Neurosurgical Forum LETTERS TO THE EDITOR

Residual meningiomas

TO THE EDITOR: We read with great interest the research published by Materi et al.¹ (Materi J, Mampre D, Ehresman J, et al. Predictors of recurrence and high growth rate of residual meningiomas after subtotal resection. *J Neurosurg*. Published online January 3, 2020. doi:10.3171/2019.10.JNS192466). Based on a retrospective cohort study, the authors explored the risk factors for recurrence and the high growth rate of residual meningiomas after subtotal resection. This article differentiates the risk stratification of residual meningiomas after subtotal resection and provides strong evidence for the diagnosis and treatment of meningiomas, which is worth encouraging and approving. However, after reading this article carefully, we have several issues to point out.

First, several data points need an explanation. For preoperative tumor volume in Table 2, the hazard ratio (HR) was 4.720, while the 95% confidence interval (CI) was between 1.042 and 3.146. The authors need to comment on this unlikely occurrence. Similarly, on page 3, the authors described that “the most significant benefit occurred with preoperative tumor volume < 10 cm³ (HR 0.396, 95% CI 1.446–4.399, $p = 0.0004$).” Here, the HR was 0.396, while the 95% CI was between 1.446 and 4.399. This represents another potential issue that requires comment. In addition, in the abstract, the p value of falx location should be 0.021, not 0.0021.

Second, in their statistical analysis, the authors did not clarify the representation of continuous variables (such as age or preoperative Karnofsky Performance Scale [KPS] score) or classified variables (such as sex or race). Additionally, the Kaplan-Meier (K-M)^{2,3} curve is mentioned twice in Figs. 1 and 2, but it is not described in the statistical analysis, which is confusing for readers. Moreover, the authors described in their statistical analysis that “stepwise multivariate proportional hazards [namely, Cox proportional hazards] regression analyses were performed to identify potential associations....” However, we disagree that this statistical analysis is appropriate. The use of Cox proportional hazards regression modeling should be in accordance with the requirement of a proportional hazard assumption.⁴ The authors did not verify the proportional hazard assumption in this study. Additionally, it is important to point out that there are noticeable intersections between the two survival curves in Fig. 2B and D, which indicate that the use of the K-M method and stepwise

multivariate proportional hazards regression analyses is inappropriate in this study. In our opinion, a competing risk model^{5,6} is more suitable for the data analysis in their study.

Rui Sui, MD

Haozhe Piao, MD

Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, Liaoning Province, China

References

1. Materi J, Mampre D, Ehresman J, et al. Predictors of recurrence and high growth rate of residual meningiomas after subtotal resection. *J Neurosurg*. Published online January 3, 2020. doi:10.3171/2019.10.JNS192466
2. Lacny S, Wilson T, Clement F, et al. Kaplan–Meier survival analysis overestimates cumulative incidence of health-related events in competing risk settings: a meta-analysis. *J Clin Epidemiol*. 2018;93:25–35.
3. van Walraven C, McAlister FA. Competing risk bias was common in Kaplan–Meier risk estimates published in prominent medical journals. *J Clin Epidemiol*. 2016;69:170–173.e8.
4. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011;378(9798):1244–1253.
5. Shen W, Sakamoto N, Yang L. Cancer-specific mortality and competing mortality in patients with head and neck squamous cell carcinoma: a competing risk analysis. *Ann Surg Oncol*. 2015;22(1):264–271.
6. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601–609.

Disclosures

The authors report no conflict of interest.

Correspondence

Haozhe Piao: drpiao_haozhe@sina.com.

INCLUDE WHEN CITING

Published online June 12, 2020; DOI: 10.3171/2020.2.JNS20447.

Response

We thank Drs. Sui and Piao for their interest in our research and for their feedback on our article. On repeated statistical analysis, we corroborate the typographical errors noted in their response. Corrected values are reflected below and will be remedied via erratum:

- Preoperative tumor volume: HR 1.008, 95% CI 1.002–1.013
- “the most significant benefit occurred with preoperative tumor volume $< 10 \text{ cm}^3$ (HR 0.396, 95% CI 0.227–0.691)”
- Falcine location: $p = 0.021$

We also confirm the variable classifications raised by Sui and Piao, where age and preoperative KPS score were evaluated as continuous variables, while sex, race, and tumor location were evaluated as nominal variables. In light of these corrections and clarifications, the overall findings and conclusions of our study remain unchanged. As it pertains to the statistical analyses selected for this study, we opted to use Cox proportional hazards modeling because it is widely accepted for time-to-event data with censoring and covariate analysis.¹ The identified factors were then presented using time-to-event curves in Figs. 1 and 2 from the original article. Sui and Piao are correct to point out that such statistical analyses potentiate inherent biases (e.g., lost to follow-up, death), resulting in overestimation of outcome, as well as proportionality assumptions. The

Fine-Gray model was reconsidered using STATA 16.0 (StataCorp LLC) to newly create Fig. 1 and account for the following competing risks: lost to follow-up and death, totaling 36 and 3 risk events, respectively. Lost to follow-up was defined based on the standard of care at our institution, which instructs for annual MR images during the first 5 years after surgery. Therefore, patients were classified as being lost to follow-up if they had surgery more than 5 years prior to our study with less than 5 years of MR images, or if they had surgery within 5 years of our study but had no MR images within 2 years prior to the start of our study. In the multivariate competing risk analysis for tumor recurrence, falcine tumor location remained significant (HR 1.973, 95% CI 1.063–3.661, $p = 0.031$), as did tentorial location (HR 2.391, 95% CI 1.127–5.072, $p = 0.023$), while African American race (HR 1.488, 95% CI 0.852–2.601, $p = 0.163$) and preoperative tumor volume (HR 1.005, 95% CI 1.000–1.010, $p = 0.062$) trended toward significance (Fig. 1).

We hope this additional analysis serves to address the comments raised by Sui and Piao. We thank them for the opportunity to bring clarity in the dissemination of our re-

FIG. 1. Competing risk curves of recurrence-free survival in all subtotally resected meningiomas dichotomized for preoperative volume $< 10 \text{ cm}^3$ (A), falcine location (B), tentorial location (C), and African American race (D). Note: new figure created based on suggested analysis from Sui and Piao.

sults to promote research and understanding that translates to the bedside.

Joshua Materi, BS

David Mampre, BS

Jeff Ehresman, BS

Jordina Rincon-Torroella, MD

Johns Hopkins University, Baltimore, MD

Kaisorn L. Chaichana, MD

Mayo Clinic, Jacksonville, FL

References

1. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457–481.

INCLUDE WHEN CITING

Published online June 12, 2020; DOI: 10.3171/2020.5.JNS20584.

©AANS 2021, except where prohibited by US copyright law

Hyperglycolysis as a common cause for elevated lactate in subarachnoid hemorrhage

TO THE EDITOR: Engquist and colleagues¹ reported that in patients with subarachnoid hemorrhage and delayed cerebral ischemia (DCI), the institution of “triple-H” therapy (hypervolemia, hemodilution, and hypertension [HHH]) increased cortical cerebral blood flow (cCBF) without improvement in the metabolic pattern as determined by cerebral microdialysis (Engquist H, Lewén A, Hillered L, et al. CBF changes and cerebral energy metabolism during hypervolemia, hemodilution, and hypertension therapy in patients with poor-grade subarachnoid hemorrhage [published online January 10, 2020]. *J Neurosurg.* doi:10.3171/2019.11.JNS192759). We suggest that hyperglycolysis may explain these findings.

Lactate, an important shuttle for metabolic fuel in the body and brain, is produced through the reduction of pyruvate by lactate dehydrogenase (LDH):

Lactate is the final product of glycolysis in most cells, including astrocytes,^{2,3} and is the main substrate for the tricarboxylic acid (TCA) cycle and subsequent oxidative phosphorylation.⁴ In the brain, lactate is shuttled from astrocytes to neurons to provide metabolic substrate,⁵ with the rate of glycolysis matched to (glutaminergic) neuronal activity.

Hyperglycolysis is suggested to be the principal driver of hyperlactatemia in sepsis. Catecholaminergic β_2 -adrenoreceptor activation increases glycolysis and Na^+ / K^+ -ATPase activity and causes dysregulation of phosphofructokinase and overall TCA cycle activity.⁶ The overarching consequence is an increase in pyruvate production.

LDH converts this pyruvate to lactate, as its K_a dictates that the reaction is mostly left-sided, that is, [lactate] is about 10- to 20-fold [pyruvate]. This ratio is maintained unless other reagent concentrations are altered, for example, changes in intracellular pH or the NADH/NAD⁺ ratio. Thus, lactate may be elevated in the setting of stress hyperglycolysis (elevated [pyruvate]), intracellular acidosis (elevated [H⁺]), or disruption of aerobic respiration (elevated NADH/NAD⁺ ratio). These latter two circumstances portend a more ominous clinical course and are associated with an elevated lactate/pyruvate ratio (LPR).

Like sepsis, subarachnoid hemorrhage, especially with DCI, is a state of high endogenous catecholamine load. Systemic adrenaline increases cerebral uptake of plasma glucose and lactate through a β_2 -adrenoreceptor-dependent mechanism, increasing cerebral nonoxidative carbohydrate metabolism 8-fold.⁷ Exogenous catecholamines are also often administered (e.g., dobutamine here), amplifying hyperglycolysis.

With these concepts in mind, we revisit the study results. Triple-H therapy improved cCBF, but [lactate] and LPR were not altered. Hemodilution reduced the oxygen carrying capacity of blood by 12%. Unfortunately, parenchymal oxygen tension was not measured.

Both [lactate] and LPR were lower in those without DCI, suggesting less “stress”; however, grossly ischemic metabolic patterns were not displayed even in DCI patients. Parenchymal [glucose] was unchanged, suggesting adequate glucose delivery and glycogen stores throughout.

Hyperglycolysis (proportionally elevated pyruvate and lactate) was common in those with DCI and was not ameliorated by triple-H therapy. Hyperglycolysis can occur with parenchymal hyperoxia⁸ and normoxia⁹ and is likely a physiological response to increased excitatory (glutaminergic) neuronal activity and catecholamines. Moreover, endothelial shear stress generated by induced hypertension in vasospastic vessels liberates nitric oxide, a potent inducer of astrocyte glycolysis.¹⁰

We conclude that in these patients who did not demonstrate conclusive evidence of ischemia, triple-H therapy increased cCBF but did not alter cerebral metabolites. Cerebral oxygenation was not addressed directly. Hyperglycolysis would not be expected to respond to increased perfusion, as cerebral oxygen tension is not one of its principal drivers, and these findings confirm that.

Dichotomization of “physiological” and “pathological” lactate using the LPR allows for specific analysis of perfusion-driven interventions on the latter, which is the objective of such therapy. Future studies are necessary to understand the mechanisms and implications of stress hyperlactatemia and perfusion-intractable dysmetabolism in subarachnoid hemorrhage.

Mendel Castle-Kirschbaum, MBBS

Monash Health, Melbourne, Australia

Scott Ayton, PhD

Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Tony Goldschlager, MBBS, PhD, FRACS

Monash University, Melbourne, Australia

References

- Engquist H, Lewén A, Hillered L, et al. CBF changes and cerebral energy metabolism during hypervolemia, hemodilution, and hypertension therapy in patients with poor-grade subarachnoid hemorrhage [published online January 10, 2020]. *J Neurosurg*. doi:10.3171/2019.11.JNS192759
- Dienel GA. Brain lactate metabolism: the discoveries and the controversies. *J Cereb Blood Flow Metab*. 2012;32:1107–1138.
- Schurr A, Payne RS. Lactate, not pyruvate, is neuronal aerobic glycolysis end product: an in vitro electrophysiological study. *Neuroscience*. 2007;147:613–619.
- Hui S, Ghergurovich JM, Morscher RJ, et al. Glucose feeds the TCA cycle via circulating lactate. *Nature*. 2017;551:115–118.
- Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci U S A*. 1994;91:10625–10629.
- Brooks GA. The science and translation of lactate shuttle theory. *Cell Metab*. 2018;27:757–785.
- Seifert TS, Brassard P, Jørgensen TB, et al. Cerebral non-oxidative carbohydrate consumption in humans driven by adrenaline. *J Physiol*. 2009;587:285–293.
- Vilalta A, Sahuquillo J, Merino M-A, et al. Normobaric hyperoxia in traumatic brain injury: does brain metabolic state influence the response to hyperoxic challenge? *J Neurotrauma*. 2011;28:1139–1148.
- Oddo M, Levine JM, Frangos S, et al. Brain lactate metabolism in humans with subarachnoid hemorrhage. *Stroke*. 2012;43:1418–1421.
- Almeida A, Moncada S, Bolanos JP. Nitric oxide switches on glycolysis through the AMP protein kinase and 6-phosphofructo-2-kinase pathway. *Nat Cell Biol*. 2004;6:45–51.

Disclosures

The authors report no conflict of interest.

Correspondence

Mendel Castle-Kirszbaum: mdck.journal@gmail.com.

INCLUDE WHEN CITING

Published online April 10, 2020; DOI: 10.3171/2020.1.JNS20191.

Response

We appreciate the interesting comments by Castle-Kirszbaum and colleagues regarding our recent article on CBF changes and cerebral energy metabolism during HHH therapy in poor-grade subarachnoid hemorrhage (SAH). In our study, we found the energy metabolic parameters, as measured by cerebral microdialysis (CMD), to be statistically unchanged despite improvement in CBF both globally and in poorly perfused regions. When patients were categorized by three energy metabolic CMD patterns (normal, ischemia, and mitochondrial dysfunction), as previously described in SAH and traumatic brain injury,^{1,2} the pattern corresponding to mitochondrial dysfunction (LPR > 30 and pyruvate > 70 $\mu\text{mol/L}$) was com-

mon during HHH therapy in the patients with a clinical diagnosis of DCI.

Several previous studies have reported that non-ischemic energy metabolic disturbances are common after SAH, and different classifications of these nonischemic energy metabolic patterns have been proposed.^{1,3–5} We agree that stress-induced hyperglycolysis with the accumulation of lactate and pyruvate, as proposed by Castle-Kirszbaum and colleagues, may be a possible explanation for the CMD findings in some of the patients in our study. Among the DCI patients receiving HHH therapy, 5 of 12 patients had elevated lactate (> 4 mmol/L) and a concurrent pyruvate level > 120 $\mu\text{mol/L}$. To our knowledge, two earlier studies (Cesarini et al. and Oddo et al.)^{5,6} found an association between a CMD pattern of hyperglycolysis and a favorable outcome in SAH patients.

Although hemodynamic optimization and restoration of regional CBF seems fundamental in the treatment of DCI, the findings in our study and the above-mentioned CMD studies suggest that other factors affecting cerebral energy metabolism at the cellular level are also important targets for future research.

Henrik Engquist, MD, PhD

Lars Hillered, MD, PhD

Per Enblad, MD, PhD

Elham Rostami, MD, PhD

Uppsala University, Uppsala, Sweden

References

- Jacobsen A, Nielsen TH, Nilsson O, et al. Bedside diagnosis of mitochondrial dysfunction in aneurysmal subarachnoid hemorrhage. *Acta Neurol Scand*. 2014;130:156–163.
- Nordström CH, Nielsen TH, Schalén W, et al. Biochemical indications of cerebral ischaemia and mitochondrial dysfunction in severe brain trauma analysed with regard to type of lesion. *Acta Neurochir (Wien)*. 2016;158:1231–1240.
- Carteron L, Patet C, Solari D, et al. Non-ischemic cerebral energy dysfunction at the early brain injury phase following aneurysmal subarachnoid hemorrhage. *Front Neurol*. 2017;8:325.
- Hutchinson PJ, Jalloh I, Helmy A, et al. Consensus statement from the 2014 International Microdialysis Forum. *Intensive Care Med*. 2015;41:1517–1528.
- Oddo M, Levine JM, Frangos S, et al. Brain lactate metabolism in humans with subarachnoid hemorrhage. *Stroke*. 2012;43:1418–1421.
- Cesarini KG, Enblad P, Ronne-Engström E, et al. Early cerebral hyperglycolysis after subarachnoid haemorrhage correlates with favourable outcome. *Acta Neurochir (Wien)*. 2002;144:1121–1131.

INCLUDE WHEN CITING

Published online April 10, 2020; DOI: 10.3171/2020.2.JNS20246.

©AANS 2021, except where prohibited by US copyright law