Textural analysis of MR images as an additional evaluation tool of Parotid Glands in Sjögren's Syndrome in children and adolescents - initial findings

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Article

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Abstract

Magnetic Resonance Imaging (MRI) is often a reference imaging method in soft tissue pathologies, particularly of the head and neck region. A significant increase in MRI popularity is observed, especially concerning salivary gland pathologies like neoplasm or chronic inflammatory processes of salivary glands like in Sjogren syndrome. The development of MRI techniques like MR sialography set a new non-invasive method alternative to classical sialography, especially in advanced cases.

Another rising MRI technique - texture analysis - appears to be a promising tool in assessing structural changes in parenchymal organs and can be an additional parameter for assessing the inflammatory process in salivary glands.

This research aimed to explore the correlation between apparent diffusion coefficient (ADC), based on T2 weighted images MRI sialography of parotid in children with and without Sjögren's Syndrome (SS).

Both groups (20 healthy and 36 patients with SS) underwent 3.0 Tesla MRI, including diffusion-weighted imaging (DWI) (b = 0, 500 and 1000 s/mm²) and T2-weighted imaging.

First-order statistics (FSO), second-order, and higher-order statistical texture analysis of the bilateral parotid glands were performed through texture analysis. A multimodal analysis, including texture analysis (TA) clinical classification; MRI evaluation for this disease entity to identify factors of disease activity. The examination group with SS was divided by the Tonami scale.

The parotid ADC values from whole volume ROI were significantly lower in group 1 than in the higher activity group. The lowest kurtosis values in the highest grade of the Tonami Scale were found. The FSO parameters showed a positive correlation in TA from T2 weighted images- a moderate correlation with individual parameters.

Our findings make TA a promising tool for assessing the grade of parotid gland inflammation. However, the effect of binning and ROI (region of interest) size is yet to be determined and needs further studies.

1. Introduction

The symptoms and course of Sjögren's Syndrome (SS) in children are often non-specific with delayed diagnosis. The SS can involve different organs like the salivary and lacrimal glands or fundamental contributions influencing the joints, lungs, kidneys, veins, and muscles [1]. Early diagnosis and evaluation of disease activity are crucial. The methods used to diagnose SS in the pediatric population are burdened with low sensitivity, especially immunologic parameters [2]. At the same time, clinical symptoms can be transient and not specific. The studies underlining the possible role of imaging methods are very promising. The new imaging methods can provide additional information in a non-invasive way.

There are numerous strategies for imaging salivary glands. Salivary gland ultrasound is a promising screening tool and a potential substitute for salivary gland biopsy [3]. Still, a validated assessment system is missing, and variability between sonographers and difficulty in objective monitoring.

The following most common imaging method in SS is sialography. A radiographic strategy can distinguish anatomic changes in the salivary gland duct system. Conversely, scintigraphy gives valuable data about salivary organ work by measuring the rate and density of technetium-99m (99mTc) pertechnetate take-up in the mouth after intravenous infusion. Both methods are invasive, with the risk of radiation exposure side effects and invasiveness [2]. MRI with sialography sequence is the alternative and very effective method, but still underrated [4]. The first studies used a multi-parametric nature of MRI to assess gland inflammation structure and function [5, 6]. The textural analysis of MRI images is a relatively new and promising method, presenting spatial patterns of signal intensity changes within the image/region of interest in a quantitative relation. In other words, texture analysis describes a wide range of techniques for quantifying gray-level patterns and the relationship between the pixels in the image. The textural parameters contain information about the extent of the heterogeneity of the region of interest in the picture. It has been shown that different areas of the picture have different texture patterns that may suggest changes at the microstructural level. Recent research indicates that the individual texture characteristics are optimally combined with dynamic progress indicators of diseases. Studies conducted so far in adult patients have shown statistically high accuracy in the differential between grades of patients with Sjögren's Syndrome based on texture analysis of ADC [7, 8]. However, there are some studies about the different approaches to analyzing MR images in diagnostic use for SS [9, 10]. Therefore, there are no unified methods of texture assessment.

2. Results

2.1. MRI sialography grades by the Tonami scale
The MR sialography grades were evaluated for each gland based on the cystic changes [11]. Grade 0 was found in 12 glands (16%), grade 1 in 8 glands (11%), grade 2 in 30 glands (42%), and grade 3 in 22 glands (31%) (Table 1).

<table>
<thead>
<tr>
<th>Index</th>
<th>Value SS group</th>
<th>Value healthy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>12.5 ± 3.4 yrs</td>
<td>13.5 ± 2.4 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>female 20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>male 16</td>
<td>12</td>
</tr>
<tr>
<td>Tonami scale</td>
<td>0 12</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>1 8</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>2 30</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>3 22</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### 2.2. ADC values

The value of ADC from SS patients and the control group was obtained from ROI in each gland; the mean value ADC depends on MR morphology grade is present in Table 3 (grade 0: 0.88 ± 0.14; grade 1: 0.86 ± 0.09; grade 2: 0.97 ± 0.17; grade 3: 1.04 ± 0.19 [10^-3 mm^2/s]). The value of ADC from the control group: 1.04 ± 0.10 [10^-3 mm^2/s]. There was a significant difference (using the Independent-Samples Kruskal-Wallis Test; \( F(4) = 25.139, p < 0.001 \)) of ADC value relative to MRI morphology grades (Tonami scale [11]) [Figure 2]. Therefore, further analysis was carried out with a pairwise comparison with Benferroni correction. An obtained significant difference \( p < 0.05 \) between groups (Table 3):

### Table 2: MRI protocol

<table>
<thead>
<tr>
<th>Sequence</th>
<th>FOV (mm)</th>
<th>Slice thickness (mm)</th>
<th>Voxel (mm)</th>
<th>Squeeze factor</th>
<th>Flip angle</th>
<th>Number of Averages</th>
<th>TE/TR (ms)</th>
<th>Matrix</th>
<th>Plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey/locator</td>
<td>256/256</td>
<td>10</td>
<td>0.98x1.98x1.98 0</td>
<td>15</td>
<td>I</td>
<td>4.5/11</td>
<td>256</td>
<td>Coronal transverse sagittal</td>
<td></td>
</tr>
<tr>
<td>T2 TSE</td>
<td>210/210</td>
<td>3/0.5</td>
<td>0.98x1.15x1.15 0</td>
<td>90</td>
<td>2</td>
<td>90/2500</td>
<td>512</td>
<td>Coronal transverse sagittal</td>
<td></td>
</tr>
<tr>
<td>T2 TSE</td>
<td>240/240</td>
<td>3/0.8</td>
<td>0.70x0.87x0.87 0</td>
<td>90</td>
<td>2</td>
<td>90/2500</td>
<td>640</td>
<td>Coronal transverse sagittal</td>
<td></td>
</tr>
<tr>
<td>T2 STIR</td>
<td>210/110</td>
<td>3/0.6</td>
<td>0.70x0.56x0.56 0</td>
<td>STIR</td>
<td>-</td>
<td>50/1400</td>
<td>560</td>
<td>Transversal</td>
<td></td>
</tr>
<tr>
<td>3D TSE_SPIR_0</td>
<td>300/245/45</td>
<td>2</td>
<td>1.25x1.25x1.25</td>
<td>SPIR</td>
<td>90</td>
<td>90/120</td>
<td>1008</td>
<td>Sagittal</td>
<td></td>
</tr>
<tr>
<td>mDixon</td>
<td>256/256/13</td>
<td>3</td>
<td>1</td>
<td>1.5x1.5x1.5</td>
<td>SPIR</td>
<td>90</td>
<td>256</td>
<td>Transversal</td>
<td></td>
</tr>
<tr>
<td>Dwi</td>
<td>240/240</td>
<td>4.5</td>
<td>1.5x2.16x1.5</td>
<td>SPIR</td>
<td>90</td>
<td>256</td>
<td>Transversal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TSE- Turbo Spin Echo, SPIR- Spectral Saturation with Inversion Recovery; 3D TSE SPIR Imaging; 3D turbo spin-echo Spectral Saturation with Inversion Recovery imaging; mDixon- time-consuming acquisition of in-phase and opposed-phase gradient-echo images; STIR- Short-TR Inversion Recovery; T2-1 is the time constant for decay/dephasing of transverse magnetization; Dwi- Diffusion-Weighted Imaging; Sialography: fast acquisition heavily T2 weighted sequence.

### Table 3: Mean values of image and texture analysis ADC images compare to MRI Tonami grades

<table>
<thead>
<tr>
<th>parameters</th>
<th>healthy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean [10^-3 mm^2/s]</td>
<td>1.04</td>
<td>0.10</td>
<td>0.88</td>
<td>0.86</td>
<td>0.97</td>
</tr>
<tr>
<td>Median [10^-3 mm^2/s]</td>
<td>1.06</td>
<td>0.10</td>
<td>0.86</td>
<td>0.86</td>
<td>0.97</td>
</tr>
<tr>
<td>Entropy</td>
<td>0.01</td>
<td>0.00</td>
<td>2.95</td>
<td>4.05</td>
<td>5.46</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>3.86</td>
<td>1.19</td>
<td>9.26</td>
<td>8.63</td>
<td>9.48</td>
</tr>
<tr>
<td>Skewness</td>
<td>-0.39</td>
<td>0.20</td>
<td>0.99</td>
<td>0.99</td>
<td>0.97</td>
</tr>
</tbody>
</table>
• 1 - healthy (p = 0.005),
• 1–3 (p = 0.046),
• 0–3 (p = 0.035),
• 0 - healthy (p = 0.001).

Worth of underling is highly significant difference between Grade 0 and 1 and the healthy group (Table 5).

Table 4
Mean values of image and texture analysis T2 images compare to MRI Tonami grades

<table>
<thead>
<tr>
<th>Texture Parameters</th>
<th>Healthy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>891.53</td>
<td>698.58</td>
<td>252.43</td>
<td>890.44</td>
<td>481.32</td>
</tr>
<tr>
<td>Median</td>
<td>887.56</td>
<td>242.88</td>
<td>697.16</td>
<td>246.50</td>
<td>880.58</td>
</tr>
<tr>
<td>Entropy</td>
<td>7.51</td>
<td>1.76</td>
<td>8.21</td>
<td>0.44</td>
<td>8.48</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>4.79</td>
<td>1.57</td>
<td>7.33</td>
<td>3.58</td>
<td>4.89</td>
</tr>
<tr>
<td>GLDM_Dependence NonUniformity</td>
<td>5791</td>
<td>3201</td>
<td>13600</td>
<td>669</td>
<td>11600</td>
</tr>
<tr>
<td>GLDM_Small Dependence High Gray Level Emphasis</td>
<td>95569</td>
<td>563232</td>
<td>115000</td>
<td>887000</td>
<td>203000</td>
</tr>
<tr>
<td>GLCM_Imc1</td>
<td>-0.32</td>
<td>0.09</td>
<td>-0.27</td>
<td>0.06</td>
<td>-0.31</td>
</tr>
<tr>
<td>GLRLM_Run Entropy</td>
<td>7.67</td>
<td>1.21</td>
<td>8.26</td>
<td>0.43</td>
<td>8.53</td>
</tr>
<tr>
<td>GLSZM_Zone Entropy</td>
<td>8.11</td>
<td>1.19</td>
<td>8.69</td>
<td>0.38</td>
<td>8.89</td>
</tr>
</tbody>
</table>

Table 5
Pairwise Comparisons of ADC value with MRI Tonami grades

<table>
<thead>
<tr>
<th>Sample 1-Sample 2</th>
<th>Test Statistic</th>
<th>Std. Error</th>
<th>Std. Test Statistic</th>
<th>Sig.</th>
<th>Adj. Sig. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>-39.756</td>
<td>14.033</td>
<td>-2.833</td>
<td>.005</td>
<td>.046</td>
</tr>
<tr>
<td>1-healthy</td>
<td>46.178</td>
<td>13.180</td>
<td>3.504</td>
<td>&lt;.001</td>
<td>.005</td>
</tr>
<tr>
<td>0–3</td>
<td>-33.905</td>
<td>11.605</td>
<td>-2.922</td>
<td>.003</td>
<td>.035</td>
</tr>
<tr>
<td>0 -healthy</td>
<td>40.327</td>
<td>10.558</td>
<td>3.820</td>
<td>&lt;.001</td>
<td>.001</td>
</tr>
</tbody>
</table>

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .050.

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

2.3. Whole-volume ADC image analysis

Whole-volume ADC analysis was calculated for each gland without dividing for the left or right gland. As shown in Table 3, a moderate correlation was observed between texture features and MRI morphology grades. The most common correlation is between MRI positive sialography and almost every texture parameter with higher statistics parameters. The correlation was negative for First order Statistics (FSO), like skewness, kurtosis, and entropy. The parotid ADC values from whole volume ROI were significantly lower in group 1 on the Tonami scale than in the groups with advanced changes - a Kruskal-Wallis H test showed a statistically significant difference (p > 0.05), where pairwise...
comparisons of the Tonami Scale for group 1–2 and 1–3, where p < 0.05 (Table 3). The most important for this research is the statistically significant difference between 0 grade and healthy group and grade 3, where p < 0.05.

2.4. Whole-volume T2 analysis

Analysis was calculated for each gland without dividing for the left or right gland. Table 4 shows a moderate correlation between texture features and MRI morphology grades. Noteworthy is the fact that the FSO parameters showed a positive correlation-a moderate correlation with individual parameters.

3. Discussion

This is the first study analyzing salivary gland texture in MRI in a group of children with Sjogren syndrome. This study compared the differences between textural features in two types of images in routine MRI examination in patients with Sjogren Syndrome-ADC maps and T2 weighted images. In total, 36 patients were qualified for the analysis, with each salivary gland being analyzed separately (N = 72); for the control group, we used 20 examinations in total were analyzed 40 glands.

The most important part of this study was to check which type of MRI images would be most compatible with grades of disease in use for texture analysis. The Tonami scale for MRI positive sialography was used to compare obtained data from TA. Information from the intensity of each voxel was gained from the ROI of the whole volume from each gland.

The parotid ADC values from whole volume ROI were significantly lower in grades 0 and 1 on the Tonami scale than in the high activity group. It should also be noted that the average ADC value in the reference group differs significantly from grade 1. If we consider that ADC can also be used as an inflammatory marker, we need to consider what happened in parameters like entropy, kurtosis, and skewness. Previous research has found that parotid ADC value rises in the early grades (short time between first clinical symptoms and high grade of inflammation) of SS due to parotid edema and increased vascular permeability based on adults patients [12, 13], which was provided by us and presented in Fig. 2 and Table 5. This can improve quality and speed up diagnosis in the early grades of SS. Our study shows that higher grades of sialographic changes present higher ADC values. Besides, we obtained the lower kurtosis and skewness values in the highest grade in Tonami Scale. It could be indicated by the high heterogeneity of examined tissue, which may be associated with tissue atrophy replaced with fibrotic tissue and fluid-filled sialectasis, causing disturbances in tissue structure in advances changes [9, 18, 19]. This results can be explained by higher spread of cystic changes of higher diameter and fibrotic process in parenchyma which can influence on an increase in ADC values. Unlike in previous studies the unchanged glands or low grade changes in MR sialography showed significantly decrease in ADC values. The finding suggests an active inflammatory process which is beforehand with architectural remodeling. The finding is promising for diagnosis early stage of SS in children which is most difficult for the pediatric population also in ultrasound studies [2].

The FSO parameters in T2 image TA analysis presented a moderate correlation between the individual parameters. Nevertheless, in FSO analysis, lower values in the highest activity SS on Tonami Scale in kurtosis were obtained. However, it is needed to mention that entropy is comparable through every grade. The speculated reason may be lower sensitivity to inflammation than the DWI sequence. However, still, this can give the highest repeatability and lowest artifacts arising from the nature of this sequence. The signal intensity in T2-weighted MR images is primarily derived from intracellular and extravascular extracellular space [10, 16]. The activity of SS disease is associated with higher T2 signal intensity, likely reflecting acute inflammation [16].

The present study has a few limitations. Firstly, the group number is relatively small, but we need to consider that the group is all about children. Secondly, optimal MRI protocol is crucial and worth remembering about the field inhomogeneity correction. Thirdly, it needs to be considered to apply in the future study to the excluded signal from cysts in the high grade level of SS, which can artificially boost the signal on adc maps. All these limitations require investigation. Besides this, it may be speculated that the association between histological activity and simple, unfiltered texture parameters on a T2-weighted image and ADC maps appears to be an overly simplistic method of assessing disease activity. We consider using both sequences to fill the gap and possible problem with signal-to-noise ratio and volume averaging in ADC maps. The textural analysis accompanied by sialography sequence and ADC maps opens new insight on early stage diagnosis of SS in children and possible monitoring of the disease more accurately.

4. Conclusion

The textural TA parameters in the degree of parotid glands inflammation can be a potential tool for early diagnosis SS and monitoring of salivary gland remodeling due to inflammatory process. Based on the study the main focus needs to be potentially increasing role of textural analysis of MRI in the evaluation of SS especially in the early stage in children.
5. Methods

5.1 patients

The Independent Bioethics Committee approved this study for Scientific Research at the Medical University of Gdansk. All analysis images were obtained respectively with consent from all subjects.

The 36 patients were to undergo primary analysis; the inclusion criteria were positive small labial salivary gland biopsy for SS. The patient went under routine clinical control; the age of patients was from 5 to 20 years old (mean age 12.5 years old; median 12 years old; male:16, female:20, IQR: 5). The control group included 20 children or young adolescents (mean age 13.5 years old; median 14 years old; male: 12, female: 8, IQR: 4). The demographic information of patients is shown in Table 1.

5.2 MRI examination

The examinations were performed using a Philips Achieva 3T TX magnetic resonance scanner (Philips Healthcare; Best. The Netherlands) with a 16-channel coil dedicated to neurovascular examinations with part to examination neck. After taking the localizer sequence (a set of three-plane. low-resolution. large field-of-view images to localize part of the body to examination), morphological imaging sequences were acquired in three planes to provide anatomical orientation (Table 2), including diffusion-weighted imaging and T2 weighted imaging, which were the primary sequences for our analysis.

5.3 Image analysis

An experienced radiologist evaluated the image findings of MR imaging with blind clinical findings. The MR images were determined according to the high T2 signal intensity size through all areas of glands in the MR sialography sequence. The Tonami modified criteria [11]:

- grade 0 (normal)- no evidence;
- grade 1 (punctate)- areas ≤ 1mm in diameter;
- grade 2 (globular)- 1–2 mm in diameter;
- grade 3 (cavitary)- up to 1 cm in diameter;
- grade 4 (destructive)- the complete destruction of the gland parenchyma.

The ADC maps are automatically generated from DWI (b = 0. 500 and 1000 s/mm²) scans by the software, which is integrated with the workstation using the monoexponential model:

\[ S = S_0 \cdot e^{-b \cdot ADC} \] [20].

To correct the field inhomogeneity, we used the N4 algorithm [21]. Then, texture analysis was performed in Pyradiomics (v3.0.1), using Radiomics modules [14]- absolute bound and bin width fixed. The ROI was drawn manually, covering all glands and keeping approximately 1 mm distance from the edge to avoid signal out of the gland. The ROI was drawn in all volumes of each parotid in ADC maps and T2 sequences.

The texture features obtained from these ROIs following formulas were divided into subgroups [22] [Figure 1]:

1. First Order Statistic (FSO);
2. Gray Level Co-occurrence Matrix (GLCM) Features;
3. Gray Level Size Zone Matrix (GLSZM) Features;
4. Gray Level Run Length Matrix (GLRLM) Features;
5. Neighbouring Gray Tone Difference Matrix (NGTDM) Features;

5.4 Statistical analysis

Statistical analysis was performed using SPSS Statistics 27 (IBM. Armonk. NY. United States). All results were tested for normal distribution, and the Shapiro-Wilk test for each parameter has shown a non-normal distribution. For this reason, we used the Spearman correlation test to show the correlation between obtained data and to find if it is a correlation between texture features in sick and healthy glands. For the difference between groups in glands, the Independent-Samples Kruskal-Wallis Test was used. Determining which of these groups differ from each other was analyzed by post hoc analysis, where a significant difference between groups was found when p < 0.05.

Declarations
Additional Information

The MRI examination was financed by the National Science Center – NCN 2020/04/X/NZ5/00599.

References


**Figures**

**Figure 1**

Axial images of T2 weighted imaging, Diffusion-weighted imaging (DWI), And apparent diffusion coefficient (ADC), Histogram correlated with T2 images. For tonami scale: a) grade 0, b) grade 1, c) grade 2, d) grade 3.
Figure 2

Graphic presents the value of First-Order statistics from ADC depending on MR Tonami's grades