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Patients' recollection about the onset of Sjögren's disease – a mixed methods study on the patients' perspective

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Abstract

Background Little is known about the symptoms at the onset of Sjögren's Disease (SjD) and it is unclear whether SjD starts with characteristic symptoms that could be differentiated from dryness of other origin (sicca syndrome). The aim of this study was to investigate patients' recollection of initial events and first symptoms of SjD. The second aim was to verify and quantify these aspects in a representative cohort.

Methods All SjD patients fulfilled the EULAR/ACR 2016 classification criteria. In the first part of the study, consecutive SjD patients were recruited for individual, semi-structured interviews. All interviews were audio-recorded and transcribed verbatim, and an inductive thematic data analysis was performed. In the second part, the identified aspects of the qualitative analysis were grouped into a checklist with ten items.

Results One-hundred and thirty-four patients participated in the study. 31 SjD patients completed the qualitative part. Major aspects emerged of how patients experienced the beginning and first symptoms of SjD: (1) "classic" SjD symptoms (fatigue, pain, dryness) (2), sicca symptoms started after initial swelling of parotid and/or lymph nodes (3), after hormonal transition or infections before the onset of SjD symptoms. In the second part of the study, the previous identified major aspects were verified in an independent cohort of 103 SjD patients. The main symptom before diagnosis was dryness ($n=77$, 74.8%) with migratory joint pain ($n=51$, 49.5%) and fatigue ($n=47$, 45.6%). In 38.8% ($n=40$), patients reported a swelling/inflammation of the parotid gland at the onset of disease.

Conclusions We describe patients' recollection of the onset of SjD. Raising awareness of the symptoms identified among physicians and among the general public may allow earlier diagnosis of SjD.

Keywords Sjögren's syndrome, Disease onset, Qualitative study, Early diagnosis, Patients' perspective, Early disease

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Introduction

Sjögren's Disease (SjD) is a systemic autoimmune disease characterized by the lymphocytic infiltration of salivary and lacrimal glands. Patients often suffer from fatigue and arthralgia in addition to "classic" sicca symptoms. Furthermore, systemic complications like respiratory, neurological, articular or renal symptoms may occur [1, 2]. The risk of B-cell lymphoma is 5 to 10 times higher in SjD patients compared to the general population [3]. Physical and mental impairment (fatigue, anxiety and depression) commonly appear in SjD patients. These complaints are only in part related to inflammatory activity; however, they significantly contribute to an impaired quality of life [4, 5]. Sicca symptoms and dryness-related complaints were reported to hardly impair patients' health-related quality of life (HRQL) [6]. SjDsymptoms are initially often ignored by both - patients and physicians- leading to a mean delay of diagnosis of up to seven years [7]. Patients often need to consult multiple specialists until diagnosis is established. This results in a feeling of not being taken seriously by physicians and social environment [6]. An earlier diagnosis could possibly prevent organ damage. Therefore, it is important to shorten the delay of diagnosis to improve health-related quality of life (HRQL) and prognosis.

The etiology of SjD remains unknown: there is evidence of a genetic pre-disposition and the presence of family clusters [8, 9]. Moreover, disease-associated autoantibodies are detectable several years before the onset of disease and symptoms [10]. Also, environmental and hormonal factors are thought to be part of the disease's pathogenesis [11].

Little is known about the symptoms at the onset of SjD. It is unclear whether SjD starts with characteristic symptoms that could be differentiated from dryness of other origin (sicca syndrome). Qualitative research provides the opportunity to evaluate the onset of SjD with the existing symptoms in a holistic way including the patients' perspective and experiences [12].

Objectives

The aim of this study was to (1) investigate patients' recollection of the first symptoms at the onset of disease and before diagnosis of SjD, and (2) to verify the identified themes of the qualitative analysis in a quantitative way.

Methods

This study is divided into two parts: the qualitative interview part and the quantitative verification part. In the first part of the study, we performed interviews and asked patients about their recollection on the beginning of SjD. In the second part, we verified the results of the interviews in a larger cohort. For both study parts, patients from the rheumatology outpatient clinic of the Medical University Graz with a diagnosis of SjD according to the 2016 ACR/EULAR classification criteria were asked to participate in this study. Purposeful sampling was conducted for selecting participants who shared particular characteristics referring to sex, age, and disease duration. Oral and written informed consent was obtained and the study was approved by the institutional review board and ethical committee of the Medical University of Graz (EK 30–193 ex17/18).

First part of the study: interviews-qualitative analysis

We performed semi-structured interviews in the first part of the study, which were all conducted by the same moderator (A.L.). The moderator did not have any pre-existing relationship with the participants, and she was employed as a research fellow, respectively at the department of Rheumatology of the Medical University Graz. The moderator was well trained in qualitative research techniques. Interviews were in German language, and they were conducted in a quiet room at the rheumatology outpatient clinic of the Medical University of Graz.

A discussion guide according to the aim of the study was developed for all interviews with an opening question (patients' introduction with disease duration, beginning of the disease etc.) and five open- ended questions about the patients' experiences at the beginning and the course of the disease.

At the beginning of each interview, the moderator explained the interview process, the aim of the study and started the discussion with interview question number 1 (interview guide is attached in supplemental Table 1). Data saturation was determined as the point when sufficient information about the study aim was obtained and no further concepts were identified.

All interviews were audio-recorded and transcribed verbatim; thereby the patients' data were anonymised. The software MAXQDA (VERBI, Berlin, Germany) was used for transcription, analysis and organization of the transcribed data. We used an inductive thematic analysis method for analysis of the qualitative data [13]. First, transcripts were read and reread for an understanding of the issues. Secondly, small units of meaning were identified and given descriptive labels/codes. Third, the results were explored to see how codes can be grouped to form subthemes and fourth, these subthemes were regrouped to form overarching themes [13] – according to the aim of the study.

Second part of the study: verification of interview data – quantitative analysis

In this second part of this study, the identified themes from the qualitative analysis were grouped into a checklist with ten items and one comment section (see supplemental Fig. 1a, 1b). A group of three patients were asked

to evaluate the developed checklist according to overall clearness and understanding. After small corrections of the checklist, patients were asked to complete it before their routine clinical assessment. Only patients who did not participate in the previous qualitative interview were asked to complete the checklist.

Statistical analysis was performed using IBM SPSS statistics (Version 26, Armonk, New York: IBM Corp). Descriptive statistics were used to summarize the data and frequencies were displayed by percentages. Group differences were calculated by Chi^2 test. Two groups were built according to patients' age at the recognized beginning of sicca symptoms: younger/older than 50 years of age. We conducted the Spearmans Correlations coefficient to screen for correlations of current clinical variables and the symptoms from the checklist.

Figures were generated using GraphPad Prism (Version 9, San Diego, California, USA) and R (version 4.2.1, R Core team 2022, Vienna, Austria).

Results

In total, 134 SjD patients participated in this mixed-method study with 31 patients in the qualitative analysis and 103 patients in the quantitative part. Detailed demographic data are depicted in Table 1. There were no statistically significant differences between the two cohorts.

First part of the study: interviews-qualitative analysis

Characteristics of SjD patients who participated in the interview cohort included following information: 90.3% ($n=28$) were female, with a mean age of 58.1 ± 12.6 years and a mean disease duration of 6.9 ± 5.7 years. The average duration of each interview was 14.8 min.

The following themes emerged of how patients experienced the beginning and first symptoms of SjD [1] "Classic" SjD symptoms (fatigue, pain, dryness) [2], symptoms started after initial swelling of parotid and/or lymph nodes [3], symptoms started after hormonal changes or infections.

(1) "Classic" SjD symptoms (fatigue, pain, dryness)

Patients complained about migratory joint pain several years before diagnosis. In addition, patients described dryness of the eyes and mouth, joint pain, chronical malaise, and fatigue over months. Patients recognized the beginning of e.g., xerostomia or dry eyes in daily life.

> *I20: 'I always had a dryness feeling in my mouth. It felt like having straw in my mouth.'*
> *I4: 'It started with pain in my joints. The small joints, hands and then the ankle. They would hurt and were swollen for time periods.'*
> *I29: 'It started with burning sensation in my mouth. The mouth burnt as if there was pepper in my mouth. The doctor did not take this seriously. I insisted on carrying out a detailed blood analysis. '.*
> *I8: 'It had started with dry eyes five years ago. I had dry eyes, reddened eyes and mucus in the eyes '.*
> *I1: 'I felt my eyes. Especially a gritty eye sensation in the afternoon.'*

Additionally, we found a sub-group of patients that reported a slow progression of symptoms with no initial recognition of sicca discomfort. Within these patients, recurrent dental problems and loss of teeth over the years prior to diagnosis was common. Patients did not realize that they had sicca complaints, because it started slowly over years. Compared to the domain "classic symptoms", patients did not realize that symptoms are due to dryness. Patients reported that they thought these complaints are normal when getting older. They did not pay attention to the slowly changing dryness.

> *I9: 'Dryness of the mouth was present for several years. I didn't notice. I just thought, that's just how it is. '.*
> *I23: 'I just realized the coated tongue, but that was just how it is. I ignored it more and more. '.*
> *I2: ,It started slowly, and I didn't think anything of it. But now, I know what's the matter. So, I thought: Oh, I have experienced these symptoms since a longer time.'*

Table 1 Demographic data of the two SjD cohorts

	Cohort - qualitative part ($n=31$)	Cohort - quantitative part ($n=103$)	*p*-value
Age, years (mean ± SD)	58.1 ± 12.6	59.9 ± 13.7	$p>0.05$
Sex (female, n (%))	28 (90.3)	97 (94.2)	$p>0.05$
Disease duration, years (mean ± SD)	6.9 ± 5.7	6.3 ± 5.3	$p>0.05$
ESSDAI (median [min, max])	4 [0–14]	4 [0–15]	$p>0.05$
ESSPRI (median [min, max])	4.0 [0.3-9]	4.3 [0.3–9.7]	$p>0.05$
PSS-QoL (median [min, max])	28 [6–69]	33 [6–72]	$p>0.05$
Sicca-duration before diagnosis, years (mean ± SD)	12.4 ± 7.8	11.6 ± 6.7	$p>0.05$

SD = standard deviation, ESSDAI = EULAR Sjögren Syndrome disease activity index, ESSPRI = EULAR sjögren syndrome patient reported index, PSS-QoL = primary Sjögren Syndrome quality of life questionnaire.

(2) Symptoms started after initial swelling of parotid and/or lymph nodes

PSS patients also reported that sicca symptoms like dryness, pain and fatigue, started after initial swelling of parotid and/or lymph nodes.

Patients expressed these experiences as following:

I28: 'Sjögren's Syndrome symptoms started, when I had an inflammation of the parotid. After that inflammation, I was diagnosed. '.
I6: ,It was always when the lymph node was swollen. Then, I always experienced that extreme fatigue.'

(3) Symptoms started after hormonal changes or infections

Patients reported initial PSS symptoms after hormonal changes, like after giving birth, during pregnancy or after gynaecological surgery.

I31: ,I feel the disease and symptoms started after surgery of the uterus and ovaries. '.
I18: 'During pregnancy I got a swollen wrist. But this never happened again.'

Other patients experienced a PSS symptom start after an infection with or without antibiotic therapy.

I9: 'I had Bronchitis and had to take an antibiotic. A few weeks later, joint pain started.

We observed that the major themes had an overlap among each other - no theme or symptom stood on its own. For example, one female patient reported that after giving birth to her second child, she experienced an initial swelling of the parotid, with further recognition of dryness of the mouth. The characteristic sicca symptoms occurred in all SjD patients independent of the presence of hormonal or glandular features.

One patient reported this overlap after a tick bite:

I24:'I actually didn't recognize it. After a tick bite, borreliosis was diagnosed and I had to take an antibiotic. A few months later, I had the feeling that I couldn't go out of bed anymore. Everything, the whole body hurts and then I realized that oral and vaginal dryness. I felt that the whole body is dry.'

Changes of symptoms over time

Patients reported changes of symptoms, specially worsening of dryness over time.

I14: 'Dryness got worse in the last years - that changed. I also recognized that I am exhausted very easily. When I had a tough week at work, I recognize earlier that the power is gone. Then I need a day off (…) then I need to do nothing. I am really exhausted.'

Besides, patients felt that of all the symptoms dryness was the worst and impaired their daily life. Moreover, when they had a feeling of stress, the symptoms worsened.

I24: 'Dryness is really bad. Especially at night. I can use chewing gum or candies by day. But at night, when I wake up, I have a feeling that I cannot breathe. The tongue sticks to the roof of the mouth and that's really bad.'
I1: ,For me it is the mouth, it always burns in the mouth. As if I have burnt my tongue. Because it is so dry. That's the feeling that I have now. '.
I15: '…only when there are stressful situations, then I need a third pill [pilocarpine].'
I1: 'Stress is really bad. Yes, stress is really bad.'

In a further step, we developed a checklist with the identified main themes. This checklist should help to verify the data from the qualitative interview part.

Second part of the study: verification of interview data – quantitative analysis

The major themes from the qualitative part were verified in this second part of the study, where 103 patients completed the developed checklist (supplemental Fig. 1a, 1b). The frequencies of patients' answers are depicted in Fig. 1. Patients were 59.9 (±13.7) years old and six (5.8%) patients were male. The time between first symptoms and diagnosis was 11.6 (±6.7) years (Table 1).

As shown in Fig. 2, the main symptom before diagnosis was dryness (n=77, 74.8%) with migratory joint-pain (n=51, 49.5%) and fatigue (n=47, 45.6%). 38.8% (n=40) of patients reported a swelling/inflammation of the parotid before the disease and after symptoms started. A slow progression of dryness symptoms occurred in 49.5%

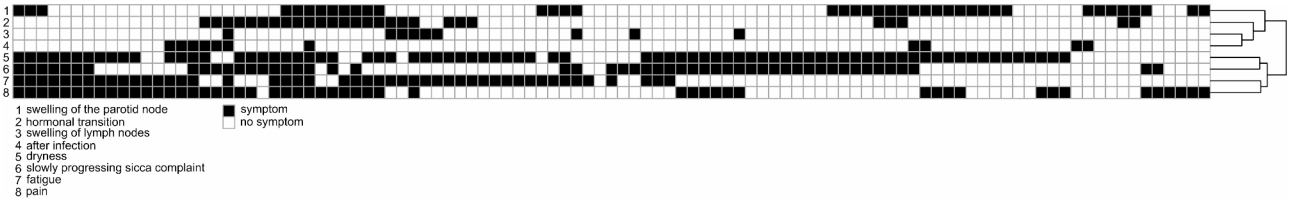

Fig. 1 Frequencies of symptoms. Appearance or absence of symptoms depicted for each patient (column)

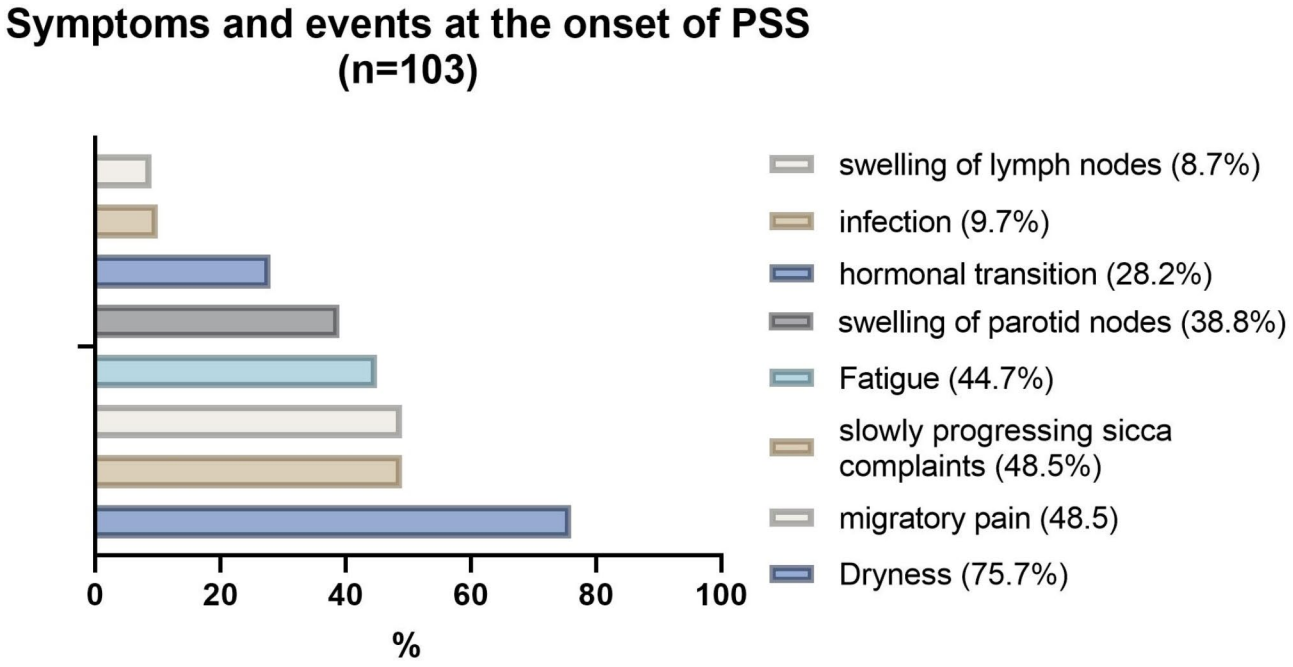

Fig. 2 Symptoms and events at the onset of the disease. The frequencies of the symptoms and events are displayed according to the completed checklists

before diagnosis. In about 30% of the patients, symptoms started after a hormonal change like gynecological surgery, menopause or pregnancy. No additional symptoms or events were added by the patients at the comment section of the checklist.

The identified symptoms were not associated with each other (Phi – coefficient < 0.1).

Furthermore, patients' symptoms at the beginning of the disease were categorized into two groups: patients with a sicca symptom start before and after the age of 50 years (Fig. 3): Patients older than 50 years of age at symptom start reported significantly more often ($p < 0.05$) a "slow progression of dryness symptoms". Whereas significantly more patients younger than 50 years of age reported about first symptoms after a "hormonal transition" ($p < 0.05$) (e.g. after giving birth or surgery). A correlation analysis of identified symptoms and the current ESSPRI and ESSDAI did not reveal any significant results. For further analysis, we combined all classic symptoms from the checklist (dryness, pain and fatigue) into one variable (at least one symptom must be present). In a correlation analysis with current clinical variables, the variable ‚classic symptoms' showed a weak correlation with age ($corr_{coeff}$=0.245, $p < 0.05$), ESSPRI ($corr_{coeff}$=0.298, $p < 0.05$) and quality of life ($corr_{coeff}$=0.314, $p < 0.05$)(PSS-QoL questionnaire).

Discussion

In our mixed methods study, we were able to identify major themes about the onset of SjD, categorized in: [1] initial swelling of parotid gland and/or lymph nodes [2], "classic" SjD symptoms (fatigue, pain and dryness) and [3] hormonal changes or infections.

We validated and quantified the qualitative interview results by asking a cohort of 103 patients about these major themes at disease onset with a symptom checklist. This checklist has the potential to be further developed into a tool that could increase awareness of the disease, thereby shortening the diagnosis process. An earlier diagnosis can improve patients' outcomes with better health-related quality of life, reducing the economic burden. This checklist could be used as a diagnostic screening tool by general practitioners and lead to faster referral of patients to a rheumatological specialist.

Most SjD patients reported a slow progression of dryness symptoms. Patients could not imagine that dryness symptoms or fatigue could be symptoms of a disease. Young patients thought they were tired because of their small children. They were surprised when the kids were older but their fatigue was just the same or even worse. Older patients thought that dryness was part of the menopause or caused by stress. In total, the slow progression of dryness symptoms seems to be a major obstacle for early diagnosis of SjD. However, we do not know if the first subtle sicca would be detectable by objective measures of salivary and lacrimal flow [14, 15]; nor if a lip salivary gland biopsy at this early time point would

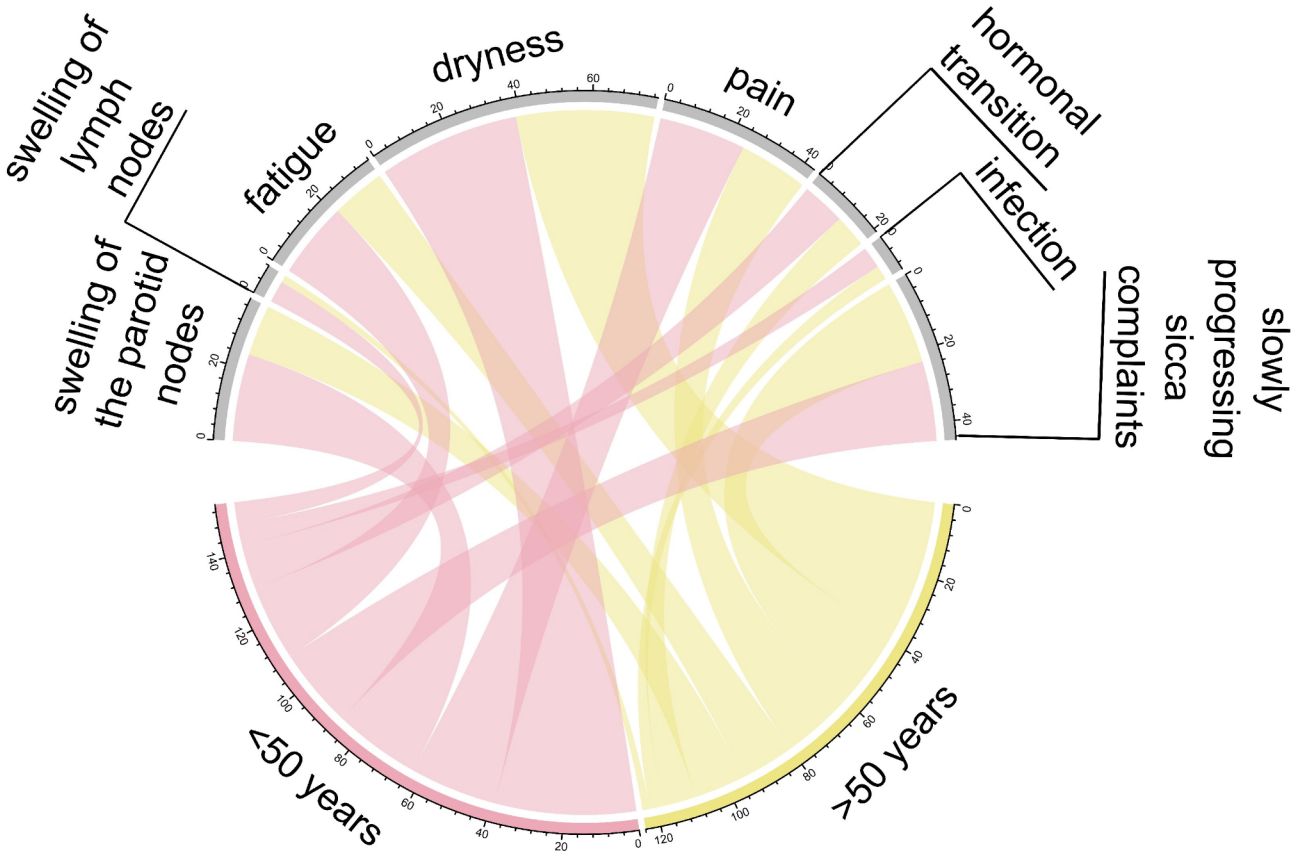

Fig. 3 Distribution of symptoms at the onset of primary Sjögren Disease between age groups (onset before (red) or after (yellow) years of age). Patients were split to groups of patients more/less than 50 years of age. Younger patients experienced the first symptoms more often after a hormonal change. Patients with a disease onset after 50 years of age experienced a slowly, often unrecognized start of sicca complaints

already show hallmarks of SjD. Therefore, diagnosis of early SjD might still be difficult even if patients and doctors are aware of sicca as a potential symptom of SjD.

The correlation analysis with a selection of current clinical parameters showed that if classic symptoms are present at the onset of the disease, patients have a higher impairment of quality of life and distressing symptoms in the further course of the disease.

It is known that certain autoantibodies (anti-nuclear antibodies, anti-Ro52/SSA, anti-RO60/SSA, anti-LA/SSB, rheumatoid factor) also occur pre-symptomatically. The literature assumes that these are already present 4–6 years before the onset of the disease [16]. Patients with positive auto-antibodies have a higher risk for high disease activity with severe disease manifestations (e.g. interstitial lung disease or lymphoma). It is therefore very important to diagnose the disease as early as possible [17, 18].

Swelling/inflammation of the parotid gland was present in 38.8% of our patients at the onset of SjD. De Vita et al. reported that SjD patients developing lymphoma experienced swelling of the parotid gland already before diagnosis. They found that the risk for the development of a lymphoma increased depending on the duration of gland swelling (2–12 months or ≥12 months) [19]. Immune activation typical for SjD might be present or even precede the first symptoms at the onset of disease. Auto-antibodies against Ro and La proteins develop years before the first symptoms of SjD [20, 21] suggesting the induction of autoantibody-producing B cells by autoreactive T cells long before the first clinical manifestation of the disease [22, 23]. In line with these findings, signs of extensive replicative history of CD4+T-cells were reported even in young patients with SjD [24]. These data suggest that immune activation might precede the first symptoms of SjD and anti-Ro antibodies could be helpful for early diagnosis.

An older age at diagnosis was associated with a higher extent of mouth dryness compared to younger SjD patients [25]. In contrast, early-onset PSS patients have a higher frequency of salivary gland enlargement with immunological activity and a higher lymphoma risk [25]. These observations are in line with our results. Additionally, we found that patients older than 50 years, experienced a slow and initially unrecognized start of sicca symptoms more often.

In roughly one third of our patients, symptoms started after hormonal transitions, such as giving birth, menopause, or undergoing ovariectomy. Hormonal factors are considered to contribute to the disease pathogenesis. The obvious female predominance in SjD indicates that sex hormones likely play an important role in disease development [26]. Mouse models have demonstrated the importance of sex hormones in the development of SjD. More severe autoimmune lesions in salivary and lacrimal glands after ovariectomy were observed in two different mouse models of SjD [27, 28]. Interestingly, McCoy et al. 2019 showed that women suffering from SjD had lower estrogen exposure and cumulative menstruating cycles compared to sicca only controls. The authors suggested that higher levels of estrogen could protect against the development of SjD [26].

9% of our patients reported a temporal association of symptom onset with infections. A possible link between viral infections and the development of SjD has been reported previously [25]. Viral infections like Epstein-Barr-Virus, cytomegalovirus, hepatitis C or Coxsackievirus could act as environmental triggers of SjD [29, 30]. Furthermore, a history of frequent infections and hospitalization for infection within the last month are associated with development of SjD [31].

An important limitation of our study is that the sample included only patients from one region in Austria, although patients were of different genders, age groups and professional backgrounds. The themes identified here should be validated in other countries.

Another limitation of this study is the retrospective nature of the reported symptoms. There is a potential for a recall bias while patients were interviewed about the symptoms experienced in the past. This risk was minimized by having the majority of patients describing the same symptoms. In addition, the symptoms were subsequently verified in a larger cohort using the checklist.

Diagnosis of SjD is based on a set of features (clinical, laboratory, imaging and pathology) [32]. The developed checklist provides an overview about the symptoms that patients recognized at the beginning of the disease. The time between first symptoms and diagnosis could be possibly shortened using this checklist. The awareness of the disease in general and the possible symptoms at the beginning of the disease have a high importance and should also be in mind of general practitioners. Awareness campaigns about the symptoms at the disease start are highly recommended to gain more visibility of the disease. An earlier diagnosis could improve patients' disease outcomes and improve their health-related quality of life.

In future projects, the checklist could be evaluated and adapted for use in clinical practice. Multi-centre studies in different countries would enable international applicability and improve the quality of psychometric evaluation. A suitable cohort for use in this context would be the preSStige study, where patients with positive antibodies are regularly examined until SjD is diagnosed [33, 34]. Subsequently, the checklist could support earlier diagnosis and thus improve patient outcomes.

Conclusions

In summary, we identified important themes in the patients' perspective at the onset of SjD. Our results show that some symptoms like sicca, parotitis or migratory pain emerged in a sneaky and can be the first evidence for the development or presence of SjD. More awareness of these symptoms could allow an earlier diagnosis. Further studies should evaluate a possible screening checklist to shorten the time to diagnosis and improve patients' quality of life.

Supplementary Information

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Supplementary Material 1

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Author contributions
A.L. and M.S. have made substantial contributions to the conception and design of the work; and the acquisition, analysis, and interpretation of data; and have drafted and revised the work.B.D. , J.F., J.H., S.Z. and J.T. have made substantial substantial contributions to analysis and interpretation of data and substantively revised the work. All authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study) and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate
Oral and written informed consent was obtained and the study was approved by the institutional review board and ethical committee of the Medical University of Graz (EK 30–193 ex17/18).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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