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

Conflict of interest: none
Funding statement: none
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)[1,2,3,4] . 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 apoptosis[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] .

REFERENCES

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9(7):689-701.
2. Rosenberg GA, Wallin A, Wardlaw JM, Markus HS, Montaner J…Hachinski V. Consensus statement for diagnosis of subcortical small vessel disease. J Cerebral Blood Flow Metabol 2016;36(1):6-25. doi: 10.1038/jcbfm.2015.172
3. Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann NY Acad Sci 2008;1142, 266.
4. Wang Y, Yang Y, Wang T, Nie S, Yin H, Liu. Correlation between White Matter Hyperintensities Related Gray Matter Volume and Cognition in Cerebral Small Vessel Disease. J Stroke Cerebrovasc Dis 2020;29(12):105275.
5. Hachinski V, Potter P, Merskey H. Leuko-Araiosis: An Ancient Term for a New Problem. Can J Neurol Sci / J Can Sci Neurol 1986;13(S4):533-534.doi: 10.1017/S0317167100037264
6. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biological Psychiatry 2008;64(4):273-280.doi:10.1016/j.biopsych.2008.03.024
7. Bigler ED. Structural neuroimaging in neuropsychology: History and contemporary applications. Neuropsychology 2017;31(8):934-953. doi: 10.1037/neu0000418.
8. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR Signal Abnormalities at 1.5 T in Alzheimer's Dementia and Normal Aging. AJR 1987;149:351-356.
9. De Leeuw F, de Groot JC, Achten E, Oudkerk M, Ramos L… Breteler MMB. Prevalence of cerebral white matter lesions in elderly people:a population based magnetic resonance imaging study. The Rotterdam scan study. J Neurol Neurosurg Psychiatry 2001;70:9-14. doi: 10.1136/jnnp.70.1.9
10. Bombois S, Debette S, Delbeuck X, Bruandet A, Lepoittevin S…Pasquier F. Prevalence of subcortical vascular lesions and association with executive function in mild cognitive impairment subtypes. Stroke 2007;38:2595-2597. doi: 10.1161/STROKEAHA.107.486407
11. Frey BM, Petersen M, Mayer C, Schulz M, Cheng B, Thomalla G. Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies. Front Neurol 2019;10:238. doi: 10.3389/fneur.2019.00238
12. Gouw AA, Seewann A, Van Der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry 2011;82(2):126-135.
13. Maniega SM, Hernández MCV, Clayden JD, Royle NA, Murray C, Morris Z ...Wardlaw JM. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. Neurobiology of Aging 2015;36(2):909-918.
14. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Ass 2015;4(6):e001140.
15. Engelhardt E, Sudo FK, Alves GS, Moreira DM. White Matter Hyperintensities: Initial Assessments. Rev Bras Neurol 2021;57(2):14-17.
16. Wycoco V, Shroff M, Sudhakar S, Lee W. White matter anatomy: what the radiologist needs to know. Neuroimaging Clinics 2013; 23(2):197-216.
17. Catani M, De Schotten MT. Atlas of human brain connections. Oxford: Oxford University Press, 2012.
18. Mandonnet E, Sarubbo S, Petit L. The nomenclature of human white matter association pathways: proposal for a systematic taxonomic anatomical classification. Frontiers in Neuroanatomy 2018;12, 94.
19. Matute C, Ransom BR. Roles of white matter in central nervous system pathophysiologies. ASN Neuro 2012;4(2):AN20110060.
20. Sporns O. The human connectome: origins and challenges. Neuroimage 2013; 80: 53-61.
21. Engelhardt E, Moreira DM. A substância branca cerebral. Localização dos principais feixes com anisotropia fracionada direcional [The cerebral white matter. Localization of the main tracts with directional fractional anisotropy]. Rev Bras Neurol 2008;44 (2):19-34.
22. Dziedzic TA, Balasa A, Jeżewski MP, Michałowski Ł, Marchel A. White matter dissection with the Klingler technique: a literature review. Brain Structure and Function 2021;226(1):13-47.

23. Ludwig E, Klingler J. Atlas cerebri humani: the inner structure of the brain demonstrated on the basis of macroscopical preparations. Boston: Little, Brown and Co.1956.
24. Engelhardt E, Moreira DM. A substância branca cerebral. Dissecção virtual dos principais feixes: tratografia [The cerebral white matter. Virtual dissection of the main tracts: tractography]. Rev Bras Neurol 2008;44(4):19-34.
25. Meynert T. Von Gehirn der Säugethiere. In: Handbuch der Lehre von den Geweben des Menschen und der Thiere. 2 Band. Stricker S ed. Leipzig: Wilhelm Engelman, 1872 , pp 694-808.
26. Catani M, Ffytche DH. The rises and falls of disconnection syndromes. Brain 2005;128(10):2224-2239.
27. Langen CD, Zonneveld HI, White T, Huizinga W, Cremers LGM, de Groot M, Ikrama MA, Niessen WJ, Vernooij MK. White matter lesions relate to tract-specific reductions in functional Connectivity. Neurobiology of Aging 2017; 51:97-103.
28. Sporns O, Tononi G, Kötter R. The human connectome: a structural description of the human brain. PLoS computational biology2005;1(4), e42.
29. Sporns O. The human connectome: Origins and challenges. NeuroImage 2013;80:53-61.
30. Wakana S, Jiang H, Nagae-Poetscher LM, Van Zijl PC, Mori S. Fiber tract–based atlas of human white matter anatomy. Radiology 2004;230(1):77-87.
31. Holly Bridge H, Gordon T. Plant GT. Conclusive Evidence for Human Transneuronal Retrograde Degeneration in the Visual System. Clin Exp Ophthalmol 2012;S:3. doi:10.4172/2155-9570.S3-003
32. Beatty RM, Sadun AA, Smith LEH, Vonsattel JP, Richardson EP. Direct demonstration of transsynaptic degeneration in the human visual system: a comparison of retrograde and anterograde changes. J Neurol Neurosurg Psychiatry 1982;45(2):143-146.
33. Nagappan PG, Chen H, Wang D-Y. Neuroregeneration and plasticity: a review of the physiological mechanisms for achieving functional recovery postinjury. Military Medical Research 2020;7:30.
34. Viswanathan A, Gray F, Bousser M-G, Baudrimont M, Chabriat H. Cortical Neuronal Apoptosis in CADASIL. Stroke 2006;37:2690-2695. doi: 10.1161/01.STR.0000245091.28429.6a
35. Yamada K, PateI U, Shrier DA, Tanaka H, Chang J-K, Numaguchi Y. MR Imaging of CNS Tractopathy: Wallerian and TransneuronalDegeneration. AJR 1998;171:813-â18.
36. Cheng B, Schulz R, Bönstrup M, Hummel FC, Sedlacik J… Thomalla G. Structural plasticity of remote cortical brain regions is determined by connectivity to the primary lesion in subcortical stroke. J Cerebr Blood Flow Metabol 2015;35:1507-1514.
37. Reid AT, van Norden AGW, de Laat KF, van Oudheusden LJB, Zwiers MP… Kötter R. Patterns of Cortical Degeneration in an Elderly Cohort with Cerebral Small Vessel Disease. Human Brain Mapping 2010;31:1983-1992. doi: 10.1002/hbm.20994
38. Rizvia B, Narkhedea A, Lasta BS, Budgea M, Tostoa G… Brickman AM. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. Neurobiol Aging 2018; 64: 25–32. doi:10.1016/j.neurobiolaging.2017.12.006
39. Tuladhar AM, Reid AT, Shumskaya E, de Laat KF, van Norden AG, van Dijk EJ ...de Leeuw FE. Relationship between white matter hyperintensities, cortical thickness, and cognition. Stroke 2015;46(2):425-432.
40. Rossi R, Boccardi M, Sabattoli F, Galluzzi S, Alaimo G, Testa C, Frisoni GB. Topographic correspondence between white matter hyperintensities and brain atrophy. J Neurol 2006;253:919-927. doi 10.1007/s00415-006-0133-z
41. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Longstreth Jr WT…Becker JT. White Matter Lesions and Brain Gray Matter Volume in Cognitively Normal Elders. Neurobiol Aging 2012;33(4):834.e7834.e16.doi:10.1016/j.neurobiolaging.2011.08.010
42. Zhuang F-J, Chen Y, He W-B, Cai Z-Y.Prevalence of white matter hyperintensities increases with age. Neural Regen Res 2018;13(12):2141-2146. doi: 10.4103/1673-5374.241465.
43. Tullberg M, Fletcher E, DeCarli C, Mungas D, Reed BR, Harvey DJ ... Jagust WJ. White matter lesions impair frontal lobe function regardless of their location. Neurology 2004; 63(2):246-253..
44. Révész T, Hawkins CP, Du Boulay EP, Barnard RO, McDonald WI. Pathological findings correlated with magnetic resonance imaging in subcortical arteriosclerotic encephalopathy (Binswanger's disease). J Neurol Neurosurg Psychiatry 1989;52(12):1337-1344.
45. Gray F, Polivka M, Viswanathan A, Baudrimont M, Bousser M-G, Chabriat H. Apoptosis in Cerebral Autosomal-Dominant Arteriopathy 2007;66(7):597-607.
46. Appelman APA, Exalto LG, van der Graaf Y, Biessels GJ, Mali WPTM, Mirjam I. Geerlings MI. White Matter Lesions and Brain Atrophy: More than Shared Risk Factors? A Systematic Review. Cerebrovasc Dis 2009;28:227-242. doi: 10.1159/000226774
47. Du AT, Schuff N, Laakso MP, Zhu XP, Jagust WJ…Weiner MW. Effects of subcortical ischemic vascular dementia and AD on entorhinal cortex and hippocampus. Neurology 2002; 58(11):1635-1641.
48. Godin O, Maillard P, Crivello F, Alpérovitch A, Mazoyer B, Tzourio C, Dufouil C. Association of White-Matter Lesions with Brain Atrophy Markers: The Three-City Dijon MRI Study. Cerebrovasc Dis 2009;28:177–184. doi: 10.1159/000226117
49. Kril JJ, Patel S, Harding AJ, Halliday GM. Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. J Neurol Neurosurg Psychiatry 2002;72:747-751.
50. O'Sullivan M, Ngo E, Viswanathan A, Jouvent E, Gschwendtner A…Dichgans M. Hippocampal volume is an independent predictor of cognitive performance in CADASIL. Neurobiol Aging 2009;30:890-897.
51. Yamamoto Y, Hase Y, Ihara M, Khundakar A, Roeber S, Duering M, Kalaria RN. Neuronal densities and vascular pathology in the hippocampal formation in CADASIL. Neurobiology of Aging 2021; 97:33-40.