Disputes & Debates: Editors' Choice

Robert C. Griggs, MD, FAAN, Section Editor; Steven Galetta, MD, FAAN, Co-Editor

Editors' note: Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage

In response to "Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage," Drs. Zheng et al. share the results of their own investigation into admission serum magnesium (ASM) and spontaneous intracerebral hemorrhage (SICH) outcome. They found that patients with favorable outcomes had higher ASM levels than those patients who died within 30 days of admission. This association between low ASM levels and 30-day mortality was consistent with the results by Liotta et al. However, the data reported by Zheng et al. did not show that ASM was a predictor for 3-month outcome. Authors Liotta et al. explain this divergence may be due to differences in the statistical methodology and patient inclusion measures used in the studies.

Megan Alcauskas, MD, and Steven Galetta, MD
Neurology® 2018;90:666. doi:10.1212/WNL.0000000000005246

Reader response: Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage

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Neurology® 2018;90:666. doi:10.1212/WNL.0000000000005247

We read with interest the article by Liotta et al.,¹ in which lower admission serum magnesium (ASM) was associated with worse outcomes in spontaneous intracerebral hemorrhage (SICH). We reevaluated the prognostic role of ASM in 395 SICH patients in the West China Hospital during 2011 and 2016: 269 male (68.1%), mean age of 57.63 (13.06) years, hematoma volume of 25.599 (25.452) mL, Glasgow Coma Scale (GCS) of 12, and ASM of 2.030 (0.368) mg/dL. With *t* tests, 91 patients with favorable outcomes had higher ASM levels (2.111 [0.438] vs 2.006 [0.341] mg/dL, *p* = 0.016); lower ASM levels were found in 97 patients who died within 30 days (2.062 [0.387] vs 1.931 [0.279] mg/dL, *p* = 0.002). After adjusting for the factors seen in Liotta et al., the GCS (odds ratio [OR] 0.711, 95% confidence interval [CI] 0.652–0.777, *p* < 0.001), hematoma volume (OR 1.012, 95% CI 1.000–1.025, *p* = 0.049), hematoma volume change (OR 2.102, 95% CI 1.637–2.699, *p* < 0.001), and ASM (OR 0.673, 95% CI 0.490–0.924, *p* = 0.015) were associated with 30-day mortality. Moreover, the GCS (OR 0.642, 95% CI 0.554–0.744, *p* < 0.001) and hematoma volume (OR 1.034, 95% CI 1.013–1.056, *p* = 0.001) were associated with 3-month outcomes, which kept with previous studies.^{1–3} However, ASM was not a predictor for 3-month outcomes (OR 0.519, 95% CI 0.099–2.713, *p* = 0.437). Therefore, our findings add new and important data (i.e., ASM is associated with 30-day mortality) to the literature. However, the association of ASM and 3-month outcomes needs further study.

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Author response: Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage

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Neurology® 2018;90:667. doi:10.1212/WNL.0000000000005272

We appreciate the interest of Zheng et al. in our article on magnesium, hemostasis, and outcome in spontaneous intracerebral hemorrhage (SICH),¹ and their efforts investigating the topic. It is exciting that they observed an association between lower admission serum magnesium (ASM) and greater 30-day mortality, which is consistent with our findings and provides additional confirmatory evidence of a true ASM effect. While Zheng et al. did not demonstrate an association between ASM and 3-month mortality, there are potential reasons for this difference between our studies. We analyzed 3-month outcome using an ordinal rather than a binary mortality approach¹; it is possible the binary mortality approach missed a functional outcome effect. We also analyzed outcomes only in patients presenting within 6 hours of symptom onset and accounted for time from onset in our model. The morbid consequences of delayed medical attention in late-presenting patients may predispose them to future medical complications with an overwhelming effect on 3-month mortality. This would be consistent with our hypothesis of an acute hemostatic role of magnesium and literature, suggesting that neurologic deterioration occurs early (less than 12 hours)² and neurologic causes of death in SICH occur before 30 days while medical causes of death occur later.³

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Editors' note: 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort

Dr. Braillon raises several concerns regarding the methodology and conclusions found in the study “25-Hydroxyvitamin D (25[OH]D) deficiency and risk of MS among women in the Finnish Maternity Cohort,” including the jump from association to causality and the lack of data related to smoking history. He likens the current state of 25(OH)D and multiple sclerosis (MS) research to that of 25(OH)D and cancer, in which, he states, there is a continuous flow of flawed positive studies despite several large negative trials. Authors Munger et al. maintain that there is enough affirmative evidence to conclude that low vitamin D level is a risk factor for MS and even to support causality. The authors agree that the lack of smoking data in the Finnish Maternity Cohort was a limitation of their study, but when they excluded women with positive serum cotinine (a biomarker for nicotine metabolism), their results were unchanged.

Megan Alcauskas, MD, and Steven Galetta, MD

Neurology® 2018;90:667. doi:10.1212/WNL.0000000000005248

Reader response: 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort

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Neurology® 2018;90:668. doi:10.1212/WNL.0000000000005249

The claim by Munger et al.¹ that “These results directly support vitamin D deficiency as a risk factor for MS” deserves comment.

First, association is not causality.

Second, investigating for confounding variables is a basic prerequisite. For 25(OH)D, these are numerous (e.g., smokers have lower levels and run a dose-dependent increased risk of developing multiple sclerosis [MS] plus rapid disability progression).^{2,3}

Third, Munger et al. used flawed methods for offspring⁴: prenatal smoking exposure increases the risk for offspring adolescent daily smoking.

In a 2008 robust study in the general population (Third National Health and Nutrition Examination Survey [NHANES III]), the association between 25(OH)D and cancer mortality was not significant and disappeared after adjustment. Later, the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial failed to show evidence that 25(OH)D plays a protective role in cancer. Neither precluded a continuous flow of flawed publications about 25(OH)D and cancer. For MS, Dr. Goldberg’s hypothesis in 1986 has lasted too long. Why are there so few randomized controlled trials?⁵

Finally, why were smoking data (amount and duration) not retrieved from the Finnish Maternity Cohort? Smoking is the most important item to monitor during pregnancy—it is the first avoidable cause of preterm birth and more.

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Author response: 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort

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Neurology® 2018;90:668–669. doi:10.1212/WNL.0000000000005245

Although a randomized clinical trial of vitamin D supplementation on primary multiple sclerosis (MS) prevention would provide more compelling evidence of causality than observational studies, challenges including cost, duration, and compliance make it unlikely that such a study will be done. As is often the case in medicine, recommendations must be based on the best

available observational evidence. Our study¹ contributed to a large body of literature supporting low vitamin D levels as a risk factor for MS.²

Applying the Bradford-Hill guidelines for assessing causality,³ the vitamin D and MS association meets many, including temporality, strength of association, dose–response, biologic plausibility, and consistency and coherence of study findings. A causal interpretation is further supported by the results of multiple Mendelian randomization studies.^{4,5} Thus, when considered in the context of the current literature, a causal interpretation of the vitamin D and MS association is not inappropriate.

As discussed, one limitation to our study was lack of information on potential confounding variables, including smoking (information not collected in the Finnish Maternity Cohort).¹ However, we were able to measure serum cotinine (a biomarker of nicotine metabolism) and restrict the analyses to women negative for cotinine (60%) and the results were unchanged, with a 50 nmol/L increase in 25-hydroxyvitamin D associated with a 45% reduced MS risk (RR 0.55, 95% confidence interval 0.37–0.82).

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CORRECTION

Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy

Neurology® 2018;90:669. doi:10.1212/WNL.0000000000005461

In the article “Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy” by A. Karaa et al.,¹ there is an error in the last sentence of the “Demographic and other baseline characteristics” subsection. The average daily dose for the 0.10 mg/kg/h dose cohort should be 12.7 mg rather than 2.7 mg as was published ahead of print on March 2, 2018. The final version published with the April 3, 2018, issue is correct. The authors regret the error.

Reference

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Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy

Neurology 2018;90;669

DOI 10.1212/WNL.0000000000005461

This information is current as of April 2, 2018

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