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Microstructural tissue damage in normal appearing brain tissue accumulates with Framingham Stroke Risk Profile Score: Magnetization transfer imaging results of the Austrian Stroke Prevention Study

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ABSTRACT

Background and purpose: Magnetization transfer imaging detects cerebral microstructural tissue alterations. We examined the association between the Framingham Stroke Risk Profile (FSRP) score and magnetization transfer imaging (MTI) measures in pathological and normal appearing brain tissue in clinically normal elderly subjects to determine if stroke risk leads to brain tissue destruction beyond what is visible in conventional MRI scans.
Methods: The study cohort is from the Austrian Stroke Prevention Study (ASPS). A total of 316 subjects underwent MTI and had a complete risk factor assessment sufficient to calculate the FSRP score. There were 205 women and 111 men with a mean age of 70.2 years ranging from 54 to 82 years. Subjects were grouped into four categories of stroke risk probability ranging from 3% to 88% for men and 1% to 84% for women.
Results: A higher FSRP score was significantly and independently associated with a MTR peak position shift indicating global microstructural alterations in brain tissue (BT) and in normal appearing brain tissue (NABT). The mean MTR in white matter hyperintensities (WMH) correlated inversely with increasing stroke risk. Age explained most of the variance in MTR peak position, all other risk factors of the FSRP score contributed significantly but explained an additional 2% of the variance of this MRI measure, only.
Conclusion: Increasing risk for stroke leads to microstructural brain changes invisible by standard MRI. The validity, the underlying pathogenic mechanisms and the clinical importance of these abnormalities needs to be further determined.

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1. Introduction

Conventional MRI detects accumulation of brain tissue destruction with advancing age and increased stroke risk [1]. "Silent" lesions include white matter abnormalities, lacunes and less commonly thromboembolic infarcts [2,3]. Recent diffusion tensor imaging (DTI) studies reported increased stroke risk to result in microstructural cerebral damage invisible on standard MR scans. The data show an association between blood pressure and white matter microstructure integrity in several regions of the brain in healthy adults [4]. Accordingly, Kennedy and Raz [5] reported that increasing pulse pressure leads to loss of anterior white matter integrity and another investigation by Gons et al. [6] revealed that hypertension-related DTI changes in normal appearing white matter preceeded morphological lesion. Microstructural tissue alterations are not only detectable by DTI but also by magnetization transfer imaging (MTI). MTI is based on the exchange of magnetization between tissue water and protons that are bound to macromolecules such as myelin lipids and proteins. The rate of exchange gives an estimate of the magnitude of these compartments, such as the pool of bound protons. The efficacy of magnetization transfer is usually quantified by the magnetization transfer ratio (MTR) which is considered to largely reflect the myelin content of the investigated brain regions [7]. MTR decreases with advancing age. As to whether stroke risk per se also leads to MTR-detectable microstructural brain changes is widely unknown. We hypothesized that an increased Framingham Stroke Risk Profile Score (FSRP) which estimates the 10-year probability for incident stroke in stroke-free individuals [8] relates to a decrease in MTR metrics of normal appearing brain tissue (NABT) independently of

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concomitant visible tissue damage. We tested this hypothesis in a sample of 316 participants of the Austrian Stroke Prevention Study.

2. Methods

2.1. Subjects

The study cohort consists of participants of the Austrian Stroke Prevention Study (ASPS) a single-center prospective follow-up study in residents of the city of Graz, Austria. The ASPS examines the frequency of cerebrovascular risk factors and their effect on cerebral morphology and function in the normal elderly. The study design and methods have been described previously [9,10]. On the basis of a structured clinical interview and a physical and neurologic examination, participants were free of overt neurologic or psychiatric disease including previous cerebrovascular attacks and dementia. A randomly selected sub-sample of 1073 ASPS participants took part in neuroimaging studies including brain MRI. Enrollment into the MR study of ASPS was started in 1991. Between 2001 and 2005 MTI was added to the scanning protocol. During this time period a total of 372 subjects entered the study. All of them underwent MTI. For the current investigation we included those 316 subjects (205 women, 111 men; mean age 70.2 years; range 54–82 years) who underwent both MTI scanning and a complete risk factor assessment according to the FSRP. The study protocol was approved and accepted by the ethics committee of the Medical University of Graz, Austria, and informed consent was obtained from all study participants.

2.2. Vascular risk factors

Risk factors were determined based on the participants' history and findings at the examination as previously described [10]. Diabetes was considered if a subject was treated for diabetes at the time of examination or if the fasting blood glucose level was above 126 mg^{-1} dl^{-1} at the time of examination. Blood pressure was measured by a random-zero sphygmomanometer, after 5 min of rest, and at the end of the study visit. The mean of the two measurements was used. Subjects were classified as former, current smokers or non-smokers. Cardiac disease was assumed to be present if there was an evidence of cardiac abnormalities known to be a source of cerebral embolism, evidence of coronary heart disease according to the Rose questionnaire or appropriate ECG findings (Minnesota codes: III, 1–3, IV, 1–3; or V, 1–2) or if individual presented signs of left ventricular hypertrophy on echocardiography or ECG (Minnesota codes: III, 1; or IV, 1–3). Atrial fibrillation was diagnosed based on electrocardiogram findings obtained at the study visit.

2.3. Framingham Stroke Risk Profile (FSRP)

The Framingham stroke risk predicts the probability of incident strokes within 10 years in stroke-free individuals and was calculated as described [8]. Briefly, the risk factors included in the FSRP are age, systolic blood pressure, use of antihypertensive medication, diabetes, smoking status, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. The FSRP provides specific risk estimates for men and women. The score ranges from 1 to 30 points for men and 1 to 27 points for women. The sex-specific score is then converted to 10 year probability of strokes ranging from 3% to 88% for men and 1% to 84% for women.

2.4. Conventional MRI

The MRI methodology used in the Austrian Stroke Prevention Study has been described [10,11]. MRI was performed on 1.5-T magnets (Gyroscan S 15 and ACS, Philips, Eindhoven, The Netherlands) using proton density- and T2-weighted sequences (repetition time [TR]/echo time [TE], 2000–2500 ms/30–90 ms) in the transverse orientation. T1-weighted images (TR/TE, 600/30 ms) were generated in the sagittal plane. The slice thickness was 5 mm and the image matrix was 128 × 256 pixels. The scanning plane was always determined by a sagittal and coronal pilot scan to ensure consistency in image angulation throughout the study [10]. White matter hyperintensities (WMH) were specified and graded by the Fazekas Score [12] into absent (grade 0) punctuate (grade 1), early confluent (grade 2) and confluent (grade 3) WMH, and semiautomated WMH volume measurements were done as described in previous publications [13]. Scans were also analyzed for the presence of clinically silent cortical infarcts and lacunes. Cortical infarcts were lesions that had consistent signal characteristics involving the cortex and following a typical branch pattern [14,15]. Lacunes were focal lesions isointense to CSF involving the basal ganglia, the white matter, the internal capsule, the thalamus or the brainstem ranging in maximal diameter between 3 mm and 10 mm [16].

2.5. Magnetization transfer imaging (MTI)

MTI was performed after conventional MR imaging with a spoiled 3D gradient-echo sequence (TE = 4 ms, TR = 26 ms, FA = 20°, section thickness = 3 mm, FOV = 250 mm, matrix = 256 × 256) with and without a binomial saturation pulse (90–180–90°, maximum amplitude = 21 μT) covering the whole brain. MTR maps were calculated according to the formula MTR = (Mss-Mo)/Mo, where Mss and Mo are the signal intensities obtained with and without MT saturation, respectively. Then they were registered to the FLAIR scans using an automated affine registration tool (FLIRT, FMRIB Image Analysis Group Oxford).

MTR metrics were assessed for the whole brain tissue (BT) including the cerebellum and the brain stem. They were also recorded in normal appearing brain tissue (NABT) which was all brain tissue outside WMH and lacunes as well as for WMH. The definition of NABT and assessment of WMH were based on FLAIR scans. A mean MTR was calculated for each WMH by masking the registered MTR maps with the WMH masks. To reduce partial volume effects, which might have taken place due to image registration and subsequent interpolation, we eroded all WMH masks by 1 pixel. The MTR of all WMH was averaged to obtain a mean lesional MTR for each subject. MTR data in WMH follow a Gaussian distribution. Therefore mean MTR is the appropriate measure to describe lesional MTR data. To analyze the MTR metrics of NABT and BT, MTR maps were masked out with the WMH masks after dilating them by 1 pixel and after removing nonbrain tissue with a brain extraction tool (BET as a part of FSL, http://www.Fmnb.ox.ac.uk/fsl/bet2/index.html). All remaining voxels in the MTR maps were then considered for the MTR histogram analysis. For each histogram, we calculated the peak position (i.e. the MTR value with the highest frequency) and the relative peak height (i.e. the relative voxel count at the peak position). Mean MTR in NABT is not displayed because the MTR histogram of this tissue compartment does not follow a Gaussian distribution. To correct for differences in individual brain volumes, we normalized the histograms by the total number of voxels contributing to the histogram [17,18].

2.6. Statistical analysis

Multiple linear regression analysis was used to correlate the FSRP score with MTR metrics. The analyses were adjusted for presence of lacunes, and cortical infarcts as well as for white matter hyperintensity volume. In separate analyses adjustment was also done for number of lacunes and cortical infarcts. For each regression coefficient, the 95% confidence interval and the *p*-value were

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