Radiol Oncol 1999; 33(2): 101-9.

Quantitative and qualitative assessment of contrast-enhanced magnetic resonance imaging of the parotid gland in Sjögren's syndrome

Michael Stiskal[1], Dieter Szolar[2], Erich Steiner[3], Hans Hitzelhammer[4], Klaus W. Preidler[2], Heinrich Czembirek[1]

Departments of Radiology, [1]KH Lainz-Vienna, [2]University of Graz, [3]University of Vienna, [4]Department of Internal Medicine KH Lainz-Vienna, Austria

Background. *The aim of this study was to evaluate the potential of unenhanced and contrast-enhanced MR imaging for providing diagnostic information of the parotid gland in patients with Sjögren's syndrome.*
Subjects and methods. *In 27 patients with Sjögren's syndrome, unenhanced and GdDTPA-enhanced spin-echo MR imaging was performed. The morphologic MR findings were compared to the signal intensity (SI) measurements of unenhanced T1-weighted, T2-weighted and contrast-enhanced T1-weighted MR imaging. Quantitative and qualitative data were compared with those of normal subjects (n=12).*
Results. *T1 and T2 values on the unenhanced MR images of the patients with Sjögren's syndrome were significantly lower than those of normal subjects (T1: 62+/-4%, T2: 71+/-2% of baseline). Quantitative analysis of contrast-enhanced MR imaging showed a significant SI increase in all patients with Sjögren's syndrome. Even in 4 patients with no morphologic findings on MR imaging, the increase of SI on enhanced MR imaging was significantly higher than in normal subjects (34+/-3% versus 17+/-3%; p<.05. The extent of morphologic changes correlated with quantitative data. The sensitivity and specificity for MR imaging was 85% and 100%, respectively.*
Conclusions. *The use of paramagnetic contrast media provides additional diagnostic information, particularly in the patients without apparent changes in morphology as indicated by a significantly greater tissue enhancement compared to normal subjects. The extent of morphologic alterations correlates with the quantitative data of Gd-DTPA-enhanced MR imaging but not with those of unenhanced MR imaging.*

Key words: Sjögren's syndrome, parotid diseases; magnetic resonance (MR) imaging, image enhancement, paramagnetic contrast media, morphology

Introduction

In 1933, Sjögren first described a syndrome characterised by the triad of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), with the evidence of a systemic autoimmune disease.[1-3] Sicca syndrome or

Received 20 July 1998
Accepted 29 November 1998

Correspondence to: Stiskal M, MD, Department of Radiology, Welkerbergenstr.1, A-1130 Vienna, Austria; Tel.: +43 222 80 110 2610; Fax: +43 222 80 110 2614.

the primary form of Sjögren's syndrome refers to the patients without underlying systemic autoimmune disease, whereas the secondary is associated with the connective tissue disease.[2-5] The secondary form is more frequent than the primary, with rheumatoid arthritis being the most common associated autoimmune disease (35%).[2-5] However, no therapeutic cure is currently available for this disorder. Hence, the care of the patients is confined to the alleviation of symptoms and prevention of tissue damage. The efficacy of the therapy of the patients with Sjögren's syndrome relies ultimately on early findings.

Magnetic resonance (MR) imaging is well suited to imaging the patients with inflammatory disease because of its potential to visualise inflamed tissue.[6-9] Former data suggest that the difference in signal intensity between normal and pathologic tissues can be increased by administering MR contrast medium;[6-9] it alters both T1 and T2 relaxation times in tissue by creating local magnetic fields that fluctuate with appropriate frequency components. For instance, Gadolinium-chelates produce significant enhancement on the T1-weighted images in the areas with blood supply, oedema, and necrosis.[10-13] This class of agents has been previously used for the delineation and characterisation of inflamed tissue in rheumatoid arthritis.[6,8,9,14]

However, there is no information available regarding the characterisation and staging of Sjögren's syndrome using contrast-enhanced MR-imaging. Accordingly, this study was designed (1) to evaluate the potential of MR imaging in the assessment of morphologic changes, and (2) to evaluate the potential of unenhanced and contrast-enhanced MR imaging for additional diagnostic information of the parotid gland in the patients with Sjögren's syndrome

Patients and methods

Study population

The study protocol comprised 12 normal subjects (7 female, 5 male, average age 48 years) without evidence of parotid disease and 27 patients with Sjögren's syndrome (25 female, 2 male, age 29-79, mean 51). All patients had signs and symptoms that met the criteria for the diagnosis of Sjögren's syndrome as defined by Sjögren's Disease Research Committee of Europe.[15] The diagnosis was pendent if the patients met 4 of the following 6 criteria; (1) xerophtalmia, (2) xerostomia, (3) positive Schirmer test results (<10 mm of wetting in 5 minutes), (4) positive lip biopsy, (5) positive scintigraphy of the salivary glands, and (6) evidence of auto antibodies (anti-Ro/SS-A and anti-La/SS-B). All patients had xerophtalmia and xerostomia. In 21 patients, the Schirmer test was positive. Scinitgraphy of the salivary glands was obtained in 13 patients (positive n=12). Fourteen patients had the biopsy of the salivary glands performed (positive n=12, not specific n=2) The diagnosis of Sjögren's syndrome was made after the identification of a periductal lymphocytic infiltration. The evidence of anti-Ro/SS-A antibodies and anti-La/SS-B (n=19) was positive in 14 patients. The patients with an associated pre-existing lymphoma, a HIV-related infection, a Sarcoid or a graft versus host reaction were excluded from the study. Twenty-two patients (81.5%) had a primary Sjögren's syndrome and 5 (18.5%) had a secondary form. The duration of the disease was from 1 to 7 years (mean 3). None of the studied patients underwent surgery of the parotid gland before. Sialography was not performed in the present population because of the reported evidence of serious exacerbation of the inflammatory process.[16-18]

MR Imaging

MR imaging was performed with 1.0 T unit (Siemens-Impact; Erlangen, Germany) using a commercially available head coil. The T2-weighted turbospin-echo(TSE) sequence followed by the T1-weighted SE sequence before and after the contrast medium application in coronal and axial scan planes were obtained. Gadopentetate dimeglumine (0.1 mmol/kg) (Gd-DTPA) (Magnevist; Schering, Berlin, Germany) was administered intravenously. For a direct comparison of the T1- and T2-weighted images, the same slices in the same location spacing were used. Imaging parameters for the T1- and T2-weighted (T)SE sequences were the following; repetition time (TR)/echo time (TE):600/15 msec and TR/TE:2000/15-90 msec, respectively. The acquisition matrix was 256x256, slice thickness 4 mm, intersection gap 0.4 mm, and field of view 23 cm. All images were displayed on the monitor with the same gray-scale level and window.

The qualitative analysis of the parotid gland on the unenhanced MR images entailed the following criteria; (1) enlargement present-absent, (2) parenchymal structure: homogeneous-inhomogeneous, and (3) presence of pseudotumors (parenchyma alterations with a size > 5 mm). The findings of the inhomogeneous gland parenchyma were further divided into two groups; mottled pattern (lesions < 2 mm in diameter) and honeycomb-like pattern (lesions 2-5 mm in diameter), known as "salt and pepper" appearance.[1]

On the unenhanced T1-weighted images, the signal intensity (SI) of the masseter muscle was defined as isointense. A circular region of interest (ROI) (4 mm^2; pixel size 0.14 cm^2) was used in order to quantify regional signal intensity (SI). For each image before and after the administration of contrast medium, ROIs were placed at the identical location bilaterally in the centre of the parotid gland. The co-ordinates of each region of interest were fixed in the first image and remained constant for the analysis of the subsequent post-contrast media injection images. The signal-intensity-time curves were generated with an implemented evaluation program. SI was calculated with the following equation; $SI = (SI_{max} - SI_0)/SI_0 \times 100$, ($SI_{max}$: maximal signal intensity following the administration of the contrast agent; SI_0: signal intensity before the injection of the contrast agent).

Data analysis

For morphological findings, MR images were interpreted independently by three radiologists. The final diagnosis was made following the agreement of at least two readers. All values were expressed as mean +/-standard error of mean value (SEM). The paired two-tailed Student's t-test was used for comparison of SI within the groups before and after the administration of the contrast agent. The unpaired Student's t-test was used for the comparisons between the groups to determine the differences of SI increase. A probability level of less than 0.05 was considered as significant.

Results

Normal subjects

Morphologic findings and signal intensity analysis

On MR imaging, the parotid gland showed homogeneous low level signal and intermediate signal on the T1- and T2-weighted MR images, respectively. Following the administration of contrast agent the increase in signal intensity was 17±3%.

Patients with Sjögren's syndrome

Morphologic findings

Morphologic findings on MR imaging are summarised in Table 1. In 23/27 patients

Table 1. MR imaging findings of the parotid gland in 27 patients with Sjögren's syndrome

Morfologic findings	MRI
Normal size	6
Enlargement	21
Homogeneity	8
Mottled pattern	8
Salt and pepper pattern	11

(85%), alterations in regard to the size or parenchymal homogeneity of the parotid gland were evident on the unenhanced T1- and T2-weighted MR images. In 4/23 patients, MR imaging showed only an enlargement of the gland. Unenhanced MR imaging was normal in 4 patients (15%). Post-contrast scans did not improve the delineation of parenchymal inhomogeneities.

Signal intensity analysis

Signal intensity of all alterations of the gland compared to normal gland tissue was hypointense on the unenhanced T1- and T2-weighted images in all patients (Figures 1-3). Figure 4 shows a significant difference in SI values on the unenhanced T1- and T2- weighted images between normal subjects and the patients with Sjögren's syndrome ($p<0.05$). No significant difference in SI values on the

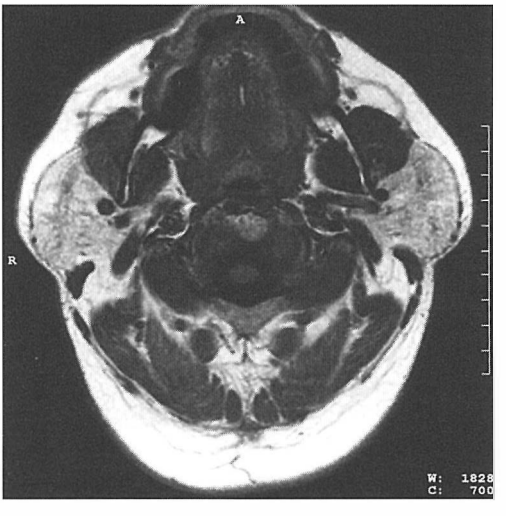

Figure 1a. Sjögren's syndrome – mottled appearance. Transverse (trans.) T1-W SE image (600/15 msec, TR/TE) precontrast: The gland appears enlarged with a granular internal structure.

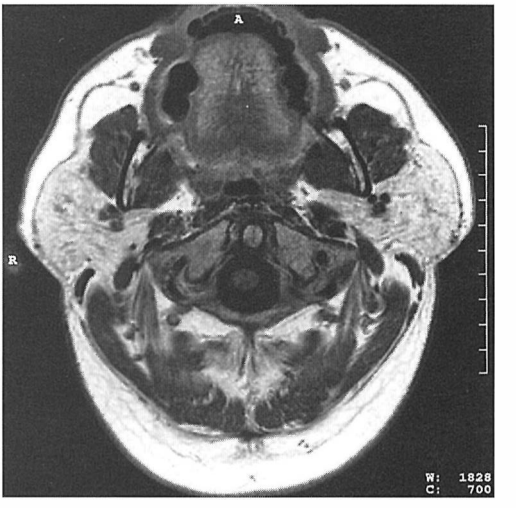

Figure 1b. Sjögren's syndrome – mottled appearance. Gadolinium-enhanced trans. T1-W SE image: The same pattern is seen on the enhanced image; no additional morphological information concerning the gland structure can be obtained using contrast medium in comparison to T2-weighted image.

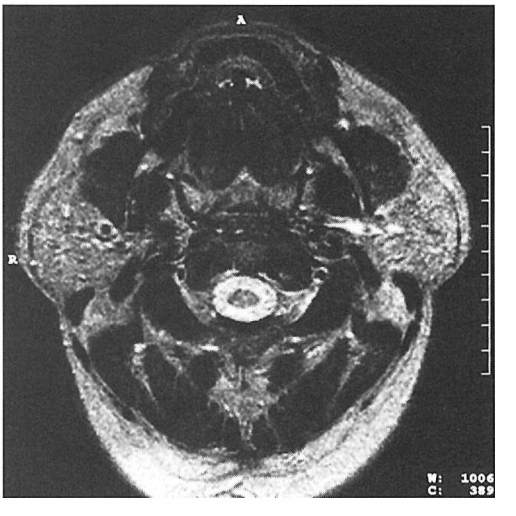

Figure 1c. Sjögren's syndrome – mottled appearance. Trans. T2-W SE image (2500/90 msec, TR/TE): The inhomogeneous granular internal structure is best seen on the T2-weighted image.

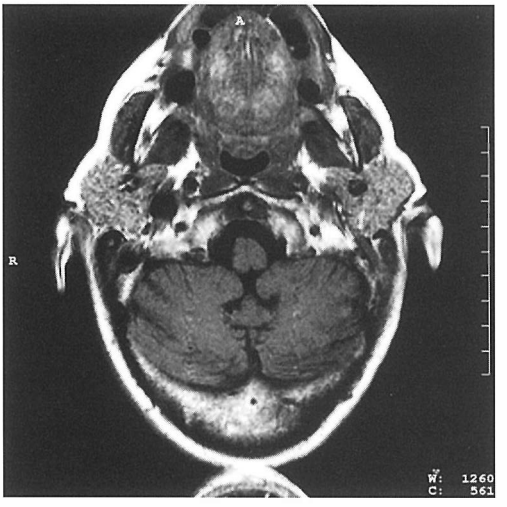

Figure 2a. Sjögren's syndrome – honeycomb-like appearance. Transverse (trans.) T1-W SE image (600/15 msec, TR/TE) precontrast: Significant enlargement of the gland with coarse nodular internal structure.

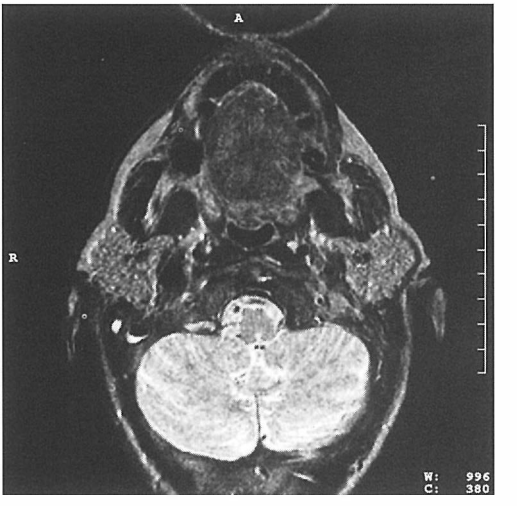

Figure 2c. Sjögren's syndrome – honeycomb-like appearance. Trans. T2-W SE image (2500/90 msec, TR/TE): The T2-weighted image represents best the typical salt and pepper appearance of the parotid gland in Sjögren's syndrome.

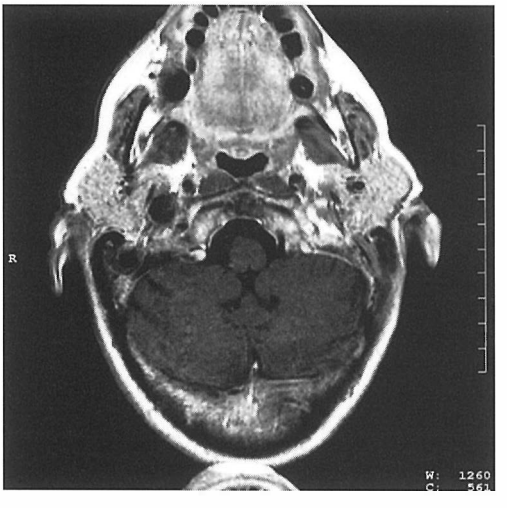

Figure 2b. Sjögren's syndrome – honeycomb-like appearance. Gadolinium-enhanced trans. T1-W SE image: Contrast medium outlines the coarse nodular internal structure but with no additional morphological information in comparison to the T2-weighted image.

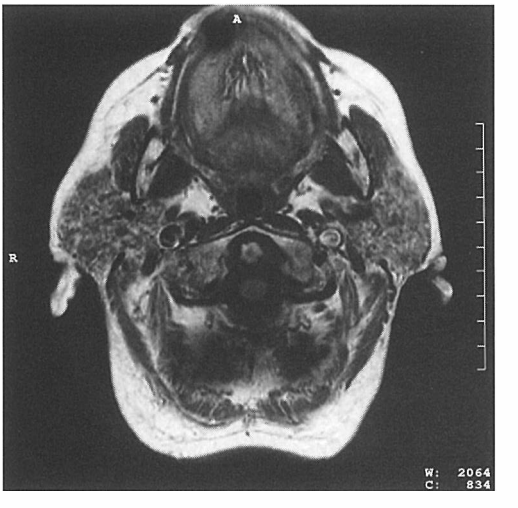

Figure 3a. Sjögren's syndrome – patient with honeycomb-like appearance on MRI. Transverse (trans.) T1-W SE image (600/15 msec, TR/TE) precontrast: Enlarged gland with coarse nodular internal structure.

unenhanced T1- and T2- weighted images was found between the patients with mottled and nodular honeycomb-like patterns.

Following the administration of the contrast medium, a significant increase of signal intensity in all patients with Sjögren's syndrome (46+/-19% versus 17+/-3% increase of the baseline value, $p<0.05$) was noted in com-

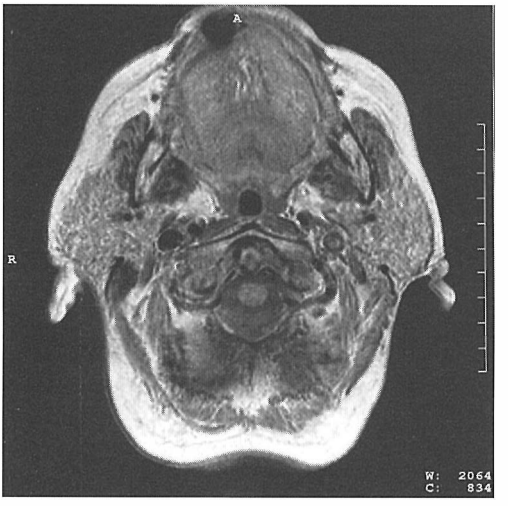

Figure 3b. Sjögren's syndrome – patient with honeycomb-like appearance on MRI. Gadolinium-enhanced trans. T1-W SE image: Honeycomb-like appearance is clearly shown on enhances T1-weighted image.

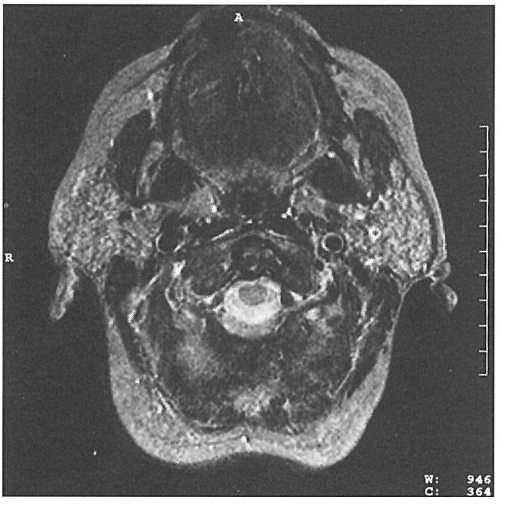

Figure 3c. Sjögren's syndrome – patient with honeycomblike appearance on MRI. Trans. T2-W SE image (2500/90 msec, TR/TE): Honeycomb-like appearance is represented best on enhances T2-weighted image.

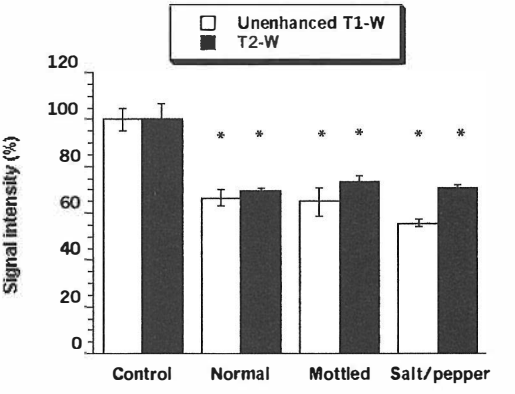

Figure 4. Difference in mean signal intensity between control group, patients with Sjögren's syndrome and no morphological findings, mottled pattern, and nodular honeycomb-like pattern of parotid gland parenchyma at T1-weighted unenhanced and T2-weighted image. Data are expressed as mean +/-SEM. (*significant compared with control group).

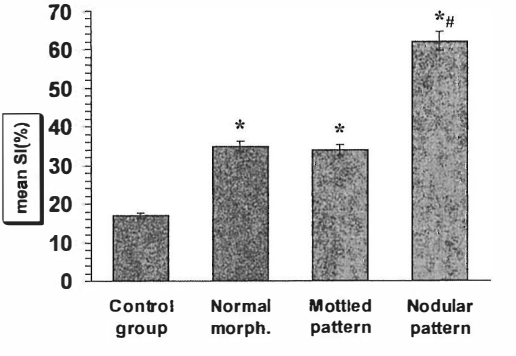

Figure 5. Comparison of differences in mean signal intensity (SI) on contrast-enhanced MR imaging between control group and MR-morphology of patients with Sjögren's syndrome with no morphological findings, mottled pattern, and nodular pattern of parotid gland parenchyma. Data are expressed as mean +/-SEM. (*significant compared with control group, # significant compared with patients with either no morphological findings or mottled pattern).

parison to that in normal subjects. Moreover, 8 patients (4 patients with the enlargement and 4 patients with no enlargement of the gland), in whom MR morphology was negative, showed a significantly higher SI_{max} (34+/-3% of baseline) than normal subjects. In the patients with mottled pattern of the parotid gland, SI_{max}, compared to normal, increased significantly (37+/-4% versus 17+/-3% of baseline, $p<0.05$). However, the magnitude of enhancement was similar to that in the

patients with no morphological findings. SI_{max} on MR imaging was significantly higher in the patients with nodular honeycomb-like pattern than in normal subjects and all other patients (59+/-6% of baseline, $p<0.05$). Figures 4 and 5 summarise the data of contrast-enhanced MR scans in the patients with or without Sjögren's syndrome.

Discussion

The major findings of the current study are as follows; the T2 and T1 signal intensity values on the unenhanced MR images were significantly lower than in normal subjects. The decrease of the T2 and T1 signal intensity values on the unenhanced MR imaging was not concordant to pathologic MR-morphology in the patients with Sjögren's syndrome. The signal intensity measurements following the administration of contrast media showed a significant increase of the signal intensity in patients compared to normal subjects. Even in the patients with no pathologic gland morphology, the signal intensity increase was significantly higher than in the subjects of the control group. The contrast-enhanced MR imaging is superior to the unenhanced MR imaging as indicated by a significantly different increase of the signal intensity in the patients with nodular pattern compared to the patients with either no morphologic findings or mottled pattern. The signal intensity increase did correlate with the extent of morphologic findings on MR imaging.

Sjögren's syndrome is believed to be a chronic inflammatory disease of autoimmune origin affecting usually postmenopausal women (90%).[5] The criteria for Sjögren's syndrome have not been universally established because of the lack of clarity in the diagnostic evaluation.[15] While some authors call for sialography, others see the salivary gland biopsy as an indispensable diagnostic tool.[19-24] Recent trials to stage Sjögren's syndrome on the basis of MR imaging are also not too satisfying because they are missing a reasonable pathological grading system.[25] Moreover, the underlying pathogenesis of Sjögren's syndrome is still not known. The antibodies to SS-A and SS-B are often detected both in the patients with sicca syndrome (70% and 48%, respectively) and in the patients with rheumatoid arthritis and Sjögren's syndrome (9% and 3%, respectively);[2] the antibodies to SS-B are considered highly specific for Sjögren's syndrome.[5] The clinical features in our patients were compatible with those reported in the literature.

MR imaging showed a high accuracy in revealing the mottled and/or honeycomb-like patterns ("salt and pepper"). Both pattern of inhomogeneity, defined also as granular for mottled and speckled for honeycomb-like pattern,[25] have been demonstrated with equal image quality on the unenhanced T1- and T2-weighted MR images as hypointense areas of varying size, which is in accordance with previous reports.[25,26] Microscopically, a periductal mononuclear cell infiltrate consists, initially, of small lymphocytes and, during the course of disease, of large lymphocytes and reticular cells. Vascular disease seems to be responsible for extravasation of lymphocytes. Mitchell and Sundaram *et al.* suggested that aggregates of lymphocytes might be responsible for this specific pattern in Sjögren's syndrome.[27,28] Our findings are consistent with those of previous studies which demonstrated a "salt and pepper" appearance in plain MR imaging.[25,26] In contrast to the inhomogeneity of the gland parenchyma, the enlargement of the parotid gland is an unreliable sign because the term 'enlargement of the gland' still lacks exactness in definition.

The significant decrease in signal intensity on the unenhanced T1-weighted images can be explained by interstitial oedema. However, this finding is not specific to Sjögren's syndrome as reported by others.[1,25,27] In contrast to previous studies, the T2-weighted MR

images demonstrated a significant decrease of signal intensity in patients compared to normals.[1,25] Furthermore, the calculations of signal intensity on the T2-weighted images did not allow to differentiate between the patients with mottled and nodular honeycomb-like pattern of the parotid gland. In agreement with previous reports, the data of the present study suggest that the amount of lymphocytic infiltration and fibrotic tissue might be responsible for an absolute decrease in signal intensity. This observation is also supported by a significant increase in signal intensity following the administration of contrast medium compared to normal subjects. Moreover, even the patients with no morphologic findings demonstrated a significant increase in signal intensity after the contrast medium administration. This marked tissue enhancement can be related to vasculitis which causes lymphocytic extravasation due to capillary permeability. This leads to an increased leaking of small GdDTPA molecules through the capillary endothelium in the surrounding tissue causing an increase in SI_{max}. This is in contrast to previous MR imaging studies which hypothesised that hyperperfusion may account for this phenomenon.[30]

In conclusion, MR imaging is a suitable non-invasive method to detect morphologic changes in Sjögren's syndrome. The mandatory use of paramagnetic contrast media to rule out lymphoma in Sjögren's syndrome provides additional diagnostic information, particularly in the patients without apparent morphologic changes. Future work may prove contrast-enhanced MR imaging an important diagnostic method for monitoring the response to therapeutic interventions in the patients with Sjögren's syndrome.

References

1. Takashima S, Takeuchi N, Morimoto S, Tomiyama N, Ikezoe J, Shogen K, et al. MR imaging of Sjögren syndrome: correlation with sialography and pathology. *J Comput Assist Tomogr* 1991; **15:** 393-400.

2. Whaley K, Buchanan WW. Sjögren syndrome and associated disease. In: Parker CW, editor. *Clinical immunology.* Philadelphia: WB Saunders; 1980. p. 632-66.

3. Mandel L. Inflammatory disorders. Part I. Clinicopathologic considerations. In: Rankow RM, Polayers IM, editors. *Diseases of the salivary glands.* Philadelphia: WB Saunders; 1976. p. 202-28.

4. Hardin JA, Bloch KJ. Sjögren syndrome. In: Samter M. *Immunological diseases.* Boston: Little Brown; 1978. p. 1151-7.

5. Robbins S, Cotran R, Kumar V. Pathological basis of disease. 3rd ed. Philadelphia: WB Saunders; 1984. p. 202-28.

6. Harve-Somma CMP, Sebag GH, Prieur AM, Bonnerot V, Lallemand DP. Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. *Radiology* 1992; **182:** 93-8.

7. Köning H, Sieper J, Wolf KJ. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. *Radiology* 1990; **176:** 473-7.

8. Kursunoglu-Brahme S, Riccio T, Weisman MH, Resnick D, Zvaifler N, Sanders ME, et al. Rheumatoid knee: role of gadopentetate-enhanced MR imaging. *Radiology* 1990; **176:** 831-5.

9. Winalski CS, Aliabadi P, Wright RJ, Shortkroff S, Sledge Cb, Weissman BN. Enhancement of joint fluid with intravenously administered gadopentetate dimeglumine: technique, rationale, and implications. *Radiology* 1993; **187:** 179-85.

10. Doucet D, Meyer D, Bonnemain B, Doyon D, Caille JM. Gd DOTA. In: Runge VM, editor. *Enhanced magnetic resonance imaging.* St. Louis: Mosby; 1989. p. 87-104.

11. LeMignon MM, Chambon C, Warrington S, Davies R, Bonnemain B. Pharmacokinetics and tolerability after intravenous injection into healthy volunteers. *Invest Radiol* 1990; **25:** 933-7.

12. Nelson KL, Runge VM. Basic principles. In: Runge VM, editor. *Enhanced magnetic resonance imaging.* St. Louis: Mosby; 1989. p. 57-73.

13. Weinmann HJ, Press WR, Radüchel B, Platzek J, Schmitt-Willich H, Vogler H. Characteristics of Gd-DTPAA and new derivates. In: Bydder G, Felix R, Bücheler E, editors. *Contrast media in MRI.* Berlin: Medicom; 1990. p. 19-29.

14. Reiser MF, Bongartz GP, Erlermann R, Schneidre M, Pauly T, Sittek H, et al. Gadolinium-DTPA in rheumatoid arthritis and related diseases: first results with dynamic magnetic resonance imaging. *Skeletal Radiol* 1989; **18:** 591-7.

15. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome. *Arthritis Rheum* 1993; **36:** 340-7.

16. Patey DH, Thackray AC. Chronic "sialectatic" parotitis in the light of pathological studies on parotidectomy material. *Br J Surg* 1995; **43:** 43.50.

17. Ericson S. Sialographic study of the parotid glands in rheumatoid arthritis. *Odont Rev* 1967; **18:** 163-72.

18. Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ, et al. Sjögren's syndrome. A clinical pathological and serological study of sixty-two cases. *Medicine* 1992; **71:** 386-401.

19. Daniels TE. Labial salivary gland biopsy in Sjögren's syndrome. *Arthritis Rheum* 1984; **2:** 147-56.

20. Daniels TE. Salivary histopathology in diagnosis of Sjögren's syndrome. *Scand J Rheumatol* 1986; **61(Suppl 1):** 36-43.

21. Fox RI Howell FV, Bone RC, Michelson P. Primary Sjögren's syndrome: clinical and immunopathologic features. *Arthritis Rheum* 1984; **2:** 77-105.

22. Marx RE, Hartman KS, Rethman KV. A prospective study comparing incisional labial to incisional parotid biopsies in the detection and confirmation of sarcoidosis, Sjögren's disease, sialosis and lymphoma. *J Rheumatol* 1988; **15:** 621-9.

23. Schiodt M, Daniels TE, Greenspan JS, Ortholm P, Prause JU, Manthorpe R. Comparing diagnostic criteria for the salivary component of Sjögren's syndrome. *Scand J Rheumatol* 1986; **61(Suppl 1):** 44-6.

24. Scully C. Oral parameters in the diagnosis of Sjögren's syndrome. *Clin Exp Rheumatol* 1989; **7:** 113-7.

25. Vogl TJ; Dresel ST, Späth M, Grevers G, Wilimzig C, Schedel HK, et al. Parotid gland: Plain and gadolinium-enhanced MR imaging. *Radiology* 1990; **177:** 667-74.

26. Späth M, Krüger K, Dresel St, Grevers G, Vogl T, Schattenkirchner M. Magnetic resonance imaging of the parotid gland in patients with Sjögren's syndrome. *J Rheumatol* 1991; **18:** 1372: 8.

27. Mitchell DG Jr, Burk DL, Vinitski S, Rifkin MD. The biophysical basis of tissue contrast in extracranial MR imaging. *AJR* 1987; **149:** 831-7.

28. Sundaram M, McGuire MH, Schajowicz F. Soft-tissue masses: histologic basis for decreased signal (short T2) on T2-weighted MR images. *AJR* 1987; **148:** 1247-50.

29. Takashima S, Nagareda T, Noguchi Y, Takeuchi N, Johkoh T, Ikezoe J, et al. CT and MR appearances of parotid pseudotumors in Sjögren syndrome. *J Comput Assist Tomogr* 1992; **16:** 376-83.

30. Steiner E, Graninger W, Hitzelhammer J, Lakits A, Petera P, Franz P, et al. Farbkodierte duplexsonographie der glandula parotis beim Sjögren syndrom. *Fortschr Röntgenstr* 1994; **160:** 97-101.

31. Whaley K, Buchanan WW. Sjögren syndrome and associated disease. In: Parker CW, editor. *Clinical immunology.* Philadelphia: WB Saunders; 1980. p. 632-66.

32. Talal N, Bunim JJ. The development of malignant lymphoma in the course of Sjögren's syndrome. *Am J Med* 1964; **36:** 529-40.