Characteristics of Cerebral Hemodynamics in Patients with Ischemic Leukoaraiosis and New Ultrasound Indices of Ischemic Leukoaraiosis

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Objective: The diagnosis of ischemic leukoaraiosis (ILA) is based on head magnetic resonance imaging (MRI) and exclusion of other causes of white matter hyperintensities (WMHs). Recent studies have shown increased arterial stiffness and diminished carotid flow in ILA patients. So far, there are very little data on intracerebral hemodynamic parameters in ILA. Due to the specific structure of the intracranial arteries, our aim was to investigate intracerebral hemodynamic parameters in ILA patients and, possibly, to find a reliable ultrasound index of combined intra- and extracranial cerebral arteries. *Methods:* We compared different hemodynamic parameters in the middle cerebral artery (MCA) and local carotid stiffness parameters in 53 ILA patients to 40 gender and risk factor-matched controls with normal head MRI. The ILA diagnosis was based on head MRI and exclusion of other causes of WMH. In addition, we introduced new ischemic leukoariosis indices (ILAi) that are ratios of carotid stiffness parameters and MCA mean blood flow velocity. The diagnostic significance of ILAi for the prediction of ILA was analyzed. *Results:* We found significantly lower diastolic, systolic, and mean MCA blood flow velocities and increased carotid stiffness in the ILA group ($P \leq .05$). All ILAi significantly differed between the groups ($P < .05$), were significantly associated with ILA ($P < .01$), and were sensitive and specific for predicting ILA ($P < .05$). *Conclusion:* MCA blood flow velocities in ILA patients are lower compared to risk factor-matched controls. A combination of lower velocities and increased carotid stiffness represented as ILAi could have a potential diagnostic value for ILA.
Key Words: Carotid Doppler ultrasound—carotid stiffness—cerebral blood flow—leukoaraiosis—transcranial Doppler sonography—white matter hyperintensities.

Ischemic leukoaraiosis (ILA) is a neuroimaging term for magnetic resonance imaging (MRI) white matter hyperintensities (WMHs).[1] In its progressed form, ILA is associated with cognitive decline, functional loss, psychiatric disorders, gait disturbance, and higher risk for stroke.[1-3] Its pathophysiological mechanisms are poorly understood,[1,4] but due to its association with age and cerebrovascular risk factors as well as similar location as lacunar infarctions, ILA is currently presumed to be ischemic in origin.[5,6] So far there are no known confirming diagnostic tests of ILA and its diagnosis is made by exclusion of other radiologically similar causes of WMH. Because of its mortality and morbidity, early diagnosis of ILA and its prompt treatment are very important.[1,3]

Due to its applicability and noninvasiveness, ultrasound (US) has been tried as a diagnostic test for ILA. Different authors have shown that aortic stiffness correlates well with the development, progression, and degree

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of ILA.[7-13] US studies including our previous work have also shown increased carotid stiffness in ILA patients.[14,15] Furthermore, we found increased resistance parameters and lower blood flows in the internal carotid arteries (ICAs) of ILA patients.[16] Because the structure and anatomy of intracranial arteries are different from extracranial arteries (they have no external elastic lamina, the adventitia is very thin, and they have a lower wall : lumen ratio), the hemodynamic parameters of intracranial arteries could give us more insight into the ILA pathophysiology than the parameters of the carotid arteries.[17]

Transcranial Doppler (TCD) enables real-time measurements of the blood flow velocity in larger intracranial arteries with the insight into hemodynamic changes and direction of the flow.[18] Although monitoring of the blood flow velocity enables only speculations about blood flow, it has been shown that the velocities correlate well with the cerebral blood flow (CBF) measured by other MRI techniques.[19] Besides, TCD can detect the velocity in different stages of the cardiac cycle (systole and diastole), which is therefore not automatically lowered in the already ischemic region as it is on perfusion MRI.[20] Although some studies have shown a relationship between higher middle cerebral artery (MCA) pulsatility index (PI) and WMH,[17,21-27] they mostly focused on this parameter, so other characteristics of cerebral flow parameters in ILA remain unclear. Furthermore, none of these studies has included a cerebrovascular disease (CVD) risk factor-matched control group. Because patients with ILA are usually older and have several CVD risk factors, these factors strongly influence cerebral hemodynamics; hence, it is important to compare them to a well-matched control group.

Moreover, it is possible that the presence of stiff large arteries in combination with lower CBF could act synergistically and cause insufficient perfusion that could cause ILA. In this case, the ratio between local carotid stiffness parameters and MCA velocities representing CBF could be used as a diagnostic index of ILA. According to our knowledge, so far there are no studies taking into account the combined US markers of intra- and extracranial cerebral artery manifestations of ILA.

The aim of our study was to compare the MCA hemodynamic parameters of ILA patients to a risk factor-matched control group. In addition, we determined ratios of carotid stiffness parameters and MCA mean blood flow velocity as parameters of combined intra- and extracranial cerebral vasculature to find a useful and clinically reliable diagnostic tool for ILA.

Methods

Patients with ILA (ILA group) and age, sex, and CVD risk factor-matched controls without ILA (control group) participated in the present study. The current study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

The present study was a continuation of our previous study on carotid stiffness parameters in ILA patients with the previously described experimental protocol.[15]

The patients were included in the study based on the previously performed brain MRI. The ILA patients were chosen among patients that have been treated in our outpatient clinic because of ILA and were up to 65 years old. Acute stroke patients as well as patients with nonlacunar strokes or any intracranial pathology other than ILA were excluded based on MRI findings and clinical data. ILA diagnosis was based on WMH findings on brain MRI and some additional tests excluding other causes of WMC (demyelination, vasculitis, Fabry disease, etc.).

All patients were thoroughly examined (neurological status was assessed; blood pressure measured; body mass index calculated; alcohol, drugs, and cigarette consumption noted; and 12-channel electrocardiogram and laboratory blood tests [hemogram, electrolytes, 4-fractioned lipidogram] performed to define CVD risk factors and additionally exclude nonvascular causes of WMH). We also excluded patients with cardiac arrhythmia, signs of ischemic heart disease, insulin-dependent diabetes, clinical signs of stroke, carotid artery stenosis higher than 50%, or hemodynamically important vertebral artery stenosis.

The control group patients were selected among patients with similar CVD risk factors and patients who already underwent brain MRI and have been treated in neurological outpatient clinics because of other symptoms such as headache and vertigo. They were chosen based on the normal brain MRI and the above exclusion criteria. They were thoroughly examined—the same protocol was followed as for the ILA group.

CVD risk factors were evaluated based on a standardized interview, which included patient history, clinical examination, body mass index determination, laboratory tests, blood pressure measurement, and electrocardiography. The laboratory tests included total cholesterol, low-density lipoprotein, high-density lipoprotein, and glucose.

Experimental Protocol

The patients were included in the study based on an already performed brain MRI. A brain MRI was performed in all patients using axial T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and proton–density-weighted scans on a 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 2 experienced radiologists who were blinded to the US parameters, laboratory findings, and clinical variables of the study population.

Color-coded duplex sonography and power Doppler sonography equipped with echo-tracking system were performed on all patients. The protocols were already described in our previous article.[15]