Neurosurgical Forum LETTERS TO THE EDITOR

Delayed facial palsy after microvascular decompression for hemifacial spasm

TO THE EDITOR: We read with great interest the article by Lee et al.³ (Lee JM, Park HR, Choi YD, et al: Delayed facial palsy after microvascular decompression for hemifacial spasm: friend or foe? *J Neurosurg* [epub ahead of print September 1, 2017. DOI: 10.3171/2017.3.JNS162869]). The authors reported that 45 of 310 patients (14.5%) with hemifacial spasm (HFS) developed delayed facial palsy (DFP) after microvascular decompression (MVD). At final follow-up, 44 patients (97.8%) completely recovered after corticosteroid treatment. In addition, they found that patients who experienced an immediate disappearance of spasm after MVD had a higher risk of DFP, and they also found that preoperative botulinum neurotoxin injections negatively influenced the occurrence of DFP. We commend the authors for their study, which is a valuable contribution to our understanding of DFP after MVD in patients with HFS. However, we hold that several controversies still exist in DFP that should be further discussed.

Although facial nerve weakness following MVD is unusual, when it happens, it usually has a negative effect on patients' quality of life, increasing their psychological pressure and causing them to question the efficacy of the operation. Generally, the facial palsy can be divided into two types, immediate facial palsy (IFP) and DFP, based on when it occurs. IFP occurs at once after the operation, and is mainly due to the intraoperative damage to the facial nerve. However, there is no consensus definition of DFP. In order to differentiate DFP from IFP, most authors have used the criterion that the facial palsy occurs over a 24-hour period after the operation,^{4,6} just as the authors of the present study.

Notably, the incidence of DFP following MVD in the present study (14.5%) was close to twice as high as that reported in previous studies.^{2,4–6} The authors speculated that the higher rate of DFP observed at their institution might result from the stimulation of the facial nerve by the moved long-shape Teflon felts. This hypothesis might be true or at least plausible. Nevertheless, we wonder why they insert at least 3 Teflon felts in every patient. In our opinion, the number of Teflon felts should be moderate, as

too many Teflon felts might lead to a higher risk of nerve compression. Furthermore, the authors found that a high House-Brackmann (HB) grade correlated with late onset of DFP, but the recovery time from the onset of DFP was not related to the HB grade. These results are interesting but seem a little different from what might be more common sense—that is, that patients with higher grade of facial palsy might require longer recovery periods. In a similar study performed by our team earlier,⁴ we demonstrated that the time of onset was correlated with the duration of DFP; earlier development of DFP corresponded with a shorter duration, whereas later development of DFP corresponded with a longer duration. Unfortunately, we didn't analyze the correlation between the onset time and the HB grade of DFP in that study.

In addition, in their study, patients with DFP after MVD were treated with oral or intravenous steroid therapy. However, the best method of treatment for patients with DFP remains debated because the pathophysiological mechanism of DFP is unclear, and it is also puzzling why DFP usually occurs up to several days after surgery. Evidence suggests that multiple factors, acting in isolation or as collaborating mechanisms, may underlie the pathophysiology. These factors include viral reactivation, facial nerve exit zone injury via the Teflon felt, local perineural edema, and vasospasm.^{1,4,6} Hence, the treatments for DFP are all empirical therapies. Fortunately, however, the prognosis of DFP is favorable, with almost all reported patients recovering normal or near-normal facial function within a few months.^{2,4–6} In our prior study,⁴ most patients with DFP recovered spontaneously, although without any treatment. Therefore, it is still unclear whether treatment is necessary for patients with DFP. In addition, further large-sample controlled studies are obviously needed for evaluating how the effects of treatment such as corticosteroid administration or antiviral medication would influence the length of recovery when DFP occurs.

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References

1. Carlstrom LP, Copeland WR III, Neff BA, Castner ML,

- Driscoll CL, Link MJ: Incidence and risk factors of delayed facial palsy after vestibular schwannoma resection. **Neurosurgery** **78**:251–255, 2016
2. Hua Z, Da TY, Hui WX, Tingting Y, Jin Z, Yan Y, et al: Delayed facial palsy after microvascular decompression for hemifacial spasm. **J Craniofac Surg** **27**:781–783, 2016
  3. Lee JM, Park HR, Choi YD, Kim SM, Jeon B, Kim HJ, et al: Delayed facial palsy after microvascular decompression for hemifacial spasm: friend or foe? **J Neurosurg** [epub ahead of print September 1, 2017. DOI: 10.3171/2017.3.JNS162869]
  4. Liu LX, Zhang CW, Ren PW, Xiang SW, Xu D, Xie XD, et al: Prognosis research of delayed facial palsy after microvascular decompression for hemifacial spasm. **Acta Neurochir (Wien)** **158**:379–385, 2016
  5. Lovely TJ, Getch CC, Jannetta PJ: Delayed facial weakness after microvascular decompression of cranial nerve VII. **Surg Neurol** **50**:449–452, 1998
  6. Rhee DJ, Kong DS, Park K, Lee JA: Frequency and prognosis of delayed facial palsy after microvascular decompression for hemifacial spasm. **Acta Neurochir (Wien)** **148**:839–843, 2006

Disclosures

The authors report no conflict of interest.

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Response

We are grateful to Dr. Lei and colleagues for their detailed and thoughtful letter regarding our article. Our goal was to report that the disappearance of spasms immediately after MVD was the only prognostic indicator of DFP.

Dr. Lei correctly points out 3 important issues. First, should we insert at least 3 Teflon felts in every patient? (Too many Teflon felts may lead to a higher risk of nerve compression.) Second, was the recovery time from the onset of DFP related to the HB grade of DFP? (This article demonstrated that there is no relation to HB grade.) Third, even though the method of treatment for DFP remains controversial and the prognosis of DFP is favorable, does one have to use steroid for treatment of DFP?

First, as the authors have pointed out, we agree that the number of Teflon felts can have an effect. However, Teflon felt is not standardized in size, length, and shape, and there is no objective comparison of the size, shape, and number of Teflon felts used according to the surgeon. Since the thickness, length, and shape of the Teflon used by each surgeon differ, the number of Teflon felts may not be an objective parameter. Additionally, it is difficult to generate enough space with one or two pieces of the felt because we use thin Teflon felt to enable easier handling. Therefore, we made space by using more than 3 pieces. The effect of thickness, length, shape, and number of Teflon felts is also likely to be worthy of objectification.

Second, if DFP were caused by a mechanical injury, it is obvious that the degree of severity would affect the recovery period. The exact cause of DFP has not been determined to date. Since it is known that the cause is not a mechanical injury, it is presumed that it will not be

correlated with the recovery period. Naturally, there may also be cases in which an author finds a correlation with a previously published article. Accordingly, more studies of this issue are required.

Finally, treatment of DFP is not standardized. Patients are worried about a full recovery, as mentioned earlier. Although DFP is said to be self-limiting from the point of treatment, we hope for a more rapid recovery. Among the estimated causes of DFP, steroid therapy is preferred in terms of treatment in cases of edema and immune factors for its effectiveness. Accordingly, our hospital has generally used steroids as a protocol for the treatment of DFP. However, in our opinion, a study is needed to compare the effects and necessity of steroids because we did not analyze the effects of treatment on DFP in this study.

Many future studies should refine treatment and improve results in the future. Once again, we appreciate the response of Dr. Lei and colleagues, and these ongoing debates should help our community make HFS treatment an increasingly effective and safe endeavor.

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Utility of folate receptor–targeted fluorescent dye for resection of pituitary adenomas

TO THE EDITOR: I read with keen interest the article by Lee et al.³ (Lee JYK, Cho SS, Zeh R, et al: Folate receptor overexpression can be visualized in real time during pituitary adenoma endoscopic transsphenoidal surgery with near-infrared imaging. **J Neurosurg** [epub ahead of print August 25, 2017. DOI: 10.3171/2017.2.JNS163191]). The technique of intraoperative pituitary tumor visualization using a folate analog conjugated to a near-infrared (NIR) fluorescent dye is a promising contribution as an adjunct technique in the surgeon's armamentarium. In their limited series of 3 patients with folate receptor alpha (FR α) overexpression, intraoperative fluorescence perfectly predicted the postoperative MRI findings. Based on

these findings the authors believe that this novel optical contrast technique may “provide important intraoperative information that influences surgical decision making and allows the surgeon to improve resection” in nonfunctioning pituitary macroadenomas. However, I respectfully disagree, in part, with their opinion.

Invasion of the cavernous sinus by pituitary tumor is associated with unfavorable surgical outcomes.⁴ Greenman et al.,² using multiple logistic regression analysis, have reported invasion of the cavernous sinus as the strongest independent negative predictor of complete tumor resection.⁴ In their series that included 233 patients with nonfunctioning pituitary macroadenomas without cavernous sinus invasion, Paluzzi and coworkers⁵ achieved gross-total resection (GTR) in 195 patients (83.6%). However, the percentage dropped to 35.4% (44 of 124) in patients with cavernous sinus invasion. In addition, they concluded that resectability was correlated with the Knosp grade, with grade 4 tumors undergoing intentional incomplete resection in consideration of the high risk of damage to the cavernous internal carotid artery and cranial nerves lateral to it. This suggests that any intraoperative imaging modality would be of little use in resecting this part of the tumor using the endonasal endoscopic approach. Hence, the utility of this technique is questionable for pituitary macroadenomas with cavernous sinus invasion. In macroadenomas without cavernous sinus invasion, the technique could hold some promise, but even in these cases, whether an improved optical contrast actually translates into improved resection and decreased recurrence is yet to be proven. Larger studies comparing FR α overexpressing and non-overexpressing tumors for differences in rates of GTR and recurrence need to be performed in the future.

Precise localization of pituitary tumors is of utmost importance in achieving the goal of transsphenoidal pituitary surgery, which is complete resection of the pituitary adenoma with preservation of pituitary function.¹ This is particularly true for secreting microadenomas. In the absence of intraoperative visualization of a secreting microadenoma, surgeons may have to resort to performing a total hypophysectomy to achieve endocrinological remission at the expense of panhypopituitarism.⁶ A novel optical contrast technique such as the one in the paper by Lee et al.³ holds more significance for such lesions. Unfortunately, none of the 9 secretory adenomas exhibited folate receptor overexpression in the present study. Future preclinical and clinical studies should be directed at searching for similar compounds directed at receptors on functional tumors.

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References

1. Eljamel MS, Leese G, Moseley H: Intraoperative optical identification of pituitary adenomas. *J Neurooncol* **92**:417–421, 2009
2. Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N: Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour

quiescence and regrowth. *Clin Endocrinol (Oxf)* **58**:763–769, 2003

3. Lee JYK, Cho SS, Zeh R, Pierce JT, Martinez-Lage M, Adappa ND, et al: Folate receptor overexpression can be visualized in real time during pituitary adenoma endoscopic transsphenoidal surgery with near-infrared imaging. *J Neurosurg* [epub ahead of print August 25, 2017. DOI: 10.3171/2017.2.JNS163191]
4. Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, Marzoli SB, et al: Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. *J Neurosurg* **108**:525–532, 2008
5. Paluzzi A, Fernandez-Miranda JC, Stefkó ST, Challinor S, Snyderman CH, Gardner PA: Endoscopic endonasal approach for pituitary adenomas: a series of 555 patients. *Pituitary* **17**:307–319, 2014
6. Prevedello DM, Pouratian N, Sherman J, Jane JA Jr, Vance ML, Lopes MB, et al: Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *J Neurosurg* **109**:751–759, 2008

Disclosures

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Response

We agree with Dr. Agarwal's contention that invasion of the cavernous sinus is the most important predictor of GTR in patients with pituitary adenoma. In addition, we agree that more patients are needed to evaluate the value of folate receptor imaging for pituitary adenoma. We also agree that a dye that can image functioning adenomas for patients with Cushing's disease is sorely needed.

However, we disagree with Dr. Agarwal's dismissal of the value of targeted tumor imaging. Reaching and returning from the moon cannot start without the early work by the Wright brothers who pioneered human airplane flight. We acknowledge the limitations of this fluorescent imaging technique, but novel dyes are currently in development by a host of different companies, and novel cameras will be needed to visualize the fluorophores. Our work may not yet have achieved true flight, but we have learned just a little bit more on the way to the stars.

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Statistical analysis is not always needed for rare informative complications

TO THE EDITOR: I read with great interest the article by Matsukawa and colleagues¹ (Matsukawa H, Kamiyama H, Tsuboi T, et al: Subarachnoid hemorrhage after surgical treatment of unruptured intracranial aneurysms. *J Neurosurg* [epub ahead of print October 27, 2017. DOI: 10.3171/2017.3.JNS162984]). They reported their surgical result in the treatment of unruptured cerebral aneurysms (UIAs) including many difficult-to-treat lesions with robust outcome criteria (modified Rankin Scale score > 1 or worsening of more than one point after the operation). They showed that basilar artery (BA) aneurysms and infarction in the perforating artery area, presumably partly due to the aneurysm size, are still significant risk factors for poor outcome in the surgical treatment of UIAs.

In addition, they presented 4 cases in which subarachnoid hemorrhage occurred after the surgery, and, using Cox regression hazard analysis, they stated that the BA location, giant aneurysms, and nonclippable aneurysm were statistically significant risk factors. These illustrated cases are very informative since 3 nonclippable BA aneurysms ruptured relatively shortly after revascularization treatment. With another anterior communicating artery aneurysms, careful observation should be needed after appropriate surgical treatment. However, it seemed odd to state the risk of subarachnoid hemorrhage in the context of statistical meaning, because the number of the events that they observed was too small to be statistically meaningful. In addition, I could not find in the manuscript how the log-rank test was used in the survival analysis. What survival curves or events did they compare by log-rank test?

Otherwise, I do respect their prodigious result in a large number of UIAs.

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References

1. Matsukawa H, Kamiyama H, Tsuboi T, Noda K, Ota N, Miyata S, et al: Subarachnoid hemorrhage after surgical treatment of unruptured intracranial aneurysms. *J Neurosurg* [epub ahead of print October 27, 2017. DOI: 10.3171/2017.3.JNS162984]

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Response

We appreciate the critical comments from Dr. Kimura

regarding our manuscript on the subarachnoid hemorrhage after the surgical treatment of UIAs.

As Dr. Kimura suggested, the number of postoperative subarachnoid hemorrhages was small ($n = 4$, Table 4 in our article). At first, we compared clinical and radiological characteristics using the log-rank test as a univariate analysis. The present study was not the randomized controlled trial. The log-rank test itself could not show significant meaning, and we regarded the finding as a reference with which to perform a multivariate analysis (a Cox proportional hazards model). The log-rank test showed that basilar artery location, giant size, and nonclippable aneurysms were related to postoperative subarachnoid hemorrhage. Other variables showed no significant relationship. We then performed a Cox proportional hazards analysis using these 3 variables. The result was that basilar artery location and nonclippable aneurysms remained significant (Table 5 in our article). Although the range of their 95% confidence interval was wide, it indicated the small number of events. Therefore, we determined that statistical analysis could be performed. Actually, only this model could not be adjusted for the other confounding factors; however, as stated above, other variables showed no significant association with postoperative subarachnoid hemorrhage. In addition, in the real world, we consider basilar artery location and nonclippable morphology to be serious risk factors for postoperative subarachnoid hemorrhage. Therefore, the results of the present study could strengthen our consideration.

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How to provide intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection

TO THE EDITOR: We read with great interest the article by Seo et al.⁴ (Seo H, Kim E, Jung H, et al: A prospective randomized trial of the optimal dose of mannitol for intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection. *J Neurosurg* 126:1839–1846, June 2017). The authors studied a total of 124 adult patients scheduled for craniotomy for supratentorial brain tumor resection under general anesthesia. They found the use of 1.0 g/kg of intraoperative mannitol provided satisfactory brain relaxation with the fewest adverse effects.

We commend the authors for performing a prospective randomized trial of a large number of adult patients (age range 20–80 years) scheduled for craniotomy for supratentorial brain tumor resection. They tried to determine the optimal dose of mannitol to provide adequate brain relaxation with the fewest adverse effects. A previous study had revealed that mannitol has several adverse effects, such as hypochloremic metabolic alkalosis associated with volume contraction and diuresis, hyponatremia, hypokalemia, and renal failure.³ Consequently, we have several concerns. First, the exclusion criteria did not exclude the patients with hyperkalemia or hypokalemia, which could influence the result of the experiment. Second, preoperative hypertonic saline use was not excluded from the study. A previous study had proved that brain relaxation can be achieved with intravenous fluids such as mannitol or hypertonic saline. Third, the authors report that the serum potassium level (mean [SD]) was higher in Group D than in Groups A and B at 60 minutes after the end of mannitol administration (4.2 [0.4] vs 3.9 [0.3] and 3.9 [0.3] mmol/L; $p < 0.001$ and $p = 0.004$, respectively). So we wonder how could the p value not be same as the numbers we showed (4.2 [0.4] vs 3.9 [0.3] and 3.9 [0.3] mmol/L). Fourth, the authors made a mistake in calculating the ratio in Tables 1 and 2. The ratio should be 2 (6.5%), 3 (9.7%), and 6 (19.4%)—not 2 (6.4%), 3 (9.6%), and 6 (19.2%).

In a report by Raghava et al.,² 50 patients were enrolled in a prospective, randomized study; patients received 5 ml/kg of either 3% hypertonic saline ($n = 25$) or 20% mannitol ($n = 25$). The authors ultimately found that brain relaxation was comparable in the two groups and there was no significant difference ($p = 0.633$). So, they came to a conclusion that 3% hypertonic saline and 20% mannitol are equally effective for brain relaxation in supratentorial brain tumor resection. And in another study by Hernández-Palazón et al.,¹ 60 patients undergoing elective supratentorial craniotomy were randomized 1:1 to receive 3 ml/kg of either 20% mannitol or 3% hypertonic saline, and they ultimately got the same conclusion that there was no difference in brain relaxation ($p = 0.55$).

In conclusion, single doses of 3 ml/kg of 20% mannitol and 3% hypertonic saline are safe and effective for intraoperative brain debulking during elective supratentorial craniotomy.¹ We appreciate Seo et al. for exploring an appropriate mannitol dose for satisfactory brain relaxation with the fewest adverse effects.

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References

- Hernández-Palazón J, Fuentes-García D, Doménech-Asensi P, Piqueras-Pérez C, Falcón-Araña L, Burguillos-López S: A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation during elective supratentorial craniotomy. *Br J Neurosurg* 30:70–75, 2016
- Raghava A, Bidkar PU, Prakash MV, Hemavathy B: Comparison of equiosmolar concentrations of hypertonic saline and mannitol for intraoperative lax brain in patients undergoing craniotomy. *Surg Neurol Int* 6:73, 2015
- Ropper AH: Hyperosmolar therapy for raised intracranial pressure. *N Engl J Med* 367:746–752, 2012
- Seo H, Kim E, Jung H, Lim YJ, Kim JW, Park CK, et al: A prospective randomized trial of the optimal dose of mannitol for intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection. *J Neurosurg* 126:1839–1846, 2017

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Response

First, we thank Mr. Kong and Dr. Liu for their interest in our article.

Mr. Kong and his colleague raised 4 issues with the article. First, they were concerned whether patients with hyperkalemia or hypokalemia at baseline were included in the exclusion criteria in our study. Serum potassium abnormality was not included in the exclusion criteria in our study. However, in our study, the nadir and zenith of serum potassium were 2.9 and 4.4 mEq/L, respectively, at baseline. Hypokalemia (< 3.5 mEq/L) at baseline was shown in 11 (35.5%), 8 (25.8%), 7 (22.6%), and 10 (32.3%) patients in groups A, B, C, and D, respectively ($p = 0.724$). In their serial follow-up, hypokalemia was observed in 3 (3/11, 27.3%), 5 (5/8, 62.5%), 2 (2/7, 28.6%), and 2 (2/10, 20.0%) patients in groups A, B, C, and D, respectively ($p = 0.494$). Hypokalemia during the entire study period, in patients showing normokalemia at baseline, was shown in 1 (5.0%), 3 (12.5%), and 2 (9.5%) patients in groups A, C, and D, respectively ($p = 0.268$). Hyperkalemia was observed in 4 patients in group D only ($p = 0.007$). Although there was no significant statistical difference in serum potassium concentration at baseline among the 4 groups, serum potassium concentration at baseline was not well controlled in our study. A further study is required to closely evaluate the effect of mannitol on serum potassium disturbance.

Second, they were concerned whether hypertonic saline was used preoperatively, because preoperative hypertonic saline can affect intraoperative brain condition and thereby act as a major confounder in interpreting our results. In the present study, no patient received hyperosmolar therapy such as hypertonic saline or mannitol administration before the surgery. However, all except 1 of the patients in group B received intravenous dexamethasone administration preoperatively to control peritumoral edema.

Third, Mr. Kong and his colleague wanted to know why there was a difference in the p value in group A and group B versus group D, even though the serum potassium level in group A was the same as that in group B. Because we needed to simplify the results, the numbers were rounded to one decimal place. The mean (SD) concentration of serum potassium at 60 minutes following mannitol administration was 4.236 (0.425) in group D, 3.852 (0.337) in group A, and 3.913 (0.288) in group B. Therefore, there

was a difference in the p value between group D and group A and between group D and group B.

Fourth, as Mr. Kong and his colleague indicated, we made a mistake in calculating the ratios in Tables 1 and 2. We appreciate them for their meticulous advice.

Mr. Kong and Dr. Liu suggest that a single dose of 3 ml/kg of 20% mannitol rather than 5 ml/kg of 20% mannitol is safe and effective for intraoperative brain relaxation in patients undergoing elective supratentorial craniotomy, based on results shown in a previous study conducted by Dr. Hernández-Palazón and coworkers.¹ However, we do not totally agree with their suggestion; 3 and 5 ml/kg of 20% mannitol correspond to doses of 0.6 and 1 g/kg mannitol, respectively. With respect to the experimental methodology, there is a significant difference between our study and the one conducted by Dr. Hernández-Palazón and coworkers. The number of patients with preoperative brain midline shift is dramatically different between the two studies. In our study all patients showed preoperative brain midline shift of more than 3 mm, whereas in their study approximately one-third of patients showed preoperative brain midline shift. They also demonstrated that patients with brain midline shift had an approximately 7 times worse response to hyperosmolar therapy compared to those without midline shift.

Quentin et al.² demonstrated that the incidence of satisfactory brain relaxation was 55% when 0.7 g/kg of mannitol was administered for intraoperative brain relaxation. In our study, the incidence of satisfactory brain relaxation was 52% and 68% after administration of 0.5 and 1.0 g/kg of mannitol, respectively. Taken together, we believe that administration of 1.0 g/kg mannitol may be preferred to 0.6–0.7 g/kg mannitol in view of the incidence of satisfactory brain relaxation. However, an increased mannitol dose was associated with increased adverse effects such as increased serum osmolar gap and potassium concentration, and decreased serum sodium concentration. Therefore, when using mannitol in clinical practice, the balance between benefits and risks should be considered.

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References

1. Hernández-Palazón J, Fuentes-García D, Doménech-Asensi P, Piqueras-Pérez C, Falcón-Araña L, Burguillos-López S: A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation during elective supratentorial craniotomy. *Br J Neurosurg* 30:70–75, 2016
2. Quentin C, Charbonneau S, Moumdjian R, Lallo A, Bouthillier A, Fournier-Gosselin MP, et al: A comparison of two doses of mannitol on brain relaxation during supratentorial brain tumor craniotomy: a randomized trial. *Anesth Analg* 116:862–868, 2013

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Transcranial versus endonasal approaches in tuberculum sellae meningioma surgery

TO THE EDITOR: We read with great interest the article by Bander et al.¹ regarding the comparison of the endoscopic endonasal approach (EEA) versus the transcranial approach (TCA) in patients with tuberculum sellae meningioma (TSM) or planum sphenoidale meningioma (Bander ED, Singh H, Ogilvie CB, et al: Endoscopic endonasal versus transcranial approach to tuberculum sellae and planum sphenoidale meningiomas in a similar cohort of patients. *J Neurosurg* 128:40–48, January 2018). In the same issue of JNS, we published our experience with endoscope-assisted frontolateral approaches in patients with TSM.²

We appreciate the intelligent scientific approach of Bander et al. in comparing both approaches to tumors that would have been accessible by both approaches *per se*. However, we have some questions arising in our point of view.

Very surprising for us was the poor visual outcome in the TCA group of Bander et al. (deterioration in 44% of patients). We have not seen any visual deterioration in our published series. Of course, we do EEA for TSM as well; however, only in smaller lesions or when the patient demands this approach and we think it is feasible. Nevertheless, we think that a TCA is the better choice in most TSMs. In two of our cases, we saw tumor growing en plaque laterally over the optic nerve and the carotid artery, which was not expected based on the preoperative MRI (Fig. 1). This tumor part would have definitely been missed by an EEA. Furthermore, branches of the superior hypophyseal artery (SHA) may run straight through the tumor (Fig. 2) and are more difficult to dissect via an EEA, at least in our hands.

Bander et al. did not state if they used an endoscope as an assistive device. In TSM surgery, the tumor part underneath the ipsilateral optic nerve is not visible with the operating microscope during TCA. Therefore, we use an endoscope to visualize tumor in that region. When there is tumor extension in only one optic canal, we approach these tumors from the contralateral side because this tumor part is very well seen with the operating microscope and can easily be removed.

The second finding of Bander et al. that is very surprising to us is that patients treated via a TCA have a rate of 27% for postoperative seizures. We did not see any seizures in our series. We do not administer antiepileptic drugs prophylactically. Bander et al. explain this frequency of seizures by the brain trauma due to brain retraction during TCA. However, significant brain retraction is not required if patient and head positioning is done in a proper way (body 15° elevated, hyperextension of the head in a way that the zygoma is the highest point). With this positioning and abundant release of CSF, the frontal lobe falls back by gravity and minimal traction, which will not damage the frontal lobe, is required to expose the tumor.

FIG. 1. Intraoperative microscopic view showing the tumor growing en plaque laterally over the optic nerve and the carotid artery.

FIG. 2. Branches of the SHA run straight through the tumor.

Of course individual decision making is necessary in approaching TSM. However, according to our own surgical experience we do not agree with the main conclusion of Bander et al. that the TCA per se has a worse visual outcome and more postoperative seizures.

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References

1. Bander ED, Singh H, Ogilvie CB, Cusick RC, Pisapia DJ, Tsiouris AJ, et al: Endoscopic endonasal versus transcranial approach to tuberculum sellae and planum sphenoidale meningiomas in a similar cohort of patients. *J Neurosurg* **128**:40–48, 2018
2. Marx S, Clemens S, Schroeder HWS: The value of endoscope assistance during transcranial surgery for tuberculum sellae meningiomas. *J Neurosurg* **128**:32–39, 2018

Disclosures

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Response

We thank the authors for their comments on our paper. Their results using a transcranial approach for tuberculum and planum meningiomas appear to be quite good. However, we take issue with their criticism of the transcranial results we report in our paper. First, we wish to point out that the transcranial surgeries were done by other surgeons at our institution who are not practitioners of extended endonasal surgeries. These surgeons, like Drs. Marx and Schroeder, are convinced that the transcranial approach is superior to the endonasal approach and continue to offer it exclusively for their patients. The results we report were obtained by reviewing the medical records in a blinded fashion without knowledge of the approach used. The results are not falsified or fabricated. If Drs. Marx and Schroeder are convinced that the transcranial approach is superior, this must be proven in a multicenter study with tumors of comparable shape and size, removed by surgeons with equal experience in the chosen approach, and not surgeons who do a particular approach rarely, only at the patients' insistence. Until such a study is performed, the opinions they profess are based on their own unique experience at their institution and may not be applicable globally in others' hands. Likewise, our results arise from our own institution and, as such, are unique to this one hospital setting.

In closing, we would like to point out that every meta-analysis ever published comparing endonasal to transcranial surgery for tuberculum and planum meningiomas shows that the endonasal approach leads to better visual outcome and a lower rate of seizures than the transcranial approach.^{1–6}

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References

1. Clark AJ, Jahangiri A, Garcia RM, George JR, Sughrue ME, McDermott MW, et al: Endoscopic surgery for tuberculum sellae meningiomas: a systematic review and meta-analysis. *Neurosurg Rev* **36**:349–359, 2013
2. Gadgil N, Thomas JG, Takashima M, Yoshor D: Endoscopic

resection of tuberculum sellae meningiomas. **J Neurol Surg B Skull Base** 74:201–210, 2013

3. Kitano M, Taneda M, Nakao Y: Postoperative improvement in visual function in patients with tuberculum sellae meningiomas: results of the extended transsphenoidal and transcranial approaches. **J Neurosurgery** 107:337–346, 2007
4. Komotar RJ, Starke RM, Raper DMS, Anand VK, Schwartz TH: Endoscopic endonasal versus open transcranial resection of anterior skull base meningiomas: a systematic meta-analysis of outcomes. **World Neurosurg** 77:713–724, 2012
5. Muskens IS, Briceno V, Ouwehand TL, Castlen JP, Gormley WB, Aglio LS, et al: The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas—a meta-analysis. **Acta Neurochir (Wein)** 160:59–75, 2018
6. Song SW, Kim YH, Kim JW, Park CK, Kim JE, Kim DG, et al: Outcomes after transcranial and endoscopic endonasal approach for tuberculum meningiomas—a retrospective comparison. **World Neurosurgery** 109:e434–e445, 2018

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Endoscopic endonasal versus transcranial approach to tuberculum sellae and planum sphenoidale meningiomas: unanswered questions

TO THE EDITOR: We read with keen interest the article by Bander et al.¹ (Bander ED, Singh H, Ogilvie CB, et al: Endoscopic endonasal versus transcranial approach to tuberculum sellae and planum sphenoidale meningiomas in a similar cohort of patients. *J Neurosurg* 128:40–48, January 2018). In their small single-institution study of similar cohorts of patients with tuberculum sellae and planum sphenoidale meningiomas they highlighted the benefits of the endoscopic endonasal approach (EEA) over the transcranial approach (TCA) in that there were fewer overall complications and better visual outcomes. We have some questions regarding their findings.

First, when was postoperative MRI done? A mention of the timing of postoperative MRI holds importance because findings on diffusion-weighted imaging (DWI) in the same patient may resolve over a period of time. In their study of 44 consecutive patients with newly diagnosed gliomas, Smith et al. prospectively investigated the incidence, time course, and ultimate outcome of postoperative DWI abnormalities by using serial MRI. In 24 of 28 patients with reduced diffusion on immediate postoperative DW MRI, complete resolution of this reduced diffusion was noted within 90 days.⁶

Second, it would be interesting to know the length of hospital stay in the 2 patients with CSF leakage following EEA. In the present study, the mean length of hospital stay is longer in patients undergoing EEA compared to those undergoing TCA (4.6 vs 4.3 days), although this difference did not reach statistical significance. Whether the patients with CSF leakage had an effect on these results is of significant interest.

Last, were prophylactic anticonvulsants given to patients in the TCA group during the early postoperative period? There is conflicting evidence in the literature regarding use of prophylactic anticonvulsants in the postoperative period.^{3,4,7} Sayegh et al.,⁵ in their review of 6 meta-analyses published between 1996 and 2011, have concluded that this management strategy should not be used. However, many studies included in the meta-analyses did not differentiate between early and late postoperative seizures. Also, the use of prophylactic anticonvulsants during the first week after surgery, and then tapering and stopping thereafter, is consistent with American Academy of Neurology guidelines.² This uncertainty raises a question—could anticonvulsants decrease the incidence of early postoperative seizures, if not in all patients, then at least in patients with significantly higher DWI signal following craniotomy? Further research should be directed toward answering this question.

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References

1. Bander ED, Singh H, Ogilvie CB, Cusick RC, Pisapia DJ, Tsiouris AJ, et al: Endoscopic endonasal versus transcranial approach to tuberculum sellae and planum sphenoidale meningiomas in a similar cohort of patients. **J Neurosurg** 128:40–48, 2018
2. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. **Neurology** 54:1886–1893, 2000
3. Komotar RJ, Raper DMS, Starke RM, Iorgulescu JB, Gutin PH: Prophylactic antiepileptic drug therapy in patients undergoing supratentorial meningioma resection: a systematic analysis of efficacy. **J Neurosurg** 115:483–490, 2011
4. Perry J, Zinman L, Chambers A, Spithoff K, Lloyd N, Laperriere N: The use of prophylactic anticonvulsants in patients with brain tumours—a systematic review. **Curr Oncol** 13:222–229, 2006
5. Sayegh ET, Fakurnejad S, Oh T, Bloch O, Parsa AT: Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence. **J Neurosurg** 121:1139–1147, 2014
6. Smith JS, Cha S, Mayo MC, McDermott MW, Parsa AT, Chang SM, et al: Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury. **J Neurosurg** 103:428–438, 2005
7. Temkin NR: Prophylactic anticonvulsants after neurosurgery. **Epilepsy Curr** 2:105–107, 2002

Disclosures

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Response

In response to your questions we propose the following answers. First, postoperative MRI scans were generally done within 2–3 days after surgery during the patients' first admission. Although we admit that DWI changes can resolve over time, it is a marker of brain injury at the time of surgery. We used DWI to compare the amount of brain trauma at the time of surgery. We are not drawing conclusions about long-term brain injury or even cognitive sequelae because we do not have data to support such a claim. Also, I would caution the authors that DWI after glioma surgery may not be the same as DWI after meningioma surgery. Second, the length of hospital stay in the patients with CSF leakage was clearly longer than if they did not have a leak. One had an initial stay of 5 days, was readmitted with a leak, and stayed an extra 5 days after lumbar drain placement. The second stayed a total of 11 days. Even with these 2 patients, there was no statistically significant difference in length of stay between the 2 groups. If these patients are eliminated, the patients who underwent EEA stayed for a shorter period of time. This implies that as CSF leak rates are reduced, eventually the length of stay may be shorter for patients treated with the EEA. As for postoperative antiepileptic drug usage, these were only given to the patients who underwent a TCA and not to the EEA patients. In spite of this fact, the rate of seizure was higher for the TCA patients.

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Multimodal opioid-minimizing pain management regimens following transsphenoidal surgery

TO THE EDITOR: We read with great interest the article of Shepherd and colleagues⁴ in a recent issue (Shepherd DM, Jahnke H, White WL, et al: Randomized, double-blinded, placebo-controlled trial comparing two multimodal opioid-minimizing pain management regimens following transsphenoidal surgery. *J Neurosurg* 128:444–451, February 2018). The authors performed a randomized controlled trial to compare the analgesic efficacy of scheduled intravenous (IV) ibuprofen on 62 patients undergoing transsphenoidal surgery and concluded that IV ibuprofen resulted in significantly improved pain scores and significantly decreased opioid use compared with placebo. The authors should be congratulated for performing a study on an important topic (i.e., acute pain) in patients undergoing surgery.^{1,2} The current emphasis on the need to use multimodal analgesics to improve patient recovery after surgery makes the topic very relevant in perioperative medicine.^{3,5}

Although the study of Shepherd et al. was well conducted, there are some concerns that need to be clarified by the authors. First, it is not clear if the authors standardized the intraoperative analgesic consumption for all patients, as this can significantly alter the outcomes. Second, it is unclear why the authors choose to use IV ibuprofen and oral acetaminophen when they could have used all medications by the same route of administration (e.g., oral administration). Last, the lack of improvement in other outcomes (e.g., postoperative nausea and vomiting) suggests that the opioid-sparing effects were not clinically significant, and therefore more studies using other patient-centered outcomes to evaluate the intervention are needed.

We would welcome some comments by the authors, as this would help to further substantiate the findings of this important clinical trial.

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References

- Herbst MO, Price MD, Soto RG: Pain related readmissions/ revisits following same-day surgery: have they decreased over a decade? *J Clin Anesth* 42:15, 2017
- Lee JYK, Pierce JT, Sandhu SK, Petrov D, Yang AI: Endoscopic versus microscopic microvascular decompression for trigeminal neuralgia: equivalent pain outcomes with possibly decreased postoperative headache after endoscopic surgery. *J Neurosurg* 126:1676–1684, 2017
- Li XD, Han C, Yu WL: Is gabapentin effective and safe in open hysterectomy? A PRISMA compliant meta-analysis of randomized controlled trials. *J Clin Anesth* 41:76–83, 2017
- Shepherd DM, Jahnke H, White WL, Little AS: Randomized, double-blinded, placebo-controlled trial comparing two multimodal opioid-minimizing pain management regimens following transsphenoidal surgery. *J Neurosurg* 128:444–451, 2018
- Zhang Z, Xu H, Zhang Y, Li W, Yang Y, Han T, et al: Nonsteroidal anti-inflammatory drugs for postoperative pain control after lumbar spine surgery: a meta-analysis of randomized controlled trials. *J Clin Anesth* 43:84–89, 2017

Disclosures

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Response

We thank Drs. Kendall and Castro-Alves for their interest in the results of our study, and we appreciate the opportunity to address their questions.

First, we wish to clarify that the “intraoperative analgesia consumption” was not standardized in the study. The actual amount of intraoperative analgesic medication that was administered outside of the study protocol, which was to give one dose of the study drug or placebo at the time that the sella turcica was opened, was determined at the

discretion of the anesthesiologist, per standard operative protocol. We regret not stating this part of the procedure in the description of our protocol.

Second, we chose IV ibuprofen as a representative non-steroidal antiinflammatory drug because the manufacturer was willing to provide it free of charge for this study. The manufacturer of IV acetaminophen was not willing to provide that drug gratis, and our hospital was not willing to subsidize its use in the context of this research. Therefore, we opted to use oral acetaminophen, which is much less expensive and which was acceptable to our institution. Although perhaps not optimal, this decision is one of the compromises we had to make within our health care setting in order to conduct the study.

Third, we disagree with Drs. Kendall and Castro-Alves' conclusion that the lack of improvement in nausea and vomiting (which we did not measure per se; we measured the use of antiemetic medications) somehow undermines the validity of our primary finding, which is improvement in pain scores with the use of IV ibuprofen. We firmly believe that pain scores are the most patient-centered end point one can evaluate in a pain study. The study also demonstrated that the use of rescue opioids was substantially reduced, thereby supporting our conclusions. Although further study of opioid-minimizing pain control with additional agents is certainly desirable, not only for transsphenoidal surgery for pituitary tumors but also for other types of surgery, we remain convinced that our findings contribute substantively to this area of research.

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Disclosures

Dr. Little is an investor in Kogent Surgical, LLC. The study drug (IV ibuprofen [Caldolor]) was provided by Cumberland Pharmaceuticals, Inc., which had no role in study design, data collection, data analysis, or manuscript preparation.

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Posterior pseudocapsule in macroadenomas

TO THE EDITOR: We have read with high consideration the article by Taylor and colleagues⁵ (Taylor DG, Jane JA Jr, Oldfield EH: Resection of pituitary macroadenoma via the pseudocapsule along the posterior tumor margin: a cohort study and technical note. *J Neurosurg* 128:422–428, February 2018). We completely agree with

the authors' conclusion that use of the posterior pseudocapsule dissection plane in macroadenomas significantly decreases the incidence of postoperative residual tumor without increasing the risk of intraoperative cerebrospinal fluid (CSF) leakage or postoperative endocrine deficits and provides a similar rate of recovery of prior endocrine deficiencies.

It is important to identify the pseudocapsule early for successful gross-total tumor resection. We also apply pseudocapsulectomy for resection of pituitary adenomas; however, following sufficient internal decompression of the tumor and creation of a wide working space, we start our pseudocapsulectomy by approaching the lateral interface between the pseudocapsule and the anterior lobe of the normal pituitary gland. In our experience it is easy to peel the pseudocapsule off of the normal pituitary gland at this lateral point after creating a wide working space for safer pseudocapsulectomy. To the best of our knowledge, it is a common technique.^{1,2,4} However, in the authors' technique, in order to reach the posterior pseudocapsule, they applied a limited central tumor debulking that resulted in a deep and narrow (cone-like) working corridor. Moreover, the initial dissection plane of pseudocapsulectomy was very close to the posterior lobe. Here, we would like to ask the authors: does such a narrow working space put the posterior pituitary gland at risk? Perhaps additional details regarding the incidence of diabetes insipidus (DI) in correlation to this technique⁵ might be helpful.

In addition, we prefer to use an angled endoscope (rather than a straight scope or microscope)³ while dissecting the pseudocapsule from surrounding structures in order to look around corners. In reviewing Video 2, we were not able to identify different angled operative views.

The importance of pseudocapsulectomy in the removal of functioning pituitary adenomas is well recognized.¹ However, the necessity of pseudocapsulectomy for nonfunctioning pituitary adenomas is controversial.³ We apply pseudocapsulectomy for nonfunctioning pituitary adenomas only when uncontrollable intraoperative bleeding from the pseudocapsule occurs (to avoid postoperative bleeding). We would like to know the authors' experience regarding this point.

Finally, we would like to congratulate the authors for their unique technique that improves the surgical results for pituitary adenoma.

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References

1. Kawamata T, Kubo O, Hori T: Surgical removal of growth hormone-secreting pituitary adenomas with intensive microsurgical pseudocapsule resection results in complete remission of acromegaly. *Neurosurg Rev* 28:201–208, 2005
2. Kim EH, Ku CR, Lee EJ, Kim SH: Extracapsular en bloc resection in pituitary adenoma surgery. *Pituitary* 18:397–404, 2015
3. Kinoshita Y, Tominaga A, Usui S, Arita K, Sakoguchi T, Sugiyama K, et al: The surgical side effects of pseudocapsu-

lar resection in nonfunctioning pituitary adenomas. **World Neurosurg** 93:430–435, 435.e1, 2016

4. Prevedello DM, Ebner FH, de Lara D, Ditzel Filho L, Otto BA, Carrau RL: Extracapsular dissection technique with the cotton swab for pituitary adenomas through an endoscopic endonasal approach—how I do it. **Acta Neurochir (Wien)** 155:1629–1632, 2013
5. Taylor DG, Jane JA Jr, Oldfield EH: Resection of pituitary macroadenomas via the pseudocapsule along the posterior tumor margin: a cohort study and technical note. **J Neurosurg** 128:422–428, 2018

Disclosures

The authors report no conflict of interest.

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Response

We would like to thank Ogiwara et al. for their interest in our work, their comments, and their contributions to pituitary surgery. The authors offer their insights to utilization of the pseudocapsular dissection plane in the treatment of pituitary adenomas, suggesting that utilizing the lateral margins of the tumor may be sufficient for tumor resection. The authors also propose that a posterior pseudocapsule technique may place increased risk on the development of DI due to proximity to the neurohypophysis.

Microadenomas and small macroadenomas are often amenable to circumferential dissection beginning at the lateral margins. The authors suggest that use of the lateral interface between the tumor and displaced anterior pituitary provides an easily accessible dissection plane. However, the authors do not comment on whether there are restrictions to the lateral approach as may be appreciated with large macroadenomas. In our experience, larger adenomas often efface the adenohypophysis anteriorly and laterally to such a degree that there is insufficient tensile strength to provide the necessary counter-tension for the pseudocapsular dissection. In contrast, the gland is most reliably displaced posteriorly or posterolaterally, and so our technique attempts to identify this dissection plane first. Once established, the integrity of the surgical plane will keep the surgical instruments within this working space, and the dissection can be then carried laterally to improve direct visualization.

The authors also requested further information regarding the incidence of DI in our series. As reported, the onset of new endocrinopathy was equivocal between techniques, but we did not comment on DI specifically. Among the piecemeal resection cohort, 2 patients (7%) required continued desmopressin at follow-up compared to 0 patients (0%) in the posterior pseudocapsule cohort ($p = 0.08$). Although we understand the authors' concern given the proximity to the posterior pituitary, because the posterior pseudocapsule technique begins at the interface between the posteriorly displaced adenohypophysis and macroadenoma, rather than at the posterior pituitary itself, there

is minimal risk of DI, and our results demonstrate a lower incidence than those reported elsewhere.¹

Lastly, the authors note that a pseudocapsule technique has demonstrated the greatest utility among functional tumors, but they suggest that a piecemeal technique may be sufficient for nonfunctioning macroadenomas. Among functional tumors, pseudocapsule technique leads to more rapid resolution of endocrinopathy.^{2,3} Surgically, resection of encapsulated functional and nonfunctional tumors is largely identical, and any method that provides greater opportunity for gross-total resection without increased risk to pituitary function or the surrounding structures should be utilized. Given the reliability with which gross-total resection by the pseudocapsular approach can be achieved, we advocate its use whenever possible to attenuate the potential risk of tumor recurrence or need for adjuvant therapies.

Again, we thank Ogiwara et al. for their comments and their interest in our work. To be concise, surgical acumen must be used when considering the appropriate technique; lateral dissection may indeed be the most applicable for mid-sized tumors with a laterally displaced anterior pituitary, but posterior dissection most reliably establishes the appropriate working plane with larger adenomas.

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References

1. Chen CJ, Ironside N, Pomeranec II, Chivukula S, Buell TJ, Ding D, et al: Microsurgical versus endoscopic transphenoidal resection for acromegaly: a systematic review of outcomes and complications. **Acta Neurochir (Wien)** 159:2193–2207, 2017
2. Kawamata T, Kubo O, Hori T: Surgical removal of growth hormone-secreting pituitary adenomas with intensive microsurgical pseudocapsule resection results in complete remission of acromegaly. **Neurosurg Rev** 28:201–208, 2005
3. Monteith SJ, Starke RM, Jane JA Jr, Oldfield EH: Use of the histological pseudocapsule in surgery for Cushing disease: rapid postoperative cortisol decline predicting complete tumor resection. **J Neurosurg** 116:721–727, 2012

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Influence of rare *RNF213* variants other than p.R4810K on the clinical outcomes of moyamoya disease

TO THE EDITOR: We thoroughly read the article by Kim et al.,² which reports that the homozygous c.14429G>A (p.R4810K) variant in *RNF213* is related to early-onset, severe symptomatic manifestations at the diagnosis and poor prognosis of moyamoya disease (MMD) (Kim EH, Yum MS, Ra YS, et al: Importance of *RNF213* polymorphism on clinical features and long-term out-

FIG. 1. FLAIR MRI (axial images, **A** and **B**) and MRA (**C** and **D**) performed at the patient's initial presentation with right lower-extremity weakness showed bilateral cerebral infarction due to MMD. Diffusion-weighted MRI (axial image, **E**) performed after left combined bypass surgery revealed an unexpected cerebral infarction in a region distant from the bypass. DNA sequence analysis (chromatogram, **F**) identified the heterozygous c.12185G>A (p.R4062Q) variant (G>A substitution indicated by R in the chromatogram). MRA performed 5 years after the onset (**G** and **H**) showed significant progression of stenosis of major intracranial arteries. Figure is available in color online only.

come in moyamoya disease. *J Neurosurg* 124:1221–1227, May 2016). Their results, which were derived from Korean samples, were identical to those from previous Japanese studies,^{6,7} because c.14429G>A (p.R4810K) and c.14576G>A (p.R4859K) are the same variants, represented by NC_000017.10:g.78358945G>A (rs112735431, https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=112735431). The misunderstanding that these were different variants, which was also present in the other study,⁵ was because of the updated reference transcriptional sequence of *RNF213*. c.14429G>A (p.R4810K) is the presently accepted nomenclature according to NM_001256071.1, which lacks the fourth exon of the previously suppressed NM_020914.4 (NCBI Reference Sequence, <https://www.ncbi.nlm.nih.gov/refseq/>).⁴

In this article, Kim et al.² also mentioned the necessity of analyzing the entire *RNF213* gene because of the etiological role of other variants in this gene, which has been increasingly recognized by recent genetic studies on MMD.^{1,7} Herein, we present an illustrative case in which the patient harbored a rare missense variant other than R4810K. An 8-year-old boy developed bilateral cerebral infarctions resulting in motor weakness of the right lower extremity due to a left medial parietal lesion (Fig. 1A and B). Magnetic resonance angiography (MRA) demonstrated bilateral steno-occlusive changes around the circle of Willis with moyamoya vessel formation, leading to the diagnosis of MMD (Fig. 1C and D). Bilateral combined direct and indirect bypass surgeries were performed in stages, but another cerebral infarction occurred in a region distant from the bypass (Fig. 1E) immediately after the

initial left-side surgery. Because of this unusual course, a comprehensive analysis of *RNF213* was performed in a previous genetic study using a large series of Japanese MMD patients.⁷ As a result, the patient was found to be heterozygous for c.12185G>A (p.R4062Q) (Fig. 1F), which was one of the most reliable MMD susceptibility variants among previously reported *RNF213* variants, because it was nonexistent in the general population, but our patient shared it with an affected relative with MMD, and it was also reported in a European MMD patient.^{1,4,6,7} Our patient recovered without significant disabilities; however, he developed a transient ischemic attack with repeated left hemiparesis 5 years after the surgical revascularization and the genetic diagnosis. MRA revealed the disappearance of the middle and anterior cerebral arteries and progressive stenosis of the posterior cerebral arteries (Fig. 1G and H). An additional bypass was created at the right middle cerebral artery using the right occipital artery as a donor artery, and the patient's postoperative course has been good so far.

Kim et al.² reported on one patient harboring a novel heterozygous c.12086A>G (p.Q4029R) variant, whose angiographic findings were typical of MMD. This c.12086A>G (p.Q4029R) is regarded as pathogenic because its C-score (16.46) of Combined Annotation Dependent Depletion (CADD; <http://cadd.gs.washington.edu/>)³ version 1.3 is markedly higher than that of c.14429G>A (p.R4810K) (7.374). c.12185G>A (p.R4062Q) in our patient has an even higher C-score of 31, and therefore, he showed severe clinical manifestations, despite its heterozygous genotype. To better predict clinical outcomes according to *RNF213*

genotypes, it is necessary to accumulate improved knowledge about the patients having different sites and types of variants in *RNF213*.

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References

1. Cecchi AC, Guo D, Ren Z, Flynn K, Santos-Cortez RL, Leal SM, et al: RNF213 rare variants in an ethnically diverse population with moyamoya disease. **Stroke** **45**:3200–3207, 2014
2. Kim EH, Yum MS, Ra YS, Park JB, Ahn JS, Kim GH, et al: Importance of *RNF213* polymorphism on clinical features and long-term outcome in moyamoya disease. **J Neurosurg** **124**:1221–1227, 2016
3. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J: A general framework for estimating the relative pathogenicity of human genetic variants. **Nat Genet** **46**:310–315, 2014
4. Liu W, Morito D, Takashima S, Mineharu Y, Kobayashi H, Hitomi T, et al: Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. **PLoS One** **6**:e22542, 2011
5. Ma J, Liu Y, Ma L, Huang S, Li H, You C: RNF213 polymorphism and moyamoya disease: a systematic review and meta-analysis. **Neurol India** **61**:35–39, 2013
6. Miyatake S, Miyake N, Touho H, Nishimura-Tadaki A, Kondo Y, Okada I, et al: Homozygous c.14576G>A variant of RNF213 predicts early-onset and severe form of moyamoya disease. **Neurology** **78**:803–810, 2012
7. Moteki Y, Onda H, Kasuya H, Yoneyama T, Okada Y, Hirota K, et al: Systematic validation of RNF213 coding variants in Japanese patients with moyamoya disease. **J Am Heart Assoc** **4**:e001862, 2015

Disclosures

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Response

No response was received from the authors of the original article.

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