Advanced Journal of Microbiology Research Vol. 2016
Available online at http://internationalscholarsjournals.org/journal/ajmr

Full Length Research Paper

Evaluation of salivary gland scintigraphy, magnetic resonance and diffusion-weighted imaging in clinical diagnosis of Sjögren's Syndrome

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Accepted 15 March, 2015

To assess diagnostic effectiveness of Sjögren's syndrome (SS), salivary gland scintigraphy (SGS), magnetic resonance (MR) and diffusion-weighted imaging (DWI) were performed in 54 patients (primary SS, secondary SS and connective tissue disease (CTD) but without SS). Results showed that SGS and diffusion-weighted magnetic resonance imaging (MRI) provided high-resolution images of the parotid glands that enabled apparent diffusion coefficient (ADC) measurements. After overall analysis, all of the oral activity indices, the maximum accumulation (MA) and uptake rate (UR) of the parotid gland clearly decreased as clinical severity progressed, and statistically significant differences were observed. Our technique may prove helpful in diagnosing the progression of SS beyond its early stages.

Key words: Diffusion-weighted imaging, salivary gland scintigraphy, Sjögren's syndrome, receiver operating characteristic curve.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of exocrine glands, involving in particular the salivary and lacrymal glands. This leads to diminished secretion of saliva and tears, resulting in xerostomia and keratoconjunctivitis sicca, respectively. SS can be observed as a clinically isolated syndrome (primary SS) or associated with other autoimmune diseases (secondary SS) including rheumatoid arthritis and systemic lupus erythematosus. Extraglandular manifestations occur in one-third of the affected patients with primary SS, represented by arthritis, Raynaud's phenomenon, lymphadenopathy, vasculitis, interstitial pneumonia, renal and neurological disorders, and malignant lymphoma (Moutsopoulos, 2001; Li et al, 2009; Winchester, 1982). Using a validated questionnaire, it was found that the prevalence of definite and probable Sjögren's syndrome in women in a Greek town was 0.6 and 3%, respectively. In another epidemiologic study, the calculated prevalence of Sjögren's syndrome in 705 randomly selected women aged 52 – 72 years was 2.7% (Jacobsson et al., 1989). Sjögren's syndrome was considered rare in young people. Age at onset tends to be between the ages of 40 to 60 years (Ostuni et al., 1996; Chen et al., 2009; Pérez Leirós et al., 1999). SS in children has been described primarily in case histories (about 50 patients) in the past 15 years (Bemstein et al., 1977; Hearth-Holmes et al., 1993).

The primary symptom in the majority of these young patients was unilateral or bilateral recurrent parotitis. Salivary gland scintigraphy is a sensitive and valid method for evaluation of the function of the salivary glands. Scintigraphy results correlate with clinical and histopathological features of the salivary glands in patients with SS. Scintigraphy is relatively safe, well tolerated and easy to perform, and enables an assessment of the function of all major salivary glands. Recently, MRI techniques have been introduced for salivary gland evaluation in patients with Sjögren's syndrome (Shizukuishi et al., 2003). More recently, Sumi et al. (2002) applied diffusion-weighted MRI to the assessment of impaired salivary gland function in patients with Sjögren's syndrome

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to show that the apparent diffusion coefficients (ADC) of the parotid glands were significantly lower than those of the healthy control subjects and inflammatory glands.

In this study, we assessed the quantitative indices of oral radioactivity in healthy volunteers and in patients with Sjögren's syndrome. We performed quantitative salivary gland scintigraphy, magnetic resonance (MR) imaging and diffusion- weighted imaging (DWI) to choose the simplest, reliable and sensitive variables for determination of the clinical stage of Sjögren's syndrome.

MATERIALS AND METHODS

Subjects

From July 2008 to January 2009, we investigated 42 patients with Sjogren's syndrome (SS) and 12 of them with connective tissue disease (CTD) but without SS. Patients with primary Sjögren's syndrome (pSS) (n = 32) and secondary Sjögren's syndrome (sSS) associated with rheumatoid arthritis (n = 10) were included in the study, all displaying sicca symptoms. Controls included 17 healthy volunteers without known inflammatory or autoimmune disease. Diagnoses were based on the 2002 revised European criteria for primary and secondary Sjögren's syndrome (Vitali et al., 2002), the 1982 revised ACR criteria for classification of SLE (Tan et al., 1982) and the 1980 ACR Criteria for the Classification of Systemic Sclerosis (1980).

All patients underwent conventional salivary gland scintigraphy (SGS), magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) studies. All patients and healthy subjects gave their informed consent and the Declaration of Helsinki (September 1989) was followed throughout the study.

Quantitative salivary gland scintigraphy

The quantitative salivary scintigraphy was performed using a standard protocol (Munter et al., 2004; Bohuslavizki et al., 1997). In short, salivary scintigraphy was performed after a 4 h fasting. After intravenous injection of the tracer (technetium-99 m pertechnetate) sequential images of 1 min/frame were acquired for 30 min using a gamma camera. After 20 min, salivary flow was stimulated with 10 ml of diluted lemon juice administered to the dorsal tongue. Time-activity curves were calculated using manually drawn oval regions - of-interest around both the parotid and the submandibular glands. Glandular uptake is given as percentage of the admi-nistered activity. For background correction, a fifth region-of-interest of similar size was drawn over the cerebrum. The maximum tracer uptake (Umax) was a priori chosen as parameter for the parotid parenchymal function. The maximum tracer uptake (Umax) before and after treatment was determined for each gland separately (averaged over three subsequent 1-min frames). The change in the maximum tracer uptake between pre- and post-treatment was expressed as proportion of the pre-treatment maximum tracer uptake: U = Umax(post)/Umax(pre).

For the analysis of the effect of chemoradiotherapy (CRT) with amifostine or intensity-modulated radiotherapy (IMRT) on the parotid function, the mean U of both parotid glands of a patient was used. A maximum tracer uptake of 0.17% was considered normal. Follow-up salivary gland scinti-graphies were usually scheduled every 3 months after completion of the radiotherapy for the first year, than yearly. A dose–response curve was calculated for the follow- up category of 13 – 47 months after radiotherapy (RT) to assess the impact of the parotid dose on late complications. For the dose–response calculation, the U of individual parotid glands was used because the intraindividual dose to the parotid glands Varied considerably in many patients.

Magnetic resonance (MR) imaging and diffusion-weighted imaging (DWI)

Preoperative magnetic resonance imaging (MRI) was performed using a 1.5-Tesla magnetic field (Siemens Magnetom Vision, Germany). MRI sequences were as follows: T1-weighted imaging (T1WI: TR, 528 ms; TE, 17 ms; FOV, 23 × 23 cm; matrix, 256 × 256; slice thickness, 5 mm with a 2.5-mm gap); T2-weighted imaging (T2WI: TR, 3000 ms; TE, 90 ms; FOV, 23 × 23 cm; matrix, 256 × 256; slice thickness, 5 mm with a 2.5-mm gap); and DWI (TR, 0.8 ms; TE, 123 ms; FOV, 23 × 23 cm; matrix, 128 × 128; slice thickness, 5 mm with a 2.5-mm gap). Region of interest (ROI) analysis was performed on the axial images as described (Brunberg et al., 1995; Ulug et al., 1997; Izumi et al., 1996). The current hardware allowed diffusion gradients of up to 1.1 G/cm, with a rise time of 320 s. The length of the diffusion gradients was 26 ms and the diffusion-time was 60.1 ms. ROI was made from the center of the DWI abnormality. ADC maps were generated from 2 or more b value images by filtering the data on a pixel-by-pixel basis. The exponential function that describes the change in magnetic resonance signal intensity with the diffusion weighting b value is $S = S0\exp(-b\times ADC)$, where S and S0 are the pixel signal intensity with (S) and without (S0) diffusion weighting applied. A set of diffusion weighted images was evaluated in each of the 3 orthogonal directions (x, y and z). When diffusion information from all 3 directions was available, ADC maps were generated for each direction and then averaged together to remove contrast due to diffusion anisotropy.

Statistical analysis

A two-tailed Mann–Whitney U test was used to compare continuous variables in the different groups. $P < 0.05$ was considered statistically significant. The SPSS program (SPSS 13.0, Chicago, IL, USA) was used to calculate area under ROC curves and ANOVA.

RESULT

Clinical information

Age of sSS group was significantly ($P < 0.05$) lower than that of pSS and CTD groups (Table 1). Course of disease of sSS group patients was significantly shorter ($P < 0.05$) than that of pSS group patients. This indicated that degree of salivary gland damage of sSS group was lower than that of pSS group. However, there was significant difference between sSS and CTD groups.

SGS analysis

All test indices between bilaterally salivary glands and between parotid glands did not significantly differ ($P > 0.05$) in pSS patients. In pSS patients, maximum accumulation (MA, 48 ± 19 (left), 49 ± 19 (right)) and excretion fraction (EF, 28 ± 16 (left), 29 ± 16 (right)) in bilaterally salivary glands were higher than those [MA, 33 ± 18 (left), 28 ± 18 (right); EF, 17 ± 14 (left), 19 ± 16 (right)] in

Table 1. Clinical information in 54 patients.

Group	Number	Range (year)	Female : Male	course of disease (month)	Aiti-SSA positive rate (%)	Anti-SSB positive rate (%)	Positive rate of saliva flow (%)
pSS	32	54(35-70)	34:0	88 (12-240)	77	76	100
sSS	10	41(36-51) *	9:1	20 (1-72) *	80	80	0
CTD	12	52(36-76)	9:1	51 (1-240)	90	0	0
Control	17	29 (18-32)	14:3				

*P < 0.05, compared with pSS and CTD groups.

Table 2. Comparison in four test indices between bilaterally salivary glands and between bilaterally parotid glands of different groups.

Group	UP		UR		MA		EF	parotid gland (P)
	salivary gland (S)	parotid gland (P)	salivary gland (S)	parotid gland (P)	salivary gland (S)	parotid gland (P)	salivary gland (S)	
normal	24±9	30±9*	21±7	25±8*	35±16	65±9*	43±9	54±9*
pSS	13±10	15±7 **	11±8 *	13±6	30±15	48±16 *	17±15 *	27±15 *
sSS	16±9	20±6 *	13±6 *	16±6 *	31±14	49±15	35±13	44±14
CTD	20±6	29±17	15±6	21±11	33±18	58±12 *	33±15	54±9 **

UP: uptake percentage; UR: uptake rate; MA: maximum accumulation; EF: excretion fraction; *p < 0.05, **p < 0.01, significant difference between bilaterally salivary glands and between bilaterally parotid glands in same group.

Table 3. Comparisons of functional parameters (PRI, POI) of oral cavity between groups.

	Normal group	pSS group	sSS group	CTD group
PRI	41±15	11±11	19±5 *	30±13
POI	63±10	31±20	42±16 *	53±19

PRI: the prestimulatory oral activity index; POI: poststimulatory oral activity index. * P < 0.05, sSS group vs. Normal group.

bilaterally parotid glands.

All test indices between bilaterally salivary glands and between salivary parotid glands did not significantly differ (P > 0.05) in sSS patients. In sSS patients, maximum accumulation (MA, 52 ± 18 (left), 54 ± 19 (right)) and excretion fraction (EF, 33 ± 17 (left), 35 ± 15 (right)) in bilaterally salivary glands were higher than those (MA, 35 ± 16 (left), 33 ± 17 (right); EF, 22 ± 16 (left), 25 ± 16 (right)) in bilaterally parotid glands.

All test indices between bilaterally salivary glands and between salivary parotid glands did not significantly differ (P > 0.05) in CTD patients. In CTD patients, maximum accumulation (MA, 57 ± 13 (left), 59 ± 16 (right)) and excretion fraction (EF, 40 ± 18 (left), 47 ± 16 (right)) in bilaterally salivary glands were higher than those (MA, 34 ± 23 (left), 32 ± 15 (right); EF, 31 ± 14 (left), 32 ± 14 (right)) in bilaterally parotid glands.

Comparisons of functional parameters (UP, UR, EF, MA) among the four groups were summarized in Table 2. ANOVA analysis showed that no statistically significant MA differences were found in the evaluation of oral or glandular parameters of salivary gland scintigraphy between groups. In this study, we investigated the quantitative indices of oral radioactivity in healthy volunteers and in patients with Sjögren's syndrome and CTD (Table 3). The prestimulatory oral activity index (PRI) and poststimulatory oral activity index (POI) in pSS group was lowest among all groups. There was no significant difference (P = 0.075, P = 0.079) in PRI and POI between pSS and sSS groups.

Compared with normal group, PRI and POI in sSS patients was significantly (P < 0.05) reduced. Compared with CTD patients, PRI and POI in sSS patients appeared reduced, although POI did not reach statistical significance (P = 0.15). In CTD patients, the PRI and POI appeared reduced relative to normal controls, although POI did not reach statistical significance (P = 0.178).

Comparisons of salivary and parotid glands functional parameters (SUP, SUR, SEF, PUP, PUR, PMA, PEF, PRI and POI) among the four groups showed significant difference. The groups of variables identified by the discriminant function analysis (DFA) are statistically interrelated implying a possible functional relationship. Functional parameters (SUP, SUR, SEF, PUP, PUR,

Table 4. Analysis of standard index of SGS.

Quantitative index	Correlation discriminant coefficient	Standardized discriminant coefficient
PRI	0.733	0.806
PEF	0.597	0.686

PRI: prestimulatory oral activity index; PEF: parotid glands excretion fraction.

Table 5. MRI morphological changes of parotid glands of pSS, sSS and CTD groups.

	group				
	0	**1**	**2**	**3**	**4**
high-intensity areas					
T1WI	-	+	+	++	+++
T2WI	-	-	+	+	-
SS group					
pSS group	0	8	4	6	14
sSS group	0	4	4	2	0
ADC mean ($\times 10^{-3}$ m^2/s) of SS group		0.98±0.54	1.02±0.44	0.87±0.07	0.85±0.14
CTD group	12	0	0	0	0
ADC mean ($\times 10^{-3}$ m^2/s) of CTD group	0.97±0.10				

Grade (0, 1, 2, 3, 4 and 5) was made according to literature (Schall, 1971).

Table 6. Comparison of apparent diffusion coefficient of bilaterally parotid glands between groups.

Group	Left gland ($\times 10^{-3}$ m^2/s)	Right gland ($\times 10^{-3}$ m^2/s)	Bilaterally parotid glands ($\times 10^{-3}$ m^2/s)
Normal	1.00 ±0.10	1.02±0.06	1.01±0.08
pSS	0.87 ±0.21	0.89 ±0.18	0.88 ±0.18 *
sSS	0.96 ±0.11	0.98 ±0.12	0.98 ±0.10
CTD	0.95 ±0.10	0.99 ±0.11	0.99 ±0.08

*$p < 0.05$, pSS group vs. CTD group; pSS group vs. normal group.

PMA, PEF, PRI and POI used a variable for classification) was calculated to determine the relative discriminatory contribution of each variable. PRI and PEF demonstrated the strongest effect. Moreover, both correlation discriminant coefficent and standard discriminant coefficient of PRI were stronger than those of PEF (Table 4). Therefore, PRI was the best predictors of classification.

MR-DWI

Relevant image distortion of salivary glands of some patients was detected on the DW MR images. This was caused by weak signal intensity. A right diagnosis could not be made. Therefore, data of parotid glands were used in this study.

MRI signals of bilaterally parotid glands of normal group were similar. Pathologic changes were not found. Pathologic change in bilaterally parotid glands of pSS, sSS and CTD groups was found (Table 5). Comparison of apparent diffusion coefficient of bilaterally parotid glands between groups was summarized in Table 6.

We did not find significant difference in ADC between left and right parotid glands. We compared the ADC of the bilaterally parotid glands between groups and found that the ADCs of bilaterally parotid glands in pSS group ($0.88 \pm 0.18 \times 10^{-3}$ m^2/sec) were significantly lower than those of the parotid glands in normal group ($1.01 \pm 0.08 \times 10^{-3}$ m^2/sec) and CTD group ($0.99 \pm 0.08 \times 10^{-3}$ m^2/sec) ($P < 0.05$, Mann-Whitney U test) (Table. 6). There was no significant difference in ADCs between pSS ($0.88 \pm 0.18 \times 10^{-3}$ m^2/sec) and sSS ($\times 10^{-3}$ m^2/sec $\times 10^{-3}$ m^2/sec) groups (Table 6). Although ADC of bilaterally parotid glands in sSS group was higher than those of in normal group, the ADCs did not show significant difference ($P = 0.26$).

After acid stimulation, three time stages of ADC changes

Table 7. ADC changes after acid stimulation.

ADC ($\times 10^{-3} m^2/s$)	Stage 1	Time 1	Stage 2	Time 2	Stage 3	Time 3
pSS	0.82±0.16*	2.4±2.3			1.02±0.15*	13.6±5.5
sSS	1.00±0.13	1.5±1.3	0.91±0.10	6.7±5.3	1.05±0.08*	17.3±5.6
CTD	1.07±0.10*	1.9±2.1	0.95±0.16	7.7±4.5	1.10±0.1*	16.1±3.4
Normal	1.04±0.10*	2.0±1.8	0.93±0.06*	5.2±2.4	1.12±0.1*	14.4±4.6

Stage 1: the first stage after acid stimulation; stage 2: the second stage after stimulation; stage 3: the third stage after acid stimulation. * $p < 0.05$, pSS group vs. sSS group; pSS group vs. CTD group; pSS group vs. normal group; sSS group vs. normal group; vs. rest.

Table 8. Discriminant analysis of quantitative index of SGS and ADC before and after acid stimulation.

Quantitative index	Correlation discriminant coefficient	Standardized discriminant coefficient
PRI	0.611	0.722
PEF	0.507	0.632
ADC after stage 1	0.428	0.558

Stage 1 = the first stage after stimulation.

in pSS group were observed. During the first 3 min (range, 0 – 2 min 25 s) of parotid stimulation, a overall decrease in ADC was observed in both the parotid of pSS group (Table 7). During the next 12 min, the ADC increased steadily to a significantly higher value ($P < 0.01$) compared with the baseline value (at rest) in the parotid glands (Table 7), with a maximum ADC at a time of 13.6 ± 5.5 min (range, 3 – 14 min) after acid administration. The maximum ADC of pSS group was still significantly lower ($P < 0.01$) than that of normal group after stimulation.

During the first 7 min (range, 1 min 30 s – 6 min 40 s) of parotid stimulation, a overall decrease in ADC was observed in both the parotid of sSS group (Table 7). During the next 10 min, the ADC increased steadily to a significantly higher value ($P = 0.01$) compared with the baseline value (at rest) in the parotid glands (Table 7), with a maximum ADC at a time of 17.3 ± 5.6 min (range, 7 – 18 min) after acid administration. The maximum ADC of sSS group was still significantly ($P = 0.002$) lower than that of normal group after stimulation.

During the first 8 min (range, 1 min 30 s – 7 min 40 s) of parotid stimulation, a significant overall decrease in ADC was observed in both the parotid in CTD group ($P < 0.01$) (Table 7). During the next 10 min, the ADC increased steadily to a significantly higher value ($P = 0.01$) compared with the baseline value (at rest) in the parotid glands (Table 7), with a maximum ADC at a time of 16.1 ± 3.4 min (range, 7 – 17 min) after acid administration.

After stimulation, there was no significant difference in ADC between different time stages of normal groups. The ADCs in cerebrospinal fluid of the between patients and healthy people showed no significant (6.55×10^{-3} mm^2/s ± 0.2×10^{-3} mm^2/s) ($P = 0.09$) change during the entire investigation period.

SGS and MR-DWI

Statistics analysis showed significant difference in ADC of parotid gland at rest and after acid stimulation. Therefore, ADC of parotid gland was investigated by using leave-one-out linear discriminant analysis, the results of which were summarized in Table 8.

Linear discriminant analysis revealed that the determination of PRI in the parotid gland could therefore be used diagnostic as a measurement for the high validity and reliability of the classification criteria of the diagnosis Sjögren's syndrome (Table 8). PEF was a direct index in evaluating function of parotid gland. To evaluate diagnostic value of PEF and ADC (stage 1) in Sjögren's syndrome, PEF area under the receiver operating characteristic (ROC) curve was compared with that of ADC (stage 1) (Figure 1 and 2).

Receiver operating characteristic (ROC) curve analysis demonstrated that areas under the ROC curve of 0.92 for PEF area was bigger than areas under the ROC curve of 0.914 for ADC area in the first stage after stimulation. The cutoff points of PEF was 47%. The cutoff points of ADC was 0.932×10^{-3} mm^2/s (Figure 1 and 2).

DISCUSSION

Clinically, it may be difficult to distinguish the early stage of Sjögren's syndrome from normal findings. However, it is important to make an accurate diagnosis because Sjögren's syndrome can be treated by various trial therapies, including corticosteroids and other

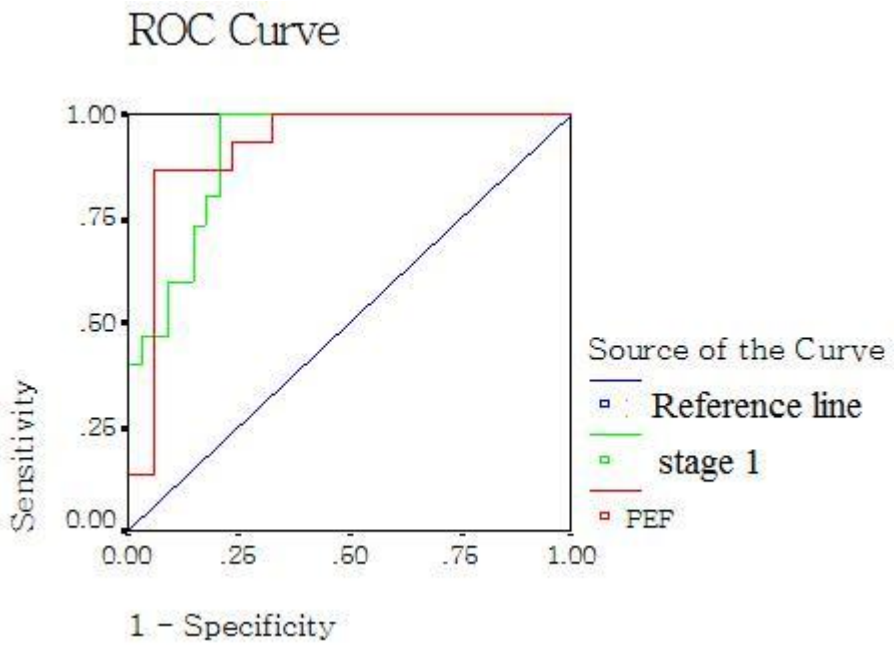

Figure 1. Evaluation of diagnostic value of PEF in Sjögren's syndrome by comparing its areas under the ROC curve with ADC (pSS group, stage 1) area under the ROC curve. Stage 1: the first stage after stimulation.

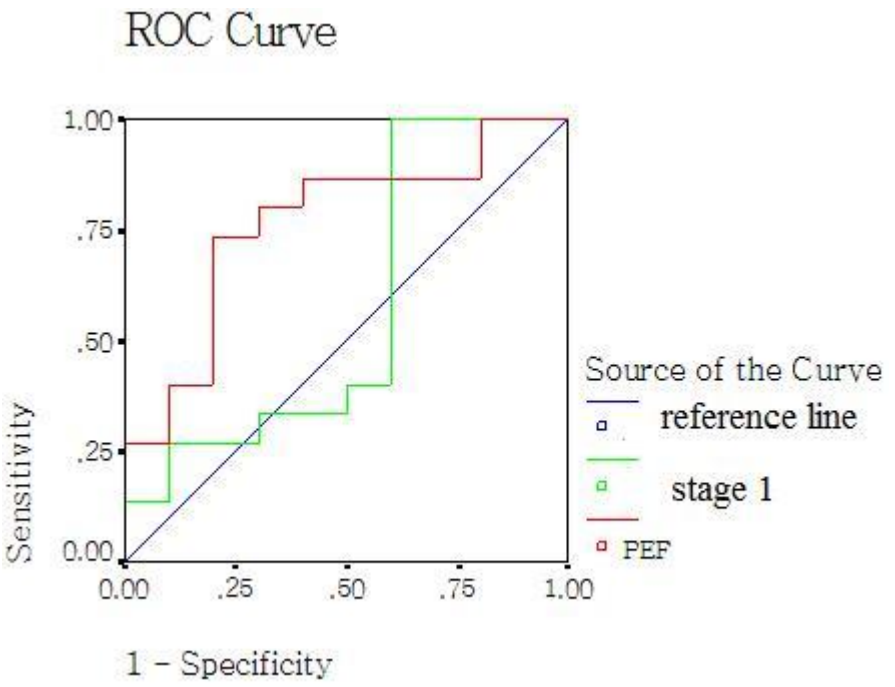

Figure 2. Evaluation of diagnostic value of PEF in Sjögren's syndrome by comparing its areas under the ROC curve with ADC (sSS group, stage 1) area under the ROC curve. Stage 1: the first stage after stimulation.

immunosuppressants. Salivary gland scintigraphy has been attempted as a substitute for labial salivary gland biopsy, the most specific and definitive diagnostic method for detection of impaired salivary function in Sjögren's syndrome (Schall et al., 1971; Umehara et al., 1999; Aung et al., 2000). However, there has been uncertainty

as to which of several scintigraphic parameters are most useful diagnostically. Some investigators have described the origin and location of radioactive saliva (van et al., 1974, 1976), and some have proposed coordinated evaluation of oral activity and salivary glandular activity (Hermann et al., 1999) but, to our knowledge, no quantitative studies of oral radioactivity have been reported to date.

In this study, we investigated the quantitative indices of oral radioactivity in healthy volunteers and in patients with Sjögren's syndrome and CTD. To cover the wide individual variation in frequency, magnitude and evolution of spontaneous and stimulated oral salivary secretion, the PRI was used to quantify the amount of spontaneous salivary secretion and the POI was used to quantify the amount of salivary secretion after stimulation.

The results of this study indicate that, despite a slight discrepancy, decreases in oral activity indices correlate significantly with the histopathologic grade of parotid gland and the stage of Sjögren's syndrome. In addition, comparisons of other glandular parameters and overall analysis revealed that the three groups (healthy subjects, pSS, sSS and CTD patients) were distinguished by decreased oral activity indices and MA and UR of the submandibular gland. MA and UR are parameters indicating the quantity of glandular accumulation. Decreased accumulation in the submandibular gland is a highly sensitive indicator of salivary gland disease in Sjögren's syndrome (Pérez et al., 1999). In normal condition, saliva excretion volume varied with different glands. At rest, excretion volume of salivary gland account for 60 - 65% of total saliva and parotid gland account for 22 - 33%. Salivary gland in SS patients was more sensitive to stimulation than parotid gland. Both salivary and parotid gland scintigraphy results showed more severe functional defects in patients with SS than in patients with CTD. Oral function indices in CTD patients were lower than those of normal subjects. Therefore, the data indicate that decreased accumulation and decreased secretion in the parotid gland are highly sensitive indicators of salivary gland disease in Sjogren's syndrome.

In the past few years, MR studies have been performed to assess functional changes in salivary glands after gustatory stimulation using diffusion-weighted imaging (DWI). DWI provides apparent diffusion coefficient values reflecting molecular diffusion in biological tissues (Tsubota et al., 2000). Diffusion-weighted MRI allows evaluation of differences in the extracellular space through variations in molecular water mobility at the microscopic level. Diffusion of water molecules depends on structures within tissues (intracellular organelles, macromolecules, membranes, and so on), viscosity, temperature, fiber packing and the cell types present (Gray and MacFall, 1998). MR imaging revealed a broad spectrum of signal intensity patterns. MR imaging reflects changes in 54 parotid glands. We therefore tentatively categorized MR images of the parotid glands in patients with definite and probable SS on the basis of the appearance of signal intensities on T1- and T2-weighted images. Calculations of SD for each grade showed that SD continued to increase up to grade 3 and then leveled off. The change was statistically significant ($P < 0.01$). We found that the parotid glands of patients with Sjögren's syndrome exhibited significantly decreased ADCs compared with those of the healthy control subjects. Therefore, the net changes in tissue ADCs may result from the balance between extracellular and intracellular spaces for freely diffusing water. In the parotid glands of patients with Sjögren's syndrome, ADCs were found to decrease and were correlated with the severity of the disease (Izumi et al., 1996). This was in agreement with our work. The parotid glands affected by Sjögren's syndrome were characterized histopathologically by the infiltration of mononuclear leukocytes, destruction of gland acini and progressive fat deposition (Håkansson et al., 1994).

Quantitative oral activity indices together with certain glandular parameters (mainly PRI and PEF of the submandibular gland) were sensitive enough to distinguish the disease severity of Sjögren's syndrome. These quantitative variables may be used to identify the stage of Sjögren's syndrome, and thereby replace the labial gland biopsy, or they can be used to determine the clinical stage in equivocal cases. Our technique may prove helpful in diagnosing the progression of SS beyond its early stages. The method will help assess treatments and prognoses for patients with definite and probable SS.

Conclusion

New oral activity indices correlated with the stage of Sjögren's syndrome and these quantitative oral indices together with certain glandular parameters (mainly MA and UR of the parotid gland) were found to be sensitive enough to distinguish the disease severity of Sjögren's syndrome. The results of salivary scintigraphy can be predicted by diagnosis. Distinction between SS and patients with CTD but without SS is difficult. Diffusion-weighted imaging including an assessment by ADCs may be able to predict SS.

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