Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study

In "Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study," Phyu et al. reported that patients with Fabry disease (FD) have significantly higher cerebral blood flow (CBF) in the white matter than normal controls, and that this difference is most notable in the splenium of the corpus callosum (SCC). Based on these findings, they proposed that white matter hyperintensities (WMH) in patients with FD are the result of hyperperfusion. In their experience, Coccozza and Quarantelli note that the SCC is infrequently hyperintense in patients with FD and suggest that a mechanism other than hyperperfusion is responsible for WMH in FD. In response, Werring et al. acknowledge that (1) the correlation between hyperperfusion in the SCC and WMH in the SCC is not indicative of causation and (2) there is a low prevalence of SCC hyperintensities in patients with FD compared with patients with multiple sclerosis, though they note that prior studies also demonstrate increased CBF in the SCC of patients with FD. Further multimodal studies are needed to assess the relationship between CBF and WMH in patients with FD.

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study

Sirio Coccozza (Naples, Italy) and Mario Quarantelli (Naples, Italy)
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We read the article by Phyu et al.¹ that confirmed increased perfusion in the brain of patients with Fabry disease (FD), essentially involving white matter (WM), mainly at the splenium of the corpus callosum (SCC), correlating with WM hyperintensity (WMH) load. The authors hypothesized a causal role of hyperperfusion in determining WM damage, supporting a causative chain linking hyperperfusion, increased interstitial pressure, and demyelination, resulting in WMH.¹ However, this chain of events does not completely fit with the currently available diffusion tensor imaging data in FD that indicate that microstructural alterations do not correlate with WMH load,^{2–4} and are lacking in the structure with the highest hyperperfusion (i.e., the SCC).

Further, a very low incidence of WMH affecting the corpus callosum has been described in patients with FD,⁵ thus questioning a possible causative role of perfusion changes in the development of WMH. Although methodologic differences and population heterogeneity may partly justify these inconsistencies, these results seem to indicate that additional, relatively independent mechanisms are at work in determining, respectively, microstructural alterations and WMH in FD. Additional multimodal studies are warranted to define the possible role of these noninvasive MRI-derived metrics as biomarkers.

1. Phyu P, Merwick A, Davagnanam I, et al. Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study. *Neurology* 2018;90:e1379–e1385.

2. Albrecht J, Dellani PR, Müller MJ, et al. Voxel based analyses of diffusion tensor imaging in Fabry disease. *J Neurol Neurosurg Psychiatry* 2007;78:964–969.
3. Coccozza S, Pontillo G, Quarantelli M, et al. Default mode network modifications in Fabry disease: a resting-state fMRI study with structural correlations. *Hum Brain Mapp* 2018;39:1755–1764.
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5. Coccozza S, Olivo G, Riccio E, et al. Corpus callosum involvement: a useful clue for differentiating Fabry disease from multiple sclerosis. *Neuroradiology* 2017;59:563–570.

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Author response: Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study

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We thank Drs. Coccozza and Quarantelli for their interest in our article.¹ We agree that correlations in our cross-sectional case-control study cannot confirm the presence or direction of causal pathways in Fabry disease (FD).

Although cerebral blood flow (CBF) was statistically higher only in the corpus callosum, it was elevated in almost all white matter regions, with a statistically significant overall elevation in white matter.¹ We did not aim to definitively investigate CBF in individual regions, so caution is needed when interpreting findings in the corpus callosum. Nevertheless, increased CBF in the corpus callosum splenium (supplied by distal posterior cerebral artery branches) was consistent with previously reported elevated CBF in the posterior circulation in FD,² and microstructural alterations in white matter, including in the splenium.³

We agree that CBF changes are not necessarily causal in the development of FD white matter injury, and acknowledge the reported low prevalence of corpus callosum lesions in FD compared to multiple sclerosis.⁴ Small patient samples and technical factors are likely important in interpreting MRI findings in FD, but further multimodal studies are justified to help clarify links between CBF, microstructural alterations, and white matter hyperintensities.

1. Phyu P, Merwick A, Davagnanam I, et al. Increased resting cerebral blood flow in adult Fabry disease: MRI arterial spin labeling study. *Neurology* 2018;90:e1379–e1385.
2. Moore DF, Scott LT, Gladwin MT, et al. Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001;104:1506–1512.
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4. Coccozza S, Olivo G, Riccio E, et al. Corpus callosum involvement: a useful clue for differentiating Fabry disease from multiple sclerosis. *Neuroradiology* 2017;59:563–570.

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Editors' note: Body composition status and the risk of migraine: A meta-analysis

In "Body composition status and the risk of migraine: A meta-analysis," Gelaye et al. reported that a meta-analysis of 12 studies revealed that the risk of migraine is increased in persons who are underweight. Dr. Gupta attributes the fact that this finding was statistically significant to the methodology of the meta-analysis, rather than to a true relationship, noting that he does not believe uncomplicated low body mass index (BMI) is associated with migraine. In support of this conclusion, he remarks that (1) Addison disease, a disorder that causes low body weight, is not associated with migraine; and (2) thyrotoxicosis, which also leads to low body weight, is associated with cephalgias of unclear etiology. Gelaye et al. respond that they were unsurprised by the relationship they observed between low BMI and migraine. They support the validity of their finding by noting that migraine is associated with altered levels of adipocytokines and that, correspondingly, their meta-analysis also showed an association between obesity and migraine.

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: Body composition status and the risk of migraine: A meta-analysis

Vinod K. Gupta (New Delhi, India)
Neurology® 2018;91:1073. doi:10.1212/WNL.0000000000006623

I read with interest the article by Gelaye et al.¹ regarding influence of body mass index (BMI), at both ends of the spectrum, on incidence of migraine. Meta-analyses are susceptible to all intrinsic biases of all observational studies and have spurred a quest for statistical truth that risks drawing clinicians away from clinical reality or common sense.^{2,3} In addition, there is no requirement for a generalized robust overarching theoretical matrix to conduct a meta-analysis, pooling—as they do—data from several studies that frequently do not ask the same research question.

The emphasis of low BMI on migraine prevalence on the basis of age- and sex-adjusted pooled risk of migraine, which was only marginally increased by 13% compared with those of normal weight (odds ratio 1.13; 95% confidence interval 1.02, 1.24, $p < 0.001$) and remained increased after multivariate adjustments,¹ is a good example of statistical truth prevailing over biological common sense. Addison disease, the prototypical low body mass disorder, does not show any increased susceptibility to development of migraine attacks. Thyrotoxicosis, another low body mass inducing illness, is associated with headache, but has a hyperkinetic cardiovascular system like patent foramen ovale,⁴ of which the cephalalgic mechanism remains unknown.

Uncomplicated low BMI is very unlikely to be associated with migraine. Such studies make the evolution of comprehensive pathophysiologic framework impossible.

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Author response: Body composition status and the risk of migraine: A meta-analysis

Bizu Gelaye (Boston), Simona Sacco (L'Aquila, Italy), Wendy Brown (Brisbane, Australia), Haley Nitchie (Baltimore), Raffaele Ornello (L'Aquila, Italy), and B. Lee Peterlin (Lancaster)
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We thank Dr. Gupta for the interest in our article,¹ in which we evaluated the relationship between body composition and migraine. The commentary raised an interesting point about biological plausibility and how observed association between low body mass index (BMI) and migraine might be attributable to underlying illness such as thyrotoxicosis. Biologically, it is well-known that there are several potential mechanisms for the BMI–migraine association.² Adipose tissue is a neuroendocrine organ. Like the thyroid gland, too much or too little can both be associated with medical symptoms or disorders. Adipose tissue is centrally regulated by the hypothalamus and its connections, and peripherally participates in modulation of hormones, immune cells, and inflammatory-related proteins (e.g., adipocytokines).^{2,3} With adipose tissue expansion, or reduction, changes in macrophage recruitment, receptor expression, and the secretion of cytokines and adipokines occur.^{2,4} As such, it is not surprising that low BMI is associated with migraine. Is it possible that undetected illness could lead to low BMI? Yes, it is possible. However, as noted in our article, most of the studies included for meta-analysis are population-based studies.¹ It is highly unlikely these rare complications can introduce bias in population-based studies. Finally, we would like to clarify that our meta-analysis was not a data-driven exercise. Rather, it was guided by a fundamental biological question with priori set procedures and consistent operational definitions of exposure and outcome variables. The details are summarized in the Methods of our article.¹

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CORRECTION

Data-driven analyses revealed the comorbidity landscape of tuberous sclerosis complex

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In the article “Data-driven analyses revealed the comorbidity landscape of tuberous sclerosis complex” by Yu et al.,¹ there was an error with one of the co-authors’ names published ahead of print on October 17, 2018. The co-author’s name should appear as Dario R. Lemos. The correct spelling of the author’s name published online with the full article on November 20, 2018. The authors regret the error.

Reference

1. Yu KH, Miron O, Palmer N, et al. Data-driven analyses revealed the comorbidity landscape of tuberous sclerosis complex. *Neurology* 2018;91:974–976.

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Data-driven analyses revealed the comorbidity landscape of tuberous sclerosis complex

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