The Enigma of Migraine, Platelet Dysfunction, and White Matter Hyperintensities

Significant advancements in the understanding of the pathophysiology of migraine have resulted in the development of highly specific and efficient medications for their treatment.[1] The scientific consensus is that migraine does not have any lasting impact on brain function. Despite this, migraineurs, especially those with aura, have a higher risk of stroke.[2,3] Several neuroimaging studies have demonstrated a higher incidence of silent infarct-like lesions (SIL) and white matter hyperintensities (WMH) in migraineurs.[4,5] The reason behind the elevated chances of MRI abnormalities in individuals with migraines remains uncertain. Antimigraine medication and traditional cardiovascular risk factors have no impact on the association between migraine and structural brain lesions, suggesting the plausibility of a non-atherosclerotic mechanism.[6] Iyigundogdu *et al*.[7] in their study have attempted to clarify the role of platelet activation in the development of SIL and WMH in migraine patients using mean platelet volume (MPV) and platelet distribution width (PDW) as markers of platelet activation and aggregation. The role of platelets in the genesis of migraine was first indicated by McIntyre *et al*.,[8] who observed that migrainous headache is the most common vaso-occlusive symptom of essential thrombocytosis. Several studies have found spontaneous platelet activation and aggregation during and between migraine attacks.[9,10] This platelet activation and aggregation probably occur because of the neurogenic inflammation characterized by the release of various neuropeptides. These neuropeptides include pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) and calcitonin gene-related peptide (CGRP); platelet-activating factor (PAF), and other pro-inflammatory cytokines which may cause platelet hyperaggregability.[11] This can increase the risk of intravascular platelet aggregation or mural thrombi formation, leading to stroke and WMH.

The risk of ischemic stroke is nearly twice as high in people with migraine with aura (MA) compared to those without migraines.[12] This association is most potent in women under 45 who use oral contraceptives or smoke. The risk for stroke is also greater in those with active migraine and more frequent migraine attacks. The association is less robust for females with migraine without aura [odds ratio: 1.83 (95% CI = 1.06 – 3.15)] and men [OR = 1.37 (95% CI = 0.89 – 2.11)].[13] There is no conclusive evidence that the severity of migraine and cumulative exposure to MA increases the risk of stroke. A possible connection between MA and stroke is cortical spreading depression (CSD), which causes a reduction of 20–30% in blood flow to the brain. On rare occasions, especially in the migraine susceptible brain, which is more vulnerable to ischemia, this hypoperfusion may be severe enough to cause ischemia and infarction.[14] Another putative mechanism is the association of MA with patent foramen ovale (PFO). PFO is common in patients with MA and cryptogenic stroke and may be a shared risk factor. Young migraineurs who smoke or use high-dose estrogen oral contraceptives have a higher risk of stroke due to an increased risk of embolism through a PFO.[14]

Several studies have found an increased risk of WMH in patients with migraine with reported prevalence rates of 4–59%, with a higher risk in those with more frequent and severe attacks.[15] Longitudinal studies have failed to find any association with cognitive decline in migraineurs with WMH, though there may be an enhanced risk of stroke with increasing WMH volume.[16] The pathophysiological mechanisms leading to the development of WMHs in migraine are not fully understood. It could be due to ischemic microvascular disturbances with subsequent focal hypoperfusion, systemic arterial stiffness, lower carotid pulsatility index, decreased resistance in intracranial arteries, and neurogenic inflammation causing the release of pro-inflammatory prostaglandins, nitric oxide with resultant platelet aggregation, and oxidative stress.[17] Choi *et al*. found that MPV, a marker for platelet activation, is associated with cerebral WMH in 870 non-stroke outpatient subjects. However, patients with higher MPV were older and had a higher prevalence of hypertension and diabetes mellitus.[18] Similar results have not been replicated in the migraine population with younger and non-diabetic, non-hypertensive patients, indicating that platelet activation and aggregation may not be the primary mechanism for the presence of WMH and SIL in migraine. So, while platelet aggregation and activation may have a role in the pathophysiology of migraine, its role in the genesis of SIL and WMHs requires further evaluation.

The role of PFO in migraine and associated brain lesions requires special mention. PFO is not only responsible for cryptogenic stroke but also has a role in the pathophysiology of MA. It is believed that small particles, air bubbles, and prothrombotic substances circulating in the venous blood gain direct access to the arterial blood, triggering CSD with MA and ischemic stroke. A recent study by Trabattoni *et al*. (LEARNER Study) found that patients with MA and PFO had a prothrombotic state characterized by marked thrombin generation capacity sustained by an elevated number of platelets and microvesicles expressing functionally active tissue factor. It was associated with increased platelet reactive oxygen species. Aspirin administration did not affect this prothrombotic state, which reverted entirely upon PFO closure. Additionally, the prothrombotic state was better controlled by $P2Y_{12}$ antagonists.[19] To conclude, although the study

by Iyigundogdu *et al*. did not show any correlation between MPV and PDW, other markers of prothrombotic state such as P-selectin, activated-glycoprotein IIb/IIIa (aGPIIb/IIIa), tissue factor reactive oxygen species, and microvesicles may shed some light on the pathogenesis of SILs and WNHs in migraineurs.[7]

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References

1. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. BMJ 2010;341:c3666.
2. Schürks M, Kurth T. is migraine a predictor for identifying patients at risk of stroke? Expert Rev Neurother 2011;11:615-8.
3. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischemic stroke in people with migraine: Systematic review and meta-analysis of observational studies. BMJ 2005;330:63.
4. Kruit MC, van Buchem MA, Hofman PAM, Bakkers JT, Terwindt GM, Ferrari MD, *et al*. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-34.
5. Kurth T, Mohamed S, Maillard P, Zhu Y-C, Chabriat H, Mazoyer B, *et al*. Headache, migraine, and structural brain lesions and function: Population-based epidemiology of vascular Ageing-MRi study. BMJ 2011;342:c7357.
6. Stam AH, Weller CM, Janssens ACJ, Aulchenko YS, Oostra BA, Frants RR, *et al*. Migraine is not associated with enhanced atherosclerosis. Cephalalgia 2013;33:228-35.
7. Iyigundogdu I, Derle E. Do mean platelet volume and platelet distribution width have an association with white matter hyperintensities in migraine patients? Ann Indian Acad Neurol 2023;26:435-40.
8. McIntyre KJ, Hoagland HC, Silverstein MN, Petitt RM. Essential thrombocythemia in young adults. Mayo Clin Proc 1991;66:149-54.
9. Couch JR, Hassanein RS. Platelet aggregability in migraine. Neurology 1977;27:843-8.
10. Wachowicz B. Platelet activation: Its possible role in the migraine mechanism. Adv Neurol 1982;33:243-6.
11. Ramachandran R. Neurogenic inflammation and its role in migraine. Semin Immunopathol 2018;40:301-14.
12. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: Systematic review and meta-analysis. BMJ 2009;339:3914.
13. Øie LR, Kurth T, Gulati S, Dodick DW. Migraine and risk of stroke. J Neurol Neurosurg Psychiatry 2020;91:593-604.
14. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, *et al*. Migraine. Nat Rev Dis Primers 2022;8:2.
15. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: A systematic review and meta-analysis. Neurology 2013;81:1260-8.
16. Rist PM, Dufouil C, Glymour MM, Tzourio C, Kurth T. Migraine and cognitive decline in the population-based EVA study. Cephalalgia 2011;31:1291-300.
17. Gryglas A, Smigiel R. Migraine and stroke: What's the link? what to do? Curr Neurol Neurosci Rep 2017;17:22.
18. Choi JW, Lee KO, Jang YJ, Kim H-K, Seo T, Roh YJ, *et al*. High mean platelet volume is associated with cerebral white matter hyperintensities in non-stroke individuals. Yonsei Med J 2023;64:35-41.
19. Trabattoni D, Brambilla M, Canzano P, Becchetti A, Teruzzi G, Porro B, *et al*. Migraine in patients undergoing PFO Closure: Characterization of a platelet-associated pathophysiological mechanism: The LEARNER study. JACC Basic Transl Sci 2022;7:525-40.

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