Involvement of the somatosensory pathways in primary Sjögren's Syndrome: a diffusion-weighted imaging study

Poster No.: C-2198
Congress: ECR 2011
Type: Scientific Paper
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Keywords: Neuroradiology brain, MR, MR-Diffusion/Perfusion, Imaging sequences, Statistics, Connective tissue disorders
DOI: 10.1594/ecr2011/C-2198

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Sjögren's syndrome (SS) is a chronic, systemic, autoimmune disease affecting 2-3% of the adult population. It can be classified as primary (pSS) when presenting in isolation, or secondary when associated with a connective tissue disease [1]. PSS is characterized by mononuclear infiltration and destruction of the exocrine glands, mainly the lachrymal and salivary glands, resulting in xerophthalmia and xerostomia [1]. Apart from the glandular features of the disease there are also extraglandular manifestations (e.g. arthralgia, pulmonary involvement, renal tubular acidosis, etc.) [2]. Since its original clinical description, neurological involvement has been reported in pSS [2,3]. Involvement of the peripheral nervous system (PNS) is a well-documented feature of the disease, with a reported prevalence of 20-25%, and is commonly manifested as ganglionopathies/sensory neuronopathies, axonal sensory and sensorimotor polyneuropathies, multiple mononeuropathies, autonomic neuropathies, small-fiber neuropathies, cranial neuropathies, and inflammatory myopathies [4,5]. The prevalence and the type of central nervous system (CNS) involvement, however, still remains a matter of controversy. The estimated frequencies of CNS findings are reported to range from 10% to 60%, depending on the parameters studied (e.g. patient selection, diagnostic criteria, etc.) [2,6].

The apparent diffusion coefficient value (ADC) is a parameter derived from diffusion-weighted MR images, which describes basic diffusion properties of the tissue [7]. The ADC depends on several aspects of tissue microstructure, including the diffusion across membranes and the tortuosity of extra-cellular space, influenced by extracellular matrix molecules [8]. Other microscopic features include the relation of ADC to electrical conductivity [7] and aspects of neurotransmission such as volume transmission [8]. To our knowledge changes in ADC values have never been addressed in patients with pSS.

Our purpose was to assess changes in ADC values in a group of unselected patients with pSS using a voxel-based analysis.
Methods and Materials

Sixteen consecutive, unselected patients with pSS, representative of our pSS population (16 females), aged 39-78 years (mean ± SD; 65.0±8.6 years), with disease duration of 2-28 years (mean ± SD; 10.5±5.75 years) were evaluated. The diagnosis of SS was established according to the American-European Consensus Criteria (AECC). Association with other connective tissue diseases was ruled out and only cases of pSS were included. The control group consisted of 16 age-matched healthy subjects, aged 39-77 (mean ± SD; 63.2±10.4 years). The study was performed with the approval of the Institutional Review Board, and the participants signed a written informed consent agreement.

Exclusion criteria included a history or clinical signs of cardiovascular disease, peripheral arterial disease, hepatic dysfunction (levels of transaminases > 1.5 times the upper limit of normal), renal insufficiency (serum creatinine > 1.6 mg/dl), proteinuria (more than 0.5 g/day), diabetes mellitus (DM) (fasting plasma glucose concentration ≥ 126 mg/dl or use of antidiabetic medication), hypertension (arterial blood pressure > 140/90 mmHg or use of antihypertensive medication), thyroid-stimulating hormone levels > 5 mU/ml and treatment with corticosteroids during the last months six months before the study. None of the study patients or control subjects had findings suggestive of CNS or psychiatric disorder.

MRI data were acquired using a 1.5-T scanner (Gyroscan ACS NT; Philips Medical Systems, Best, The Netherlands). The MRI protocol included a multi-slice, spin-echo planar diffusion weighted sequence (TE: 131 msec, TR: 9807 msec, matrix size: 112 x 128, thickness: 3 mm, FOV: 230 mm, max b-value: 700 sec/mm²). Maps of the ADC values were reconstructed for each diffusion weighted image using the DTI studio software.

Data pre-processing and analysis for the VBM were performed using MATLAB 7.0 (MathWorks, Natick, MA, USA) and Statistical Parametric Mapping SPM 5.0 (Wellcome Department of Cognitive Neurology, London, UK). For each b0 EPI image, normalization parameters were estimated with 12-parameter affine and 16 nonlinear iterations using the b0 EPI template supplied with SPM 5.0 and then applied to the corresponding ADC map. Normalized ADC and MTR maps were smoothed with a 10-mm, full-width, half maximum Gaussian kernel to improve normal distribution and increase signal-to-noise ratio.

Differences between the patients and healthy control subjects were estimated using a two-sample t test. Inferences about regional differences in ADC values were made using a significance threshold level of p < 0.05 with FWE correction with multiple comparisons.
Results

Patients with pSS demonstrated areas of statistically significant reduced ADC values when compared to controls (figures 1-3). Restricted diffusion was observed in patients with pSS when compared to controls in the midbrain and pons. The distribution of these areas was along the somatosensory pathways bilaterally (P < 0.05, FWE correction for multiple comparisons).
**Fig. 0:** Differences in Apparent Diffusion Coefficient (ADC) values between patients with primary Sjögren’s syndrome (pSS) and healthy control subjects. The results of the voxel-based analysis for differences in ADC values are superimposed on an axial T1-weighted brain template. The colour scale (z-score) encodes areas of significant differences in ADC values between patients with pSS and control subjects. Colour represents regions of decreased ADC values in patients with pSS.

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Fig. 0: Differences in Apparent Diffusion Coefficient (ADC) values between patients with primary Sjögren's syndrome (pSS) and healthy control subjects. The results of the voxel-based analysis for differences in ADC values are superimposed on a coronal T1-weighted brain template. The colour scale (z-score) encodes areas of significant differences in ADC values between patients with pSS and control subjects. Colour represents regions of decreased ADC values in patients with pSS (P

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Fig. 0: Differences in Apparent Diffusion Coefficient (ADC) values between patients with primary Sjögren's syndrome (pSS) and healthy control subjects. The results of the voxel-based analysis for differences in ADC values are superimposed on a sagittal T1-weighted brain template. The colour scale (z-score) encodes areas of significant differences in ADC values between patients with pSS and control subjects. Colour represents regions of decreased ADC values in patients with pSS

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Conclusion

Involvement of the PNS is a well documented feature in patients with pSS [4,5]. Several neuropathy subtypes have been described in pSS. PNS manifestations include ganglionopathies/sensory neuronopathies, axonal sensory and sensorimotor polyneuropathies, multiple mononeuropathies, autonomic neuropathies, small fiber neuropathies and cranial neuropathies [4,5]. Predominantly, sensory or pure sensory neuropathies are most common (about 50-60%) [4,5]. Dorsal root ganglionitis and vasculitis are the main pathogenetic mechanisms of PNS manifestations [5]. Vasculitic neuropathy; inflammation of the vasa nervorum serving the peripheral sensory nerves, through the ascending sensory pathways may be at the basis of the restricted diffusion observed in the present study in patients with pSS. Similarly, restricted diffusion has been described along the neuronal pathways in cases of inflammation of the vessels serving the cranial nerves [9].
References

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