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Association between leukoaraiosis and cerebral blood flow territory alteration in asymptomatic internal carotid artery stenosis

Y.-F. Chen [d], Y.-S. Kuo [c,f], W.-C. Wu [a,b,c,d,*], S.-C. Tang [e], S.-F. Jiang [d]

[a] Graduate Institute of Medical Device and Imaging, National Taiwan University, Taipei, Taiwan
[b] Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan
[c] Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan
[d] Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan
[e] Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[f] Department of Radiology, Cathay General Hospital, Taipei, Taiwan

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AIM: To test the hypothesis that leukoaraiosis (also known as white matter lesion) is associated with cerebral blood flow territory change as revealed by territorial arterial spin-labeling (TASL) magnetic resonance imaging (MRI) in patients with asymptomatic internal carotid artery stenosis (aICAS).

MATERIALS AND METHODS: The institutional review board approved this study. Thirty-three patients with aICAS were included prospectively and divided into high-grade (ultrasonographic stenosis ≥70%, n=17) and low-grade (n=16) groups; 16 healthy subjects were also included. Cerebral flow territory was delineated for left ICA, right ICA, and vertebral arteries using TASL MRI and fuzzy clustering. Two licensed neuroradiologists independently and dichotomously rated the hemispherical asymmetry of flow territories. Flow territories were finalised by consensus, and when asymmetry was present, these were divided into normal and abnormal areas where the raters separately assessed leukoaraiosis based on fluid-attenuated inversion recovery images and the Fazekas scale.

RESULTS: The inter-rater agreement in the evaluation of flow territory asymmetry with TASL imaging in conjunction with time-of-flight angiogram is substantial (Cohen's kappa=0.82). Multinomial logistic regression (reference group=healthy subjects) indicates that global leukoaraiosis is not a predictor of aICAS after controlling for age, whereas in high-grade patients, the deep white matter lesion is more severe in the area receiving collateral circulation than in the area with normal flow territory (Wilcoxon signed-rank test, p=0.03).

CONCLUSION: TASL MRI is clinically feasible in aICAS and shows that more severe deep white matter lesions are associated with collateral circulation in high-grade patients.

Introduction

Internal carotid artery (ICA) stenosis (ICAS) has been identified as a risk factor of stroke.[1] According to published

* Guarantor and correspondent: W.-C. Wu, Graduate Institute of Medical Device and Imaging, National Taiwan University, No. 1, Sec. 1, Ren-Ai Road, Taipei, 100, Taiwan. Tel.: +886 2 23123456, ext: 88658; fax: +886 2 33936523.
E-mail address: wenchau@ntu.edu.tw (W.-C. Wu).

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guidelines,[1] immediate surgery is recommended for ICAS with sudden neurological symptoms referable to the appropriate ICA, whereas the management of asymptomatic ICAS (aICAS) remains controversial. Decreased cerebral blood flow has been considered as a diagnostic index of ischaemic stroke[2,3] and symptomatic ICAS.[4,5] By contrast, patients with aICAS were found to have a better preserved cerebral haemodynamic status,[6,7] commonly through collateral circulation to provide adequate perfusion, which warrants the exploration of compensatory alterations, such as varied route/source of blood flow.

Free of exogenous contrast medium and ionising radiation, territorial arterial spin labelling (TASL)[8] is a magnetic resonance imaging (MRI) technique with the ability to depict the arterial flow territory by using tailored radiofrequency pulses to magnetically label a single or a subset of arteries. So far, only a few studies have explored ICAS-induced flow territory change with TASL imaging. Van Laar *et al.*[9] reported significant difference in the flow territories between patients with symptomatic ICA occlusion and control subjects. Kansagra & Wong[10] demonstrated in one asymptomatic patient (unilateral ICA stenosis >90%) that TASL was able to detect flow territory normalisation after endarterectomy. Chen *et al.*[11] recently showed that arterial transit time and flow territory may be better predictors of high-grade aICAS than cerebral blood flow.

Leukoaraiosis is considered a manifestation of ischaemic white matter lesion and its presence and severity has been related to the presence of hypertension or other small vessel disease. It is a common finding (as hyperintensities in fluid-attenuated inversion recovery (FLAIR) MRI) in stroke patients and is a risk factor of recurrent stroke, especially lacunar infarctions. By contrast, ICAS is a type of large vessel disorder and usually accounts for border zone infarction or thromboembolic infarction. The relationship between leukoaraiosis and ICAS is less well known and remains to be elucidated. The aim of this study was to investigate the association between white matter hyperintensities and flow territory alteration as measured by TASL MRI in aICAS.

Materials and methods

Participants

This study was approved by the Institutional Review Board and conducted in compliance with the Helsinki Declaration.[12] Eighty patients were recruited prospectively, in whom carotid ultrasonography indicated stenosis in ICAs and adequate flow amount in the vertebral arteries (VAs). Forty-seven patients were excluded because they had symptoms during the past six months (n=10) or neurological diseases (n=12), did not have TASL data (n=15), or TASL imaging was inadequate due to excessive motion (n=7) or technical problems (n=3). Thirty-three patients were finally included and divided into two groups: high-grade group (group 1) ultrasonographic stenosis ≥70% and low-grade group (group 2) ultrasonographic stenosis <70%; 16 healthy volunteers (group 3) who had no abnormality in the ICAs and VAs as revealed by time-of-flight (TOF) MR angiogram were also included. Table 1 summarises the subject demographics. None of the included patients and healthy volunteers had a known history of multiple sclerosis or other inflammatory demyelinating disease, or a history of irradiation to the brain. No included patients had bilateral high-grade stenosis. All participants provided informed written consent.

MRI

MRI was conducted on a 3 T clinical system (Tim Trio, Siemens) using the body coil to transmit radiofrequency pulses and phased-array coils (a 12-channel head coil and a four-channel neck coil) to receive signals. The protocol included fluid attenuated inversion recovery (FLAIR), T1-weighted three-dimensional magnetisation-prepared rapid gradient echo, T2-weighted turbo spin-echo, time of flight (TOF) angiogram, and TASL imaging. For TASL imaging, pseudo-continuous labelling[13,14] was employed (labelling duration=2 seconds, post-labelling delay=2 seconds, harmonic encoding[15] with 4–8 steps and 10 measurements for each step), followed by single-shot gradient-echo echo-planar readout (field-of-view=20 cm, in-plane matrix=64×64, repetition time [TR]=5 seconds, echo time [TE]=13 ms, 14 sections, section thickness=5 mm, intersection gap=1 mm). Based on TOF angiogram, the labelling plane was chosen such that ICAs and VAs were mostly perpendicular to the plane and separable from one another. Reference scans were also obtained for labelling efficiency calibration and coil sensitivity correction.[16]

Data analysis

Complex data were reconstructed online into magnitude images and exported to a laptop computer for further analysis. ASL images were realigned series by series to remove head motion during the scan, pair-wise subtracted, and averaged to generate the difference image (ΔM). ΔM was corrected for spatial variation of receiver sensitivity to remove signal modulation that was unrelated to flow.[16] Fuzzy clustering was applied to the feature space constituted by the ΔMs derived from harmonic encoding to estimate each voxel's membership level in the territories of the left ICA, right ICA, and VAs.[15] The membership levels range from 0 to 1 and add up to 1 for each voxel.

Two licensed neuroradiologists (with 17 and 10 years of experience, respectively) independently and dichotomously rated the hemispherical asymmetry of flow territory, when blinded to clinical findings and TOF data. They rated the flow territory maps again after 3–5 weeks but with TOF data revealed. By consensus, flow territories were finalised and when asymmetry was present, divided into normal area and abnormal area (where the flow territory appeared to decrease or deviate beyond normal variations). The raters evaluated leukoaraiosis in the normal area and the abnormal area separately by viewing the FLAIR images and based on the Fazekas scale[17]: score=0, 1, 2, and 3, with 0 being absent and 3 the more severe. Periventricular

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