

# White matter hyperintensities and the pulsatility index: fellow travelers or partners in crime?

Hiperintensidades de substância branca e índice de pulsatilidade: companheiros de viagem ou parceiros no crime?

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**A**lthough cognitive and vascular neurology are separate divisions within a major neurological department, the spectrum of vascular disease process is part of the cognitive decline seen in the brains of the aging population<sup>1</sup>.

In 1987, Prof. Hachinski et al.<sup>2</sup> introduced the term “leukoaraiosis” to designate bilateral and symmetrical areas in the periventricular white matter and centrum semi-ovale that appeared hypodense on brain tomography. The equivalent to leukoaraiosis seen on magnetic resonance imaging (MRI) are referred to as white matter hyperintensities (WMHs). These are seen as diffuse areas of high signal intensity on T2-weighted or fluid-attenuated inversion recovery sequences<sup>3</sup>. Aging is a risk factor associated with leukoaraiosis: most of the individuals older than 60 years of age have some degree of WMHs, and the prevalence increases with aging<sup>4</sup>. Both WMHs and aging are associated with an increased risk of dementia and cognitive decline<sup>5</sup>.

There are few visual rating scales available to quantify the severity of these lesions on computed tomography (CT) or MRI. The Fazekas scale divides white matter into periventricular and deep white matter, and each region is classified by grade depending on the size and confluence of WMHs combined on a 0–3 point scale<sup>6,7</sup>. The Scheltens scale rates these lesions separately in the periventricular (0–6 points) and in the subcortical regions (0–24 points)<sup>8</sup>. In addition, the Scheltens scale includes ratings for the basal ganglia and infratentorial region. Wahlund et al.<sup>9</sup> introduced a scale that is easy to use and compare between CT scans and MRI.

The WMHs may represent only the extreme end of a continuous spectrum of white matter disease. It is important to observe that the visual rating scales have broad categories for severity and ceiling effect<sup>10</sup>. The visual rating scales were designed for cross-sectional rating, whereas the automated WMH detection methods allow the most precise quantification of WMH progression through the use of image subtraction<sup>11</sup>. In addition, diffusion tensor imaging and tractography should be the technique of choice to evaluate more subtle changes and the white matter integrity<sup>12</sup>.

Various conditions may be considered in the differential diagnosis of WMHs on MRI. White matter hyperintensities due to multiple sclerosis and other inflammatory brain diseases or metabolic leukodystrophies can be challenging<sup>13</sup>. Among vascular WMHs, cerebral amyloid angiopathy is another common age-related cerebral small vessel disease, and results from deposition of amyloid  $\beta$  in the media and adventitia of small arteries and capillaries of the leptomeninges and cerebral cortex<sup>14</sup>.

Cerebral small vessel disease is a chronic disorder of cerebral microvessels that causes WMHs and several other common abnormalities<sup>15</sup>. Research in humans has identified several manifestations of cerebral microvessel endothelial dysfunction including blood-brain barrier dysfunction, impaired vasodilation, vessel stiffening, dysfunctional blood flow and interstitial fluid drainage, white matter rarefaction, ischemia, inflammation, myelin damage, and secondary neurodegeneration<sup>15</sup>. Biochemical markers may identify the cerebral small vessel disease impairment and must be integrated with neuroimaging to improve the accuracy of the disease etiologies<sup>16</sup>. Furthermore, a similar condition related to small vessel disease that appears

in the brain may be part of a multisystem disorder affecting other vascular beds, such as the kidney and heart<sup>17,18</sup>. Renal failure is associated with both stroke and WMHs<sup>17</sup>, whereas unrecognized myocardial infarction may be associated with risk of dementia<sup>18</sup>.

The strongest modifiable risk factor associated with cerebral small vessel disease is hypertension. In the Rotterdam Scan Study, elevated blood pressure was associated with increased risk of WMHs, five and 20 years later.<sup>4</sup> The white matter microvascular network likely contributes to the pathogenesis of WMHs, with different presentations of WMHs indicating different underlying pathological changes<sup>19</sup>. There are differences in the arteries supplying the periventricular and subcortical white matter. While long perforating branches supply the periventricular white matter, shorter branches supply the subcortical white matter. Different types of concomitant lesions at different anatomic WMH locations related to cerebral small vessel disease also interact to affect cognitive domains. Periventricular WMH progression and incident lacunar infarcts are associated with a decline in general cognitive function, in particular, the speed of information processing. Lacunar infarcts on follow-up MRI were found in 12% of patients in the Rotterdam Scan Study<sup>4</sup>. Lacunar infarcts and WMHs share similar susceptibility to the same cluster of risk factors resulting in a common pathological substrate<sup>4</sup>.

A T2\* gradient-recalled echo and susceptibility-weighted MRI sequences may visualize another type of cerebral small vessel disease: the cerebral microbleeds. Microbleeds are also associated with WMHs and lacunar infarcts on MRI, linking arteriolosclerosis and cerebral amyloid angiopathy<sup>20</sup>.

Transcranial Doppler is a feasible tool to evaluate the cerebral hemodynamics, the arterial perfusion integrity, and the intracranial small vessel compliance<sup>21</sup>. Large artery stiffening results in increased arterial pulsatility with transmission to the cerebral small vessels resulting in leukoaraiosis<sup>22</sup>.

In this issue of *Arquivos de Neuro-Psiquiatria*, Fu et al.<sup>23</sup> report on an evaluation of 184 elderly patients with cerebral small vessel disease as shown by transcranial Doppler and MRI<sup>23</sup>. They observed that the elevated pulsatility index obtained in the middle cerebral artery was significantly correlated with severe WMHs, using the Fazekas scale. They confirmed the growing evidence supporting the association

between increased intracranial pulsatility and cerebral small vessel disease<sup>24</sup>.

Although the authors attempted to establish a cut-off for the pulsatility index of the middle cerebral artery to identify severe WMHs, they obtained an extremely low positive predictive value in this high-risk cohort. There is certainly more work to be done in this area. Perhaps the authors had simplified the topic, underestimating important variables that may have had relevant interaction with the variables in their model.

The discordance observed in several studies using transcranial Doppler as a tool for an indirect measurement of cerebral blood flow must consider the technical aspects of the examination. The choice of intracranial arterial segments and how they were evaluated is one of the first questions to ask. The M1 segment of the middle cerebral artery is usually examined at a 50-65 mm depth to obtain the most reliable spectral waveform. In addition, the pulsatility index described in most scientific papers should be cited as the Gosling pulsatility index<sup>25</sup>. Another important consideration is related to the ethnic group in the study by Fu et al.<sup>23</sup>. Cerebral blood flow velocities and pulsatility index patterns may be affected by ethnicity not only during the examination, with respect to the temporal window, but also by the predominance of specific vascular diseases. In the Chinese population, there is a predominance of intracranial arterial disease, that may indirectly compromise the pulsatility index even without the presence of arterial stenosis<sup>26</sup>. In addition, there is reduced cerebrovascular reactivity in WMHs<sup>27</sup>. This could be another important piece of information that could have been added in this study to improve the selection of patients with severe white matter impairment.

Refined diagnostic criteria, taking into account the questions raised above, are likely to be beneficial in future studies. What would have been the impact if they had used different rating scales to quantify WMHs? What is the relation of the pulsatility index with WMHs in patients with lacunar infarcts and/or microbleeds? Is there any biomarker that can optimize the findings? Do the selected patients with severe WMHs present with systemic small vessel disease?

Previously, Prof. Hachinski questioned whether stroke and Alzheimer's disease were fellow travelers or partners in a crime<sup>28</sup>. We still question this role in the relationship between WMHs and the pulsatility index as surrogate markers of cerebral small vessel disease.

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