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● *Original Contribution*

ULTRASOUND DIAGNOSIS OF CAROTID ARTERY STIFFNESS IN PATIENTS WITH ISCHEMIC LEUKOARAIOSIS

Monika Turk, Janja Pretnar-Oblak, Matija Zupan, Bojana Zvan, and Marjan Zaletel
Department of Vascular Neurology and Intensive Neurologic Therapy, University Medical Center Ljubljana, Ljubljana, Slovenia

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Abstract—The pathophysiology of ischemic leukoaraiosis (ILA) is unknown. It was recently found that ILA patients have increased aortic stiffness. Carotid stiffness is a more specific parameter and could have value as a non-invasive diagnostic value for ILA. Therefore, using color-coded duplex sonography, we compared local carotid stiffness parameters of 59 patients with ILA with those of 45 well-matched controls. The diagnosis of ILA was based on exclusion of other causes of white matter changes seen on magnetic resonance imaging. Pulse wave velocity β (PWVβ, m/s), pressure–strain elasticity modulus (E_p, kPa), β index and augmentation index (A_{ix}, %) values were higher and arterial compliance (AC, mm^2/kPa) values were lower in the ILA group; however, only E_p and PWVβ reached statistical significance ($p \leq 0.05$). β, E_p and PWVβ exhibited an increasing trend with higher Fazekas score, though only E_p reached significance ($p = 0.05$). The main conclusion was that E_p and PWVβ could have a diagnostic role in patients with ILA. (E-mail: monika.turk84@gmail.com) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Carotid arterial stiffness, Doppler sonography, Echo tracking system, Leukoaraiosis, Vascular risk factors, White matter changes.**

INTRODUCTION

Leukoaraiosis is a neuroimaging term for periventricular and subcortical white matter hyper-intensities seen on magnetic resonance imaging (MRI), also called white matter changes (WMCs) (O'Sullivan 2008). The most common cause of WMCs is ischemic leukoaraiosis (ILA), which is diagnosed after the exclusion of other possible causes of WMCs that appear radiologically similar (demyelinization, vasculitis, Fabry's diseases, *etc*.). The prevalence of ILA increases with age and reaches almost 100% in the eighth decade (de Leeuw et al. 2001). WMCs are often found incidentally on MRI scans of clinically asymptomatic individuals (Vernooj et al. 2007). However, in its advanced form, ILA is associated with cognitive decline, functional loss, psychiatric disorders and gait disturbance (Leukoaraiosis and Disability [LADIS] Study Group 2011; O'Sullivan 2008; Pantoni 2010). A severe form of ILA more than doubles the risk of the patient's transition to a dependent status in 3 y (LADIS Study Group 2011).

The pathophysiologic mechanisms causing ILA are not well known (LADIS Study Group 2011; O'Sullivan 2008; Pantoni 2010). Mostly because of its association with age and cerebrovascular risk factors, as well as its similarity in location to lacunar infarctions, ILA is today recognized as one of the manifestations of cerebral small-vessel disease (Pantoni 2010). One of the recently discussed possible mechanisms is ischemic microvascular injury associated with atherosclerosis of large arteries (Brisset et al. 2013; Mitchell et al. 2011; Poels et al. 2012; Webb et al. 2012). It is well known that aging and vascular risk factors contribute to the stiffening of the large elastic arteries (Benetos et al. 2002; Lee and Oh 2010). Increased large artery stiffness exposes the small vessels in the brain to abnormal flow pulsations and, as such, may contribute to the pathogenesis of ILA (O'Rourke and Safar 2005; Poels et al. 2012). Aortic arterial stiffness has already been reported to correlate with development, progression and degree of ILA (Hatanaka et al. 2011; Henskens et al. 2008; Kearney-Schwartz et al. 2009; Kuo et al. 2010; Mitchell et al. 2011; Ohmine et al. 2008; Poels et al. 2012; van Elderen et al. 2010; Webb

Address correspondence to: Monika Turk, Department of Vascular Neurology and Intensive Neurologic Therapy, University Medical Center Ljubljana, Zaloska 2, 1000 Ljubljana, Slovenia. E-mail: monika.turk84@gmail.com

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et al. 2012). However, it is still not known if carotid stiffness is also related to ILA.

Recently, echo tracking ultrasound methods have enabled a non-invasive and easy determination of several local arterial stiffness parameters in the carotid artery (Jaroch et al. 2008, 2012; Laurent et al. 2006; Myung et al. 2012; Niki et al. 2002; Núñez et al. 2010; Rhee et al. 2008). Although carotid–femoral pulse wave velocity is still considered the "gold standard" for evaluation of arterial stiffness (Laurent et al. 2006), the sensitivity and specificity of local carotid parameters has been reported (Laurent et al. 2006). However, studies have found that aortic stiffness and carotid stiffness cannot be used as interchangeable predictors (Paini et al. 2006). So far, local carotid arterial stiffness parameters have not been systematically studied in patients with ILA.

To our knowledge, there is only one study that has already reported increased carotid arterial stiffness in a relatively old population of ILA patients (Brisset et al. 2013). Because age is an important risk factor for arterial stiffness as well as for ILA (Benetos et al. 2002; Lee and Oh 2010; Pantoni 2010) it would be wise to study younger patients and compare them to a control group without ILA matched with respect to risk factors. In addition, it is still not clear which parameter of carotid stiffness is the most sensitive and specific for ILA. Early non-invasive detection of increased carotid stiffness could have diagnostic and prognostic value for ILA patients. Therefore, our aim was to systematically study the most frequently used parameters of local carotid stiffness in a relatively young patient group with ILA and compare them with those for a well-matched control group.

METHODS

Fifty-nine patients, aged 53.2 ± 6.4 y, with ILA participated in the study (ILA group), together with 45 controls without leukoaraiosis matched for age, sex and cerebrovascular disease (CVD) risk factors (control group). The study was prospective. It was approved by the National Medical Ethics Committee of the Republic of Slovenia.

Patients were included in the study on the basis of an already performed brain MRI. The ILA patients were chosen from patients who have been treated in our outpatient clinic because of ILA and were up to 65 y old. ILA diagnosis was based on WMC findings on brain MRI and some additional tests excluding other causes of WMCs (demyelinization, vasculitis, Fabry's disease). We screened all for hypovitaminosis (vitamin B_{12} and folic acid), thyroid hormones, vasculitis and chronic vessel inflammation factors (C-reactive proteins, homocysteine) and rheumatoid factors. In some patients, cerebrospinal fluid was checked for oligoclonal bands.

Magnetic resonance images were evaluated by two radiology specialists based on the semiquantitative Fazekas scale (Fazekas et al. 1987). The patients were additionally divided into three groups according to the Fazekas scale: group 1 = Fazekas score 0, group 2 = Fazekas score 1 and group 3 = Fazekas score ≥ 2.

All patients were thoroughly examined (neurologic status; blood pressure; body mass index [BMI]; drug, alcohol and cigarette consumption; electrocardiogram; laboratory blood tests) to define CVD risk factors and exclude non-vascular causes of WMCs. We also excluded patients with cardiac arrhythmia, signs of ischemic heart disease, insulin-dependent diabetes, clinical signs of stroke and >50% carotid artery stenosis.

Cardiovascular disease risk factors were evaluated on the basis of a standardized interview, which included patient history, clinical examination, BMI determination, laboratory tests, blood pressure measurement and electrocardiography. The laboratory tests included total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and glucose. Control group subjects were selected from among patients of our outpatient clinic with similar CVD risk factors based on the normal brain MRI and the listed exclusion criteria. They were thoroughly examined according to the same protocol followed for the ILA group.

EXPERIMENTAL PROTOCOL

All patients gave informed consent to their participation in the study. The trial was performed in a quiet room under constant conditions. In preparation for the test, each subject rested for 10–15 min. Mean arterial blood pressure (MAP) and heart rate (HR) were measured continuously over a 5-min interval using non-invasive plethysmography (Colin CBM 7000).

Brain MRI was performed in all patients using axial T1-weighted, T2-weighted, fluid-attenuated inversion–recovery (FLAIR) and proton density-weighted scans on 1.5-T MRI scanner (Signal General Electric, GEMS, Philips Healthcare, Best, The Netherlands) in the axial and sagittal planes with a slice thickness of 5 mm. All MRI scans were evaluated by two experienced radiologists who were blinded to the ultrasound parameters, laboratory findings and clinical variables of the study population. Grading was performed using the Fazekas scale. The Fazekas score represents the sum of deep white matter corps and periventricular corps divided into three groups of increasing severity (Fazekas et al. 1987). The Fazekas score has the advantage of displaying the highest interrater agreement and correlation with volumetric measurements: 0 = no lesion, 1 = punctuated foci,