



Migraine with aura, thrombophilia, and the debate on white matter hyperintensities

Enxaqueca com aura, trombofilia e o debate sobre hiperintensidades da substância branca

Raffaele Ornello¹ Federico De Santis¹ Matteo Foschi¹

¹ University of L'Aquila, Department of Biotechnological and Applied Clinical Sciences, L'Aquila, Italy.

Arq. Neuro-Psiquiatr. 2024;82(7):s00441790571.

White matter hyperintensities (WMHs) on brain magnetic resonance imaging (MRI) are a common finding in migraine with aura¹ whose nature remains debated as they may represent vascular or non-vascular phenomena.² The vascular hypothesis is supported by migraine, especially with aura, being a risk factor for ischemic stroke and other vascular events,³ possibly due to prothrombotic factors, occult embolism, and/or endothelial dysfunction.⁴

In a study published in this issue of *Arquivos de Neuro-psiquiatria*, Can investigated thrombophilia in individuals with migraine with aura. The author found an association between resistance to activated protein C and WMHs in this population.⁵ Notably, thrombophilia was present in up to one third of subjects, a high prevalence consistent with previous literature.⁶

While the study found a link between WMHs and resistance to activated C protein, other thrombophilic factors might also influence WMH occurrence in migraine with aura. Clinically, these results suggest a comprehensive investigation of thrombophilia in individuals with migraine with aura and WMHs.

Pathophysiologically, the study does not definitively resolve the origin of WMHs in migraine with aura. Although WMHs were more prevalent in individuals with thrombophilia, they were also common in those without it. This suggests that WMHs may not be solely related to factors leading to thrombophilia in individuals with migraine. The increased risk for thrombotic events in individuals with migraine can be explained by several factors different from thrombophilia, such as microembolism or microvascular dysfunction.^{4,7} Besides, WMHs can have non-vascular causes such as inflammation.² The results of Can's study suggest that at least some WMHs in migraine with aura may have a vascular origin due to their association with thrombophilia.

Should individuals with migraine with aura and WMHs receive antithrombotic treatment given their high suspect for thrombophilia? Currently, there is no indication for universal antithrombotic therapy in individuals with migraine with aura, as its benefits for WMH progression or migraine management are unclear. Antithrombotic treatments should be prescribed only if some forms of thrombophilia are found. The study suggests screening for thrombophilia in individuals with migraine and WMHs, given its high prevalence, and treating accordingly if found.

As a further therapeutic implication, the study does not address patent foramen ovale, which has been associated with migraine, particularly with aura.⁸ However, closure of patent foramen ovale is not generally indicated for migraine, even with aura, due to uncertain outcomes in available literature.⁹ Thrombophilia might increase the susceptibility to paradoxical embolism in individuals with migraine and consequently contribute to triggering migraines; however, there is no study addressing the benefits of patent foramen ovale closure in individuals with migraine with aura and thrombophilia, likely because of the very low prevalence of those individuals.

In conclusion, this study highlights a potentially significant comorbidity in migraine with aura that may be associated with WMHs and requires attention to avoid missing treatable diagnoses. Questions remain regarding the role of various thrombophilia forms in migraine, the nature of WMHs, and the optimal management of individuals with comorbid migraine with aura, WMHs, and thrombophilia.

Authors' Contributions

RO: conceived the paper and drafted the manuscript; FdS, MF: revised the manuscript for intellectual content.

Address for correspondence
Raffaele Ornello
(email: raffaele.ornello@univaq.it)

DOI <https://doi.org/10.1055/s-0044-1790571>.
ISSN 0004-282X.

received
August 14, 2024
accepted
August 15, 2024

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution 4.0 International License, permitting copying and reproduction so long as the original work is given appropriate credit (<https://creativecommons.org/licenses/by/4.0/>).

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Conflict of Interest

RO reports personal fees or non-financial support from AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva. FdS and MF report no conflict of interest.

References

- 1 Hamedani AG, Rose KM, Peterlin BL, et al. Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology* 2013;81(15):1308–1313. Doi: 10.1212/WNL.0b013e3182a8235b
- 2 Eikermann-Haerter K, Huang SY. White Matter Lesions in Migraine. *Am J Pathol* 2021;191(11):1955–1962. Doi: 10.1016/j.ajpath.2021.02.007
- 3 Sacco S, Ricci S, Carolei A. Migraine and vascular diseases: a review of the evidence and potential implications for management. *Cephalalgia* 2012;32(10):785–795. Doi: 10.1177/0333102412451361
- 4 Øie LR, Kurth T, Gulati S, Dodick DW. Migraine and risk of stroke. *J Neurol Neurosurg Psychiatry* 2020;91(06):593–604. Doi: 10.1136/jnnp-2018-318254
- 5 Yilmaz Can F. Investigation of the relationship between thrombophilic disorders and brain white matter lesions in migraine with aura. *Arq Neuropsiquiatr* 2024;82(07):1. Doi: 10.1055/s-0044-1787762
- 6 Cavestro C, Degan D, Micca G, et al. Thrombophilic alterations, migraine, and vascular disease: results from a case-control study. *Neurol Sci* 2021;42(09):3821–3828. Doi: 10.1007/s10072-020-05006-z
- 7 Sacco S, Harriott AM, Ayata C, et al. Microembolism and Other Links Between Migraine and Stroke: Clinical and Pathophysiologic Update. *Neurology* 2023;100(15):716–726. Doi: 10.1212/WNL.0000000000201699
- 8 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia* 2008;28(05):531–540. Doi: 10.1111/j.1468-2982.2008.01554.x
- 9 Zhang Y, Wang H, Liu L. Patent Foramen Ovale Closure for Treating Migraine: A Meta-Analysis. *J Interv Cardiol* 2022;2022:6456272. Doi: 10.1155%2F2022%2F6456272