SSB (61.9%), RF (67.6%) and lower prevalence of cryoglobulins (4.7%)</td>
<td>Only a patient with lymphoma</td>
</tr>
<tr>
<td>Luo et al. 2022</td>
<td>105/742 (14%)</td>
<td>&lt;35</td>
<td>35-65, &gt;65</td>
<td>American-European, 2002 or EULAR/ACR, 2016</td>
<td>Lower prevalence of dry mouth (78.1%) and abnormal Schirmer I tests (81.9%)</td>
<td>Lower prevalence of ILD (14.3%); No differences in laboratory tests</td>
<td>Higher prevalence of ANA (78.8%), anti-SSA (88.9%), anti-SSB (48.5%), RF (60.2%), low C3 (33.3%) and low C4 (51%)</td>
<td>Higher prevalence of dental caries</td>
</tr>
</tbody>
</table>

jSS: juvenile Sjögren’s disease; EGM: extra-glandular manifestations; MSGB: minor salivary glands biopsy; PNS: peripheral nervous system; CNS: central nervous system; ILD: interstitial lung disease; SLE: systemic lupus erythematosus; SSDDI: Sjögren’s Syndrome Disease Damage Index.
patients with different manifestations, further complicating the understanding of the disease in younger populations (17).

The most significant and recent studies on jSS are reported in Table II.

**Immunologic profile**

A hallmark of juvenile patients is a pronounced humoral activity, with a higher prevalence of autoantibodies such as Antinuclear antibodies, anti-Ro SSA (particularly anti-Ro52), anti-La SSB, anti-RNP, and rheumatoid factors. Furthermore, younger patients have hypergammaglobulinemia and lower levels of C3, C4, cryoglobulins, circulating CD4+ T-cells and CD16/56+ NK cells (18, 42, 44). Theander et al. (45) demonstrated that jSS patients, when compared to Eo-SS, showed a higher prevalence of autoantibodies before diagnosis with a less extended time between the appearance of autoantibodies and diagnosis (5.1±3.6 vs. 6.8±4.7). Interestingly, pre-diagnostic autoantibodies are associated with a more systemic disease, including elevated IgG values, decreased C4, CD4+ T-cell lymphocytes and skin involvement, typical features of younger patients. Autoantibodies are associated with specific genes (HLA) thus suggesting a potential genetic role in determining juvenile phenotype.

### Glandular and extra-glandular manifestations

Juvenile SS, compared to adults, is a more severe disease with a higher systemic involvement and is frequently associated with other autoimmune diseases (15, 42, 46).

Salivary gland enlargement is a key feature of juvenile Sjögren’s Syndrome. In adult-onset cases, parotitis is one of the main determinants of prognosis, and the correct assessment of the swelling (as persistent) allows the identification of a phenotype at high risk of lymphoma. In younger patients differentiating between SS-related swelling and other causes of parotitis may be particularly challenging, especially in juvenile recurrent parotitis (JRP) of the children. Salivary gland ultrasonography has emerged as a valuable diagnostic tool to rule out other causes of sialadenitis (47, 48). In addition, it offers high negative predictive value in paediatric cases, being positive in almost all these patients (47). Despite the frequency of recurrent parotid inflammation, jSS patients often exhibit milder sicca symptoms. This dissociation between sicca symptoms and ultrasonographic findings could suggest that in younger patients the disease may represent an early stage of SS where the glands have not yet sustained significant damage. In contrast to this hypothesis, younger patients present a higher frequency of positive oral tests compared to SS adults (22, 49).

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**Table III. Male patients.**

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>n° of male SS pts</th>
<th>Age</th>
<th>Comparison group (yrs)</th>
<th>Classification criteria</th>
<th>Glandular manifestations</th>
<th>EGM</th>
<th>Serology</th>
<th>Outcome and lymphoma risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramirez Sepúlveda et al. 2017</td>
<td>13/199 (7%)</td>
<td>No differences</td>
<td>186 females</td>
<td>American-European, 2002</td>
<td>No differences in prevalence of positive oral tests, ocular tests and MSGB</td>
<td>Higher prevalence of ILD (15%), cutaneous vasculitis (23%)</td>
<td>No differences in prevalence of anti-SSA, anti-SSB, Higher levels of anti-Ro52</td>
<td>None of the patients developed lymphoma</td>
</tr>
<tr>
<td>Ramirez Sepúlveda et al. 2017</td>
<td>68/967 (7%)</td>
<td>No differences</td>
<td>899 females</td>
<td>EULAR/ACR, 2016</td>
<td>No differences in prevalence of positive MSGB</td>
<td>Higher prevalence of ILD (17%), lymphadenopathy (16%); lower frequency of hypothyroidism</td>
<td>Higher prevalence of ANA (87%), anti-SSA and anti-SSB (52%)</td>
<td>Higher prevalence of lymphoma (10%)</td>
</tr>
<tr>
<td>Retamozo et al. 2017</td>
<td>622/9032 (7%)</td>
<td>No differences</td>
<td>860 females</td>
<td>American-European, 2002</td>
<td>Lower prevalence of dry eyes (89%) and dry mouth (90%)</td>
<td>\</td>
<td>\</td>
<td>Higher prevalence of RF (54%)</td>
</tr>
<tr>
<td>Park et al. 2020</td>
<td>33/107 (3%)</td>
<td>No differences</td>
<td>353 matched females</td>
<td>EULAR/ACR, 2016</td>
<td>Lower prevalence of dry eyes (78.8%), dry mouth (84.8%) and higher values of Schirmer’s test (3 mm) and Unstimulated Salivary Flow Test (0.3)</td>
<td>Higher prevalence of pulmonary involvement (21.2%); and lower prevalence of autoimmune thyroid disease (0%)</td>
<td>Lower prevalence of anti-SSA (71.9%), RF (41.4%); Higher prevalence of anti-RNP (17.4%)</td>
<td>No differences in SDDI, higher prevalence of lymphoma (9%)</td>
</tr>
<tr>
<td>Chatzis et al. 2020</td>
<td>96/1987 (5%)</td>
<td>192 matched females</td>
<td>EULAR/ACR, 2016</td>
<td>Lower prevalence of dry mouth (91%)</td>
<td>No differences in EGM manifestations</td>
<td>Higher prevalence of anti-SSB (50%)</td>
<td>Higher prevalence of lymphoma (18%)</td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 2023</td>
<td>140/961 (15%)</td>
<td>Higher age at onset and higher at diagnosis</td>
<td>821 females</td>
<td>American-European, 2002 or EULAR/ACR, 2016</td>
<td>Higher prevalence of PGE (19.3%), lower dry eyes (67.1%), dry mouth (79.3%)</td>
<td>Higher prevalence of ILD (62.1%); Lower prevalence of rheumatoid arthritis (28.1%)</td>
<td>Lower prevalence of ANA (42.5%), anti-SSA (38.4%), anti-Ro52 (22.4%), anti-CENPB (1.5%); anti-RF (8.3%); Lower IgM levels</td>
<td>Lower prevalence of dental caries (23.2%)</td>
</tr>
</tbody>
</table>

EGM: extra-glandular manifestations; MSGB: minor salivary glands biopsy; RF: rheumatoid factor; SGUS: salivary glands ultra-sound; PNS: peripheral nervous system; CNS: central nervous system; ILD: interstitial lung disease; SLE: systemic lupus erythematosus; SDDI: Sjögren’s Syndrome Disease Damage Index.
Regarding extra-glandular manifestations, younger patients showed a higher frequency of fever, lymphadenopathy, haematological involvement, skin and kidney involvement. Instead, considering only the patients under the age of 18, children more frequently showed central nervous system and biological involvement. Finally, peripheral nervous system involvement and interstitial lung disease appear less frequently in juvenile cases (15).

**Outcome and lymphoma risk**

The risk of lymphoma is increased in patients with juvenile Sjögren’s Disease (10-11%) (15). Interestingly, the distribution pattern of lymphoma occurrence in jSS exhibits a bimodal trend. One peak incidence is observed within the first three years and a second peak arises after a decade of disease duration. Patients with jSS demonstrate robust B-cell responses, which are classical risk factors for the development of lymphoma. Consequently, B-lymphocyte hyperactivity may lead to the early development of lymphoma. On the other hand, the late onset of lymphoma in jSS patients could be due to strong immunoregulatory mechanisms. Indeed, the immune system could counteract the lymphomagenesis process, delaying the onset of lymphoma (15).

JSS has the potential to evolve into a more intricate autoimmune condition. Studies have reported that approximately 8% of younger patients develop poly-autoimmunity. Notably, patients with JSS appear to be at an elevated risk for developing SLE (2.78%), thus requiring a long-term follow-up (50).

**Sjögren’s syndrome in male sex**

SS is quite rare in males. According to a recent systematic review by Qin et al. (51) the SS estimated incidence rate ratio (IRR) for females versus males was 9.29 (95% 6.61–13.04). The pooled prevalence rate (PR) of SS in the female population was 116.72 (95% CI 70.39–163.05) per 100,000 inhabitants and the pooled PR in the male population was 5.53 (95% CI 2.49–8.58) per 100,000 with an overall female/male ratio of 10.72 (95% CI 7.35–15.62). Noteworthy, by using the most recent ACR/EULAR 2016 criteria in Europe, the overall female/male ratio was approximately 1:20, higher than the ratio reported in previous studies (52).

**Immunologic profile**

Anaya et al. in one of the oldest studies investigating SS in males reported a lower frequency of antinuclear antibodies (ANA) in male with respect to female patients (53). By contrast, recent studies have described a similar frequency of autoantibodies between the two sexes or even a higher frequency of Ro52(54) and La/SSB in males (52). These discrepancies could be partially explained considering that to be included in observational studies males needed to satisfy the recent classification criteria that requires a positivity for anti-Ro/SSA autoantibodies to be satisfied.

**Glandular and extra-glandular manifestations**

Sex differences in SS presentation and in patients’ perception between men and women, have been widely reported in the existing literature as summarised in Table III (49, 52, 55-57). More specifically, oral and ocular dryness seems to be less pronounced in male patients, apparently leading to a longer diagnostic delay compared to females (58). By contrast, arthritis, vasculitis and ILD are apparently more frequent in male patients than in women, making SS in male patients generally more severe (52, 54).

**Outcome and lymphoma risk**

Intriguingly some studies have reported a higher prevalence of non-Hodgkin lymphoma in male patients. Anaya et al. (53) in 1995 reported a prevalence of malignant lymphoma in male of 15.4%, higher than the 9% observed in female patients. Moreover, Gondran et al. (59), reported that lymphoma apparently occurred earlier in males than females after SS diagnosis. In a large cohort of SS patients including 1115 patients (1067 women vs. 48 men) male sex was an independent risk factor for lymphoma (60). Similarly, in the recent study by Chatzis et al., lymphoma appeared independently associated with male sex. However, no differences were observed in the frequencies of lymphoma predictors between the two genders (52).

**Conclusions**

SS is a complex and heterogeneous disease with a phenotypic expression that is significantly influenced by the age at the onset of the disease and patients’ gender. Eo-SS, jSS and male patients have a distinct clinical presentation, different type of organ involvement and a different prognosis when compared with middle-aged female. Overall, these three subgroups tend to be more aggressive, particularly considering lymphoproliferative complications. A phenotypic stratification of SS patients according to age and gender appears therefore pivotal in the era of precision medicine to improve patients’ management and long-term prognosis.

**References**


34. THEANDER E, JONSSON R, SÖSTRÖM B, BROKSTAD K, OLSSON P, HENRIKSSON G: Prediction of Sjögren’s syndrome years be- fore diagnosis and identification of patients...
with early onset and severe disease course by autoantibody profiling. *Arthritis Rheumatol* 2015; 67(9): 2427-36.


