Duration till diagnosis and clinical profile of Sjögren's syndrome: Data from real clinical practice in a single-center cohort

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ABSTRACT

Aim of the work: To describe the clinical features of patients with Sjögren's syndrome (SS) in a single-center cohort and to investigate factors that may influence duration till disease diagnosis.

Patients and methods: This cross-sectional study is based on the local registry of SS patients at the Rheumatology Department of Dnipropetrovsk Mechnikov Regional Hospital, Ukraine. Data from the first admission of 24 patients; 1 male and 23 females with a median age of 54 years (45–61 years) was analyzed.

Results: In patients with primary SS (n = 19) the disease appeared at the age of 44 years (37–49 years) and the most common symptom to emerge first was ocular/oral dryness (OOD); in patients with secondary SS (n = 5) the disease mostly manifested with Raynaud's phenomenon/rash/myalgia at the age of 28.6 years (27–37 years). Patients with primary SS more commonly had elevated antinuclear antibody (ANA) titer, anemia, higher IgG and lower glomerular filtration rate; patients with secondary SS more frequently exhibited skin changes, myocarditis, heart failure and higher IgA. Median duration till diagnosis was 8.5 years (2.8–17 years). Onset of SS with fever or Raynaud's phenomenon/rash/myalgia shortened the duration till diagnosis. Presence of C-reactive protein >6 mg/dl or ANA > 1:320 may indicate primary SS in patients with symptoms of OOD. On the contrary, combination of OOD at the disease onset and positive rheumatoid factor significantly increased the duration till SS diagnosis.

Conclusions: The median duration till diagnosis of SS is prolonged. Patients with symptoms of OOD at disease onset had significantly prolonged duration till diagnosis.

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1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease, a hallmark of which is affection of lachrymal and salivary glands along with extraglandular manifestations and presence of autoantibodies [1]. SS can further be distinguished as primary (pSS), in which the disease is limited to dry eye and/or mouth symptoms, and secondary (sSS), in which above mentioned symptoms accompany another systemic disease [1]. Epidemiology and clinical manifestations of SS vary significantly among ethnic groups and geographical areas that may contribute to difficulties in diagnosis establishment [2–4]. Whereas in several countries of European region SS is considered as an orphan disease [5], it is supposed to be the second prevalent rheumatic disease [6]. Although >90% of patients present with sicca syndrome [7], these complaints are rather non-specific and are difficult to classify [8]. Patients from Northern Europe experience ocular dryness two times less frequently than in other geographical regions [4]. This leads to an average 3.9-year delay in diagnosis and treatment initiation, as well as under diagnosis of SS in more than in half affected patients [8]. Hematological and immunological markers are widely used in diagnosis of SS and prediction of its complications [9–12]. Role of autoantibodies in SS, even in the absence of systemic manifestations is highly appreciated, moreover, according to revised 2016 ACR/EULAR diagnostic criteria presence of autoantibodies has the same impact on the SS diagnosis establishment as salivary gland biopsy [12]. In the study of the Dutch prospective diagnostic cohort anti-SSA (Ro) antibody titer was even more specific for SS diagnosis, than labial or parotid salivary gland focus score [13]. Strong association of primary SS with hypergammaglobulinemia G supports the idea of autoimmune origin of SS [6,14]. Hypergammaglobulinemia and hypercomplementemia were predictive of

progression to SS in individuals with incomplete diagnostic criteria [15].

To our knowledge, this is the first study concerning clinical characteristics of the patients with SS in Ukrainian region. This study is the earliest to define how laboratory findings available in primary care may influence the time of SS diagnosis from the moment of the first symptom development. The aim of the present work is to describe the clinical features of patients with SS in a single-center cohort and to investigate factors that may influence duration of SS diagnosis.

2. Patients and methods

This cross-sectional study is based on the local registry of patients with SS at Dnipropetrovsk Mechnikov Regional Hospital, Dnipro, Ukraine. The register was established in 2018 and contains data on 24 SS patients (1 male and 23 females) with a median age of 54 years (45;61) who received medical care at the Rheumatology Department from 2007 to 2019. Data from patients' medical records on the first admission was analyzed. Diagnosis of SS was provided according to the 2002 American-European Consensus Group criteria [10]. All the patients gave their informed written consent on data collecting and processing. The study was approved by the Ethics Committee of Dnipropetrovsk Mechnikov Regional Hospital (protocol number 703/17-1 from 6 June 2017).

2.1. Symptoms of SS onset

The first manifestation of SS and time of its emergence was collected from patients' medical records. Fever was considered as rise of body temperature >37°Celsius. Arthritis was defined as swelling

and/or tenderness in ≥1 joints. Ocular/oral dryness symptoms were assessed according to the 2002 criteria [10]. SS onset with symptoms of other systemic disorders was established in patients reporting Raynaud's phenomenon, rash (any location) or myalgias as the first manifestation. All the patients with symptoms of ocular or oral dryness were prescribed cholinolytic drugs, artificial saliva and eye drops. 19 patients (79.1%) were prescribed low-dosage steroids (15 mg/day); 7 (29.1%) were treated with hydroxychloroquine and 4 patients (16.6%) were prescribed other immunosuppressive drugs (leflunomide, cyclophosphamide).

2.2. Clinical manifestations

Diagnosis of dry keratoconjunctivitis was provided by an ophthalmologist. For objective confirmation of xerostomia and evaluation of salivary glands enlargement patients were referred to oral and maxillofacial surgery department. Raynaud's phenomenon was diagnosed if patient experienced episodes of paleness/cyanosis/hyperemia of fingers after exposure to cold or emotional stress and after nail fold video capillaroscopy. Arterial hypertension was diagnosed if systolic blood pressure was ≥140 mmHg or diastolic ≥90 mmHg on hospital admission or when using antihypertensives. Diagnosis of myocarditis was taken from patients' medical records. None of the patients had acute myocarditis. The mean pulmonary artery pressure (PAPm) and presence of pericardial effusion were assessed during transthoracic echocardiography. Left ventricle hypertrophy was diagnosed using Sokolow-Lyon criteria [16]. Pulmonary fibrosis was diagnosed using chest X-ray or computerized tomography. Gastritis was diagnosed after esophago-gastroduodenoscopy. Diagnosis of pancreatitis was based on patients' complaints, changes in stool test

Table 1
Comparison of clinical characteristics of the patients in the study with primary and secondary Sjögren's syndrome.

Parameter n(%) or median (IQR)	Sjögren's syndrome patients (n = 24)			
	All (n = 24)	pSS (n = 19)	sSS (n = 5)	p
General characteristics				
Females	23 (95.8)	18 (94.7)	5 (1 0 0)	1
Age (years)	54 (45.5–61)	56 (47.5–61)	50 (36–52)	0.3
BMI	24.2 (19.8–26.5)	23.6 (20.9–25.9)	24.9 (19.4–32.7)	0.61
SBP (mmHg)	120 (110–150)	120 (117–155)	110 (110–120)	0.09
DBP (mmHg)	80 (70–82)	80 (70–90)	75 (75–78)	0.44
Age at first symptom (years)	41.5 (33.5–48.2)	44 (37–49.5)	28.6 (27–37)	0.11
Time till diagnosis (years)	8.5 (2.8–17)	8 (3–14)	13 (2–18)	0.77
First symptom				
Fever	3 (12.5)	2 (10.5)	1 (20)	0.52
Arthritis	5 (20.8)	4 (21.1)	1 (20)	1
Ocular/oral dryness	9 (37.5)	9 (47.7)	0 (0)	–
Signs of systemic diseases	8 (33.3)	6 (31)	2 (40)	1
Diagnostic criteria				
Objective xerostomia	23 (95.8)	18 (94.7)	5 (1 0 0)	1
Stomatitis	7 (29.2)	5 (26.3)	2 (40)	0.6
Decreased salivary glands	2 (13.3)	2 (15.4)	0 (0)	–
Enlarged salivary glands	10 (66.7)	8 (61.5)	2 (1 0 0)	0.52
Dry keratoconjunctivitis	21 (87.5)	17 (89.5)	4 (80)	0.52
Need for artificial eye drops	18 (75.0)	14 (73.7)	4 (80)	1
Rheumatoid factor (>14 IU/l)	13 (54.2)	11 (57.9)	2 (50)	0.62
ANA positive	5 (31.3)	5 (41.7)	0 (0)	–
Laboratory findings				
GFR (ml/min)	88 (74–101)	78 (70–97)	101 (94–102)	0.13
Proteinuria	6 (26.1)	6 (31.6)	0 (0)	–
Anemia	10 (41.7)	10 (52.6)	0 (0)	–
ESR (>25 mm/h)	12 (50)	6 (31.6)	2 (50)	1
CRP (>5 mg/l)	8 (33.3)	6 (31.6)	2 (50)	1
Cryoglobulinemia	9 (45.0)	7 (41.2)	2 (66.7)	0.56
IgG (g/l)	14 (9–19)	14.6 (9.9–20.1)	6.9 (3.7–10.2)	0.056
IgA (g/l)	3.1 (2.3–3.8)	2.9 (2.2–3.6)	3.8 (3.6–4.2)	0.16
IgM (g/l)	2.1 (1.2–3.2)	2.1 (1.2–3.4)	2.2 (1.5–2.8)	1

pSS: primary SS; sSS: secondary SS; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure, ANA: antinuclear antibodies; GFR: Glomerular filtration rate; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Ig: immunoglobulin. IQR: interquartile range.

and abdominal ultrasound. Body mass index (BMI) was recorded. Glomerular filtration rate (GFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17]. Several laboratory findings were regarded as positive if they exceeded the following thresholds: C-reactive protein (CRP) > 6 mg/dl, rheumatoid factor (RF) > 14 IU/l, erythrocyte sedimentation rate (ESR) > 25 mm/h or antinuclear antibodies (ANA) titer > 1:320.

Statistical analysis: Due to a small sample size (n < 30) nonparametric statistic tools were used. Continuous data was described as median (interquartile range) and compared with U Mann-Whitney test. Categorical data was described as n (valid %) with account for missing data and compared using Fisher's exact test. Time of SS diagnosis depending on the first symptom was analyzed using Kaplan-Meier method. Significance of divergence of survival curves was assessed with log-rank test. Data processing was performed using The R Project for Statistical Computing (GNU project, https://www.r-project.org/). The role of positive CRP, RF, ESR or ANA in augmenting the diagnostic value of symptoms of ocular/oral dryness (OOD) at the disease onset has been assessed aiming at a faster diagnosis of SS. In combination with the OOD, the effect of each factor alone or together with others was assessed. Influence of all combinations on duration of SS diagnosis was assessed using Cox proportional-hazards regression models for all patients and separately for patients with pSS. A p-values <0.05 was considered significant.

3. Results

The majority of patients were middle-aged females with normal BMI and the disease onset in fourth decade of life (Table 1). SS was primary in 19 and secondary in 5 patients (to systemic sclerosis (SSc) in 3, to mixed connective tissue disease in 1 and to rheumatoid arthritis in 1). The most frequent findings were xerostomia and dry keratoconjunctivitis. None of the patients with sSS had OOD symptoms at the disease onset. The next most prevalent were systemic manifestations, elevated inflammatory activity and signs of thyroid gland injury (Table 2). Both patients with pSS and sSS had elevated levels of IgA and IgM. IgA was higher in patients with sSS, while IgG was markedly higher in patients with pSS. ANA positivity was more common in pSS. Patients with pSS had lower GFR and higher proteinuria. Dyspnea and pulmonary fibrosis were slightly more prevalent in sSS (Table 2). Patients with pSS had a higher frequency of hypertension, left ventricle hypertrophy and arrythmia/conduction blocks while sSS patients more often suffered from myocarditis and heart failure. Signs of gastrointestinal tract involvement were evenly distributed between groups.

Patients in whom disease onset began with fever or signs of other systemic diseases had on average 6–7 years shorter duration of SS diagnosis establishment (Table 3). Those with OOD or arthritis had a prolonged time till SS diagnosis. In patients with pSS there was a significant difference in the duration till diagnosis between those with and without OOD (p < 0.05) (Fig. 1). There was significant difference for fever and a tendency for arthritis as the first manifestations of SS. Both of these trends disappeared after exclusion of patients with sSS from the analysis. For patients with pSS a significant difference of diagnosis survival curves remained.

Analysis of Cox proportional-hazards regression models for the diagnosis of SS showed no significance (Table 4). After excluding patients with sSS, addition of hematological findings in the majority of combinations had a notable effect on the duration till SS diagnosis.

Table 2
Extraglandular manifestations in patients with primary and secondary Sjögren's syndrome.

Parameter n(%) or median (IQR)	Sjögren's syndrome patients (n = 24)			
	All (n = 24)	pSS (n = 19)	sSS (n = 5)	p
Raynaud's phenomenon	9 (37.5)	7 (36.8)	2 (40)	1
Polyarthritis	19 (79.2)	14 (73.7)	5 (1 0 0)	0.54
Skin rash	5 (20.8)	4 (21.1)	1 (20)	1
Hyperpygmentation	4 (16.7)	1 (5.3)	3 (60)	**0.02**
Skin atrophy	3 (12.5)	1 (5.3)	2 (40)	0.09
Thyroid gland anomaly	12 (75)	10 (82.3)	2 (50)	0.24
Heart failure	12 (63.2)	7 (50)	5 (1 0 0)	0.12
Hypertension	7 (29.2)	7 (36.8)	0 (0)	–
Myocarditis	10 (41.7)	5 (26.3)	5 (1 0 0)	**0.01**
LVH	5 (33.3)	5 (38.5)	0 (0)	–
Arrhythmia	6 (30)	6 (35.3)	0 (0)	0.52
Hydropericarditis	3 (21.4)	2 (20)	1 (25)	1
PAPm (mmHg)	24 (22–26)	22 (20.5–25.5)	26 (25–27.5)	0.26
Dyspnea	14 (58.3)	10 (52.6)	4 (80)	0.35
Pulmonary fibrosis	2 (11.8)	1 (7.7)	1 (25)	0.42
Gastritis	14 (58.3)	10 (52.6)	4 (80)	0.69
Pancreatitis	15 (62.5)	11 (57.9)	4 (80)	0.57

pSS: primary SS; sSS: secondary SS; LVH: left ventricle hypertrophy; PAPm: mean pulmonary artery pressure. IQR: interquartile range. Bold values are significant at p < 0.05

Table 3
Time till diagnosis of Sjögren's syndrome depending on the first symptom.

Symptom median (IQR)	All SS patients (n = 24)			pSS patients (n = 19)		
	Present	Absent	p	Present	Absent	p
Fever	3 (2–5.5)	10 (3–17)	0.16	3 (4.2–6.7)	9 (3–17)	0.54
Arthritis	17 (11–20)	8 (2.5–12)	0.14	14 (8.5–17)	8 (3–10.5)	0.42
Salivary glands	11 (10–19)	5 (2.5–11)	0.08	11 (10–19)	4.5 (3–8)	**0.049**
Symptoms of AID	4.5 (2.7–10.2)	10.5 (2.7–17.5)	0.22	4.5 (3.2–7.2)	10 (3–17)	0.33

SS: Sjögren's syndrome; pSS: primary SS; AID: autoimmune disease. Bold values are significant at p < 0.05.
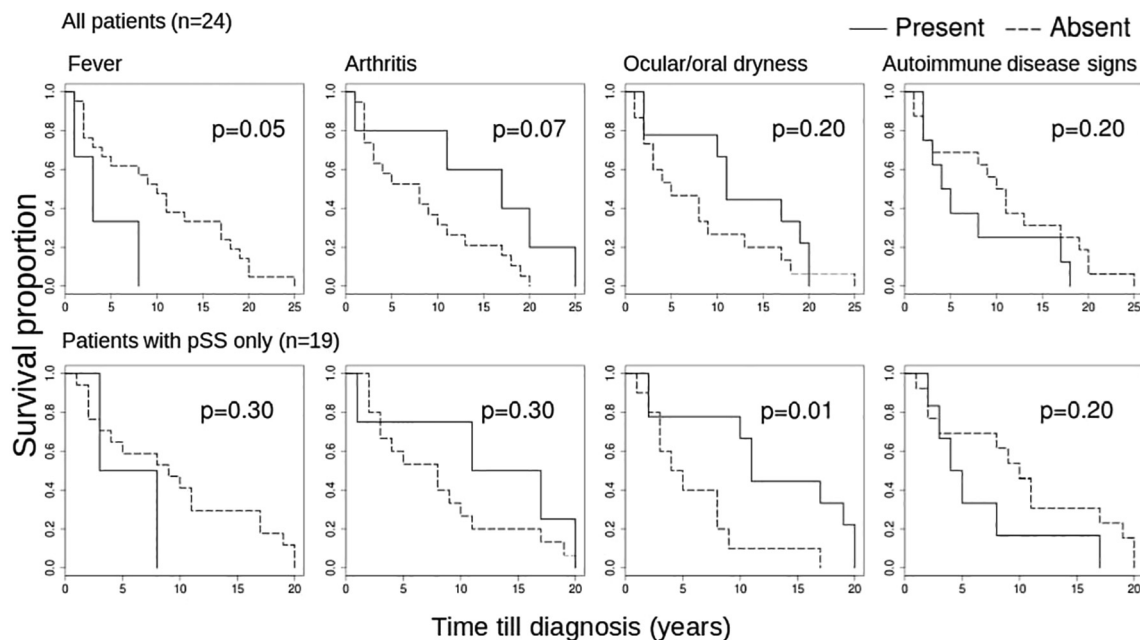
Fig. 1. Survival curves of Sjögren's syndrome duration till diagnosis depending on the first symptom.

Table 4
Cox-regression analysis of laboratory investigations for Sjögren's syndrome diagnosis in all patients (n = 24).

	Positive laboratory investigations	Sjögren's syndrome patients					
		All (n = 24)			pSS (n = 19)		
		RR	CI	p	RR	CI	p
Ocular/Oral Dryness plus	OOD only	0.61	(0.26–1.44)	0.26	0.27	(0.09–0.81)	**0.02**
	CRP	0.7	(0.16–3.06)	0.63	0.54	(0.12–2.52)	0.43
	RF	0.46	(0.18–1.22)	0.12	0.18	(0.05–0.67)	**0.01**
	ESR	0.53	(0.18–1.57)	0.25	0.39	(0.13–1.21)	0.1
	ANA	0.35	(0.05–2.69)	0.31	0.25	(0.03–2.03)	0.2
	CRP/RF	0.56	(0.22–1.42)	0.22	0.26	(0.08–0.88)	**0.03**
	CRP/ESR	0.5	(0.19–1.32)	0.16	0.22	(0.06–0.81)	**0.02**
	CRP/ANA	0.7	(0.16–3.06)	0.63	0.54	(0.12–2.52)	0.43
	RF/ESR	0.53	(0.18–1.57)	0.25	0.39	(0.13–1.21)	0.1
	RF/ANA	0.46	(0.18–1.22)	0.12	0.18	(0.05–0.67)	**0.01**
	ESR/ANA	0.53	(0.18–1.57)	0.25	0.39	(0.13–1.21)	0.1
	CRP/RF/ESR	0.58	(0.24–1.41)	0.23	0.26	(0.08–0.82)	**0.02**
	CRP/RF/ANA	0.56	(0.22–1.42)	0.22	0.26	(0.08–0.88)	**0.03**
	RF/ESR/ANA	0.5	(0.19–1.32)	0.16	0.22	(0.06–0.81)	**0.02**
	CRP/ESR/ANA	0.5	(0.19–1.32)	0.16	0.22	(0.06–0.81)	**0.02**
	CRP/RF/ESR/ANA	0.58	(0.24–1.41)	0.23	0.26	(0.08–0.82)	**0.02**

pSS: primary SS; OOD, ocular/oral dryness; CRP, C-reactive protein; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies. RR: risk ratio; CI: confidence interval. Bold values are significant at p < 0.05.

4. Discussion

Sjogren's syndrome (SS) is one of the most common chronic autoimmune rheumatic disease and considered a high burden disease [18]. SS is a connective tissue disease (CTD) that mainly affects the lacrimal and salivary glands [19]. In addition to the sicca symptoms, morbidity arises also from extra-glandular manifestations. Proper diagnosis in due time should improve the current standards of care [18]. pSS is a slowly progressive disease characterized by lymphocytic infiltration of the exocrine glands leading to sicca manifestations. It may affect any organ thus initially presenting by extraglandular manifestations causing a delay in the diagnosis. In the past years, better knowledge of the disease has led to improvement in treatment management [20].

In the present work, SS was more prominent in females. SS primarily affects women [21]. The age and gender in this work were comparable to those of previous European studies [3,4,6]. All the current patients with symptoms of OOD were prescribed cholinolytic drugs, artificial saliva and eye drops. Most of the patients received low-dosage steroids and a considerable number received immunosuppressives. Topical treatment of mucosal dryness is a mainstay therapeutic strategy and SS patients may also require treatment with immunomodulatory agents and immunosuppressives for a variety of extraglandular manifestations [21].

Even though it is 1 of the 3 most frequent CTDs alongside systemic lupus erythematosus (SLE) and progressive systemic sclerosis (PSS), SS is the least researched. SS poses a potential diagnostic challenge as it shares many clinical and immunologic features with other CTDs [19]. In this study, only 5 cases had sSS compared to 19 with pSS. sSS was found to be associated with immune dysfunction [22], disease activity and comorbidities [23] in RA patients as well as with SLE [24] and cutaneous vasculitis [25]. When SS is

secondary to RA, it is less serious and anti-SSA/SSB antibodies are found less frequently than in pSS. When SS is associated with SLE or SSc, clinical and serological patterns are similar to those of pSS [26].

The frequency of symptoms of OOD and RF positivity were comparable to those of other European studies [3,4,6], however there were substantial differences in clinical presentations from those in Asian, Hispanic and African-American patients [3,4,27]. When compared to patients from French cohort [3], our patients more often presented with Raynaud's phenomenon and cryoglobulinemia. Frequencies of articular and pulmonary involvement in both cohorts were similar. The present patients more frequently had objective oral dryness and enlarged salivary glands after ultrasound imaging which, along with cryoglobulinemia may be regarded as a predictor of lymphoma development [28].

The median duration till diagnosis of SS in this study was 8.5 years, which is longer than that in the SICCA registry report [6]. According to the SS foundation's initiative, launched in 2012, SS diagnosis duration should have decreased by 50% in five years. In 2017, the foundation reported decrease of SS diagnosis to three years and less [29]. They declared 3 helpful principles in achieving this goal including increasing public awareness, enhancing education and awareness among healthcare professionals and involving friends and partners [29].

Comparing this registry to existing reports, more similarities were found with European subgroups of the French [3] and Sjögren Big Data Project [4] cohorts rather than with the SICCA [6] study. In all of three mentioned studies there were higher rates of elevated ANA titer compared to that in this work. Patients from SICCA cohort had fewer extraglandular manifestations (Raynaud's phenomenon, rash and joint involvement), than in our and French cohorts. Although to the SICCA registry were included two European centers (in UK and Denmark), presence of patients from Asia and America may complicate comparison of this register to ours [3,6]. Patients from our study had characteristics similar to European subgroups of Sjögren Big Data Project cohort, however, they cannot be clearly relegated to either Northern or Southern European populations [4]. Thyroid gland involvement is supposed to be related to SS [6]. Patients in our study experienced a number of thyroid gland abnormalities, which, along with high rates of another extraglandular abnormality may be explained by presence of atypical antibodies [30]. On the other hand, rate of thyroid gland involvement may be influenced by another factor – Chernobyl accident [31].

There was heterogeneity of clinical presentations in primary and secondary SS cases. In both groups glandular and extraglandular manifestations were similar except for skin hyperpigmentation, atrophy and myocarditis, but underlying immunological abnormalities were quite different. The presence of 3 patients secondary to SSc affected the difference in skin changes. pSS patients were characterized by lower GFR and higher frequency of anemia and proteinuria. This finding cannot be explained by age differences or discrepancy in BP values.

There was a remarkable paradoxal impact of OOD symptoms on the duration till diagnosis of SS. In our opinion it may happen because primary care physicians are not prone to consider these complaints as a sign of autoimmune disease. According to local standards, SS is an orphan disease in Ukraine [32]. The augmentation of this phenomenon after exclusion of patients with sSS from the analysis confirms a key message that pSS and sSS patients should be analyzed separately. Thus, in an attempt to find laboratory signs that are routinely available at primary outpatient care level that could be helpful in suspecting SS, CRP, RF and ESR have been selected as markers of systemic inflammatory reaction and ANA titer as a marker of autoimmune inflammation.

Impact of different autoantibody fractions in SS diagnosis is revised constantly: both anti-SSA and anti-SSB antibodies were present in diagnostic criteria until 2012 [9–11]. In 2016 only anti-SSA antibodies were selected as the most specific for SS [12]. This decision was partly influenced by Baer et al. who showed that anti-SSB only (without anti-SSA) positivity is poorly associated with typical SS clinical manifestations [33]. Nimwegen et al. [13] and Kontny et al. [30] confirmed that anti-SSA positivity has stronger relation to symptoms of SS and immunological abnormalities.

ANA and RF, present in 1993 [9] and 2012 [11] versions of diagnostic criteria were excluded in 2016 [12]. After Cox-regression analysis we discovered that, generally, RF positive patients at the moment of SS diagnosis, had had longer course of SS before admission to the rheumatology department and was more fair for patients with pSS. It may be partly explained by low specificity of RF for SS diagnosis [3,6,8] together with high frequency of polyarthritis in the current study. In previous report RF was also associated with both glandular and articular involvement in patients with pSS [34]. It could force physicians to look for inflammatory joint diseases in RF positive patients and ignore complaints of OOD. The shortest duration till SS diagnosis was in CRP, ANA or CRP/ANA positive patients. Probably, high ANA titer and elevated CRP are associated with more aggressive course of SS or these values were more specific for pSS in this study. Elevated ANA titer was more frequent than positive RF [3,4,6] thus indicating its superiority in diagnosis of SS.

Among the limitations of this work, patients with symptoms of OOD were consulted by ophthalmologists or oral and maxillofacial surgeons, respectively. All diagnostic manipulations as the Schirmer's test, ocular staining, salivary gland visualization and biopsy were performed outside the rheumatology department. We had to rely on other physicians' conclusions regarding the diagnosis of objective xerostomy, keratoconjunctivitis and the nature of salivary gland involvement. However we had no access to the results of above-mentioned tests. Improvement in the diagnosis of SS may be achieved via implementing the following diagnostic tests for suspected patients in primary care: unstimulated whole saliva flow measurement, Schirmer's test, evaluation of CRP level and ANA titer. Of note, dental caries may be useful in suspecting SS [27].

In conclusion, a substantial time gap between the first symptoms and diagnosis of SS establishment was observed. Patients with symptoms of OOD at the disease onset had significantly prolonged duration till diagnosis. Positive CRP or a high ANA titer may indicate pSS in patients with OOD symptoms.

Declaration of Competing Interest

None.

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