Apparent Diffusion Coefficient Mapping of the Normal Parotid Gland and Parotid Involvement in Patients with Systemic Connective Tissue Disorders

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*AJNR Am J Neuroradiol* 2004, 25 (1) 16-20
http://www.ajnr.org/content/25/1/16
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PURPOSE: We hypothesized that a difference in restricted diffusion would exist in patients with connective tissue disorders (CTD) as compared with those without CTD. Our purpose was to determine whether the apparent diffusion coefficient (ADC) measurement could be used to identify parotid abnormalities in patients with CTD.

METHODS: One neuroradiologist, who was unaware of patient histories, retrospectively measured the ADC values for the parotid glands in 121 patients who underwent clinically indicated brain MR imaging in which the parotid glands were sufficiently depicted. Regions of interest were obtained from both the left and right parotid glands. After the medical records were reviewed and exclusion criteria were used, 90 non-CTD and seven CTD patients (systemic lupus erythematosus = 5; discoid lupus erythematosus = 1; Sjögren syndrome = 1) remained. The two groups were then compared. Statistical analysis consisted of Wilcoxon sign rank and Mann-Whitney tests.

RESULTS: The combined mean ADC for both parotid glands in 90 healthy patients was 0.50 ± 0.28 × 10⁻³ mm²/s (95% CI, 0.44 × 10⁻³, 0.56 × 10⁻³). The combined mean ADC for both parotid glands in the seven CTD patients was 0.96 ± 0.24 × 10⁻³ mm²/s (95% CI, 0.79 × 10⁻³, 1.14 × 10⁻³). The mean ADC for the CTD patients’ parotid glands was significantly higher than that of the non-CTD patients (P = .0001), which suggests there is less restricted diffusion in parotid glands affected by CTD when compared with normal parotid glands.

CONCLUSION: These results suggest that ADCs may be used to detect parotid abnormalities in patients with CTD that are not identified by standard imaging. Although preliminary, the results indicate a potential role for ADC mapping in detection of subclinical parotid disease.

The salivary glands, as an organ system, have one of the greatest diversities of pathology, ranging from infection and inflammation to various neoplasms (1–17). Currently, an assessment of the parotid gland can be performed with biopsy, fine needle aspiration, sialography, ultrasonography, CT, scintigraphy, and various MR imaging techniques (7, 10, 18–25). Each diagnostic technique varies in invasiveness, degree of soft tissue differentiation, and spatial resolution (10). Some imaging techniques are more appropriate for tissue assessment, whereas others are more useful for ductal evaluation (7, 18, 19).

For diffuse parotid gland disorders, such as systemic connective tissue disorders (CTD), tissue sampling through biopsy is the criterion standard, but it is highly invasive, operator dependent, and can characterize only the portion of the gland from where the sample was obtained (26). Ultrasonography, CT, and MR imaging are used routinely to assess the degree of salivary gland involvement in CTD (10, 21). Enlargement of the parotid gland in CTD patients is shown by CT in 25–55% of the cases (25). Standard T1- and T2-weighted MR imaging appears to confer additional parenchymal definition that may be useful in evaluating the degree of salivary gland involvement in patients with CTD, particularly patients with Sjögren syndrome (27); however, these abnormalities are often identified in advanced stages of the disease (27).

Diffusion-weighted imaging has been shown in the central nervous system to identify certain pathologic...
conditions, such as ischemia, earlier than standard T1- and T2-weighted MR imaging (28). Potentially, diffusion-weighted imaging could similarly reveal early pathologic abnormality in the salivary glands. Diffusion-weighted imaging with apparent diffusion coefficients (ADCs) has the advantage of determining whether increased diffusion-weighted signal intensity is due to restricted diffusion or T2-weighted shine-through (29). Although ADC values have been used in the central nervous system, little is known about ADC mapping in the head and neck structures outside of the central nervous system (30, 31). Recent studies have shown that diffusion-weighted imaging with ADC mapping can be used to characterize lesions in a variety of head and neck disorders (30, 32). The purpose of our study is twofold: 1) to quantitate whether increased diffusion-weighted signal intensity is due to restricted diffusion or T2-weighted shine-through (29). Although ADC values have been used in the central nervous system, little is known about ADC mapping in the head and neck structures outside of the central nervous system (30, 31). Recent studies have shown that diffusion-weighted imaging with ADC mapping can be used to characterize lesions in a variety of head and neck disorders (30, 32). The purpose of our study is twofold: 1) to quantitate the normal ADC values of the parotid parenchyma and 2) to compare the ADC values of the normal parotid gland with patients with CTD.

**Methods**

**Patient Selection**

Individuals in whom clinically indicated brain MR imaging had been obtained between May 2001 and September 2001 were considered for the retrospective study. To be included, the MR imaging examination must have depicted both parotid glands on axial 2D spin-echo T1-weighted and diffusion-weighted images, as determined by visual inspection of the MR imaging images. A total of 121 individuals (46 men and 75 women; 1–85 years of age [mean, 39 years]) fulfilled inclusion criteria. Because this was a retrospective review, this study was deemed exempt from continuing review by our institutional review board.

The clinical indications for the MR imaging study in these patients included psychiatric disorders (n = 2); evaluation of mass lesions, benign and malignant (n = 46); neurologic disorders, including headache, seizure, dementia, multiple sclerosis, Menière disease, Grave disease, diplopia, vertigo, neuropathy, ataxia, dystonic posturing, tremor, hemiparesis, syncope, blurred vision, aphasia, and anosmia (n = 52); hemorrhage (n = 1); infarct (n = 6); closed head injury (n = 3); anatomic disorders (n = 5); evaluation of systemic lupus erythematosus (SLE; n = 4); and parotid disorders (n = 2).

We excluded patients who were younger than 5 years (n = 6), had known parotid lesions, surgery, or trauma (n = 2), or had a history of radiation therapy (n = 16). A total of 97 patients (36 men and 61 women; 5–85 years of age [average, 42 years]) formed the study population (seven patients with known connective tissue disorder [CTD] [five with SLE, one with discoid lupus erythematosus (DLE), and one with Sjögren syndrome]; 90 without known CTD). Neither the patients with CTD nor the controls had documented complaints of salivary dysfunction. Fulfillment of the final exclusion criteria and segregation based on the presence or absence of CTD was determined by electronic records review of all available clinical data.

**MR Imaging Technique and Analysis**

All examinations were performed by using a 1.5-T system (Siemens; GE Medical Systems, Milwaukee, WI) with a standard head coil (GE Medical Systems, Waukesha, WI). The parameters for the axial 2D spin-echo T1-weighted sequence were a TR/TE of 500/14, a 6.0-mm section thickness with 0–2-mm interslice gap, a 22 × 22-cm field of view, and a 128 × 128 matrix. The parameters for diffusion-weighted images were a minimum TE of 74.9 ms, a TR of 10,000 ms, and b = 1,000 s/mm². ADC maps were generated by using a pixel-by-pixel calculation as referenced by Wang et al (30).

After confirmation of parotid gland location of diffusion-weighted images (Figs 1 and 2), ADC maps were generated by a single observer (R.R.P.) from the axial diffusion-weighted images (Figs 1 and 2). Regions of interest, measuring approximately 74 mm², were manually defined in a relatively homogeneous area in each parotid gland. If no area was deemed homogeneous, an area that was most representative of the parotid gland was selected. ADC was recorded for each defined region of interest. As an internal control, the ADC in a 51-mm² region of interest defined in the center of the spinal cord at the level of the parotid glands was recorded in all seven patients with CTD and in 54 representative non-CTD patients. Spinal cord measurements in the upper area of the neck were consistent with the measurements made by in the reference study by Wang et al (30).

**Data Analysis**

We compared the right and left parotid gland ADC data by using the Wilcoxon sign rank test. We segregated the patients into two groups on the basis of the history of underlying CTD. To determine a statistically significant difference between the two groups, the Mann-Whitney U test was employed. We fur-
A total of 90 patients with no known history of CTD (36 men and 75 women; mean age, 41 years) were included. The right and left parotid glands were initially analyzed separately. The mean ADC value of the left parotid gland was 0.47 ± 0.28 × 10⁻³ mm²/s (95% CI, 0.42 × 10⁻³, 0.52 × 10⁻³); the mean ADC value of the right parotid gland was 0.53 ± 0.29 × 10⁻³ mm²/s (95% CI, 0.47 × 10⁻³, 0.59 × 10⁻³) (Table 1). The difference between the left and right ADC values was not significant (P = .60). When the data for the left and right parotid glands were combined, the average ADC value of the parotid gland was 0.50 ± 0.28 × 10⁻³ mm²/s (95% CI, 0.44 × 10⁻³, 0.56 × 10⁻³). We further segregated patients by sex after combining parotid glands. There was a statistically significant difference (P = .01) in ADC values accounting for sex, where mean ADC in men was 0.44 ± 0.28 × 10⁻³ mm²/s; in women, 0.54 ± 0.28 × 10⁻³ mm²/s.

As an internal control, the mean ADC value of the parotid gland in a representative sample of these patients was 0.98 ± 0.18 × 10⁻³ mm²/s (95% CI, 0.93 × 10⁻³, 1.03 × 10⁻³). We validated our internal control with the previously published value (30) of 1.11 ± 0.14 × 10⁻³ mm²/s (mean ± SD) and found no statistically significant difference (P = .75).

### Results

**Non-CTD Patients**

A total of seven patients with a known history of CTD (seven women; average age, 48 years) were included. Initially, the right and left glands were analyzed separately (Table 2). There was no qualitative difference in the MR appearance on T1- and T2-weighted images between the parotid glands of patients with CTD compared with our normal cohort. There was no radiographic evidence of sialadenitis or sialosis in the parotid glands of patients with CTD.
The mean ADC value of the left parotid gland was
0.98 ± 0.31 × 10^-3 mm^2/s (95% CI, 0.75 × 10^-3,
1.20 × 10^-3); the mean ADC value of the right
parotid gland was 0.95 ± 0.29 × 10^-3 mm^2/s (95% CI,
0.73 × 10^-3, 1.17 × 10^-3). The difference between
the left and right ADC values was not significant (P = .22). When the data for the left and right parotid
glands were combined, the mean ADC value was
0.96 ± 0.24 × 10^-3 mm^2/s (95% CI, 0.79 × 10^-3,
1.14 × 10^-3) (Table 2).

As an internal control, the mean ADC value of the
spinal cord in these patients was 1.04 ± 0.29 × 10^-3
mm^2/s (95% CI, 0.83 × 10^-3, 1.25 × 10^-3), which was
not significantly different from the non-CTD group
(P = .87). Also, the mean ADC value of the spinal
cord in these patients was not significantly different
from previously published studies (P = .54) (30).

The ADC values for the left, right, and combined
parotid glands for the CTD patients, however, were
significantly higher than those of non-CTD parotid
glands (P < .005; Table 1). Because all patients with
CTD were women and we noted differences in ADC
values on the basis of sex, we further compared CTD
patients with female non-CTD patients. The differ-
ence remained statistically significant (P < .0002).

Discussion

We have characterized the distribution of the ADC
values in the normal, non-CTD parotid gland for our
study population. The lack of statistical difference
between the ADC value of the left and right parotid
glands in both groups shows consistency in our data
collection. Also, our ADC results may be translatable
to other ADC studies that have been previously pub-
lished, in light of the consistency of our spinal cord data
as compared with data of previous investigations (30).

In a recently published study by Sumi et al (32), the
ADC value in the normal parotid gland in their pop-
ulation was 0.28 ± 0.01 × 10^-3 mm^2/s. These results
are not significantly different from our data by using
the Mann-Whitney test (P = .49) and validate the
results of our non-CTD parotid gland ADC values
that we used to compare with our CTD parotid gland
results.

Our results suggest there is less restricted diffusion
(increase in ADC) in the parotid gland of CTD pa-
patients than that found in normal patients, even ac-
counting for sex. The increase in ADC seen in early
parotid involvement in CTD patients may be due to
various causes. Sumi et al (32) suggested that elevated
ADC values in the CTD population could be due to
intraparotid edema in patients with early sialadenitis
(32). By contrast, Sumi et al reported a decrease in
ADC in patients with late stage clinically evident
disease. The fact that our patients had no radi-
ographic abnormalities on standard T1- and T2-
weighted images and had no salivary dysfunction
indicates that the parotid changes in our population
are mild and are in the early stages of disease. It is
possible that the elevated ADC values in patients with
CTD may be due to early cellular infiltration. Studies
of CTD patients and CTD mouse models have shown
that early sialadenitis results in focal periductal lym-
phocytic infiltration and dilated intraglandular ducts
with a slight increase in the interlobular fibrous tissue
(33, 34). It is possible that the increase in unrestricted
diffusion identified in our affected population could
be caused by early lymphocellular infiltrate in the
parotid glands (35, 36).

We feel that ADCs may be used to evaluate the
parotid gland and to detect parotid abnormalities in
patients with systemic connective tissue disorders that
are not identified by standard imaging. It is also
possible that ADC mapping will be able to diagnose
parotid disease before the onset of clinical signs. This
may affect prognosis by allowing early intervention
of certain disorders. The treatment of salivary dysfunc-
tion in patients with Sjögren syndrome and other
connective tissue disorders is largely empirical and
symptomatic (36). Analgesics and antinflammatory
drugs are used for symptomatic relief and to reduce
further damage to tissues (36). In addition to provid-
ing symptomatic relief, treatment is aimed at reducing
the damaging effects of chronic xerostomia by substi-
tuting the missing secretions (36). Also, preventive
dental care and personal hygiene are important in
reducing the long-term complications of these disor-
ders (36). It is possible that earlier diagnosis and
treatment of parotid involvement in these patients
may lead to a reduction in symptoms and long-term
complications; however, future studies will be neces-
sary to confirm this.

This study is a preliminary evaluation of the feasi-
bility of applying ADCs in the evaluation of nonbrain
structures, in particular the parotid gland. Although
the results are encouraging, in view of the apparent
detectable differences in ADC values based on pres-
ence or absence of CTD, further studies replicating
and validating our findings need to be performed.
This may include a prospective trial enrolling patients
with and those without CTD or an assessment of the
response to therapy by using ADC values as an indi-
cator of parotid parenchymal status.

There are certain limitations associated with our
study. We present the ADC means and confidence
intervals for our population as standard descriptive
statistics, the calculations of which are based on a
normal distribution. The 95% CI of our non-CTD
population compared with Sumi et al do not overlap,
which suggests a statistically significant difference be-
tween two populations assumed to have a normal
distribution. In comparing our values with Sumi et al,
we did not make such an assumption and used a
nonparametric test. Consequently, we believe that the
results of nonparametric testing (Mann Whitney)
more accurately compare the two means, rather than
comparing them by using the 95% CI. Further, het-
erogeneity in our patient population may have con-
tributed to the relatively wide distribution of ADC
values in our study. It is interesting that there appears
to be a sex-based difference in ADC values in our
population. This is of uncertain significance and may
be related to differences in fat content of the parotids.
Diffusion-weighted imaging is based on echo-planar imaging that permits rapid imaging with reduced motion artifacts. The disadvantages are relatively low signal-to-noise ratios and image degradation due to susceptibility artifacts. Our standard echo planar imaging technique attempts to minimize susceptibility artifacts due to air-bone-tissue interfaces by using a high-bandwidth echo planar sequence with thin sections, although we do not use an antisusceptibility device. Further, heterogeneity in fat content of the parotid glands across the patient population may have manifested different levels of chemical shift artifacts, contributing to some of the variability in parotid ADC values. All patients were imaged in a standard head coil. As a result, the complete extent of the parotid gland was not included in the study. The parotid regions of interest were obtained from an area that was felt to be most representative of the parotid gland. Also, the sample size for our CTD population was relatively small.

Conclusion

Our findings indicate that the parotid glands in patients with CTD and no parotid-referable complaints have higher ADC values than the parotid glands in patients without CTD. When compared with our normal values, ADC mapping of the parotid gland may be a useful adjunct in the detection of parotid involvement in patients with CTD. This information may be used to identify patients with parotid abnormalities before development of clinical symptoms or imaging abnormalities detectable current standard techniques.

Acknowledgments

We thank Jill Philp and Claudia Koitch for their assistance in the collection of patient information and their software technical support. Also, we thank Nita Patel for assisting in the retrieval of the hardware information and image acquisition parameters. Finally, we thank Matthew Thompson for his assistance in converting images for submission.

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