Factors associated with delayed diagnosis of Sjögren's syndrome among members of the Japanese Sjögren's Association for Patients

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ABSTRACT

Objective. *The heterogeneous nature of the signs and symptoms of Sjögren's syndrome (SS) often causes delays in diagnosis. The reasons for these delays have not been investigated in Japan and need to be determined.*

Methods. *We conducted a questionnaire survey of members of the Japanese Sjögren's Association for Patients (JSAP). Questionnaire items were demographic (sex, age at diagnosis and current age) and factors associated with delayed diagnosis (age at first visit to hospital or clinic, medical department first attended, and initial symptoms). Patients were classified into those diagnosed in <1 year and those diagnosed in ≥1 year.*

Results. *Of the 510 patients questioned, 276 returned the questionnaire, and 255 questionnaires were assessed. The average time to diagnosis was 3.47 years. After adjustment, risk factors for delayed diagnosis were initial visit to an internal medicine department [adjusted odds ratio (aOR) 3.13, 95% confidence interval (CI) 1.42–6.92] or ophthalmology department (aOR, 2.63, 95% CI 1.07–6.50), younger age at initial visit to hospital or clinic (aOR, 0.96, 95% CI 0.94–0.99), and having symptoms of only dry eye (aOR, 2.69, 95% CI 1.09–6.64). Diagnosis was faster when patients had a dry mouth (aOR, 0.55, 95% CI 0.30–1.00) or cutaneous symptoms (aOR, 0.29, 95% CI 0.11–0.82).*

Conclusion. *Risk factors for delayed SS diagnosis were younger age, initial visit to internal medicine or ophthalmology department, and having only dry eye. We need to raise awareness of SS among doctors and the general public to improve early diagnosis and therapeutic potential.*

Introduction

The heterogeneous nature of the signs and symptoms of Sjögren's syndrome (SS) often causes a delay in diagnosis (1, 2). SS is a chronic systemic autoimmune inflammatory disease that is best characterized by lymphocytic infiltration of the exocrine glands and epithelia, resulting in the classic sicca symptoms of dry eye and dry mouth. Along with symptoms of extensive dryness, other serious complications include profound fatigue, chronic pain, major organ involvement, neuropathies, and lymphomas (3, 4). This heterogeneity makes early diagnosis difficult.

Early diagnosis and proper treatment are important, as they can prevent serious complications and greatly improve the patient's quality of life (5, 6). For the patient, the length of time for which the disease goes undiagnosed is the length of time for which the patient continues to tolerate the symptoms. In other words, patients must continue to tolerate their symptoms in the period between their initial visit to a hospital or clinic and their eventual diagnosis. Knowing the cause of the symptoms and being able to receive an early diagnosis can help reduce the patient's anxiety, even without active treatment. However, SS has a high chance of being overlooked or misdiagnosed (7, 8). The Sjögren's Foundation, which is a US patient association, tried to shorten the time to diagnosis of SS by 50% in 5 years; they managed to reduce the time from 4.7 years in 2012 to 3 years by the end of 2016 (8). However, delay in diagnosis continues to remain a serious issue for SS patients and results in the prolongation of patients' distress.

Delay in diagnosis in Japan may also be influenced by the atypical medical system in this country. In many Organi-

Table I. Patient demographics stratified by diagnosis of Sjögren's syndrome <1 year or ≥1 year.

			Time to diagnosis		
		Total n=255 (%)	<1 year n=118 (46.3%)	≥1 year n=137 (53.7%)	*p*
Sex	Male	8 (3.1)	3 (2.5)	5 (3.7)	0.728*
	Female	247 (96.9)	115 (97.5)	132 (96.4)	
Disease	Primary SS	206 (80.8)	101 (85.6)	105 (76.6)	0.070
	Associated SS	49 (19.2)	17 (14.4)	32 (23.4)	
Mean age at initial visit to hospital/clinic		50.5 ± 14.0	54.4 ± 11.6	47.2 ± 15.0	**0.004**
Age at initial visit to hospital/clinic	10–19	6 (2.4)	0 (0.0)	6 (4.4)	**0.002**
	20–29	17 (6.7)	1 (0.9)	16 (11.7)	
	30–39	27 (10.6)	12 (10.2)	15 (11.0)	
	40–49	54 (21.2)	26 (22.0)	28 (20.4)	
	50–59	85 (33.3)	40 (33.9)	45 (32.9)	
	60–69	46 (18.0)	26 (22.0)	20 (14.6)	
	70–79	20 (7.8)	13 (0.0)	7 5.1)	
Mean age at diagnosis		54.0 ± 12.2	54.4 ± 11.6	53.6 ± 12.6	0.347
Age when diagnosed	20–29	4 (1.6)	1 (0.9)	3 (2.2)	0.658
	30–39	31 (12.2)	12 (10.2)	19 (13.9)	
	40–49	49 (19.2)	26 (22.0)	23 (16.8)	
	50–59	85 (33.3)	40 (33.9)	45 (32.9)	
	60–69	57 (22.4)	26 (22.0)	31 (22.6)	
	70–79	27 (10.6)	13 (11.0)	14 (10.2)	
	80–89	2 (0.8)	0 (0.0)	2 (1.5)	
Mean present age		65.3 ± 11.7	65.2 ± 11.5	65.4 ± 11.9	0.741
Current age	30–39	6 (2.4)	1 (0.9)	5 (3.7)	0.538
	40–49	20 (7.8)	10 (8.5)	10 (7.3)	
	50–59	45 (17.7)	23 (19.5)	22 (16.1)	
	60–69	82 (32.2)	38 (32.2)	44 (32.1)	
	70–79	79 (31.0)	33 (28.0)	46 (33.6)	
	80–89	23 (9.0)	13 (11.0)	10 (7.3)	
Initial department visited	Rheumatology	50 (19.6)	30 (25.4)	20 (14.6)	**0.027**
	Internal medicine	72 (28.2)	23 (19.5)	49 (35.8)	
	Gynaecology	6 (2.4)	3 (2.5)	3 (2.2)	
	Ophthalmology	39 (15.3)	14 (11.9)	25 (18.3)	
	Dentistry	11 (4.3)	5 (4.2)	6 (4.4)	
	Dermatology	18 (7.1)	12 (10.2)	6 (4.4)	
	Otolaryngology	26 (10.2)	16 (13.6)	10 (7.3)	
	Orthopaedics	18 (7.1)	8 (6.8)	10 (7.3)	
	Other	15 (5.9)	7 (5.9)	8 (5.8)	
Symptoms at initial visit	Dry eye	106 (41.6)	48 (40.7)	58 (42.3)	0.789
	Dry mouth	114 (44.7)	63 (53.4)	51 (37.2)	**0.010**
	Arthralgia	47 (18.4)	19 (16.1)	28 (20.4)	0.373
	Cutaneous symptoms	22 (8.6)	14 (11.9)	8 (5.8)	0.117*
	Parotid swelling	28 (11.0)	11 (9.3)	17 (12.4)	0.432
	Headache	12 (4.7)	3 (2.5)	9 (6.6)	0.150*
	Body pain	24 (9.4)	10 (8.5)	14 (10.2)	0.634
	Limb paraesthesia	14 (5.5)	5 (4.2)	9 (6.6)	0.583*
	Fatigue	51 (20.0)	23 (19.5)	28 (20.4)	0.851
	Slight fever	28 (11.0)	8 (6.8)	20 (14.6)	0.069*
	Low mood	14 (5.5)	5 (4.2)	9 (6.6)	0.583*

p-values: chi-square test; *Fisher's exact test.

sation for Economic Co-operation and Development (OECD) countries, patients must see a general practitioner, who provides primary care, to obtain a referral to see a specialist (9). Primary care physicians have stated that mild disease and slowly progressive disease are barriers to referral, even in the case of rheumatoid arthritis (RA) (10, 11). In contrast, in Japan, patients are free to consult any provider, primary care physician or specialist, at any time without proof of medical necessity and with full insurance coverage. Japanese patients can choose their own doctors at hospital or clinic department for consultation, so the route from the initial department to referral to a specialist varies. In one Indian study, primary SS patients consulted 24 different types of specialist at their first vis-

its, and many of them visited multiple hospitals before the final diagnosis of primary SS was reached. However, in 64.84% of cases, it was a rheumatologist who initially suspected the disease (12). Therefore, due to Japan's medical system, any type of specialist, not just rheumatologists, might provide the initial consultation, so the effect of the department on potential delay in diagnosing SS must be clarified.

Here, we investigated pre-diagnosis situations such as age, symptoms, and hospital or clinic department initially visited to identify risk factors for delayed diagnosis. SS patients in the Japanese Sjögren's Association for Patients (JSAP) usually discuss in their private meetings when and which symptoms occurred or how long they waited for a diagnosis of SS. We therefore decided to survey them regarding their recall of these events. We thought that this might be the only way to find out what had happened before the diagnosis, although recall bias is a concern when tracing a patient's memory. Accordingly, our aim was to identify the risk factors associated with delayed diagnosis of SS from the patient's perspective.

Methods

Study design

In November 2019, questionnaires were sent to 510 SS patients in the JSAP. The JSAP was established in 1986 to enhance medical understanding of SS patients, collect and provide appropriate information to improve quality of life, identify potential patients, and help patients to receive appropriate diagnosis and treatment. The informed consents were obtained from the participating patients in this study.

In the questionnaire, we asked patients their age at the time of their initial visit to a hospital or clinic; age when SS was diagnosed; current age; initial department visited [rheumatology, internal medicine (general medicine apart from rheumatology), gynaecology, ophthalmology, dentistry, dermatology, otolaryngology, orthopaedics, or other department]; and symptoms at first visit (dry eye, dry mouth, arthralgia, cutaneous symptoms, parotid swelling, headache, body pain, limb paraesthesia, fatigue, slight fever, low mood). Also, we asked about current dryness symptoms, such as dry eye and dry mouth. In addition, patients were classified as having primary SS or associated SS (13, 14). Owing to the patient-reporting nature of the questionnaire, it was not possible to confirm that the diagnostic criteria for SS were met; nor was it possible to guarantee that the primary and associated SS classifications were met. However, we used the following classification. Patients initially diagnosed with only SS or with SS with Hashimoto's disease were classified as having primary SS (4, 15). Those initially diagnosed with RA, scleroderma or systemic lupus erythematosus and subsequently diagnosed with SS were classified as having associated SS. We also classified dryness symptoms at the initial visit and at present as follows: having both dry eye and dry mouth, only dry eye, only dry mouth, or no dry eye and no dry mouth.

For analysis, the patients were allocated to two groups: those whose time from first visit to a hospital or clinic to diagnosis was less than 1 year (<1 year) and those whose time to diagnosis was at least 1 year (≥1 year), with 1 year being the median.

Statistical analyses

The chi-squared test and Fisher's exact test were used to determine the associations between time to diagnosis of SS (<1 year or ≥1 year) and patient characteristics, initial department visited, initial symptoms, and dryness symptoms. We then conducted a multiple logistic regression analysis of the time to diagnosis in the <1 year and ≥1 year groups and the initial department visited, initial symptoms, and dryness symptoms at the initial visit to the hospital or clinic. Significance was set at $p<0.05$. All analyses were performed with Stata 15 software (Stata Corp LP, College Station, TX, USA).

Ethical consideration

This study was approved by the Kochi Medical School ethics committee (ERB-105381). All procedures were performed according to the declaration of Helsinki in this study.

Table II. Association between time to Sjögren's syndrome diagnosis ≥1 year and initial department visited.

	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Initial department visited				
Rheumatology	reference		reference	
Internal medicine	**3.20 (1.51–6.78)**	**0.002**	**3.13 (1.42–6.92)**	**0.005**
Gynaecology	1.50 (0.27–8.19)	0.640	1.16 (0.20–6.77)	0.869
Ophthalmology	**2.68 (1.13–6.36)**	**0.026**	**2.63 (1.07–6.50)**	**0.036**
Dentistry	1.80 (0.48–6.70)	0.381	2.28 (0.58–8.94)	0.235
Dermatology	0.75 (0.24–2.33)	0.618	0.55 (0.17–1.86)	0.340
Otolaryngology	0.94 (0.35–2.48)	0.896	0.93 (0.33–2.63)	0.898
Orthopaedics	1.88 (0.63–5.57)	0.258	1.44 (0.45–4.58)	0.538
Other	1.71 (0.54–5.48)	0.363	1.82 (0.54–6.10)	0.332

OR: odds ratio adjusted for sex, age at time of initial visit to hospital or clinic, and disease (primary or associated SS).

Results

Of the 510 members of the JSAP, 276 returned the questionnaire, giving a response rate of 54.1%. We excluded 21 respondents for whom data were missing, resulting in a final sample size of 255. Of these 255 patients, 96.9% (n=247) were women and 80.8% (n=206) had primary SS. The average delay in the diagnosis of SS, as calculated from the difference between the age at initial visit and the age at the time of diagnosis, was 3.47 years.

Of the 255 patients, 118 had been diagnosed with SS in <1 year and 137 were diagnosed after ≥1 year (Table I). Age of initial visit to the hospital or clinic was significantly younger for patients diagnosed in ≥1 year than for those diagnosed in <1 year (p=0.004). Of 23 patients who initially visited a

hospital or clinic aged between 10 and 29 years, only one was included among the patients diagnosed in <1 year; the remaining 22 patients were diagnosed in ≥1 year. In addition, significant differences between the two groups were found for initial department visited (p=0.027; significantly more patients diagnosed in <1 year than in ≥1 year had first visited a rheumatology department) and for symptoms at the initial visit (p=0.010; significantly more patients diagnosed in <1 year than in ≥1 year had presented with dry mouth). In contrast, there were no significant differences between the two groups in terms of sex, primary or associated SS, and current age or age at diagnosis.

We used a multiple logistic regression to examine the initial department visited and symptoms as risk factors for a delayed diagnosis of SS (*i.e.* ≥1 year). Initial department visits that constituted risk factors compared with visits to the rheumatology department were to internal medicine [adjusted odds ratio (aOR) 3.13, 95% confidence interval (CI) 1.42–6.92] and ophthalmology (aOR 2.63, 95% CI 1.07–6.50) after adjustment for sex, age at initial visit to hospital or clinic, and disease (primary SS or associated SS) (Table II).

In patients diagnosed after ≥1 year, the aOR values for those with symptoms at the first visit of dry mouth (aOR, 0.55, 95% CI 0.30–1.00) or cutaneous symptoms (aOR, 0.29, 95% CI 0.11–0.82) were low after adjustment for sex, age at initial visit to hospital or clinic, disease (primary SS or associated SS) and all symptoms (Table III). Thus, patients with symptoms of dry mouth or with cutaneous symptoms were more likely to be diagnosed earlier than those with other symptoms.

Dryness symptoms were classified into four categories as noted above (Table IV). Patients diagnosed at <1 year were significantly more likely than those diagnosed at ≥1 year to have both dry eye and dry mouth at the time of the initial visit (p=0.018). In this analysis, 26.7% of all patients had both dry eye and dry mouth and 40.4% had neither. In contrast to the results at the initial visit, our analysis of present symptoms revealed no difference between the two groups in terms of dryness symptoms. In this analysis, 86.7% of all patients had both dry eye and dry mouth and only 2% had neither. The incidence of dryness symptoms therefore increased over time.

Last, we used a multiple logistic regression to examine sex, age at initial visit, disease (primary SS or associated SS) and symptoms as risk factors for a delayed diagnosis of SS (Table V). Risk factors for a delayed diagnosis SS

Table III. Association between time to Sjögren's syndrome diagnosis ≥1 year and symptoms at initial visit.

	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Symptoms at initial visit				
dry eye	1.07 (0.65–1.76)	0.789	1.44 (0.80–2.57)	0.222
dry mouth	**0.52 (0.31–0.85)**	**0.010**	**0.55 (0.30–1.00)**	**0.049**
arthralgia	1.34 (0.70–2.55)	0.374	0.72 (0.32–1.62)	0.429
cutaneous symptoms	0.46 (0.19–1.14)	0.094	**0.29 (0.11–0.82)**	**0.019**
parotid swelling	1.38 (0.62–3.07)	0.433	0.98 (0.41–2.34)	0.968
headache	2.70 (0.71–10.20)	0.144	2.87 (0.67–12.36)	0.157
body pain	1.23 (0.52–2.88)	0.635	0.85 (0.28–2.57)	0.770
limb paraesthesia	1.59 (0.52–4.88)	0.419	1.64 (0.47–5.75)	0.439
fatigue	1.06 (0.57–1.97)	0.851	0.76 (0.35–1.67)	0.497
slight fever	2.35 (0.99–5.56)	0.052	2.45 (0.90–6.68)	0.081
low mood	1.59 (0.52–4.88)	0.419	2.90 (0.81–10.40)	0.101

OR: odds ratio adjusted for sex, age at time of initial visit to hospital or clinic, disease (primary or associated SS) and all symptoms.

Table IV. Dryness symptoms stratified by time to Sjögren's syndrome diagnosis <1 year and ≥1 year.

	Total n=255(%)	Time to diagnosis **<1 year** n=118 (46.3%)	Time to diagnosis **≥1 year** n=137 (53.7%)	p
Dryness symptoms at initial visit				
dry eye and dry mouth	68 (26.7)	38 (32.2)	30 (21.9)	**0.018**
only dry eye	38 (14.9)	10 (8.5)	28 (20.4)	
only dry mouth	46 (18.0)	25 (21.2)	21 (15.3)	
no dry eye and no dry mouth	103 (40.4)	45 (38.1)	58 (42.3)	
Present dryness symptoms				
dry eye and dry mouth	221 (86.7)	97 (82.2)	124 (90.5)	0.209
only dry eye	8 (3.1)	6 (5.1)	2 (1.5)	
only dry mouth	21 (8.2)	12 (10.2)	9 (6.6)	
no dry eye and no dry mouth	5 (2.0)	3 (2.5)	2 (1.5)	

p-value: chi-squared test.

Table V. Multiple logistic regression of the time to Sjögren's syndrome diagnosis ≥1 year and dryness symptoms.

	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Sex	0.69 (0.16–2.94)	0.615	0.49 (0.11–2.21)	0.355
Age at initial visit to hospital/clinic	**0.96 (0.94–0.98)**	**0.000**	**0.96 (0.94–0.99)**	**0.001**
Disease (primary SS/associated SS)	0.55 (0.29–1.06)	0.073	0.66 (0.33–1.32)	0.242
Dryness symptoms at initial visit				
dry eye and dry mouth	reference		reference	
only dry eye	**3.55 (1.49–8.43)**	**0.004**	**2.69 (1.09–6.64)**	**0.032**
only dry mouth	1.06 (0.50–2.26)	0.872	1.06 (0.49–2.28)	0.890
no dry eye and no dry mouth	1.63 (0.88–3.03)	0.119	1.12 (0.57–2.18)	0.744

OR: odds ratio adjusted for sex, age at time of initial visit to hospital or clinic and disease (primary SS or associated SS).

(≥1 year) were younger age at initial visit to the hospital or clinic (aOR 0.96, 95%CI 0.94–0.99) and having only dry eye (aOR 2.69, 95% CI 1.09–6.64), after adjustment for sex, age at initial visit to hospital or clinic and disease (primary SS or associated SS). These results suggest that the diagnosis of SS is likely to be delayed in younger patients and in patients with only dry eye symptoms.

Discussion

We found here that the risk factors for delayed diagnosis of SS were associated with age at initial visit, initial department visited, and initial symptoms. Younger age at first visit to the hospital or clinic was a risk factor for delayed diagnosis. When a patient's first visit was to the department of internal medicine or ophthalmology, diagnosis of SS was delayed compared with the rheumatology department. Also, when patients had an initial symptom of dry eye only, the diagnosis of SS was delayed. In contrast, when patients had initial symptoms of dry mouth or cutaneous symptoms, the time to diagnosis was shorter. The average period of time from the initial visit until diagnosis of SS was 3.47 years. We need to make an effort to shorten this time.

Younger age at first visit to the hospital or clinic was a risk factor for delayed diagnosis SS. Almost all patients whose initial visits were between the ages of 10 and 29 years had a delayed diagnosis of SS. Given that SS is traditionally diagnosed in middle age or at menopause because dryness is often more pronounced, physicians are trained to look for SS in patients suffering from dryness within those age groups. SS is unlikely to be suspected in patients in their teens or 20s. Moreover, some physicians may not be aware of paediatric SS as an entity. Our study showed that patients without dryness at their initial visit developed both dry eye and dry mouth over time; dryness symptoms therefore seem to appear as the disease progresses. Young people who develop the disease early and have not yet developed dry symptoms may thus be more likely to suffer a delay in diagnosis. This indicates that, if patients are examined from the perspective that SS is characterised by dryness of the eyes and mouth, patients in the early stages of the disease may be missed. If we are to treat SS at an earlier stage in the future, it would be optimal to make a diagnosis before the onset of dryness symptoms. In the past era, RA was diagnosed after the joints had been destroyed; in this regard, the dryness symptoms of SS can be considered to parallel those of destroyed joints. Just as RA can now be treated before joint destruction occurs, so it may become possible to treat SS before dryness symptoms appear.

One of the risk factors for a delay in diagnosis of SS was an initial visit to the internal medicine department rather than the rheumatology department. This finding is similar to that in the delay in diagnosis of RA resulting from delayed referral by primary care physicians to a rheumatologist; such delays in the diagnosis of autoimmune disease have been investigated extensively in the case of RA (16-18). The treatment of RA is now well established, and it is recommended that drugs be administered in the early stages after disease onset (19, 20). The median delays from the onset of RA symptoms to patients being assessed by a specialist rheumatologist range from 23 to 36 weeks in European countries (16-19). Also, the interval from RA symptom onset to rheumatology assessment is 6 months, with the percentage of patients seen within 12 weeks of symptom onset ranging from 8% to 42% (17, 19-21). In Japan, the Ministry of Health, Labour and Welfare encourages general internists to be the first point of contact as primary care physicians. Many patients therefore visit a general internal medicine department before visiting a specialist directly. In this regard, the delay in diagnosis of SS has the same problem in terms of primary care physicians as has been found in many RA studies. In a qualitative study in the United States, primary care physicians stated that mild disease and slowly progressive disease were barriers to referral (10, 11). This may explain the delay in referral by primary care physicians.

Others factors increasing the risk of delayed diagnosis of SS were initial visit to an ophthalmology department and having only dry eye symptoms. Interestingly, although the absence of any dryness symptoms tends to think to delay diagnosis, having only dry eye gave a more delayed diagnosis of SS than did having neither dry mouth nor dry eye. Diagnosis of SS may be delayed because treatment may be given solely for the dry eye, rather than determining and treating the cause of the dry eye. In the current literature on SS-associated dry eye, although there are few rigorous clinical trials to support therapeutic recommendations, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies (22). The treatment methods for normal dry eye and Sjögren's dry eye are the same. In a recent survey of ophthalmologists in the United States, although the survey return rate was low, they were found to refer fewer than 5% of their dry eye patients for SS workups, and 18% of ophthalmologists never referred any patients for this purpose (23). If the patient fails to report other systemic symptoms to the ophthalmologist, then there may be little chance for the ophthalmologist to suspect SS. Akpek *et al*. (24) say that, to prevent delays in diagnosis, there is an urgent need to develop evidence-based screening algorithms for determining which patients with dry eye should be assessed for underlying SS. Dry eye is one of the major symptoms of SS. We hope that ophthalmologists will consider the possibility of SS in all dry-eye patients and ask whether the patients have other systemic symptoms such as fatigue or chronic pain.

We found that factors accelerating the diagnosis of SS were dry mouth and cutaneous symptoms. Xerostomia and hyposalivation are symptoms and signs in most patients with SS (25). Dry mouth is a major symptom, and it is easy to suspect SS when this oral condition is observed. Also, skin symptoms can easily be observed. Recent studies have identified several distinct cutaneous manifestations related to SS, namely cutaneous vasculitis, annular erythema, subacute cutaneous lupus

erythematosus and localised cutaneous nodular amyloidosis (26). Thus, the diagnosis of SS is likely faster when the symptoms are visible.

To accelerate the diagnosis of SS, understanding of SS by the general public and by the patients themselves is essential. Many people do not know about SS; even when they do know of it, they think it is a mild disease consisting only of dry eye and dry mouth. Similarly, many people have little knowledge of RA before diagnosis, believing it to be a mild condition that affects older people (11, 27). It is important to inform the public that SS is a systemic disease and that its symptoms vary. If patients themselves know more about this disease, they will be able to convey appropriate information to doctors, thus leading to early consultation with specialists. Villeneuve *et al*. (5) identified strategies to reduce the delay in RA diagnosis; they said that public awareness and education were integral parts of early referral. Raising SS awareness and educating patients and the general public about SS is very important. We believe that improved awareness among the general public will promote the constant updating of physicians' knowledge of SS. In addition, it is also important to educate medical students about the latest knowledge of SS for future medical care.

Our study had several limitations. First, it was based on patients' reporting and might therefore have suffered from recall bias. This was the biggest limitation. However, it was essential for us to ask the patients themselves which medical service providers they had visited before their SS diagnosis, because such information was not available in the medical records. Second, the 54.1% response rate was not high, and it is possible that this low response rate affected the results. Third, because this was a questionnaire, it was difficult to clarify which diagnostic criteria had been used for each patient and whether the diagnostic criteria had been met. Especially in patients without dry eye or dry mouth, it is not clear whether the symptoms before diagnosis are those of SS and not those of other comorbidities. Fourth, our results do not necessarily reflect those of the general SS population, because we conducted this study on members of the JSAP, a population with a high percentage of primary SS. One would expect most patients with associated SS to belong to support groups for the autoimmune condition with which they were first diagnosed, such as RA and systemic lupus erythematosus. However, in light of this fact, we consider that the JSAP was an appropriate group to use in investigating delayed diagnosis of SS. Last, as mentioned above, the Japanese medical system differs from that in many other OECD countries, however, our findings could be useful in many countries.

Conclusion

We evaluated the factors associated with delayed diagnosis of SS. Such delayed diagnosis is one of the patients' unmet needs. Efforts are needed to raise awareness of SS among doctors and the general public to disseminate the early diagnostic and therapeutic potentials for SS. To relieve the patients' burden, we believe that future studies can develop strategies aimed to diagnosis the disease in its earliest stage.

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