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Neuroscience Reviews: White Matter Hyperintensities

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Summary

Abnormal patches of white matter, called hyperintensities, are thought to signal damage to neurons and surrounding fiber connections. White matter hyperintensities generally increase with age but vary among healthy and diseased individuals. There is much debate among scientists as to the significance of these lesions, particularly as they relate to certain neurological disorders.

Introduction

The human brain is made up of relatively fixed amounts of white matter (e.g., myelin) and gray matter (e.g., cell bodies) distributed throughout the brain and spinal cord. Myelin proteins surround the axons of neurons contributing to the generation and propagation of action potentials. Cell bodies, on the other hand, contain the nucleus and a mass of cytoplasm from which dendrites and axons arise (Haines, 2002). White matter can sometimes be injured as in autoimmune-mediated demyelination resulting in multiple sclerosis (MS; Doubal et al., 2010). Signs of white matter damage, however, are also seen without apparent neurologic disability. This brief review discusses the phenomena of white matter hyperintensities (WMH) which are abnormal patches of white matter material often seen in the brains of both healthy and diseased individuals (Murray et al., 2012; Wardlaw et al., 2015).

What are white matter hyperintensities?

Magnetic resonance imaging (MRI) is a useful scanning method for visualizing the human brain (Zakary et al., 2011). MRIs, for instance, allow scientists to determine the extent of brain damage and in turn provide the most appropriate treatment. This brain-image technology has also revealed the presence of abnormal bright signals in the white matter of patients with MS, obstructive sleep apnea and diffuse axonal injury (Baik et al., 2015). Mainly located in the periventricular and subcortical white matter, WMH can also be detected in deep white matter (Hachinski et al., 1987; Fig. 1). Although WMH are often seen in diseases of neuro-vascular origin, they are also visualized in the brains of elderly cohorts (Erten-Lyons et al., 2013). In this context, signs of white matter damage appear to be a prominent age-related occurrence, with an incidence of ~ 20% in adults over the age of 60 and ~ 90% in adults over the age of 90. From

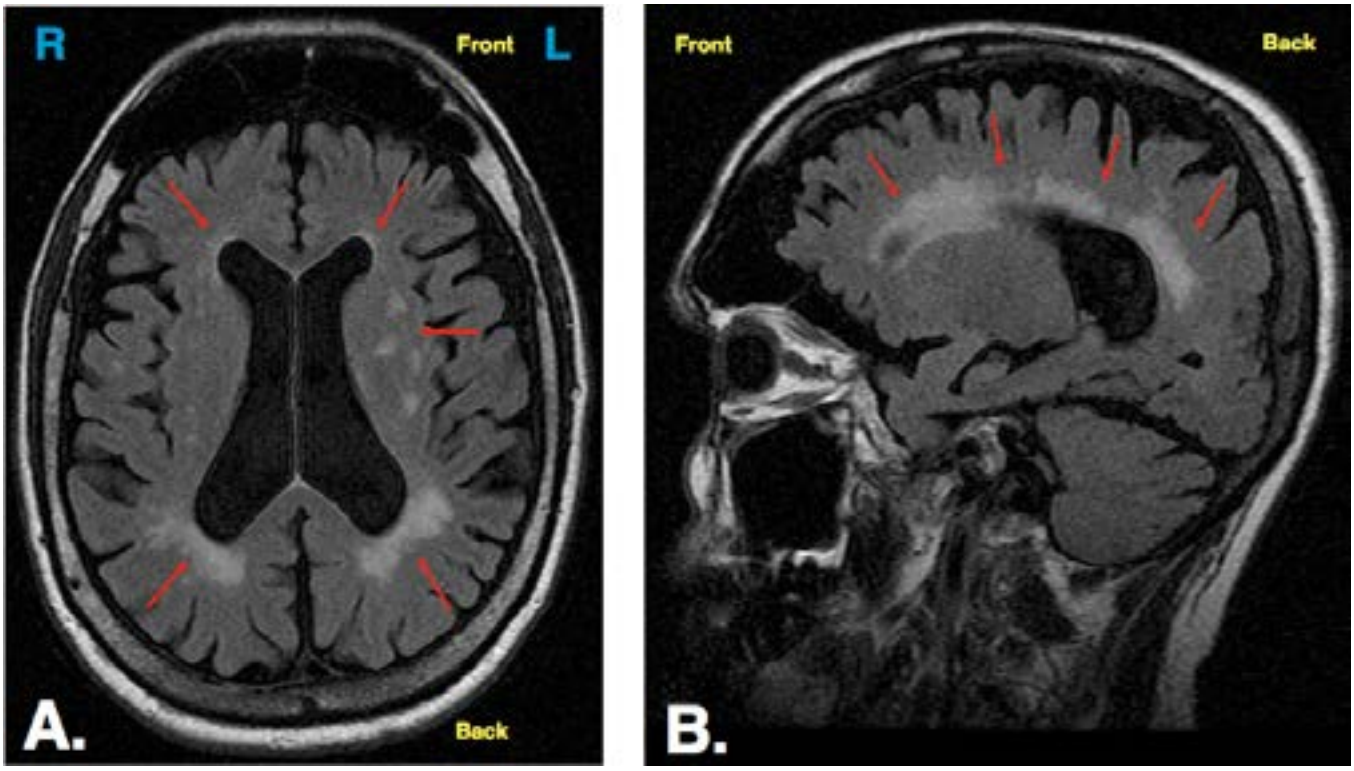

Fig. 1. Representative WMH lesions on fluid attenuated inversion recovery (FLAIR) brain MRIs (A = transverse view; B = sagittal view). Notice that most WMH lesions are mainly located in the periventricular white matter of the human brain (red arrows). Initially described in patients with cardiovascular risk factors and symptomatic cerebrovascular disease, WMH are now associated with progressive cognitive impairment in the elderly (Wardlaw, 2015). It appears that the greatest risk factor for developing white matter damage is high blood pressure. We are learning that these WMH are much more widespread than we thought as they are also detected in healthy cohorts as well. R = right; L = left.

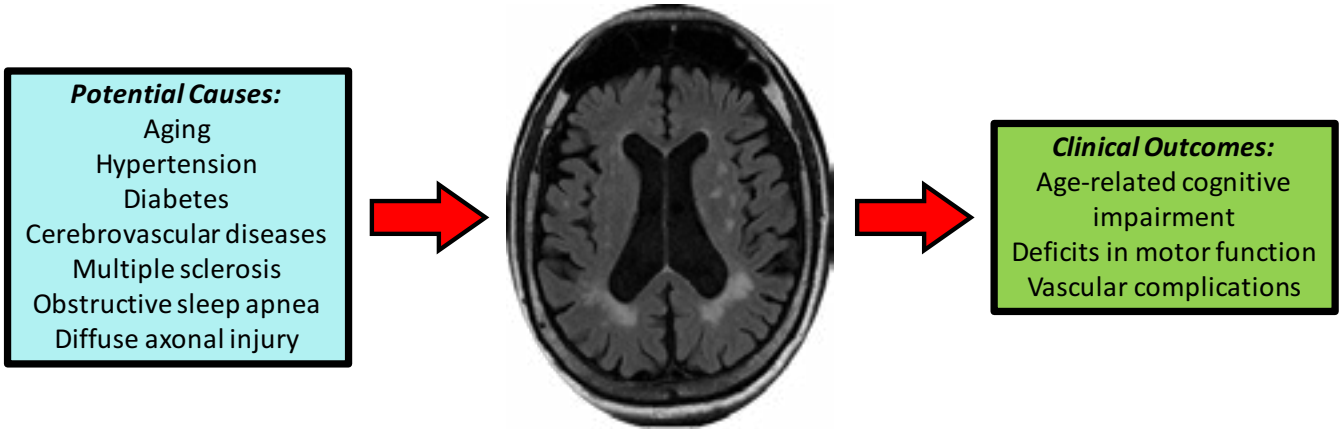

Fig. 2. We list some of the most scrutinized diseases which are increasingly associated with WMH. There are remarkable similarities among diseases, but they are also marked differences in etiology and clinical symptoms. There are still enormous gaps in our knowledge of WMH. Perhaps the most effective way to prevent the onset of WMH is to promote brain health *via* lifestyle modifications.

this point of view, WMH might be the result of intrinsic aging, with neurological deficits (e.g., motor, sensory or cognitive) only seen in patients with certain pre-morbid conditions such as high blood pressure, diabetes, obesity or a sedentary lifestyle (Fig. 2).

Why do white matter hyperintensities matter?

It is not clear whether the presence of WMH in healthy individuals represents an innocuous phenomenon or should be viewed as harmful structural lesions to the ailing brain. Regardless of functional significance, WMH are causally linked to a number of human diseases that are particularly prominent in elderly individuals. For example, Alzheimer's disease, vascular dementia, lacunar strokes and diabetes type 2 are pathologies associated with the accumulation of WMH throughout the brain (Debette and Markus, 2010; Doubal et al., 2010; Gordon et al., 2015). Of interest, among the old who escape the aforementioned diseases, their brains show little or no evidence of WMH lesions. This observation emphasizes the potentially important role of healthy aging, and suggests that there is extensive variability in age-related susceptibility to degeneration of myelin sheaths (Assareh et al., 2011).

Next steps: treatment and prevention

Do we have sufficient knowledge to substantially prevent or even reverse the gradual accumulation of WMH? Unfortunately, at the present time we know very little about the intrinsic mechanisms responsible for the formation and/or accumulation of WMH in the brain. However, there is sufficient information to draw some general conclusions. For example, it appears that WMH are closely associated with high levels of cortisol, a hormone secreted in response to psychological stress (Cox et al., 2015). Thus, reducing the amounts of stress in your daily life could dramatically improve brain health and hence minimize the loss of insulation among branched neurons. Along the same lines, simply lowering blood pressure to a threshold of systolic readings of 140 mmHg could reduce the risk of both stroke and age-related cognitive impairment which appear to be major causes of WMH (Verhaaren et al., 2013; 2015). Exercise is also thought to improve brain health by lowering blood pressure and promoting the birth of new neurons, particularly in hippocampal circuits related to memory and learning phenomena (Fleischman et al., 2010). In this context, irreversible myelin and axonal loss are the most frequently degenerative events encountered in old age, and accordingly, WMH may represent the earliest indices of cognitive aging and their relationship to disease (Gordon et al., 2015). It should be noted that the justification for interventions to prevent the accumulation of abnormal white matter in the brain before clinical symptoms manifest in patients is contentious. Nevertheless, understanding the mechanisms of WMH expressivity will undoubtedly provide critical pathophysiological clues.

Conclusions

The findings of FLAIR WMH lesions are of significant interest. WMH have been well described in MS. However, these lesions appear to be non-specific in other brain disorders. There is currently little correlation between WMH and overt clinical symptoms. The large diversity of WMH, their complex interactions with disease and ultimate clinical consequences require an integrative, systems-biology approach for understanding their functional significance in the human brain.

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Biographies

Ivan Bandovic, OMS I, received his B.S in Biology with a Specialization in Developmental Genetics from Stony Brook University in 2014. He is a candidate to receive a D.O. degree from the New York Institute of Technology, College of Osteopathic Medicine in 2019.

Mia P. Castiglione, OMS I, received her B.S. Honors Degree with Distinction in Neuroscience with a minor in Biology from University of Delaware in 2013. She is currently working as a student-research assistant in the Biomedical Sciences department at the New York Institute of Technology, College of Osteopathic Medicine. She anticipates receiving a D.O. degree from the above institution in 2019.

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Dr. Sherry M. Zakhary is currently completing her medical residency in Radiology, and will be beginning subspecialty training in Neuroradiology at Mt. Sinai Hospital of New York City this summer. She is a graduate of New York Institute of Technology, College of Osteopathic Medicine, where she was a Neuroscience Academic Medicine Fellow, and received a M.S. in Neuromusculoskeletal Sciences.

Dr. German Torres (torresg@nyit.edu) received a Ph.D. from the University of California at Santa Barbara and is currently an Associate Professor in the department of Biomedical Sciences at the New York Institute of Technology, College of Osteopathic Medicine. His specific research interests are centered on the biological basis of brain disorders.

Editor's Column

This issue of the Kopf *Carrier* features an interesting article written by German Torres, Ph.D. and his colleagues titled "White Matter Hyperintensities". These rather enigmatic structures may play a role in some brain disease states, but apparently little is known about their function. Closely related to aging and trauma, these lesions are the focus of research on altered brain function. We thank German and his colleagues for another very interesting Neuroscience Review.

This is the time of year when many academicians are taking summer breaks or using some time without teaching to work hard in their laboratories. Although I am now long retired, I remember the summer days as times to get the graduate students really up to speed and excited about turning out a lot of publishable research. It is also time to think about the upcoming Society for Neuroscience meetings in November in San Diego. Registration has begun and the usual dash for good housing is in full swing. We hope to see many of you there. I was disappointed to find out a while back, that the SfN would not be going back to New Orleans again. Apparently there were problems with many hotels and some of the other meeting arrangements, as well as the fact that the October-November time frame of our meetings is at the peak of hurricane season. New Orleans was, next to San Diego, my favorite venue.

Here it is, mid-summer. My wife and I are spending a good part of the summer in our condo in Dublin, OH and at our oldest son's home (in his grandma and grandpa apartment). Why? Grandchildren! Our youngest son and wife, here in Dublin, have three kids, two girls and a boy. The other son, just north of Detroit, has a boy and girl. So when "up north" we split out time between the two families, trying our best to spoil the kids before handing them back to their parents. Unlike many parts of the country, both the Ohio and Michigan places have been overly dry this summer, but also a bit warm. In Florida, we have been, so far, spared any hurricane activity. The second hurricane is about to hit the Mexican Yucatan peninsula but was well south of Florida. Hopefully it will continue to be a quiet hurricane season, but we have a long way to go until November 30, the official season end.

In speaking to Dawn Gelsinger, Vice President of Sales and Operations at David Kopf Instruments, the company is expanding its manufacturing operations and acquiring advanced machines to better serve the neuroscience community. The company has sponsored this publication, the Kopf *Carrier* since 1973 as a service to the community, an admirable record unsurpassed by any other. We look forward to seeing many of you at the SfN meetings. Stop by and thank Dawn and Carol Kopf (company president) for their devotion to supporting neuroscience research.

Should any of you wish to write an article for the *Carrier*, please contact me at the phone or address below.

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