Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study

In "Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study," Sen et al. followed 11,939 patients with headache and no diagnosis of atrial fibrillation for 20 years and found that after adjusting for confounders, migraine with visual aura was associated with an increased risk of atrial fibrillation. They postulated that autonomic dysfunction may be the underlying cause of both atrial fibrillation and migraine and questioned whether migraine with aura is the result of cardioembolic stroke secondary to atrial fibrillation. Gupta challenged the value of Sen et al.'s findings and commented that (1) migraine with aura and migraine without aura have the same amount of autonomic dysfunction (although no source was provided to quantify the amount of autonomic dysfunction in these 2 entities), and (2) it would be nearly impossible for thromboembolic events due to atrial fibrillation to serially occur in the same cerebrovascular territory leading to migraine with aura. In response, Sen (1) replied that migraine with aura and migraine without aura are commonly considered to be distinct entities and pathophysiologic variants and cited a document published by the International Headache Society and (2) cited a review article that concluded that migraine with aura tends to produce more significant autonomic impairment than migraine without aura. In addition, Sen reinforced that there is a relationship between both (1) migraine with aura and atrial fibrillation (as shown in the present study) and (2) ischemic stroke and migraine with aura (as shown in a previous study). However, it remains unclear whether autonomic dysfunction is responsible for, or merely related to, migraine. Last, Hsieh noted that the x-axis of the Kaplan-Meier curves showing 20-year outcome of incident atrial fibrillation in figure 1 should be labeled "Time to atrial fibrillation," not "Time to stroke," and that the log-rank p value of 0.0048 shown on the figure is different from that which is noted in the text ($p = 0.0002$). Sen replied that Hsieh is correct that the x-axis label should be changed, but said that the p value in the figure is correct (and did not clarify why it is different from the p value in the text).

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study

Vinod Gupta (New Delhi)
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I read with interest the article by Sen et al.[1] The investigators believe that migraine with aura (MwA) and migraine without aura (MwoA) are distinct clinical entities. Neuropharmacologically, both beta-blockers and tricyclic antidepressants are equally effective in the prevention of both variants. This study[1] does not distinguish between variants of migrainous visual aura.[2] Only the migrainous visual field loss without scintillation can be conceived of as being of ischemic origin. The pathognomonic scintillating scotoma was not seen in any patient.[1] Retrospective questionnaire responses for migrainous visual aura are highly subjective.

Author disclosures are available upon request (journal@neurology.org).

Recurrent stereotyped MwA-headache attacks of atrial fibrillation (AF)-related thromboembolism require the presumed passage of vascular-occluding substance(s) into the same cranial vascular territory, predictably or unpredictably, over decades—a highly unlikely to impossible clinical scenario.[3] AF begins in the right atrium. The pulmonary circulation cannot remain indefinitely spared in patients with MwA-AF. There is also no difference in autonomic dysfunction between patients with MwA and patients with MwoA, as speculated.[1]

Meta-analysis obtains bizarre associations and has introduced a façade of mathematical acceptability that draws the clinician away from reality.[4] The linkage of AF-related presumed thromboembolism to patients with MwA,[1] despite lack of commonsense and logic in closure of the patent foramen ovale to prevent migraine attacks,[3] appears to be misplaced.

1. Sen S, Androulakis XM, Duda V, et al. Migraine with visual aura is a risk factor for incident atrial fibrillation: a cohort study. Neurology 2018;91:e2202–e2210.
2. Hupp SL, Kline LB, Corbett JJ. Visual disturbances in migraine. Surv Ophthalmol 1989;33:221–236.
3. Gupta VK. Patent foramen ovale closure and migraine: science and sensibility. Expert Rev Neurother 2010;10:1409–1422.
4. Horton RC, Kendall MJ. Clinical pharmacology and therapeutics. Postgrad Med J 1991;67:1042–1054.

Reader response: Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study

Cheng-Yang Hsieh (Tainan, Taiwan)
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In figure 1,[1] the x-axis should be "Time to incident atrial fibrillation" rather than "Time to stroke." Besides, the "log-rank *p* value" in figure 1 was not consistent with that in the text (paragraph 2, page e2205). Please check.

1. Sen S, Androulakis XM, Duda V, et al. Migraine with visual aura is a risk factor for incident atrial fibrillation: a cohort study. Neurology 2018;91:e2202–e2210.

Author response: Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study

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I thank Dr. Gupta for the comment on our article.[1] Migraine with aura is considered a different clinical entity compared with migraine without aura.[2] Pathophysiologically, the 2 are considered to be variants, with the accepted notion being that visual aura is generated by cortical spreading depression.[3] We have shown that migraine with aura is a risk factor for ischemic stroke of cardioembolic subtype.[4] The migraine questionnaire was administered through a structured interview by trained personnel, similar to what a clinician may achieve at the bedside to make migraine with and without aura diagnoses. Studies have shown that migraine with aura is associated with autonomic dysfunction.[5]

I also wish to thank Dr. Hsieh for identifying the typographical errors in our article.[1] In figure 1, the x-axis label should be "Time to incident atrial fibrillation" rather than "Time to stroke." However, the "log-rank *p* value" in figure 1 is correct (0.0048).

Author disclosures are available upon request (journal@neurology.org).

1. Sen S, Androulakis XM, Duda V, et al. Migraine with visual aura is a risk factor for incident atrial fibrillation: a cohort study. Neurology 2018;91:e2202–e2210.
2. Headache Classification Committee of the International Headache Society (IHS) the International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
3. Vgontzas A, Burch R. Episodic migraine with and without aura: key differences and implications for pathophysiology, management, and assessing risks. Curr Pain Headache Rep 2018;22:78.
4. Androulakis XM, Kodumuri N, Giamberardino LD, et al. Ischemic stroke subtypes and migraine with visual aura in the ARIC study. Neurology 2016;87:2527–2532.
5. Miglis MG. Migraine and autonomic dysfunction: which is the horse and which is the jockey? Curr Pain Headache Rep 2018;22:19.

CORRECTIONS

Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG

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In the article "Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG" by Honorat et al.,[1] first published online August 1, 2019, the legend for figure 2 should have read "(A) Control CSF from normal pressure hydrocephalus patient and (B) healthy control serum do not bind to the surface of living hippocampal neurons. Neither CSF (D) nor serum (E) from patients 1–10 (representative images from patient 5) bind to the neuronal cultures. In contrast, NMDAR-IgG-positive patient CSF binds in a punctate pattern to the extracellular surface of hippocampal neurons (C, green). Cells were poststained for acetylated tubulin to identify axons (F, red). Nuclei stained with DAPI in all panels (white). Scale bar, 20 μm." The corrected version appeared in the September 3 issue. The authors regret the error.

Reference

1. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al. Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG. Neurology 2019;93:e954–e963.

Clinical trials of disease-modifying agents in pediatric MS

Opportunities, challenges, and recommendations from the IPMSSG

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In the article "Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG" by Waubant et al.,[1] first published online May 1, 2019, the Coinvestigator appendix—the list of those who reviewed and approved the consensus statement—should have included Investigators Angelo Ghezzi (Centro Studi Sclerosi Multipla, Ospedale di Gallarate, Gallarate, Italy), Amit Bar-Or (Center for Neuroinflammation and Experimental Therapeutics and the Department of Neurology, University of Pennsylvania, Philadelphia, PA), and Andrew Kornberg (University of Melbourne, Parkville, Australia), who each reviewed the manuscript. The authors regret the errors.

Reference

1. Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in pediatric MS: opportunities, challenges, and recommendations from the IPMSSG. Neurology 2019;92:e2538–2549.

Author disclosures are available upon request (journal@neurology.org).