White Matter Hyperintensities: repercussion on grey matter structures of the brain

Hiperintensidades da Substância Branca: repercussão em estruturas da substância cinzenta do cérebro

Eliasz Engelhardt [1]

ABSTRACT

The extensive white matter of the brain, which comprises about one half of its volume, is constituted by an intricate and interwoven assemble of nerve fibers. The WMH (leukoaraiosis) represent the most frequent ischemic type of lesion of SVD, affecting the white matter. These lesions may be apparent or normal appearing on neuroimaging. In both cases such lesions may interrupt the affected white matter fibers, with consequent disconnection syndromes, and atrophy of the denervated grey matter structures. These conditions affect the structural neural networks (connectome), with functional repercussion on the cognitive and behavioral domains.

Keywords: white matter, hyperintensities, leukoaraiosis, denervation, disconnection

RESUMO

A extensa substância branca do cérebro, que compreende cerca da metade do seu volume, é constituída por um intricado e entrelaçado conjunto de fibras nervosas. As HSB (hiperintensidades da substância branca) (leucoaraiose) representam o mais frequente tipo de lesão isquêmica da DPV (doença dos pequenos vasos) que afeta a substância branca. Essas lesões podem ser aparentes ou de aparência normal na neuroimagem. Em ambos os casos tais lesões podem interromper essas fibras da substância branca, com consequente síndromes por desconexão e atrofia de estruturas de substância cinzenta desnervadas. Essas condições afetam as redes neurais estruturais (conectoma), com repercussão funcional nos domínios cognitivo e do comportamento.

Palavras-chave: substância branca, hiperintensidades, leucoaraiose, desenervação, desconexão

[1] Neurology Institute Deolindo Couto – Institute of Psychiatry – Federal University of Rio de Janeiro – Rio de Janeiro – RJ – Brazil

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Correspondence: e-mail: eliasz@centroin.net.br

INTRODUCTION

The cerebral white matter is a very frequent target of "small vessel diseases" (SVD), which appear under varied kinds of ischemic lesions (white matter lesions [WML]), comprising "white matter hyperintensities" (WMH), "lacunar infarcts" (lacunes), and "enlarged perivascular spaces" (EPS), and also hemorrhagic lesions, the "micro-hemorrhages" (MI), as visualized on magnetic resonance imaging (MRI)[2,3,4] . The WMH are the most common among the ischemic WML, and are also designated by the term "leukoaraiosis" (leuko=white and araios=rarefaction), "meaning a diminution of the density of representation of the white matter"[5,6] . They appear hyperintense on MRI and hypointense (hypodense) on CT, the latter with a lesser sensitivity in comparison to MRI[7,8] .

The WMH (leukoaraiosis) are the most common visible kind of lesions of the white matter, and occur frequently in adults over 65 years old with a prevalence rate of ~60 - 80% in the general population[9] , and are even more extensive in those with cerebrovascular or Alzheimer's diseases, where they may reach ~90% when compared with cognitively normal older adults[10]. Currently, there is accumulating evidence pointing to the clinical relevance of the WMH[11] .

Additionally, lesions of the white matter not visible with the conventional MRI sequences (e.g., FLAIR), the "normal appearing white matter" (NAWM), was identified by DTI, and have also an important role in the pathophysiology, as they affect the nerve fibers and their function[12,13,14].

As already seen, the severity and the spatial distribution of WMH vary, as can be assessed by several metrics, as the Fazekas scale and others[15] .

THE WHITE MATTER

The white matter makes up approximately one half of the human brain volume, and appears relatively homogeneous as seen on gross anatomical sections and sectional MRI (e.g., on T1 sequence), where some regions can be distinguished (e.g., internal, external and extreme capsules, corpus callosum (body, genu and splenium), centrum semiovale, gyral white matter [blades]), without further detail[4,16] .

However, it is known that the white matter is constituted by a very large number of interwoven nerve fibers (axons) of variable thickness, unmyelinated and myelinated. These fibers form assembles, constituting fascicles, bundles or tracts of diverse lengths and directions. Their course varies according to the brain axis, many in a predominantly medial-lateral direction (e.g., commissural, thalamic-cortical-thalamic, and cortical-striatal), and others mainly in an anteroposterior direction (e.g., long association tracts)[16,17,18,19,20] .

These tracts were identified by anatomical dissection in the human brain by numerous authors, who provided an apparently complete picture of the macro-connections of the brain [3,16,21,22,23] . They were also revealed and identified by virtual dissection with special MRI sequences in vivo, the diffusion tensor imaging (DTI), with the obtention of color-coded fractional anisotropy (FA) mapping and tractography[17,24] .

A general classification of these bundles of fibers, mostly localized between the lateral ventricles, cerebral cortex, and deep basal nuclei, as association (short, long), commissural, and projection tracts, was established a long time ago by Meynert (1872)[25] , which endures until the present days[4,16,17].

These fascicles, bundles or tracts are responsible for connecting the varied superficial (cortical) and deep (basal nuclei) gray matter formations, and underpin, when interrupted by apparent (visible) lesions or NAWM on MRI, the concept of disconnection syndromes[25,27].

Important to stress is that these fiber assembles that interconnect varied grey matter formations represent the material substrate of the varied structural and functional networks. Among the structural networks stands out the "connectome", a concept and term first defined as a "network of elements and connections forming the human brain", fundamentally important in cognitive neuroscience and neuropsychology[28,29].

WHITH MATTER LESIONS AND NERVE FIBERS DEGENERATION

As already mentioned, the white matter is formed by nerve fibers (axons) afferent or efferent from a given cortical (laminar) and/or subcortical (nuclear) structures (e.g., thalamo-cortical, cortico-thalamic, cortico striatal, cortico-cortical)[16,30]. Lesions of these axons cause denervation (deafferentation, deefferentation) of the interconnected gray structures. The "deafferentation" is caused by "anterograde degeneration" (Wallerian), which impacts on near and/or distant target regions, with deprivation of incoming information. On the other side, the "deefferentation" results from "retrograde degeneration", which affects the neuron body (pericarion, soma), leading to its reaction, eventually harm, and in some cases even to its death (via apoptosis). Such reactions also affects the synapses that contact the affected neurons, beside the related neuroglial elements. Additionally, transneuronal (trans-synaptic) degeneration, which affect nearby related structures, increases the extension of the damage, may also be seen[31,32,33,34,35].

The result of such changes of the grey matter structures (laminar or nuclear), and loss of nervous elements, may produce disorganization of their microstructure (e.g., cerebral cortex, thalamus), grossly represented by atrophy, with reflection on the local activity, of nearby, and of distant related structures.

THE DENERVATED STRUCTURES AND THEIR CHANGES

Many studies have focused on changes of the cerebral cortex and subcortical nuclei after WML (e.g., WMH) using several kinds of metrics.

Several isolated and systematic studies have shown brain volume and cortical thickness (CT) changes among patients with symptomatic SVD (WMH), interpreted as secondary to axonal degeneration. Some studies revealed a significant decrease in CT found in specific cortical areas connected to white matter focal lesions (regional cortical atrophy), while areas with undamaged connections remained relatively unchanged. Other studies showed that higher total WMH load was associated with lower global cortical thickness (and lower cognitive performance)[36,37,38,39].

It was demonstrated a correspondence of the localization of WMH and the affected cortical regions, which revealed that the most common sites of WMH are related to frontal and parieto-occipital regions. The frontal WMH affect fibers related to frontal cortical areas, while parieto-occipital WMH affect fibers related to posterior cortical regions, including parietal and temporal areas[40]. In consequence, there is a more accentuated volume loss of the frontal lobes cortex, followed by the temporal lobes, and less by parietal and occipital cortices[41].

Another MRI study analyzed the spatial distribution of WMH in a more detailed manner, and revealed an inhomogeneous distribution of the WMH. There, among 333 cases, 56.66% were frontal, 37.54% parietal, 7.21% temporal, and 3.30% occipital. Among those, there were also 43.84% in the basal ganglia, and lesser percentages in other regions[42], certainly reflecting proportional atrophy of the related gray matter structures.

Interestingly, it was also shown that regardless their location, the lesions of the white matter impacts the function of the frontal areas[43], certainly explained by the several longitudinal tracts that converge on the frontal lobes[24,25].

Confluent WMH (leukoaraiosis) affecting large parts of the white matter, as seen in cases of Binswanger disease, permitted further information. The neuropathological examination of brains revealed global brain volume reduction, and histological analysis of the white matter revealed areas of axonal and myelin loss with gliosis, and lacunar infarcts[44]. The examination of the cerebral cortex showed occasional isolated apoptotic neurons in layers 3 and 5 of the frontal and occipital cortex, and few apoptotic neurons were present also in the hippocampus of the long-lasting cases[45].

Regarding specifically the medial temporal region, studies of patients with SVD with WML (lacunes, WMH) showed, beside a reduction of the volume of the cortical grey matter, also of the entorhinal cortex and the hippocampus, in comparison to cognitively normal controls[46,47,48]. Another study of SVD, with post-mortem analysis, showed a volumetric global brain reduction, including the hippocampus and subiculum. The neuronal count revealed a substantial loss of pyramidal neurons of the CA1 region of the hippocampus, possibly due to damage to cerebral microvasculature and neuronal apopotosis[49].

A special consideration is deserved by studies of cases of CADASIL, the traditional model of monogenic illness, which produces a slowly developing subcortical ischemic vascular disease. There, a progressive cortical atrophy, revealed by MRI, associated with progressive cognitive decline, was seen. One the studies was performed on post-mortem material, with histological and immunohistochemical techniques, aiming the identification of varied apoptosis markers. Those revealed widespread apoptotic neurons (cell death), mostly in neocortical layers 3 and 5, place of large numbers of pyramidal neurons, which was more severe in frontal and occipital lobes. The severity correlated semi-quantitatively with the extent of ischemic lesions and axonal damage in the underlying white matter, and the apoptosis of cortical neurons could be credited to the resulting denervation (deafferentation or retrograde neuronal degeneration). This supports the view that neuronal apoptosis may contribute to cortical atrophy and cognitive impairment in patients with CADASIL and that it may, at least partly, result from axonal damage in the underlying white matter. Neuronal apoptosis was minimal in hippocampus where the underlying white matter was usually devoid of ischemic lesions. Apoptosis of neurons was milder in the basal nuclei (lenticular nuclei and thalamus)[34,45]. A recent CADASIL study analyzed the hippocampal formation with histological and immunehistochemical techniques, and stereological metrics of CA1 and CA2 regions, and layer 5 of the entorhinal cortex (EC). The results showed hippocampal volume decrease as demonstrated by neuroimaging studies, related to a selective loss of neurons in the hippocampal formation (CA1 and mainly CA2)[50]. Such findings also suggest that white matter integrity in the temporal stem is compromised and is a factor in the observed cell loss in the hippocampal formation, particularly in the layer 5 of the EC[51].

Other kinds of studies in human beings (stroke and diaschisis), and on experimental laboratory animals (stroke, cortical undercutting), which affect the white matter, analyzed by neuroimaging and/or neuropathology, were not presently considered, bearing in mind that they produce acute effects, and although they may provide useful information, they are not entirely comparable to the slow developing lesions produced by the WMH and their repercussion on grey matter structures. Such studies will be focused in another opportunity.

COMMENTS

The extensive white matter of the brain, which comprises about one half of its volume, is constituted by an intricate and interwoven assemble (fascicles, bundles, tracts) of myelinated and unmyelinated nerve fibers, interconnecting gray matter formations. The WMH (leukoaraiosis) represent the most frequent kind of ischemic lesion due to SVD,

acquired or genetic, affecting the white matter. They vary in severity, size and spatial localization. These lesions may be apparent on neuroimaging (MRI-FLAIR) or be NAWM (MRI-DTI) [1,3,13] .

Such kinds of lesions interrupt, in variable degree and extension, the affected fiber assembles of the white matter. The consequence of such situation is double: [1] interruption of the connection among grey matter structures (cortical, subcortical), a situation generating disconnection syndromes, and [2] volume reduction of the denervated (deafferented, deefferented) grey matter structures, as thinning of the affected areas of the cerebral cortex, and/or atrophy of the affected subcortical nuclei. These condition appear to have a broader effect, as the affected grey matter structures are frequently connected with others, which also become compromised, enhancing the dysfunctional effect [31,33] .

The nervous fiber system interconnecting varied gray matter structure represents the structural basis of the "connectome". The WMH, lesions that affect these fibers in diverse extension, are responsible for varied degrees of connectome disruption with consequent repercussion of cognitive and behavioral functional disorders [28,29] .

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