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Voxel-by-voxel analysis of brain SPECT perfusion in Fibromyalgia

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Abstract

We evaluated brain perfusion SPECT at rest, without noxious stiumuli, in a homogeneous group of hyperalgesic FM patients. We performed a voxel-based analysis in comparison to a control group, matched for age and gender. Under such conditions, we made the assumption that significant cerebral perfusion abnormalities could be demonstrated, evidencing altered cerebral processing associated with spontaneous pain in FM patients. The secondary objective was to study the reversibility and the prognostic value of such possible perfusion abnormalities under specific treatment. Eighteen hyperalgesic FM women (mean age 48 yr; range 25–63 yr; ACR criteria) and 10 healthy women matched for age were enrolled in the study. A voxel-by-voxel group analysis was performed using SPM2 ($p<0.05$, corrected for multiple comparisons). All brain SPECT were performed before any change was made in therapy in the pain care unit. A second SPECT was performed a month later after specific treatment by Ketamine. Compared to control subjects, we observed individual brain SPECT abnormalities in FM patients, confirmed by SPM2 analysis with hyperperfusion of the somatosensory cortex and hypoperfusion of the frontal, cingulate, medial temporal and cerebellar cortices. We also found that a medial frontal and anterior cingulate hypoperfusions were highly predictive (PPV = 83%; NPV = 91%) of non-response on Ketamine, and that only responders showed significant modification of brain perfusion, after treatment. In the present study performed without noxious stimuli in hyperalgesic FM patients, we found significant hyperperfusion in regions of the brain known to be involved in sensory dimension of pain processing and significant hypoperfusion in areas assumed to be associated with the affective dimension. As current pharmacological and non-pharmacological therapies act differently on both components of pain, we hypothesize that SPECT could be a valuable and readily available tool to guide individual therapeutic strategy and provide objective follow-up of pain-processing recovery under treatment.

Keywords: Pain; Fibromyalgia; Brain SPECT; 99mTc-ECD; Voxel-based analysis

1. Introduction

Fibromyalgia syndrome (FMS) is a chronic pain condition characterized by widespread musculoskeletal aches and pain and stiffness, soft tissue tenderness, general fatigue and sleep disturbances, without a clinically demonstrable peripheral nociceptive cause [1]. Although a psychogenic cause was initially postulated, recent fMRI activation studies have clearly demonstrated global dysfunction of central pain processing, consolidating the hypothesis of central sensitization. Similar painful pressure applied in patients and in controls did not result in activation of any common cerebral areas and showed greater effects in patients [2]. In this prospective study, we evaluated brain perfusion SPECT at rest, without noxious stiumuli, in a homogeneous group of hyperalgesic FM patients. We performed a voxel-based analysis in comparison to a control group, matched for age and gender. Under such conditions, we made the assumption that significant cerebral perfusion abnormalities could be demonstrated, evidencing altered cerebral processing associated with spontaneous pain in FM patients. The secondary objective was to study the reversibility and the prognostic value of such possible perfusion abnormalities under specific treatment.

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2. Methods

2.1. Patients and control subjects

Eighteen consecutive hyperalgesic FM women (49 ± 11 yr, range 25–63) who fulfilled the American College of Rheumatology (ACR) criteria [3] were enrolled in the study. All patients underwent a general medical assessment by one investigator to confirm the diagnosis. All patients failed to respond optimally to non-opioid analgesics or weak opioids and had to be managed in a pain management unit. Patients with psychiatric disease were excluded. No patient had any other significant medical illness. No change was made in treatment during the month preceding inclusion. No patient was receiving treatment with a strong opioid, tricyclic antidepressant, selective serotonin reuptake inhibitor, benzodiazepine and anti-convulsant agents.

For comparison of imaging findings, a control group of 10 women matched for age was also included (52 ± 7 yr, $p = 0.21$, using Mann–Whitney U-test). All subjects provided informed consent according to institutional guidelines.

2.2. SPECT protocol and statistical analysis

All brain SPECT were performed before any change was made in therapy in the pain care unit. A second SPECT was performed a month later after specific treatment by Ketamine. Patients were injected with 740 MBq of 99mTc-ECD (Neurolite, BMS) and placed at rest for 1 h, in quiet surroundings with their eyes closed. A Visual Analogue Scale (VAS) score for pain, evaluated in the immediate pre-injection period, was 82 ± 4 (range 75–90). SPECT image acquisitions were performed using a double-headed rotating gamma camera (ECAM, Siemens) equipped with a fan beam collimator. Thirty-two projections of 40 s were collected per head, in a 128×128 format. Tomographic 3D reconstruction was performed using a filtered back projection algorithm (Butterworth filter of order 4 with a cut-off frequency of $0.4\,\mathrm{cm}^{-1}$) and Chang's attenuation correction. Each brain SPECT was first visually interpreted by two nuclear medicine physicians (EG and CDL). A voxel-by-voxel group study was then performed using SPM2 (Welcome Department of Cognitive Neurology, University College, London, running on Matlab 6.0 Mathworks Inc, Sherborn, MA). Images were initially converted from the DICOM to the Analyze format using MRIcro (www.mricro.com), and transferred to SPM2. The data were then standardized with the Montreal Neurological Institute (MNI) atlas by using a 12-parameter affine transformation, followed by nonlinear transformations and a trilinear interpolation. Dimensions of the resulting voxels were $2 \times 2 \times 2$ mm. Standardized data were then smoothed by a Gaussian filter (FWHM = 12 mm). FM and control groups were compared using the "compare-populations one scan/subject" routine, which carries out a fixed-effects simple t-test for each voxel. Global normalization was performed using proportional scaling. MNI coordinates were finally converted into Talairach

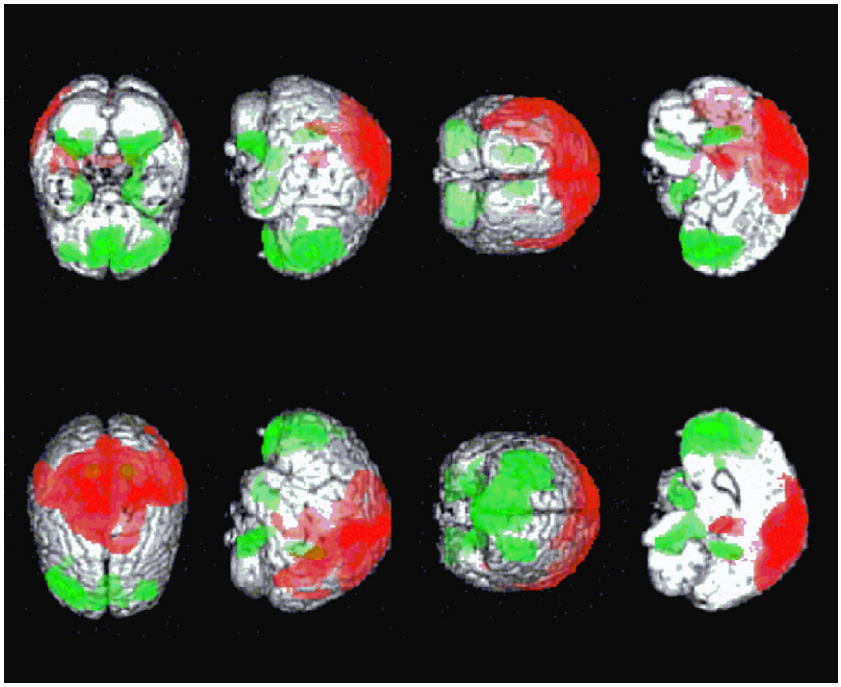

Fig. 1. Brain 99mTc-ECD SPECT abnormalities. Voxel-by-voxel SPM2 group analysis (18 FM patients vs. 10 healthy women). Anatomical localization of significant hyperperfusions (in red) and significant hypoperfusions (in green), projected on SPM2 surface rendering (P voxel level < 0.001; P cluster-level < 0.05, corrected for multiple comparisons).