RHEUMATOLOGY

Rheumatology 2022;61:1986–1996
doi:10.1093/rheumatology/keab560
Advance Access publication 16 August 2021

Original article

Comparison of salivary gland MRI and ultrasonography findings among patients with Sjögren's syndrome over a wide age range

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Abstract

Objectives. This retrospective study compared MRI and US findings among patients with SS over a wide age range.

Methods. Ninety patients with SS aged 8–84 years who had undergone both MRI and US examinations were divided into four groups according to age, as follows: <18 years (juvenile SS, JSS), 9 patients; 18–39 years, 12 patients; 40–69 years, 53 patients; >69 years, 16 patients. Imaging findings of parotid glands (PGs) and submandibular glands (SMGs) were compared among the four groups. Furthermore, the relationships within and between imaging findings and various clinical findings were examined.

Results. On MRI, patients with JSS commonly exhibited multiple high-intensity spots in the PGs on MR sialography and fat-suppressed T2-weighted imaging. With increasing SS group age, the frequencies and numbers of the high-intensity spots were lower. Fat areas on MRI and hyperechoic bands on US were rarely observed in the PGs and SMGs of patients with JSS, whereas they were more common in patients with adult SS. In addition, the presence of hyperechoic bands on US, the presence of fat areas on MRI, and decreased salivary flow were associated with one another.

Conclusion. Salivary gland imaging findings in patients with JSS were characterized by punctate sialectasis, whereas those findings in patients with adult SS were characterized by fatty degeneration. Distinct findings in patients with JSS and adult SS are likely to reflect differences in glandular lesion stage. MRI and US are presumably useful for evaluation of glandular lesion severity during follow-up.

Key words: Sjögren's syndrome, juvenile Sjögren's syndrome, magnetic resonance imaging, ultrasonography

CLINICAL SCIENCE

Rheumatology key messages

- Salivary gland imaging findings in patients with JSS were characterized by punctate sialectasis.
- Salivary gland imaging findings in patients with adult SS were characterized by fatty degeneration.
- These distinct findings are likely to reflect differences in glandular lesion severity.

Introduction

SS is a systemic autoimmune disease characterized by the infiltration of inflammatory cells into exocrine glands (e.g. lacrimal and salivary glands). This leads to gradual destruction of exocrine gland tissue, thereby causing xerostomia and keratoconjunctivitis sicca. SS is most common in women and is classified as primary or secondary, depending on its occurrence with other autoimmune diseases (e.g. RA, SLE, or scleroderma). Primary SS reportedly has two age peaks: after menarche (20–40 years of age) and after menopause (50–60 years of

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Submitted 15 May 2021; accepted 5 July 2021

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age) [1]. Because the pathology of SS involves chronic progression, a confirmed diagnosis of SS often requires several years of assessments. Younger age has been reported as a risk factor for delayed SS diagnosis [2]; accordingly, some patients with early adult SS may experience disease onset in childhood.

Thus far, the clinical findings and characteristics of patients aged <18 years [i.e. patients with juvenile SS (JSS)] have not been thoroughly elucidated. Because most patients exhibit secondary JSS, primary JSS is particularly rare and may be underdiagnosed [3–5]. Recurrent parotitis is regarded as a common early symptom of primary JSS [3–8]; xerostomia is observed less often in JSS than in adult SS [3, 4, 9, 10]. In an international cohort study of 300 patients with JSS, Basiaga *et al.* [5] reported that the majority of patients with JSS did not meet the 2016 ACR/EULAR classification criteria. Because there are differences in characteristics between JSS and adult SS, there is a need to establish JSS-specific criteria or SS classification criteria that consider differences in age, thus facilitating early diagnosis.

Labial gland biopsy is a heavily weighted item in the ACR/EULAR classification criteria; it is also included in the 2002 American–European Consensus Group classification (AECG) criteria and the 2012 ACR classification criteria. However, labial gland biopsy is difficult to perform in all patients with suspected SS because of its invasiveness. Furthermore, the results of labial gland biopsy in children often do not meet the criteria for positive diagnosis in adults [5, 6]; therefore, non-invasive and highly sensitive items (applicable over a wide age range) are desired for inclusion in the diagnostic criteria.

MRI and US are non-invasive imaging methods that have been used for evaluation of salivary glands in patients with SS since the 1990s [11–14]. US is the primary imaging modality for the assessment of SS in salivary glands because it is simple, inexpensive and versatile. On US, characteristic findings of SS include hypoechoic areas and hyperechoic bands in PGs and submandibular glands (SMGs), as well as an irregular SMG margin [13, 15–20]; various scoring systems have been proposed for the diagnosis of SS and assessment of disease stage [11, 13, 16, 21–24]. Recently, salivary gland US as a possible outcome measurement instrument have been validated [25–27], and the OMERACT US scoring system has been reported to exhibit excellent specificity for diagnosis of SS [27]. However, US is examiner-dependent and the findings can be subjective [28]. Although MRI is an expensive imaging modality, its findings are more objective than the findings of US. On salivary gland MRI, characteristic findings of SS include fatty degeneration and punctate sialectasis on MR sialography [14, 29–33].

To our knowledge, most studies thus far have focused on adult SS; it is unclear whether the imaging findings of salivary glands in JSS are similar to the findings in adult SS. Therefore, the present study compared the MRI and US findings of PGs and SMGs among patients with SS over a wide age range. Additionally, because the relationships between various MRI and US findings have rarely been examined in detail, this study assessed the relationships within and between various MRI findings, US findings, and several clinical findings.

Methods

Study population

This retrospective study included nine patients with JSS [eight girls and one boy; mean age, 13 years (range, 8–17 years)] and 81 patients with adult SS [79 women and 2 men; mean age, 58 years (range, 28–84 years)]. Of the nine patients with JSS, five had primary SS and four had secondary SS; of the 81 patients with adult SS, 58 had primary SS and 23 had secondary SS. The inclusion criteria were (i) completion of both MRI and US examinations of PGs and SMGs at our hospital between June 2008 and December 2020; (ii) diagnosis with SS by specialist rheumatologists or paediatric rheumatologists, based on the ACR/EULAR classification criteria ($n = 67$). Patients who lacked items applicable to ACR/EULAR criteria were diagnosed based on the AECG criteria ($n = 55$), the ACR criteria ($n = 24$) or the 1999 revised Japanese Ministry of Health criteria for diagnosis of SS ($n = 23$). The Saxon test (≤2.0 g/2 min) was used for salivary flow evaluation [20] because the unstimulated whole saliva test was not performed on all included patients. Demographic, clinical and laboratory characteristics of all patients are shown in Supplementary Table S1, available at *Rheumatology* online. All patients with SS were classified into four groups according to age: JSS (<18 years), adult SS-1 (18–39 years), adult SS-2 (40–69 years) and adult SS-3 (>69 years).

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval of the study was obtained from the Institutional Review Board of Nagasaki University Hospital (#0948–5). The requirement for informed consent was waived because of the retrospective nature of the study.

MRI and US examinations

MRI examination

MRI was performed using a 1.5-T magnetic resonance unit (Gyroscan Intera 1.5 T Master; Philips Healthcare, Best, the Netherlands) or a 3.0-T magnetic resonance unit (Skyra 3.0 T; Siemens Healthineers, Erlangen, Germany). All 90 patients underwent transverse T1-weighted turbo spin-echo imaging (T1WI) and fat-suppressed T2-weighted turbo spin-echo imaging (fsT2WI) of PGs and SMGs; 81 patients also underwent MR sialography through single-section single-shot turbo spin-echo imaging of the bilateral PGs and SMGs (details in Supplementary Table S2, available at *Rheumatology* online).

US examination

Grayscale US was performed at 14 MHz by four radiologists with >22 years of experience in scanning salivary

glands using a LOGIQ 9 unit (GE Healthcare, Milwaukee, WI, USA) equipped with a wide bandwidth (range, 9–14 MHz) transducer. Stored static images were used for analysis.

MRI and US qualitative assessment

Three radiologists (T.Y., S.M. and E.S.; 24, 24 and 22 years of experience in head and neck radiology, respectively) who were blinded to patient data evaluated the presence or absence of the following published characteristic findings of SS [13–20, 29–33].

- MRI: multiple high-intensity spots on fsT2WI and MR sialography in bilateral PGs and SMGs, as well as fat areas on T1WI that exhibited reduced high signal intensities on fsT2WI in bilateral PGs and SMGs (Fig. 1).
- US: hypoechoic areas and hyperechoic bands in bilateral PGs and SMGs, as well as irregular margins of bilateral SMGs (Fig. 2).

Interobserver agreement concerning the presence or absence of each finding was evaluated for each gland. If a specific finding was clearly observed in either of the bilateral glands by a consensus among the three radiologists, that finding was considered present in the affected patient.

MRI quantitative assessment

Quantitative measurement of high-intensity spots in PGs

Because multiple high-intensity spots in PGs on fsT2WI and MR sialography were characteristic findings in patients with JSS, the numbers of high-intensity spots in PGs in all patients with SS were quantitively measured using the particle analysis function of ImageJ software, version 2.1.0/1.53c, as previously reported [31]. These measurements were performed by two radiologists (T.Y. and S.M.; 24 years of experience in head and neck radiology). Interobserver agreements were determined by calculating the mean measurement performed by the two radiologists for each PG.

Grading of high-intensity spots inPGs

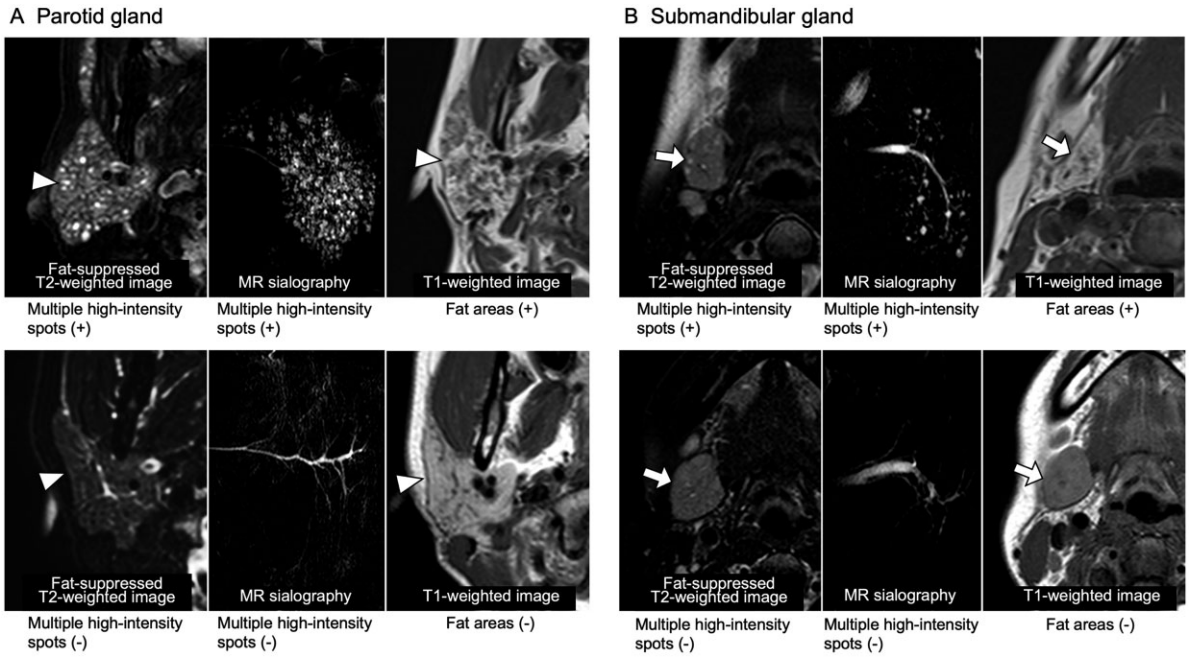
In each patient, the high-intensity spots on fsT2WI were graded as follows, based on mean number of high-intensity spots in the bilateral PGs (i.e. mean number of spots in both glands for each patient, as described in Supplementary Data S1, available at *Rheumatology* online): grade I (0–9 high-intensity spots), grade II (10–19 high-intensity spots), grade III (20–29 high-intensity spots) and grade IV (>29 high-intensity spots) (Fig. 3A).

Similarly, the high-intensity spots on MR sialography were graded as follows, based on the mean number of high-intensity spots in the bilateral PGs using the method described in Supplementary Data S1: grade I (0–19 high-intensity spots), grade II (20–39 high-intensity spots), grade III (40–59 high-intensity spots) and grade IV (>59 high-intensity spots) (Fig. 3B).

Relationships of specific findings

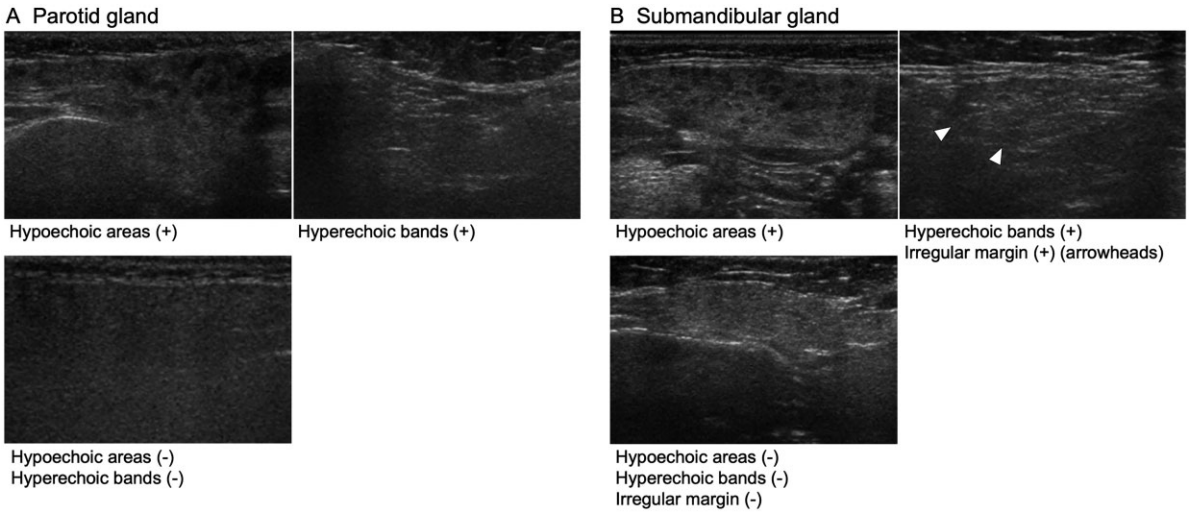
The data for all patients with SS were used for statistical analysis of the relationships between MRI, US, and clinical and laboratory findings.

Fig. 1 MRI findings of (**A**) parotid (arrowheads) and (**B**) submandibular (arrows) glands



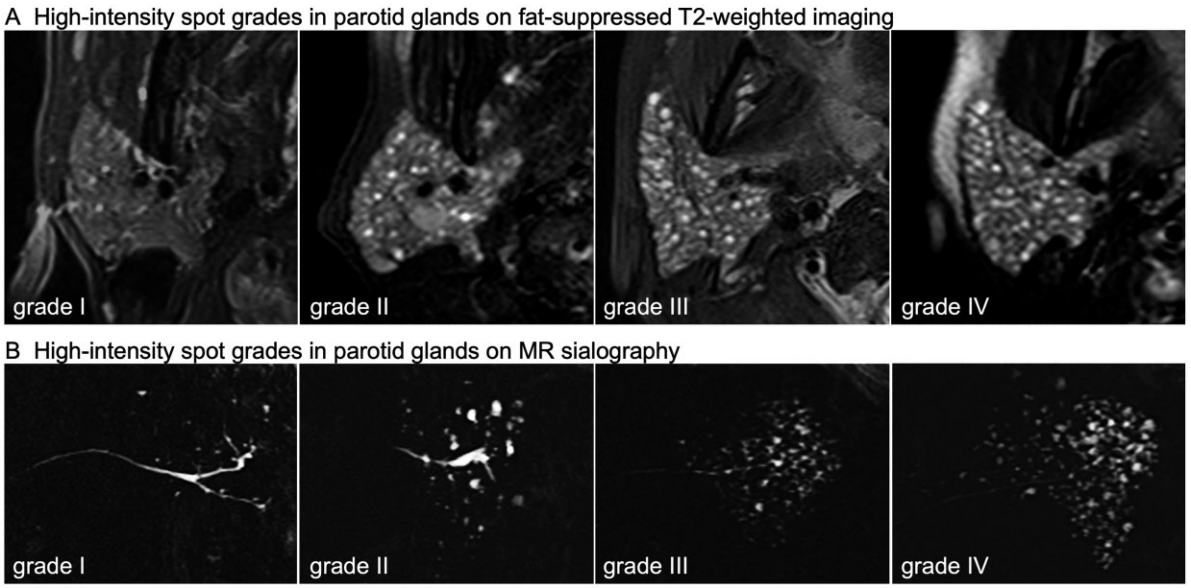
(+), presence of the finding; (−), absence of the finding.

Fig. 2 US findings of (**A**) parotid and (**B**) submandibular glands



(+), presence of the finding; (−), absence of the finding.

Fig. 3 High-intensity spot grades in parotid glands on (**A**) fat-suppressed T2-weighted imaging and (**B**) MR sialography



Statistical analysis

Statistical analyses were performed with JMP Pro, version 15.0 (SAS Institute) and IBM SPSS Statistics, version 27.0.1 (IBM Corp.). Cochran–Armitage test statistics were used to evaluate the associations between age group and the frequency of each finding. Jonckheere–Terpstra trend test statistics were used to evaluate monotone trends between age groups and high-intensity spot grades on fsT2WI and MR sialography. The correlation between fsT2WI high-intensity spot grade and MR sialography high-intensity spot grade was evaluated using Spearman's rank correlation coefficient. Associations between dichotomized findings were assessed with Fisher's exact test. Interobserver agreement concerning the presence or absence of each US and MRI finding was assessed by using Cohen's kappa coefficient. Spearman's rank correlation coefficients and intraclass correlation coefficients (ICCs) were used to assess interobserver agreement concerning the measurements of multiple high-intensity spot numbers on fsT2WI and MR sialography.

All reported *P*-values were descriptive [34]. Correlation/agreement values (for Spearman's rank correlation coefficient, ICC, and kappa coefficient assessments) were

interpreted as follows: 0–0.2, poor correlation/agreement; >0.2 and ≤0.4, fair correlation/agreement; >0.4 and ≤0.6, moderate correlation/agreement; >0.6 and ≤0.8, substantial correlation/agreement; and >0.8 and ≤1.0, almost perfect correlation/agreement.

Results

Patient characteristics

Detailed clinical and laboratory data were available for all 90 patients regarding (i) anti-Ro/SSA and/or anti-La/SSB antibodies, (ii) decreased salivary flow and (iii) xerostomia; these findings are shown in Table 1. The remaining clinical and laboratory data (results not available for all 90 patients) are shown in Supplementary Table S1, available at *Rheumatology* online.

Evaluation of trends between age groups and clinical/laboratory findings revealed that, as the SS group age increased, xerostomia and decreased salivary flow were observed with increasing frequency ($P = 0.0001$ and $P < 0.0001$, respectively). Anti-Ro/SSA and/or anti-La/SSB antibodies were present in all nine patients with JSS; patients in the older group had a lower frequency of Anti-Ro/SSA and/or anti-La/SSB antibody positivity ($P = 0.0127$).

Interobserver agreements

Kappa coefficients of interobserver agreements concerning the presence/absence of each MRI and US finding indicated moderate to almost perfect agreement (Supplementary Table S3, available at *Rheumatology* online.). Interobserver agreements concerning the numbers of high-intensity spots in PGs on fsT2WI and MR sialography were almost perfect, according to Spearman's rank correlation coefficient, as follows: $r = 0.9889$ (almost perfect), $P < 0.0001$ on fsT2WI; $r = 0.9696$ (almost perfect), $P < 0.0001$ on MR sialography. The results of ICC assessment between the two observers regarding the numbers of high-intensity spots on fsT2WI and MR sialography were also almost perfect, as follows: ICC (2.1) = 0.978 (almost perfect), 95% CI: 0.966, 0.985 on fsT2WI; ICC (2.1) = 0.968 (almost perfect), 95% CI: 0.951, 0.979 on MR sialography.

MRI and US qualitative evaluation

MRI

The frequencies of MRI findings are described in Table 1. The most frequent MRI findings in patients with JSS were multiple high-intensity spots in PGs on MR sialography and fsT2WI (100% and 89% of patients with JSS, respectively). Evaluation of trends between age groups and MRI findings revealed that, as the SS group age increased, the findings on MR sialography and fsT2WI were observed with decreasing frequency ($P = 0.0011$ and $P < 0.0463$, respectively); the frequencies of the findings were 57% and 19% in patients with adult SS who were >69 years of age.

Fat areas within PGs and SMGs were rarely observed in patients with JSS (one and none of the patients with JSS, respectively). As the SS group age increased, fat areas in PGs and SMGs were observed with increasing frequency ($P = 0.0007$ and $P < 0.0001$, respectively).

US

The frequencies of US findings are described in Table 1. The most frequent US findings in patients with JSS were hypoechoic areas within PGs and SMGs (100% and 67% of patients with JSS, respectively). Conversely, hyperechoic bands in PGs and SMGs and an irregular SMG margin were rarely observed in patients with JSS (two, two and one of the patients with JSS, respectively). Evaluation of trends between age groups and US findings revealed that, as the SS group age increased, hypoechoic areas within PGs were observed with decreasing frequency ($P = 0.0011$); in contrast, hyperechoic bands within PGs and SMGs and irregular SMG margins were observed with increasing frequency ($P = 0.0005$, $P = 0.0009$ and $P = 0.0363$, respectively).

MRI quantitative evaluation

Evaluation of trends between age groups and high-intensity spot grades revealed that, with increasing SS group age, lower high-intensity spot grades in PGs were observed on both fsT2WI and MR sialography ($P = 0.002$ and $P < 0.001$, respectively) (Fig. 4). A substantial correlation was observed between fsT2WI high-intensity spot grade and MR sialography high-intensity spot grade ($r = 0.603$, $P < 0.0001$).

Relationships of specific findings

The pairwise correlations of specific findings were evaluated by odds ratios (ORs) and *P*-values (Fig. 5) [35]. A correlation between the presence of multiple high-intensity spots in PGs on fsT2WI and the presence of multiple high-intensity spots in PGs on MR sialography was observed (OR = 15.71, $P < 0.0001$); each of these findings was correlated with the presence of hypoechoic areas in PGs on US (OR = 8.89 and OR = 7.74, $P = 0.0002$ and $P < 0.0001$, respectively). In both PGs and SMGs, correlations were observed between the presence of fat areas on MRI and the presence of hyperechoic bands on US (OR = 13.82 and OR = 5.23, $P < 0.0001$ and $P = 0.0004$, respectively); notably, these correlations were observed within and between PGs and SMGs (OR = 7.47 and OR = 5.51, $P < 0.0001$ and $P = 0.0004$, respectively). In addition, a correlation was observed between the presence of irregular SMG margins and the presence of hyperechoic bands in SMGs on US (OR = 5.29, $P = 0.0015$); the presence of irregular SMG margins on US was also correlated with the presence of hyperechoic bands in PGs on US (OR = 3.65, $P = 0.0078$) and the presence of fat areas in both SMGs and PGs on MRI (OR = 6.98 and OR = 4.70, $P = 0.0005$ and $P = 0.0052$, respectively).

Regarding the pairs of clinical and laboratory findings, decreased salivary flow was correlated with xerostomia (OR = 14.8, $P = 0.0048$). Imaging findings that had the

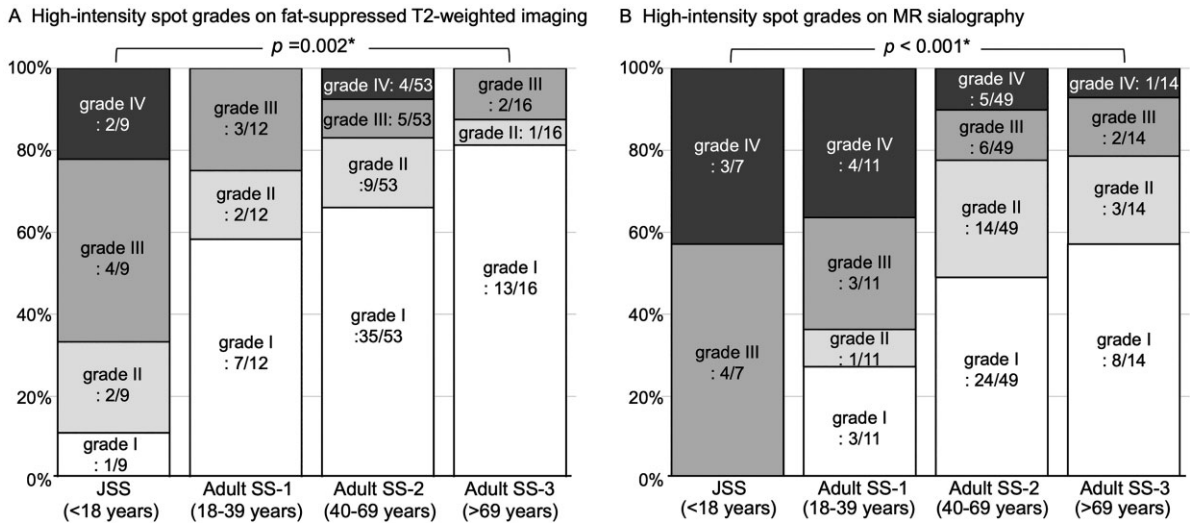
Table 1 Frequencies of MRI, US, and clinical and laboratory findings according to age group

Age group	Number of patients	MRI findings				US findings					Clinical and laboratory findings			
		Parotid glands		Submandibular glands		Parotid glands		Submandibular glands						
		Multiple high-intensity spots on fsT2WI	Fat areas	Multiple high-intensity spots on fsT2WI	Fat areas	Hypoechoic areas	Hyperechoic bands	Hypoechoic areas	Hyperechoic bands	Irregular margin	Anti-Ro/SSA and/or anti-La/SSB antibodies	Decreased salivary flow[a]	Xerostomia	Primary SS
JSS (<18 years)	9	8 (89%)	1 (11%)	1 (11%)	0 (0%)	9 (100%)	2 (22%)	6 (67%)	2 (22%)	1 (11%)	9 (100%)	4 (44%)	3 (33%)	5 (56%)
Adult SS-1 (18–39 years)	12	5 (42%)	6 (50%)	0 (0%)	5 (42%)	8 (67%)	2 (17%)	5 (42%)	3 (25%)	3 (25%)	11 (92%)	8 (67%)	12 (100%)	9 (75%)
Adult SS-2 (40–69 years)	53	19 (36%)	38 (72%)	1 (2%)	37 (70%)	37 (70%)	33 (62%)	30 (57%)	34 (64%)	19 (36%)	44 (83%)	49 (92%)	53 (100%)	35 (66%)
Adult SS-3 (>69 years)	16	3 (19%)	12 (75%)	0 (0%)	14 (88%)	8 (50%)	12 (75%)	13 (81%)	12 (75%)	8 (50%)	10 (63%)	15 (94%)	16 (100%)	14 (88%)
P-value by Cochran–Armitage trend test		0.0011	0.0007	0.1451	<0.0001	0.0217	0.0005	0.2533	0.0009	0.0363	0.0127	0.0001	<0.0001	0.1828

Age group	Number of patients	Multiple high-intensity spots on MR sialo	Multiple high-intensity spots on MR sialo
JSS (<18 years)	7	7 (100%)	1 (14%)
Adult SS-1 (18–39 years)	11	8 (73%)	0 (0%)
Adult SS-2 (40–69 years)	49	30 (61%)	2 (4%)
Adult SS-3 (>69 years)	14	8 (57%)	0 (0%)
P-value by Cochran–Armitage trend test		0.0463	0.2400

Numbers indicate number of patients with each finding (frequency in each age group). [a]≤2.0 g/2 min on the Saxon test. JSS: juvenile SS; fsT2WI: fat-suppressed T2-weighted imaging; sialo: sialography.

FIG. 4 Frequencies of high-intensity spot grades in parotid glands according to age group



Numerators indicate numbers of patients with each grade on fat-suppressed T2-weighted imaging (**A**) and MR sialography (**B**); denominators indicate numbers of overall patients in each age group. **P*-values by Jonckheere–Terpstra trend test.

FIG. 5 Relationships between MRI, US, and clinical and laboratory findings in all patients with SS

P-values (odds ratio) by Fisher's exact test			MRI findings						US findings					Clinical and Laboratory findings			
			Parotid glands			Submandibular glands			Parotid glands		Submandibular glands						
			Multiple high-intensity spots on fsT2WI	Multiple high-intensity spots on MR Sialo	Fat areas	Multiple high-intensity spots on fsT2WI	Multiple high-intensity spots on MR Sialo	Fat areas	Hypoechoic areas	Hyperechoic bands	Hypoechoic areas	Hyperechoic bands	Irregular margin	SSA/SSB	Decreased salivary flow[a]	Xerostomia	Primary SS
MRI	PGs	Multiple high-intensity spots on fsT2WI		< 0.0001 (15.71)	1.0000 (0.97)	0.1486 (8.28*)	0.5549 (3.38)	1.0000 (1.05)	0.0002 (8.89)	1.0000 (0.99)	1.0000 (1.0)	0.5140 (0.71)	0.3738 (0.65)	0.2652 (2.16)	0.3835 (0.58)	0.0313 (0.11)	0.1068 (2.15)
		Multiple high-intensity spots on MR Sialo	< 0.0001 (15.71)		0.6325 (1.34)	0.5420 (2.77*)	0.5478 (3.95*)	0.1505 (2.12)	< 0.0001 (7.74)	0.6451 (0.78)	0.6384 (1.32)	0.2492 (1.76)	0.6255 (0.78)	0.0755 (3.11)	0.5262 (0.52)	0.1582 (0.15*)	0.6255 (0.78)
		Fat areas	1.0000 (0.97)	0.6325 (1.34)		0.1318 (0.11*)	0.5549 (0.30)	< 0.0001 (16.7)	0.0996 (2.27)	< 0.0001 (13.82)	0.8241 (1.17)	< 0.0001 (7.47)	0.0052 (4.70)	0.1525 (0.34)	< 0.0001 (36.4)	0.0235 (10)	0.4754 (0.56)
	SMGs	Multiple high-intensity spots on fsT2WI	0.1486 (8.28*)	0.5420 (2.77*)	0.1318 (0.11*)		0.0009 (261.7*)	0.1401 (0.12*)	1.0000 (2.36*)	1.0000 (0.83)	1.0000 (0.66)	1.0000 (0.76)	0.5433 (0.37*)	1.0000 (1.14*)	1.0000 (0.97*)	1.0000 (0.39*)	0.5124 (2.38)
		Multiple high-intensity spots on MR Sialo	0.5549 (3.38)	0.5478 (3.95*)	0.5549 (0.30)	0.0009 (261.7*)		0.0527 (0.08*)	1.0000 (1.06)	1.0000 (1.80)	0.5692 (0.35)	0.5823 (0.39)	0.5475 (0.28*)	0.4880 (0.48)	1.0000 (1.44*)	1.0000 (0.52*)	1.0000 (1.06)
		Fat areas	1.0000 (1.05)	0.1505 (2.12)	< 0.0001 (16.7)	0.1401 (0.12*)	0.0527 (0.08*)		0.3478 (1.69)	0.0004 (5.51)	0.6577 (1.32)	0.0004 (5.23)	0.0005 (0.98)	1.0000 (0.99)	< 0.0001 (14.73)	0.0022 (25.77*)	1.0000 (1.05)
US	PGs	Hypoechoic areas	0.0002 (8.89)	< 0.0001 (7.74)	0.0996 (2.27)	1.0000 (2.36*)	1.0000 (1.06)	0.3478 (1.69)		1.0000 (1.05)	0.0363 (2.8)	0.4917 (1.48)	0.6326 (0.74)	0.2458 (1.96)	0.5359 (0.56)	0.1713 (0.15*)	0.0454 (3.54)
		Hyperechoic bands	1.0000 (0.99)	0.6451 (0.78)	< 0.0001 (13.82)	1.0000 (0.83)	1.0000 (1.80)	0.0004 (5.51)	1.0000 (1.05)		1.0000 (0.93)	< 0.0001 (9.43)	0.0078 (3.65)	0.5841 (0.67)	0.0088 (5.62)	0.0887 (6.67)	0.8192 (0.86)
	SMGs	Hypoechoic areas	1.0000 (1.0)	0.6384 (1.32)	0.8241 (1.17)	1.0000 (0.66)	0.5692 (0.35)	0.6577 (1.32)	0.0363 (2.8)	1.0000 (0.93)		0.1927 (1.9)	0.5034 (0.72)	0.5761 (0.63)	1.0000 (1.15)	0.3956 (0.28)	0.4843 (1.5)
		Hyperechoic bands	0.5140 (0.71)	0.2492 (1.76)	< 0.0001 (7.47)	1.0000 (0.76)	0.5823 (0.39)	0.0004 (5.23)	0.4917 (1.48)	< 0.0001 (9.43)	0.1927 (1.9)		0.0015 (5.29)	0.4053 (0.53)	0.0373 (4.05)	0.0813 (7.35)	0.6441 (0.76)
		Irregular margin	0.3738 (0.65)	0.6255 (0.78)	0.0052 (4.70)	0.5433 (0.37*)	0.5475 (0.28*)	0.0005 (6.98)	0.6326 (0.74)	0.0078 (3.65)	0.5034 (0.72)	0.0015 (5.29)		0.3989 (0.62)	0.1260 (3.70)	0.0897 (7.65*)	0.1477 (0.43)
Clinical and Laboratory findings		SSA/SSB	0.2652 (2.16)	0.0755 (3.11)	0.1525 (0.34)	1.0000 (1.14*)	0.4880 (0.48)	1.0000 (0.99)	0.2458 (1.96)	0.5841 (0.67)	0.5761 (0.63)	0.4053 (0.53)	0.3989 (0.62)		1.0000 (0.74)	0.5860 (0.32*)	0.5503 (0.66)
		Decreased salivary flow[a]	0.3835 (0.58)	0.5262 (0.52)	< 0.0001 (36.4)	1.0000 (0.97*)	1.0000 (1.44*)	< 0.0001 (14.73)	0.5359 (0.56)	0.0088 (5.62)	1.0000 (1.15)	0.0373 (4.05)	0.1260 (3.70)	1.0000 (0.74)		0.0048 (14.8)	0.5405 (1.69)
		Xerostomia	0.0313 (0.11)	0.1582 (0.15*)	0.0235 (10)	1.0000 (0.39*)	1.0 (0.52*)	0.0022 (25.77*)	0.1713 (0.15*)	0.0887 (6.67)	0.3956 (0.28)	0.0813 (7.35)	0.0897 (7.65*)	0.5860 (0.32*)	0.0048 (14.8)		1.0000 (0.85)
		Primary SS	0.1068 (2.15)	0.6255 (0.78)	0.4754 (0.56)	0.5124 (2.38)	1.0000 (1.06)	1.0000 (1.05)	0.0454 (3.54)	0.8192 (0.86)	0.4843 (1.5)	0.6441 (0.76)	0.1477 (0.43)	0.5503 (0.66)	0.5405 (1.69)	1.0000 (0.85)	

Numbers outside and inside parentheses indicate *P*-value and odds ratios by Fisher's exact test, respectively. [b]Odds ratios of contingency tables with 0 counts were corrected by the Haldane–Anscombe method. [a]≤2.0 g/2 min on the Saxon test. SMGs: submandibular glands; fsT2WI: fat-suppressed T2-weighted imaging; MR sialo: MR sialography.

first to fourth significant correlations with decreased salivary flow were fat areas in PGs and SMGs on MRI (OR = 36.4 and OR = 14.73, $P = 3.7 \times 10^{-6}$ and $P = 9.9 \times 10^{-5}$, respectively) and hyperechoic bands inPGs and SMGs on US (OR = 5.62 and OR = 4.05, $P = 0.0088$ and $P = 0.0373$, respectively).

A significantly different finding between primary SS and secondary SS was hypoechoic areas in PGs on US

(OR = 3.54, $P = 0.0454$) (Fig. 5, Supplementary Table S4, available at *Rheumatology* online.), although hypoechoic areas in PGs were observed in all patients with primary and secondary JSS; no difference was observed between primary and secondary JSS in our study.

Discussion

This study investigated the MRI and US findings both of PGs and SMGs in patients with JSS and adult SS; it demonstrated that the characteristics in patients with JSS were distinct from the characteristics in patients with adult SS. To our knowledge, this is the first study with the following features: (i) it investigated PGs and SMGs of patients with SS over a wide age range (8–84 years); (ii) it compared MRI and US findings among four SS groups according to age; and (iii) it examined relationships between MRI and US findings of PGs and SMGs, and clinical and laboratory findings in patients with SS over a wide age range.

In our study, the most frequent MRI finding in patients with JSS was the presence of multiple high-intensity spots in PGs on MR sialography, suggesting punctate sialectasis [31]. This result supported the findings by Sumida *et al.* [36]. The second-most frequent MRI finding in patients with JSS was the presence of multiple high-intensity spots in PGs on fsT2WI. Because there were associations between fsT2WI and MR sialography findings in terms of the frequency and grade of multiple high-intensity spots in PGs, the presence of multiple high-intensity spots in PGs on fsT2WI may be suggestive of punctate sialectasis. These findings became less common with increasing SS group age; thus, they constitute characteristic findings of JSS. Because fsT2WI is a routine conventional sequence in head and neck MRI examinations, while MR sialography is an additional sequence used for detailed examination of ductal abnormalities, JSS may be detected by multiple high-intensity spots on fsT2WI during MRI examinations for other complaints. Indeed, our hospital policy is that incidental findings of multiple high-intensity spots on fsT2WI during MRI examinations for other complaints (e.g. ranulas) [37] trigger a referral to specialist rheumatologists; these specialists confirm the diagnosis of primary SS on the basis of further assessments in accordance with ACR/EULAR or AECG classification criteria. Conversely, within SMGs, multiple high-intensity spots on MR sialography and fsT2WI were rarely observed in patients with JSS or patients with adult SS (Table 1), potentially because of differences in the PG and SMG ductal systems [38–40].

On US, hypoechoic areas within PGs and SMGs were frequently observed in patients with JSS. In PGs, hypoechoic areas were associated with multiple high-intensity spots on MR sialography and fsT2WI; similar associations were not observed in SMGs (Fig. 5). Accordingly, hypoechoic areas may not be equivalent to multiple high-intensity spots on MR sialography and fsT2WI. Hypoechoic areas have been reported to represent lymphocyte infiltration in the glandular parenchyma and/or punctate sialectasis [12, 38, 41, 42], but this relationship remains unclear [40, 43].

In contrast, the presence of fat areas on MRI and hyperechoic bands on US, reportedly characteristic of adult SS [14, 29–31, 33], was rarely observed in PGs and SMGs of patients with JSS; with increasing SS group age, these findings were observed with increasing frequency. The presence of hyperechoic bands inPGs and SMGs was associated with the presence of fat areas on MRI, implying that hyperechoic bands represent fatty degeneration similar to fat areas on MRI [38, 41]. Additionally, an irregular SMG margin was rarely observed in patients with JSS and was more common in older SS groups; it was associated with the presence of hyperechoic bands and the presence of fat areas on MRI in PGs and SMGs. These findings imply that fatty degeneration of the glandular parenchyma obscures the outline of the SMG. The difference in salivary gland characteristic findings between JSS and adult SS likely reflects differences in SS glandular lesion severity.

Importantly, decreased salivary flow was associated with fat areas on MRI and hyperechoic bands in PGs and SMGs on US, implying that the fatty degeneration findings are the most useful features for assessment of salivary gland dysfunction and may be an indicator of advanced disease. Our finding that fatty degeneration is rarely observed in patients with JSS suggests that most patients with JSS exhibit early-stage SS; the hypothesis is consistent with the findings of less frequent decreased salivary flow and xerostomia in patients with JSS. In contrast, multiple high-intensity spots in PGs on fsT2WI and on MR sialography became less common with increasing age. Therefore, the punctate sialectasis in PGs observed in patients with JSS is presumably a component of relatively early disease. This might be related to inflammatory ductal changes caused by SS, which precede atrophy and fatty degeneration in the glandular parenchyma [33].

This study had some limitations. First, because it was a single-centre study, the number of patients was small and a control group could not be established. Therefore, imaging findings specific to JSS and adult SS could not be clarified. Because fat filtration of salivary glands is often observed in elderly healthy controls, there is a need to clarify differences in fat infiltration and ductal change patterns between SS and non-SS controls in a larger cohort. Moreover, ophthalmic and labial gland biopsy findings could not be analysed because of insufficient data. Thus, multicentre studies with additional patients and control groups are needed. Second, tissue biopsy of PGs and SMGs was not performed; therefore, we could not clarify relationships between imaging findings and histological findings. Third, this study did not determine the mechanisms underlying each specific disease finding. Animal model experiments using mouse models, such as the NZB/W F1 mouse [44], are needed to clearly elucidate those mechanisms.

In conclusion, we have shown that MRI and US examinations are useful for the assessment of ductal

and parenchymal damage in salivary glands. Salivary gland imaging findings in patients with JSS were characterized by punctate sialectasis, whereas those findings in patients with adult SS were characterized by fatty degeneration. This suggests that the glandular lesions in most patients with JSS comprise relatively early disease, compared with those in patients with adult SS. MRI and US examinations will be useful for evaluation of glandular lesion severity during follow-up.

There remains a need to establish SS classification criteria that consider differences in age, thus facilitating early diagnosis. These criteria may permit earlier treatment initiation and aid in preventing disease progression in exocrine glands; they may also prevent complications in other organs. It is important to establish the diagnostic capabilities of MRI and US imaging findings in a larger cohort to enable their implementation for assessment of patients with suspected SS over a wide age range.

Acknowledgements

We thank Ryan Chastain-Gross, Ph.D., from Edanz Group (https://jp.edanz.com/expert/immunology) for editing a draft of this manuscript. The various author contributions are as follows—

(1) conception and design: M.S. and Y.T.;

(2) administrative support: M.S.;

(3) provision of study materials or patients: Y.T., I.K., K.H., H.N., T.S. and A.K.;

(4) collection and assembly of data: Y.T., M.S., S.E. and I.K.;

(5) data analysis and interpretation: Y.T., M.S., S.M.;

(6) statistical analysis: M.S. and S.M. (biostatistician);

(7) manuscript writing: M.S. and Y.T.;

(8) critical revision of the drafted manuscript for important intellectual content: all authors.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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