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White Matter Damage of the Brain is Associated with Poor Outcome in Vascular Surgery Patients with Claudication: A Pilot Study

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WHAT THIS PAPER ADDS

This study demonstrates that pre-operative brain white matter damage assessed with diffusion tensor imaging is associated with poor outcome in patients with peripheral arterial disease undergoing infrainguinal surgical revascularization. The relationship between peripheral arterial disease and other comorbidities is complex and lower brain white matter fractional anisotropy values may reflect worse overall cardiorespiratory and metabolic status in these patients. Diffusion tensor imaging of the brain may have value in risk stratification in this patient group.

Objective: Peripheral arterial disease (PAD) is a systemic atherosclerotic syndrome with high post-operative morbidity and mortality. Fractional anisotropy (FA), an index measured by magnetic resonance diffusion tensor imaging (DTI), has been shown to be exceedingly sensitive to microstructural damage in brain white matter tracts. It is hypothesized that pre-operative white matter damage is more extensive in PAD patients scheduled for vascular surgery who experience an adverse long-term outcome.

Methods: Preoperative FA values were obtained in 24 consecutive PAD patients (age >40 years) scheduled for elective infrainguinal revascularization surgery and in 15 healthy age matched participants. All patients had their clinical history taken and underwent physical examination and laboratory tests. After surgery, patients were followed for a median of 52 months (range 40–63) and major adverse cardiovascular and cerebrovascular events (MACCE) were recorded.

Results: There were no statistically significant differences in baseline demographic or clinical variables between the MACCE group and the non-MACCE group. During follow up, eight PAD patients suffered a MACCE and they had lower FA values than patients without MACCE or healthy controls (mean ± SD 0.370 ± 0.017 vs. 0.392 ± 0.023 vs. 0.412 ± 0.018, $p = .036$ and $p = .00007$, respectively). Voxelwise analysis of the FA data revealed diffuse spatial distribution of white matter damage in PAD patients. There was no statistically significant association between the FA values and other clinical variables.

Conclusion: Microstructural white matter damage was associated with poor outcome in PAD patients with claudication requiring surgical revascularization, and its extent may have clinical value in risk stratification.

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INTRODUCTION

Peripheral arterial disease (PAD) is a systemic atherosclerotic syndrome with high morbidity and mortality.[1,2] It has been estimated to affect approximately 20% of adults over 55 years of age in Europe and North America.[3] Most patients with PAD suffer from multiple comorbidities including diabetes, hypertension,[4] and obstructive sleep apnea (OSA),[5] and PAD is also known to be a risk factor for cerebral infarction.[6] Not surprisingly, patients undergoing surgical treatment of lower extremity atherosclerotic disease have significant mid-term mortality because of this heavy co-morbidity burden.[7,8]

There is evidence that PAD is associated with small artery disease of the brain.[9] The imaging manifestations of small

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vessel disease on conventional magnetic resonance imaging (MRI) are lacunar infarctions and white matter lesions. However, conventional MRI is unable to demonstrate the whole extent of white matter pathology; previous studies with diffusion tensor imaging (DTI) have shown that substantial microstructural white matter damage also occurs in areas that appear normal on conventional MRI,[10] and that changes in white matter microintegrity precede the development of lesions seen with conventional MRI.[11] DTI is a recently established MRI technique, which can be used to assess the microstructural integrity of brain white matter tracts with good sensitivity. The method permits acquisition of quantitative measurements such as fractional anisotropy (FA), which represents the directionality of water diffusion in white matter.

The purpose of this prospective follow up study was to assess microstructural white matter damage in PAD patients needing surgical revascularization. It is hypothesized that pre-operative white matter damage quantified with DTI is more extensive in those patients who experience an adverse long-term outcome. Correlation of several clinical variables with brain white matter FA values was also examined. Additionally, the difference in FA values between PAD patients and healthy control participants was investigated.

PATIENTS AND METHODS

Patients

This study is a part of the BAROSLEEP project (ClinicalTrials.gov identifier: NCT00712946), which is a large prospective study of PAD patients. The medical ethics committee of the hospital district of Southwest Finland approved the study protocol.

Patients in this study consist of a subgroup of PAD patients previously described in another study of the BAROSLEEP project.[5] Of the original 82 patients with PAD over 40 years of age scheduled for elective infra-inguinal revascularization surgery, MRI of the brain was performed on 24 consecutive patients between August 2008 and September 2010. Fifteen healthy, age matched control participants were also imaged. The control participants were recruited mainly from the hospital staff and had no known vascular or neurological disease. Exclusion criteria for patients were previously diagnosed obstructive sleep apnea syndrome, congestive heart failure, atrial fibrillation or any other non-sinus rhythm, inability to cooperate, immobility, end stage renal disease, history of coronary bypass within 3 years, or other major surgery within 3 months of enrolment. All patients had their clinical history taken and underwent physical examination and laboratory tests. To assess previously undiagnosed obstructive sleep apnea (OSA), all participants underwent an overnight polysomnography, and apnea-hypopnea indices (AHI) were calculated according to a previously described protocol.[5] After surgery, patients were followed for a median of 52 months (range 40–63). Patients were routinely seen at the outpatient ward 6 weeks and 1 year after the operation, followed by annual contacts by phone, and data on major adverse cardiovascular and cerebrovascular events (MACCE) were retrieved from hospital records. MACCE was defined as cardiac death, acute myocardial infarction (AMI), ischemic or hemorrhagic stroke, coronary revascularization or hospitalization caused by unstable angina pectoris (UAP). Presence of AMI was classified according to the third universal definition.[12] According to these criteria, patients with PAD were divided into two groups: patients with MACCE and patients without MACCE.

MRI data acquisition, image processing, and analysis

Diffusion tensor imaging and conventional MRI were performed on a 3.0T Siemens Verio scanner (Siemens Medical Systems, Erlangen, Germany) with a head coil.

The imaging protocol consisted of the following sequences:

- An axial T2-weighted turbo spin echo (TSE) sequence (repetition time (TR) 5210 ms; echo time (TE) 96 ms; section thickness 4.0 mm; intersection gap 1.2 mm; acquisition matrix 512 × 512; field of view (FOV) 220 mm).
- A sagittal 3D T2 fluid-attenuated inversion recovery (FLAIR) TSE sequence (TR 5000 ms; TE 395 ms; inversion time (TI) 1800 ms; section thickness 1.0 mm; intersection gap 0 mm; acquisition matrix 256 × 256; FOV 250 mm).
- A sagittal 3D T1-weighted gradient echo sequence (TR 1900 ms; TE 221 ms; TI 900 ms; flip angle 9°; section thickness 1.0 mm; intersection gap 0 mm; acquisition matrix 256 × 256; FOV 250 mm).
- An axial DTI sequence (TR 6100 ms; TE 100 ms; number of gradient directions 20; b-values 0 s/mm^2 and 1000 s/mm^2; section thickness 3.0 mm; intersection gap 0 mm; acquisition matrix 128 × 128; FOV 250 mm).

The structural MRI data were reviewed by two neuroradiologists (SV, RP) to rule out major intracranial lesions (tumors, large old infarcts, etc.). Analysis of the fractional anisotropy data was performed using the tract-based spatial statistics (TBSS)[13] tool of the FMRIB Software Library[14,15] toolbox. In the image analysis, raw diffusion data were corrected for the effects of eddy currents. The FA images were calculated and automatic brain extraction was performed. Thereafter all participants' FA images were aligned into a common space by means of non-linear registration and the aligned FA images were averaged to create a mean FA image of all participants. The mean FA image was thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. This mean FA skeleton was thresholded at FA value 0.2, thus suppressing areas of very low FA. Aligned FA images of each participant were then projected onto this skeleton, thus creating a skeletonized and aligned FA map for each participant. Finally, the mean FA values of each participant's skeletonized FA maps were then automatically measured to obtain a global FA value for each participant. To assess the spatial distribution of the hypothesized white matter damage, voxelwise analysis between groups was also performed.