Bleeding risk after cavernous malformation surgery: remnant or recurrence?

TO THE EDITOR: We read with great interest the article by Garcia et al. (Garcia RM, Oh T, Cole TS, et al. Recurrent brainstem cavernous malformations following primary resection: blind spots, fine lines, and the right-angle method. J Neurosurg. Published online November 20, 2020. doi:10.3171/2020.6.JNS201555) regarding management and surgical treatment of recurrent brainstem cavernous malformations (BSCMs) following primary microsurgical resection (PMR). In this article, the authors highlighted the pivotal role of the right-angle method in reducing or being aware of blind spots, underlining the importance of meticulous inspection of the resection cavity, and at the same time the need for advanced surgical experience for an effective and safe surgical management of brainstem lesions. We greatly commend the authors for this fascinating and comprehensive study; their results will be useful to aid in making balanced treatment decisions in cases of BSCMs. However, after a detailed analysis, we would like to discuss some important issues that the article raises.

First, we would like to focus on the term “recurrent” used by the authors. Etymologically, recurrent comes from the Latin re-currire, i.e., to happen again. In this sense, the “recurrent BSCM” indicates a completely removed BSCM that reappears after a variable time span, which is free of disease. In the literature, in reference to the outcomes of cavernous malformation (CM) surgery, the term “remnant” is more established than “recurrent.” We believe that in the event of a BSCM reappearance after surgery, the use of the term “remnant” is more consistent with the subjective admission of the high risk of permanent residual disease from the PMR, as admitted by the authors themselves. From a careful analysis of the provided data, there is evidence of the possible persistence of remnant BSCM after PMR in the 14 cases analyzed, even if not identifiable at 48-hour MRI. Specifically, the mean volume of the 14 recurrent BSCMs was 3209 mm³; considering the mean time of 127 days from surgery until recurrence, an average daily growth rate of 25 mm was found. This average daily growth rate appears excessive when compared to the data in the literature on the dynamic morpho-volumetry of CMs. This discrepancy might be explained by the presence of a remnant, which was not visible due to the detection limitations of early postoperative MRI (EPMRI). Indeed, the EPMRI has a sensitivity for CM remnant detection of 66.67%, specificity of 76.74%, positive predictive value of 16.67%, and negative predictive value of 97.06%, demonstrating that EPMRI is not reliable in detecting postoperative CM remnants due to its high risk of false-positive and false-negative results.

Second, the authors declare a postoperative CM remnant rate (PCRR) of 6.6%. This value is significantly lower than the PCRR range reported in the literature (10%–19%). Surely the senior author’s experience in the surgical management of BSCMs helped to reduce the PCRR; this is also supported by the 3.8% reduction of the PCRR between the first and the second half of the series. However, it is likely that the low sensitivity of the EPMRI also contributed to reducing the PCRR rate.

Third, we noted that the authors did not analyze Zabramski type and perilesional hemosiderin ring (PHR). Indeed, the presence of a PHR and Zabramski type II CM are both significantly associated with bleeding risk of the postsurgical CM remnant. If one or both of these factors are present, the surgeon should aim for complete removal of the BSCM, even if this increases the risk of neurological damage, while aiming to avoid the permanence of a postoperative BSCM remnant with high bleeding risk.

Finally, we are extremely impressed by the authors’ data and with the results that have been so honestly described: this is not common in the literature, where in many cases remnants do not appear to exist. On the contrary, we think that before CM surgery, it is necessary to clearly explain to the patient the possibility of recurrence or remnant after surgery. The authors’ data are, therefore, of paramount importance.

Eduardo Agosti, MD
Francesco Doglietto, MD, PhD
Marco M. Fontanella, MD
University of Brescia, Italy

References


**Disclosures**

The authors report no conflict of interest.

**Correspondence**

Edoardo Agosti: edoardo_agosti@libero.it.

**INCLUDE WHEN CITING**

Published online March 12, 2021; DOI: 10.3171/2020.12.JNS204192.

**Response**

We were pleased to read the review and insightful commentary provided by Agosti et al. Previously, we proposed a grading system to predict outcomes of patients after resection of BSCMs.1 As a continuation of this work, we highlight the surgical challenges for the small subset of patients needing reoperation for remnant lesions. We recognize the inconsistent and sometimes confusing semantics of “recurrent” and “residual” used in the literature. We agree with Agosti et al. that, from a pathophysiological standpoint, CMs that were “recurrent” within this series were, in fact, “remnants” or “residuals” following PMR. BSCMs do not recur after complete resection, but a small remnant can be difficult to detect on postoperative MRI. Only 2 of our patients had lesions that were immediately apparent after primary surgical intervention, and 3 additional patients demonstrated a remnant on postoperative surveillance MRI. Therefore, the detection of small remnants is challenging, but it is critical to postoperative surveillance and is made easier by the progressive growth of, or hemorrhage by, the remnant (which we have termed “recurrence”). Early aggressive surgery with the goal of complete resection is critical for a microsurgical cure in patients with BSCMs who are deemed surgical candidates.

Agosti et al. raise the concern that the frequency that BSCM remnants are reported in the literature after primary resection was significantly higher than the rate published in our series. Although some studies have reported a remnant rate greater than 10%, we argue there are arguably more reports suggesting a remnant rate of less than 10%. We believe the 6.6% remnant rate proposed in our series is consistent with other previously published series.

In our earlier analysis of patient outcomes, we did evaluate hemosiderin staining as a potential predictor of outcome, but we did not find multivariate statistical significance to support this factor as a predictor of outcome because nearly all lesions demonstrated some visible hemosiderin staining intraoperatively. The Zabramski classification has aided neurosurgeons in the basic classification of cerebral cavernomas.7 However, we find that clinical and anatomical factors are more helpful in determining the optimal moment to intervene. More than 47% of patients experienced one hemorrhagic event in our series, and 28% experienced a second event. The median time from the last hemorrhagic event was 28 days. In our experience, other factors, such as the size of the cavernoma, pial presentation, and time since the last hemorrhage, are more important classifying factors given the eloquence of brainstem anatomy.

Resection of BSCMs should be undertaken with the intent to remove the lesion completely and not harm the patient. The delicate balance of these two objectives is particularly difficult in the brainstem, much more so than in the cerebrum. As our knowledge of brainstem anatomy, safe entry zones, and exposures afforded by skull base surgical approaches has increased, it has become routine to curatively resect BSCMs and achieve favorable long-term outcomes. We hope our experience and adoption of insights such as the right-angle method will help others obtain excellent microsurgical results.

**Acknowledgments**

Dr. Roxanna Garcia served as the StrokeNet research fellow from 2018 to 2019 and was a Fogarty Global Health Trainee from 2019 to 2020. Research reported in this publication was supported under the StrokeNet award no. U24 NS107233-01 and the Fogarty International Center and National Institute of Mental Health, of the NIH, under award no. D43 TW010543. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The authors thank the staff of Neuroscience Publications at Barrow Neurological Institute for assistance with manuscript preparation.

With regard to changes in intracranial pressure (ICP) before and after cranioplasty, cerebral venous physiology may explain the postural changes between supine and sitting positions as well as the discrepancy between findings in this study and that of Fodstad et al., as the authors mention. In this scenario, an evolved protective mechanism that prevents siphoning of venous blood from the cranium known as the “Starling resistor” may become nonfunctional during craniectomy, resulting in posture-related overdrainage of venous blood from the venous outflow tracts. This seems to be related to CSF and sagittal sinus pressure dissociation as proposed by the mathematical model in the study of Piechnik et al., causing intracranial hypotension depending on varying circumstances (such as head elevation, position, individual venous anatomy, and compensatory mechanisms). It is plausible that after cranioplasty the Starling resistor becomes functional again. With regard to individual venous anatomy, Doepp et al. in a systematic ultrasound and MRI study of cranial venous outflow tracts have shown that there is predominantly jugular drainage in 72% of healthy volunteers. In 22%, the jugular drainage equals the nonjugular drainage, and in 6% the drainage pattern is nonjugular. These findings suggest that in the general population there are variations in the anatomy of cranial venous outflow.

Kaveh Barami, MD, PhD
Kaiser Permanente Northern California, Sacramento, CA
Furthermore, the intracranial pulse wave amplitude is severely diminished. When cranioplasty is performed, normal intracranial physiology appears to be re-established regarding both postural ICP changes and intracranial pulsatility. Applying the Starling resistor concept in this setting, sustained posture-related venous overdrainage following decompressive craniectomy (related to individual venous anatomy) might explain some cases of the poorly defined condition termed “syndrome of the trephined” or “sunken skin flap syndrome,” although other factors such as changes in cerebral blood/CSF flow as well as impaired cerebral metabolism probably also play important roles. Intracranial pulsatility is believed to be an important driver of intracranial fluid movements (including glymphatic flow), and normalization of this factor following cranioplasty probably is equally important in this regard.

References

Trumatic axonal injury: causes and effects

TO THE EDITOR: We read with great interest the article published by Moe et al. (Moe HK, Limandvik Myhr J, Moen KG, et al. Association of cause of injury and traumatic axonal injury: a clinical MRI study of moderate and severe traumatic brain injury. J Neurosurg. 2020;133(5):1559–1567). The authors reported their investigation of causal mechanistic effects on the incidence of traumatic axonal injury (TAI). Moe et al. accurately analyzed the role of each known cause of TAI and the underlying pathophysiology; however, some concerns need to be highlighted. It is well known that TAI is one of the main causes of impairment during the posttraumatic phase in patients who have no detectable intracranial lesions on CT, even patients with mild traumatic brain injury. Several phenomena explain how the strong acceleration-deceleration and rotational-angular acceleration forces in high-impact trauma lead to progressive changes in the axons, resulting in deformation of the brain tissue.

An external injury involves shearing forces that stimulate the formation of axon retraction balls, which result from a swelling phenomenon at the end of the axonal axis due to external shear force and tension that lead to the final breakage of the axon. During this process the permeability of the axon membrane changes and large amounts of Ca²⁺ enter the cells, reversing the flux of plasma transport and activating the cytoine protein signal pathway and caspase-3. These events lead to the degradation of the axonal cytoskeleton network. During this progressive phenomenon, axons usually maintain their morphology several hours after injury, and for that reason it is crucial to perform MRI in patients days after trauma.

Although we understand the complex nature of reporting hundreds of neuroimaging results and thank the authors for their investigation of this important topic, we have to note the highly heterogeneous rating of the samples reported by Moe et al. and the possible consequences. The fact that there is substantial agreement between raters (linear Cohen’s kappa 0.74) should be interpreted with caution given that some of the pitfalls in this study may have decreased the interrater reliability to an unknown degree. Having more than two raters may have masked valuable ratings in the analysis, and thus the generalized kappa may not have captured the range of potential agreement or disagreement between assessments by multiple raters.

Mónica Patricia Herrera-Martinez, MD1,3
Ezequiel García-Ballesteras, MD1,3
Ivan David Lozada-Martínez, MS2-4
Luis Rafael Moscote-Salazar, MD1,4
Mohammed Al-Dhahir, MD1
1Center of Biomedical Research (CIB), Faculty of Medicine, University of Cartagena, Colombia
2Medical-Surgical Research Center, University of Cartagena, Colombia
3Latinamerican Council of Neurocritical Care (CLaNi), Cartagena, Colombia
4Colombian Clinical Research Group in Neurocritical Care, University of Cartagena, Colombia
5Strong Memorial Hospital, University of Rochester, MN

References

Response
We thank authors Herrera-Martinez et al. for their interest in our paper on the association of cause of injury with traumatic axonal injury (TAI). The authors elaborate more thoroughly on the underlying cellular mechanisms behind TAI than was within the scope of our study. While TAI detectability on histopathological examination has been reported to peak at 24 hours, little is known about how the indirect signs of TAI visualized on clinical MRI develop over the first few hours and days after injury. One recent study indicated that traumatic microbleeds detected on susceptibility-weighted imaging (SWI) were more visible 1 week after injury. We also know from previous studies that almost all non-hemorrhagic TAI lesions (detected on FLAIR or diffusion-weighted imaging [DWI]) have disappeared at 3 months after injury. We want to emphasize that in the present study we performed MRI at a median of 8 days (IQR 4–17 days) post-injury, so it is unlikely that the MRIs were performed too early and thus could have affected the results in our study.

Herrera-Martinez et al. also argue that the “substantial agreement between raters . . . should be interpreted with caution,” and that “having more than two raters may have masked valuable ratings in the analysis.” We acknowledge the possibility that a misunderstanding might have occurred. The linearly weighted Cohen’s kappa (not the generalized kappa) was calculated between two raters in a previous paper, namely K.G.M. (who was able to consult with neuroradiologists K.A.K. and J.R. when needed) and M.F. Both K.G.M. and M.F. were blinded to the scores of the other rater. Interrater analyses were not performed for J.R. (n = 66) since all of his scores were also evaluated by K.A.K. or M.F. The two latter neuroradiologists had been part of the abovementioned interrater analyses. Moreover, in a recent larger study including the Trondheim cohort of patients with moderate and severe traumatic brain injury, interrater analyses were performed for multiple raters. In this more recent study, the positive and negative agreement for the presence or absence of TAI were 0.90 (95% CI 0.77–0.95) and 0.69 (95% CI 0.42–0.84), respectively, and the intraclass correlation coefficient was 0.78 for the classification of TAI grade. More details can be found in the Methods and Results sections of that paper. Hence, we hope our response has clarified some of the concerns raised by Herrera-Martinez et al.

Hans Kristian Moe, MD, PhD
Anne Vik, MD, PhD
Turid Follostad, MSc, PhD
Toril Skandsen, MD, PhD
Asta Kristine Håberg, MD, PhD
Kent Goran Moen, MD, PhD

Correspondence
Ivan David Lozada-Martínez: ivandavidloma@gmail.com.

References
6. de Vet HCW, Dikmans RE, Eekhout I. Specific agreement on dichotomous outcomes can be calculated for more than two raters. J Clin Epidemiol. 2017;83:85–89.

On the right side of history: expanding diversity within neurosurgery

TO THE EDITOR: As the US grows increasingly diverse, it is crucial to develop a healthcare system in which shared ethnic background, language, gender, and sexual orientation foster connections between physicians and their patients. The article by Corley and colleagues is instrumental in improving medical care through increased diversity, and we believe now is the time to wholeheartedly embrace and embody the changing facets of American society (Corley J, Kim E, Philips CA, et al. One hundred years of neurosurgery: contributions of American women. J Neurosurg. 2021;134[2]:337–342).

Homogeneity restricts the practice of medicine. Ignorance toward a patient’s social and cultural background can cause oversight of relevant parameters in patient pathology.
On a societal level, the “homogeneity of members’ social background and ideology [can result in] groupthink.” This psychological phenomenon leads to ideas that lack nuance; therefore, a homogenous group of physicians runs an increased risk of coming to erroneous conclusions. In medicine, this can mean inaccurate diagnoses that put patients’ lives at risk. Additionally, homogenous groups of medical students, physicians, and nurse practitioners hinder innovation and progress in the medical field. Advocacy for more diverse medical institutions allows healthcare leaders to avoid herd behavior. This is only attainable by welcoming perspectives from many walks of life.

Academic institutions have worked to foster medical student interest in neurosurgery, with efforts including creating neurosurgery interest groups, encouraging clinical exposure and research opportunities, and providing continued mentorship. Still, analysis of underrepresented minority student performance indicates that both objective and subjective measures of student critique are commonly difficult areas for minority students to excel in due to implicit bias, lack of financial support and/or mentorship, and sexual harassment, among others. Given the emphasis on measures of medical student performance in the neurosurgery match, such as the United States Medical Licensing Examination step scores, clerkship grades, and number of research projects, gender and ethnic minorities may additionally benefit from mentorship driven by residents and attending physicians.

We propose the implementation of opportunities that provide youth from underrepresented groups with the chance to pursue their interest in medicine. Establishment of scientific interest at early educational stages may increase future pools of diverse applicants interested in neurosurgery, and the medical field as a whole. At the medical student level, we recommend that the AANS be utilized to amplify the call for diversity in one of the most scientifically engaging and versatile specialties in medicine. Within the field, there is much to accomplish in the areas of increasing minorities in academic positions, promotion of women in leadership positions, and defeating barriers affecting minority medical students. Specific approaches to action may include creating a diversity section in the AANS or requesting diversity initiatives through AANS medical student chapters.

The complexities of American diversity call for an introspective look at the healthcare system. Physicians and medical providers should reflect the diverse nature of their patients for myriad reasons. Notably, the quality of patient care is heavily reliant on both proper communication and understanding of patients’ lived experiences to provide comfort and reassurance.

Marianne I. J. Tissot, BA
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Andrew E. Boyke, MS
Albert Einstein College of Medicine, New York, NY
Alvin Onyewuenyi, MPH
Chicago Medical School, Rosalind Franklin University of Medicine and Science, Chicago, IL
Gregory Glauser, MBA
Evalyn S. Mackenzie, BA

References

Disclosures
The authors report no conflict of interest.

Correspondence
Donald K. E. Detchou: donald.detchou@pennmedicine.upenn.edu.

INCLUDE WHEN CITING
Published online April 23, 2021; DOI: 10.3171/2021.1.JNS21176.

Response
Tissot et al.’s letter calls forth the need to substantially advance inclusivity and accentuate clear intentions to re-examine the fundamental aims that the field of neurosurgery should prioritize, namely, promoting diversity. While we agree with the overall goals outlined in the letter, we hope to extend beyond objectives and implement actionable and systemic approaches.

Over the past decade, the average Black, Hispanic, and Native American neurosurgical resident populations were 4.4%, 4.1%, and 0.2%, respectively. Other concerns such as improving the gender distribution among female faculty and residents, as well as establishing accommodations for individuals with disabilities, are necessary to take into account to promote an equitable neurosurgical environment. Initially released in 2018 by White Coats for Black...
Lives, the Racial Justice Report Card (RJRC) exists as a 15-point metric to critically assess the institutional climate for those Black, Indigenous, and People of Color (BIPOC). This focus efforts on representation and recruitment, institutional safety, and resource allocation. The RJRC can serve as an effective tool toward solidifying institutional changes in neurosurgery.

Attracting young and talented underrepresented minorities (URMs) will ensure that neurosurgery continues to progress in equitable clinical advancements. Research findings have demonstrated that adolescents with early clinical exposure to healthcare have an increased interest in pursuing a medical career. Partnering with communities to offer operating room tours or research mentorship would improve students’ preparedness to excel in academics and cultivate a diverse applicant pool of future neurosurgeons.

While pipeline programs help mitigate the workforce gap of URMs in medicine, enhance research productivity, and increase patient satisfaction, there must be an increase in the funding available for neurosurgeons to conduct racial- and gender-focused research to ensure that all patients have access to equitable care. National societies should encourage the development of studies that evaluate the impact of race and ethnicity on neurosurgical outcomes, residency application trends, career trajectories for underrepresented persons, or recommendations to improve race and gender inclusion in clinical trials.

Of course, renewed policies and research goals will have limited success without a culture change to one that fosters allyship. Perhaps the greatest modern example of this phenomenon is the #HeForShe movement, which has heralded a dynamism of men showing support for women with a new organized purpose. Additionally, the emergence of the term “upstander” has also changed the culture of medicine and emboldened people to stand up for discriminated and harassed minority persons.

These practices need to permeate the neurosurgery workplace through education, advocacy, and establishing entryways for other progressive like-minded people. Additionally, allyship not only involves relationships between the group majority and the group minority; partnerships should be forged with groups of all protected classes of people: from racial and gender minorities; to those of the lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ) community; and those who identify as disabled or who struggle with mental or physical illness. Ultimately, we all stand to gain from a diverse workplace, policies and infrastructure that are inclusive, research that is forward thinking, and a culture that is protective for everyone.

Antoinette J. Charles, BS
Duke University School of Medicine, Durham, NC

Julia B. Duvall, BS
Harvard Medical School, Boston, MA

Alexis O. Umoyo, BS
University of California, Davis School of Medicine, Sacramento, CA

Jacquelyn Corley, MD
Duke University School of Medicine, Durham, NC
The Gender Equity Initiative in Global Surgery, Boston, MA

References

A new approach for local tumor control

TO THE EDITOR: We read with great interest the paper by Schipmann et al. (Schipmann S, Mütter M, Stögbauer L, et al. Combination of ALA-induced fluorescence-guided resection and intraoperative open photodynamic therapy for recurrent glioblastoma: case series on a promising dual strategy for local tumor control. J Neurosurg. 2021;134(2):426–436). The authors present a combined 5-aminolevulinic acid (5-ALA) and photodynamic therapy (PDT) approach in the treatment of recurrent high-grade gliomas (HGGs). Their experience has proved to be an innovative and safe method for local tumor control, an effort for which they should be commended. In particular, they brought the discussion to bear on a crucial issue of such 5-ALA use in the treatment of recurrent HGG, which is currently done on a case-by-case basis and without a proper consensus.

In the literature and in general practice, 5-ALA’s indisputable role has been well underlined for newly diagnosed HGG cases, whereas its significance and its possible pitfalls in recurrent HGGs are de facto less clear. As is widely acknowledged, an accurate differentiation of glioma recurrence from treatment-induced changes...
is of paramount importance because it can change the patient’s management. Against this background, we want to emphasize 5-ALA heterogeneity in the “recurrent setting” and the need to properly address this feature in order to better integrate it with other techniques such as PDT.3

As a matter of fact, the presence of inflammatory tissue, as in the case of peritumoral reactive inflammation, pseudoprogression, or radiation-induced necrosis, may influence the intraoperative fluorescence detection. Therefore, surgeons must be aware that not everything that glitters is gold—a critical awareness of 5-ALA potentialities and drawbacks in recurrent gliomas is necessary.

With specific focus on pseudoprogression and radiation necrosis, we believe it is important to point out 5-ALA heterogeneous behavior in such cases in order to properly design future studies in which investigators are able to properly select patients who, during a second surgery with 5-ALA, become eligible for PDT, and to avoid resections improperly exceeding planned limits.

Pseudoprogression, which constitutes a strong reaction to effective therapy and is associated with damage to the endothelium, is linked to a high responsiveness to 5-ALA. Different studies have suggested the presence of a peritumoral inflammatory state, and an increased reactive mitotic activity could explain these false-positive results. This is relevant in order to avoid patients’ exposure to unnecessary treatment and to tailor resection, especially in eloquent areas. Furthermore, there are currently no data on PDT selectivity in this context.

A different consideration has to be made for radiation necrosis. The paper points out that PDT has high selectivity for tumor cells, having shown no effect in a patient operated on for suspected recurrence and with 5-ALA positivity, but in whom histological analysis revealed the lesion to be radionecrosis. However, we want to highlight how 5-ALA behavior in radiation necrosis has been linked to conflicting evidence—further studies are needed to better clarify this issue in order to provide an improved selection of candidates for the dual approach.6,7

In thanking the author for providing such interesting food for thought, we wish that future studies on the topic will take our suggestion.

Grazia Menna, MD
Alessandro Olivi, MD
Giuseppe Maria Della Pepa, MD
Institute of Neurosurgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University, Rome, Italy

References

Disclosures
The authors report no conflict of interest.

Correspondence
Grazia Menna: mennagrazia@gmail.com.

INCLUDE WHEN CITING
Published online May 7, 2021; DOI: 10.3171/2021.2.JNS21409.

Response
With great interest have we read the letter to the editor from Menna et al. regarding our publication on open PDT, and we thank the authors for their interest in our research.

We agree that accurate detection of tumor recurrence is of paramount importance for patient management, and we are aware that it is not always possible to reliably differentiate tumor progression from treatment-related changes with conventional imaging techniques.1

However, with our use of advanced imaging modalities and the Response Assessment in Neuro-Oncology (RANO) criteria before allocating a glioma patient with suspicion of tumor recurrence or progression to further surgical treatment (including open PDT), we reach a high certainty for the detection of tumor tissue and for distinguishing recurrent tumor from pseudoprogression or radiation necrosis.

These advanced imaging modalities include MR spectroscopy, reaching a sensitivity and specificity of 91% and 95%, respectively;2 MR perfusion;3 and PET studies using 11C-MET or 18F-FET as tracers.4–6 With the use of 18F-FET PET, a sensitivity of up to 100% and specificity of 91% can be expected.6 When in doubt, the combination of several imaging modalities can help to increase sensitivity and help in making clinical decisions. These data together with our experience in daily routine use of these advanced imaging modalities have led to the fact that distinguishing between tumor progression or recurrence and posttherapeutic changes is no longer a limiting issue. Because progression and ultimately death are inevitable in malignant gliomas, with no generally accepted treatment options after progression, early detection of progression by using multiple methods is an integral part of modern neuro-oncological management.

In addition, histological assessment of intraoperative frozen sections, a routine procedure in our department,
does also help to confirm the diagnosis of recurrent tumor before application of PDT.

With this degree of patient selection, we have a very low risk of operating on patients without real tumor progression and underestimating pseudoprogression. This lowers the remaining uncertainty of the reported higher false-positive fluorescence rate of 5-ALA in recurrent HGGs. In addition, several studies have shown a high positive predictive value for the use of 5-ALA in recurrent gliomas.\(^7\)\(^-\)\(^9\) The specificity of 5-ALA is related to the intensity of fluorescence. Areas with strong fluorescence are accompanied by a high predictive value for the presence of tumor tissue. In areas with weak fluorescence, the false-positive rate is higher. However, histologically these areas are characterized by an abundance of gliotic tissue in combination with inflammatory and reactive cells, but with only a little normal brain.\(^8\)\(^-\)\(^10\) Consequently, resection of these areas or treatment with PDT is not likely to cause functional impairment.

We agree that there are currently no data on PDT selectivity in the context of tumor recurrence. However, the fact that the one patient who was included in our study and in whom histology revealed that radiation necrosis had no effect of PDT on postoperative MRI suggests a certain selectivity of this treatment strategy.

In summary, overtreatment of patients with pseudoprogression can generally be avoided. With modern imaging modalities and intraoperative frozen sections, a high certainty for the detection of real tumor progression can be achieved. This is particularly important because patients with recurrent HGGs have a dismal prognosis and our suggested treatment strategy of re-resection and open PDT offers a promising treatment option.

Stephanie Schipmann, MD, PhD
Walter Stummer, MD, PhD
University Hospital Münster, Germany

References

Don’t blame the resilient corticotroph


Historical misunderstandings may result in the unnecessary fear of addisonian crises and subsequent blanket use of steroids in pituitary surgery. Despite the obvious utility of glucocorticoid therapy,\(^3\)\(^-\)\(^5\) its widespread use has led to tragic postoperative deaths.\(^4\)\(^-\)\(^5\) Furthermore, the perceived risk of hypopituitarism after pituitary operations has led to variable perioperative cortisol replacement paradigms largely unsupported by high-quality evidence.\(^6\)

Recently, two randomized trials supported withholding perioperative steroids in patients without preoperative adrenal insufficiency undergoing pituitary surgery.\(^7\)\(^,\)\(^8\) Lee and colleagues\(^1\) randomized patients to placebo or a single dose of 100 mg of intravenous hydrocortisone 30 minutes prior to induction of anesthesia, and their findings provide valuable insight into the resilience of the human corticotroph. The treatment group had higher serum cortisol levels throughout the operation, reflective of drug administration, followed by lower cortisol levels on all 3 postoperative days. Interestingly, adrenocorticotropic hormone (ACTH) was only suppressed at induction. Dose-dependent pharmacokinetics suggest that a 100-mg dose is expected to have a plasma half-life greater than 1.7 hours due to increased apparent distribution volume.\(^8\) We are curious to know whether the lower postoperative cortisol levels could be reflective of a longer biological half-life (i.e., an extended suppressive effect), or is the study simply underpowered to detect confounding by different rates of early adrenal insufficiency?\(^9\)

This apparent paradox between rapid pituitary corte-
coticotroph recovery and blunted adrenal response from the administration of a single dose of hydrocortisone deserves more attention, as does the fundamental historic confusion between atrophy of the adrenal cortex and secondary adrenal insufficiency as they relate to perioperative mortality.2–3 Although an Addisonian crisis can precipitate from any cause of long-term adrenal cortex atrophy, the human corticotroph has a unique ability to sustain hypothalamic-pituitary-adrenal (HPA) function in the face of direct injury.

An important goal of selective adenomectomy, the most common operation in pituitary surgery, is preservation of pituitary function. However, some injury to normal gland can occur. Therefore, how much residual healthy pituitary gland is necessary to support normal HPA axis function? Landmark studies in 1959 by H. J. Campbell from Maudsley Hospitals, London, included serial partial hypophysectomies in rabbits and compared adrenal ascorbic acid content and depletion, as well as lymphopenic response to stress.4 Campbell found that only 1% of residual anterior pituitary was required for a normal adrenal cortex response to stress, and that only 10% was required for both normal ascorbic acid concentrations and histological appearance of the adrenal gland. Likewise, studies in humans support a rapid and potent stimulatory effect of ACTH on adrenal cortisol production.5

In conclusion, for patients with normal preoperative adrenal function, endogenous ACTH secretion at induction should provide adequate support for the first 24 hours, which explains why preoperative supplementation is not routinely necessary. Thereafter, recovery room and daily fasting morning cortisol evaluations are adequate to safely diagnose early ACTH deficiency in the perioperative setting. The pituitary surgeon and endocrinologist can rest assured that the resilient corticotroph will not let us, or our patients, down.

Michael P. Catalino, MD, MSc
Carolyn S. Quinsey, MD
G. Stephen DeCherney, MD, MPH
University of North Carolina, Chapel Hill, NC

References

Disclosures
The authors report no conflict of interest.

Correspondence
Michael P. Catalino: michael.catalino@unchealth.unc.edu.

INCLUDE WHEN CITING
Published online May 14, 2021; DOI: 10.3171/2021.2.JNS21473.

Response
First, we thank Dr. Catalino and coworkers for their great enthusiasm about our recent article, in which we compared intraoperative serum cortisol and ACTH concentrations after preoperative administration of 100 mg of hydrocortisone (HC group) versus placebo (C group) in patients without adrenal insufficiency undergoing endoscopic transphenoidal pituitary surgery. Our results showed that serum cortisol levels were significantly higher in the group HC throughout the operation, but no patient showed intraoperative hypotension due to adrenal insufficiency. For that reason, we totally agree with Catalino et al.’s statement that for patients with normal preoperative adrenal function undergoing pituitary surgery, preoperative hydrocortisone supplementation is not routinely necessary.

With respect to early postoperative cortisol levels, they wonder why morning cortisol levels were relatively low in the group HC from 1 to 3 days postoperatively. The exact underlying mechanism of early adrenal insufficiency after pituitary surgery has not been fully revealed.1–3 Three possibilities may be considered to explain this finding. First, long-lasting feedback suppression of the HPA axis caused by exogenous steroid administration may be responsible for relatively low cortisol levels during the early postoperative period. Second, serum cortisol levels and the incidence of adrenal insufficiency during the early postoperative period were secondary outcome measures in our study. Moreover, sample size was calculated based on immediate postoperative cortisol level. Therefore, there is a possibility that our study is underpowered to detect significant differences in both secondary outcome measurements between the two groups. Third, in our study, early adrenal insufficiency was shown on postoperative day 2 or 3, not on postoperative day 1. Early adrenal insufficiency after pituitary surgery may be reflective of temporary or permanent HPA axis suppression by surgical manipulation of normal pituitary gland. Indeed, 20% of patients in our study demonstrated early (3 days) or delayed (3 months) ACTH deficiency after surgery, although the human pituitary gland has a wide range of ability for functional resilience.
Taken together, our study suggests that in patients undergoing pituitary surgery, preoperative preserved HPA axis can provide adequate endogenous pituitary ACTH and adrenal cortisol secretions intraoperatively as well as for at least the first 24 hours postoperatively, which explains why preoperative steroid supplementation is not routinely necessary in such patients. However, to adequately diagnose and treat early postoperative ACTH deficiency, daily fasting morning cortisol evaluation should be done postoperatively. Moreover, a large-scale prospective study is needed to clarify the exact mechanism of postoperative adrenal insufficiency and to help patient stratification in individuals with preoperative normal adrenal function who undergo pituitary surgery.

Hyung-Chul Lee, MD, PhD
Yong Hwy Kim, MD, PhD
Hee-Pyoung Park, MD, PhD
Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

References

INCLUDE WHEN CITING
Published online May 14, 2021; DOI: 10.3171/2021.3.JNS21487.
©AANS 2021, except where prohibited by US copyright law