

# Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

## **Editors' note: Meta-analysis of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy**

In their systematic review and meta-analysis of magnetic resonance spectroscopy (MRS) findings associated with hepatic encephalopathy (HE) due to cirrhosis, Zeng et al. observed a statistically significant increase in glutamine/glutamate metabolites with a decrease in myo-inositol and choline concentrations throughout the parietal, occipital, and basal ganglia regions among patients with HE vs those without HE. Of these metabolites, glutamine/glutamate presence in the parietal lobe was the most robust predictor of HE. In response to these findings, Dr. Gupta expresses concern as to the utility of advanced MRS imaging, given that HE remains a clinical diagnosis. The authors respond that MRS may be useful for earlier identification of mild or subclinical HE, which may lead to earlier, targeted treatment in patients at risk for later decompensation.

James E. Siegler III, MD, and Steven Galetta, MD  
*Neurology*® 2020;95:984. doi:10.1212/WNL.00000000000011039

## **Reader response: Meta-analysis of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy**

Vinod K. Gupta (New Delhi)  
*Neurology*® 2020;95:984–985. doi:10.1212/WNL.00000000000011038

I read the article by Zeng et al.<sup>1</sup> Magnetic resonance spectroscopy (MRS) changes—particularly in the parietal lobe related to glutamine/glutamate, choline, and myo-inositol—correlate with the severity of hepatic encephalopathy (HE), helping to distinguish between cirrhotic patients with and without minimal hepatic encephalopathy (MHE).

The clinical picture of the cirrhotic patient is generally clinically evident.<sup>2</sup> Most commonly used tools to predict outcomes in patients with cirrhosis include assessing severity of portal hypertension using hepatic venous pressure gradient measurements, using scoring systems such as the Model for End-stage Liver Disease and Child-Pugh-Turcotte scores, and recently, clinical staging systems based on cirrhosis-related clinical complications.<sup>2</sup> Slipping of the cirrhotic patient in to the MHE or HE is frequently marked by elevations of blood ammonia and the highly characteristic flapping tremor, besides constructive apraxia.<sup>3</sup> MHE/HE in patients with cirrhosis is a clinical diagnosis of exclusion based on a high index of suspicion that should, however, not be based solely on ammonia levels.

MRS changes of MHE should be correlated with early clinical signs of hepatic decompensation to augment clinical utility. Cirrhosis and cirrhotic decompensation are not clinically subtle issues that might benefit clinically to any extent with MRS findings.

Utility of MRS with brain parietal changes in the outpatient settings would indeed be clinically valuable in the predecompensated nonhospitalized cirrhotic patient. Correlation of MRS

findings with hepatic venous pressure gradient measurements or other clinical scores would be useful. Otherwise, such studies will remain purely academic and clinically unhelpful, even in tertiary care centers.

1. Zeng G, Penninkilampi R, Chaganti J, et al. A meta-analysis of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy. *Neurology* 2020;94:e1147–e1156.
2. Haj M, Rockey DC. Predictors of clinical outcomes in cirrhosis patients. *Curr Opin Gastroenterol* 2018;34:266–271.
3. Ninan J, Feldman L. Ammonia levels and hepatic encephalopathy in patients with known chronic liver disease. *J Hosp Med* 2017;12:659–661.

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## Author response: Meta-analysis of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy

Mark Danta (Sydney, Australia), Georgia Zeng (Sydney, Australia), and Sara Montagnese (Padua, Italy)  
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The authors thank Dr. Gupta for the comment on our article.<sup>1</sup> Hepatic encephalopathy (HE) is associated with significant morbidity and mortality in cirrhosis; its pathophysiology is incompletely understood. Our meta-analysis was a review of magnetic resonance spectroscopy (MRS) data in HE, which confirmed a specific metabolic pattern, consisting of increased glutamine/glutamate—with reduced choline—and myo-inositol, particularly in the parietal lobes.<sup>1</sup> The changes increased with the severity of HE. We agree that this would have limited diagnostic utility in overt HE, which is clinically obvious. We strongly disagree, however, about covert or minimal HE (MHE), which are defined as the presence of neuropsychologic or neurophysiologic abnormalities in patients with no obvious—i.e., at least disorientation for time or asterix—clinical signs of overt HE. Here, there is a potential role for MRS in diagnosis, monitoring, and investigation. In a recent French cohort of cirrhotic individuals with and without MHE, HE pattern MRS changes in the pallidum were present in 95% of MHE vs 0% of unimpaired patients ( $p < 0.001$ ), suggesting MRS could outperform other modalities of MHE diagnosis.<sup>2</sup> MRS may also have a significant role in future pathophysiologic and pharmacologic HE studies.

1. Zeng G, Penninkilampi R, Chaganti J, et al. A meta-analysis of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy. *Neurology* 2020;94:e1147–e1156.
2. Hermann B, Rudler M, Galanaud D, Thabut D, Weiss N. Magnetic resonance spectroscopy: a surrogate marker of hepatic encephalopathy? *J Hepatol* 2019;71:1055–1057.

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## Editors' note: Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants

Using pooled patient-level data from 5 randomized clinical trials, Dr. Carcel et al. evaluated sex disparities in the management and outcomes of patients with acute ischemic or hemorrhagic stroke. Compared with men, women were more frequently treated with antihypertensives and admitted to an acute stroke unit but were otherwise less frequently given acute antithrombotics, antipyretics (when fever was present), glucose- or lipid-lowering agents, or treated in an intensive care unit. With the exception of an antipyretic for fever, it is unclear whether these disparities in treatment reflect missed opportunities in care or suggest sex differences in the presence (or severity) of preexisting comorbidities. Incompletely characterized is the disparity in treatment with glycemic agents, which could be confounded by severity of hyperglycemia during hospitalization, whereas the differential use of antithrombotics could be confounded by the inclusion of both ischemic and hemorrhagic stroke trials. Compared with men in this cohort, women were more likely to survive stroke at 3 months, albeit with greater disability than male survivors. This disability difference likely has several explanations, as Drs. Ganesh and Varma indicate in their response to the article, with the big confounder being survival bias. Furthermore, the disparate premorbid disability between sexes before stroke could have contributed to the higher mortality rate seen in men, as pointed out by Drs. Ganesh and Varma. A more detailed analysis on the impact of premorbid disability is presently under review and will illustrate what sex differences in outcome exist—if any—when patients are stratified by premorbid disability.

James E. Siegler III, MD, and Steven Galetta, MD  
*Neurology*® 2020;95:986. doi:10.1212/WNL.00000000000011040

## Reader response: Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants

Aravind Ganesh (Calgary, Canada) and Malavika Varma (Calgary, Canada)  
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We thank Drs. Carcel et al.<sup>1</sup> for helping advance our understanding of sex differences in stroke treatment and outcome. The accompanying editorial astutely suggested that the greater poststroke disability seen among the women in this study may reflect a survivor bias effect.<sup>2</sup> However, we would also like to highlight the sex difference in premorbid disability per the modified-Rankin Scale (mRS) that was evident in the ENCHANTED, SCAST, and HeadPoST trials (unavailable for INTERACT) in table 2. Men were more likely to have premorbid mRS of 0 (no symptoms). Sex differences in premorbid mRS may account for apparent differences in stroke outcomes between men and women.<sup>3</sup> It would be interesting to further validate the disability analysis using ordinal rather than dichotomous analysis of the mRS (allowing more premorbidly disabled patients to contribute to treatment effect)<sup>4</sup> or by comparing the difference between poststroke and prestroke mRS (“delta-mRS”) in men and women, which has predictive validity for long-term poststroke outcomes.<sup>5</sup> Alternatively, if numbers permit, perhaps the dichotomous mRS analysis could be stratified by premorbid disability (e.g., premorbid mRS = 0 together, mRS = 1 together, and so forth) to see if the difference remains.

1. Carcel C, Wang X, Sandset EC, et al. Sex differences in treatment and outcome after stroke. *Neurology* 2019;93:e2170–e2180.
2. Sposato LA, Brown DL. Sex differences in the use of therapeutic resources and stroke outcomes in 5 randomized trials. *Neurology* 2019; 93:1025–1027.
3. Renoux C, Coulombe J, Li L, et al. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke* 2017;48:2731–2738.

4. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM. Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology* 2018;91:e1951–e1960.
5. Ganesh A, Luengo-Fernandez R, Pendlebury ST, Rothwell PM. Long-term consequences of worsened poststroke status in patients with premorbid disability. *Stroke* 2018;49:2430–2436.

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## Author response: Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants

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The authors thank Drs. Ganesh and Varma for their interest in our article.<sup>1</sup> We agree with Drs. Ganesh and Varma's comments on premorbid disability potentially influencing the sex differences in 90-day mRS. Indeed, the findings from the INternational STroke oUtcomes sTudy (INSTRUCT),<sup>2</sup> which was individual participant data (IPD) for incident strokes obtained from 13 population-based incidence studies, showed that prestroke functional limitation was one of the confounding factors—along with age, stroke severity, and history of atrial fibrillation—that reversed the greater mortality in women compared with men after adjustments.

In our IPD, only HeadPoST has complete premorbid mRS data—SCAST excluded patients with an mRS of 4 or more, ENCHANTED excluded those with an mRS of 2 or more, and INTERACT had no premorbid mRS data. However, the results of this analysis are under peer review in another journal. We will share the results in this post once the article has been published.

1. Carcel C, Wang X, Sandset EC, et al. Sex differences in treatment and outcome after stroke: pooled analysis including 19,000 participants. *Neurology* 2019;93:e2170–e2180.
2. Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (International Stroke Outcomes Study): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes* 2017;10:e003436.

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### CORRECTION

## Nusinersen in SMA 2 and 3

Risks vs benefits

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In the editorial “Nusinersen in SMA 2 and 3: Risks vs benefits” by Deymeer,<sup>1</sup> the name of the corresponding author of a cited article should be spelled as “Mercuri” in the 3 locations it is listed within the editorial. The author regrets the error.

### Reference

1. Deymeer F. Nusinersen in SMA 2 and 3: risks vs benefits. *Neurology* 2020;95:151–152.

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## Nusinersen in SMA 2 and 3: Risks vs benefits

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