Dumbbell-shaped pituitary adenomas

TO THE EDITOR: We read the article by Micko et al. with interest (Micko ASG, Keritam O, Marik W, et al. Dumbbell-shaped pituitary adenomas: prognostic factors for prediction of tumor nondescent of the supradiaphragmatic component from a multicenter series. J Neurosurg. Published online December 24, 2021. doi:10.3171/2021.9.JNS211689). In this article Micko et al. discuss dumbbell-shaped pituitary adenomas and their relationship with the diaphragma sellae. It is unfortunate that the authors seem to have ignored the articles that my colleagues and I have published on the subject.2–5

In our several published articles on this topic, my colleagues and I have discussed the pattern of growth of pituitary tumors, particularly those that acquire a giant size, and their relationship with the dural layers of the region that includes the diaphragma sellae.2–5 My coauthors and I reported for the first time in the literature, to our knowledge, that in a large majority of such dumbbell-shaped tumors the diaphragma sellae “dura” is elevated on the dome of the tumor.2,3 Previously the understanding was that pituitary tumors emerged out of the aperture of the diaphragma sellae that is normally occupied by the pituitary stalk. The elevated diaphragma sellae may be thinned out in larger tumors and the thickness and consistency may resemble that of the arachnoid membrane. This anatomical observation has major surgical implications, because the elevated dural layer of the diaphragma forms a distinct layer of compartmentalization and a reliable barrier for resection of the tumor away from the arteries of the circle of Willis, optic chiasma, and other critical neural structures. The diaphragma sellae falls into the surgical field at the end of tumor resection, signaling the radicality of resection.

My colleagues and I have classified giant pituitary tumors into 4 grades.2–5 Grade 1 pituitary tumors were those that remained confined to the sella and supradiaphragmatic space and did not invade into the cavernous sinus. Such tumors formed a majority of giant pituitary tumors. Although transgression of the medial dural wall of the cavernous sinus was a more frequent event in tumors of this grade, transgression of the diaphragma sellae was infrequent. Grade 4 pituitary tumors were those that extended into the supradiaphragmatic space, were located in the subarachnoid space, and had intimate relationships with arteries of the circle of Willis. The exact site of communication of the sellar and supradiaphragmatic part of the tumor could not be confirmed. However, transgression from the diaphragma sellae opening appeared to be infrequent. We observed that radical resection of grade 4 pituitary tumors was technically difficult and was fraught with the possibility of postoperative hemorrhagic complications. We also observed that grade 4 giant pituitary tumors were inherently more aggressive in nature. Recurrences of these tumors were high, and such tumors merited consideration of postoperative upfront radiation treatment.

This understanding regarding the relationship of pituitary tumors with the diaphragma sellae has had a significant impact in the shifting of neurosurgeon preference toward transsphenoidal surgery when transcranial surgery was previously the more frequently chosen approach for pituitary tumors with suprasellar extension.

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Disclosures
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Response
We appreciate Dr. Goel’s comments. As we have mentioned in our previous publication concerning the management of giant pituitary adenomas (GPAs), we value his surgical experience on this topic. However, GPAs comprised only 20 of the 99 cases of the series of dumbbell pituitary adenomas reported in our article.

We agree with Dr. Goel that the thin diaphragma sellae layer is elevated to the dome of the suprasellar adenoma component in the majority of pituitary adenomas with suprasellar extension. This elevation to the dome provides the rationale for the success of resection of pituitary adenomas from below via the transsphenoidal route.

Independently of this thin diaphragm layer, however, a narrow sellar entry level is the underlying cause for the development of dumbbell-shaped pituitary adenomas. In these cases, the narrow neck is known to prevent the successful removal of the suprasellar component (and subsequent downward herniation of the thin diaphragm) in some cases.

As such, non-descent has important therapeutic implications, and our current study was designed to elucidate the risk factors for non-descent of the suprasellar component. We identified a neck-to-dome area ratio ≥ 2 as a predictive factor for intraoperative tumor non-descent in our multicenter series of endoscopic cases.

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Risk factors for postoperative DI after transsphenoidal surgery: missing a pinch of SALT

TO THE EDITOR: Joshi et al. have reported their findings from the largest study to date assessing postoperative diabetes insipidus (DI) after transsphenoidal surgery (TSS) (Joshi RS, Pereira MP, Osorio RC, et al. Identifying risk factors for postoperative diabetes insipidus in more than 2500 patients undergoing transsphenoidal surgery: a single-institution experience. J Neurosurg. Published online January 28, 2022. doi:10.3171/2021.11.JNS211260). Their results further our understanding of this important potential complication of pituitary surgery.

The authors use a stringent definition of DI, requiring the presence of hypernatremia for diagnosis. Patients with DI may maintain a “normal” plasma tonicity so long as their thirst response remains intact, enabling them to match their output with oral intake. Thus, the strict definition used in this study may in fact have led to some cases of DI being left undiagnosed, particularly transient ones.

Diagnostic sensitivity may be improved by employing an alternative definition of postoperative DI, such as that proposed by De Vries et al. However, the normonatremic patient with DI would be difficult to recognize in a retrospective study, and this broader definition may decrease diagnostic specificity. Urinary tonicity is a helpful diagnostic measure that could also be added to the diagnostic criteria used by Joshi et al., as evaluating urinary concentration is vital to establishing whether the renal system is responding appropriately or inappropriately to plasma tonicity and the volume state. Regardless, the definition chosen by Joshi et al. in their reported study is practical, captures the majority of patients with DI, and (importantly) includes all patients who required intervention with an arginine vasopressin (AVP) analog.

On multivariate analysis, the authors found that younger age, intraoperative CSF leak, craniopharyngioma histology, and postoperative hyponatremia were all associated with the development of postoperative DI. In a recent prospective study of endoscopic endonasal transsphenoidal surgery (EEA), we found craniopharyngioma histology, suprasellar extension, Kelly grade 3 intraoperative CSF leak, and age < 50 years to independently predict the development of postoperative DI. Together, these factors formed the SALT (suprasellar, age, lesion, three) score, which we have used to predict postoperative DI with good accuracy. It would be interesting to see whether the SALT score could be independently validated in the Joshi et al. study cohort.

The association of DI with postoperative hyponatremia is consistent with the triphasic (or occasionally biphasic) response to stalk injury. The known association between hyponatremia and DI has limited clinical utility in predicting the development of DI, as classically DI occurs before the development of hyponatremia. Was this temporal relationship observed in the current study?

The cohort of participants in the study by Joshi et al. was recruited over a 13-year period beginning in 2007, and thus microscopic approaches predominated. A total of 19.8% of patients treated with endoscopic approaches experienced postoperative DI, compared to 8.6% of patients in whom a microscopic method was used (p < 0.001). These results contrast with the findings of the prospective, multicenter Transsphenoidal Extent of Resection (TRANSSPHER) Study, in which new DI was more common in the micro-
scopic treatment arm (8.9% vs 2.4%, p = 0.04). Joshi et al. appear not to have included “surgical approach” in their multivariate analysis, leaving one to ponder whether this finding is indicative of the learning curve for performing the EEA, or that the EEA was used in more complex cases. Despite a predominance of microscopic cases, predictors of DI are concordant with more modern, purely endoscopic cohorts, suggesting good generalizability of results.

We congratulate the authors on their important contribution to pituitary surgery. A greater understanding of the risk factors for DI will guide the development and validation of predictive tools, such as the SALT score. With better prediction of this complication, preoperative patient counseling, postoperative management, and resource allocation will be improved.

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Disclosures
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Response
We appreciate the opportunity to respond to the letter to the editor written by Dr. Castle-Kirsbaum et al. We additionally thank Castle-Kirsbaum et al. for their insights and questions regarding our study and have responded to each below.

We agree with the authors that capturing every case of postoperative DI is a difficult feat, as DI is likely to be missed in patients who compensate for their increased urine output by drinking more fluids. In future prospective studies in which all pertinent data can be actively collected during the postoperative window, it would be sensible to use a more rigorous diagnostic criterion, such as the one offered by de Vries et al. However, while the use of this method would likely lead to uncovering more DI cases, we feel confident that our study captured all clinically relevant cases of DI, as we included desmopressin (ddAVP) therapy as a diagnostic criterion.

The authors’ questions regarding their previously verified SALT scoring system are intriguing, and we agree that it would be interesting to see if the SALT system was verified by our dataset. In its current version, our database lacks Kelly grading for patients who experienced intraoperative CSF leak, but collecting these data and assessing SALT scores would indeed be an intriguing future study.

Castle-Kirsbaum et al. also note that since postoperative hyponatremia is classically uncovered after DI diagnosis, our findings of hyponatremia following a triphasic/occasionally biphasic response to stalk injury would not help in diagnosing DI, unless a different temporal relationship was seen in our study. We agree that these authors have raised an important question that can be answered by returning to the data to assess the temporal relationship between DI and hyponatremia diagnoses, and we would love to include our findings in a follow-up study.

Finally, Castle-Kirsbaum et al. note how our lower rate of DI among microscopic resections contrasts with the findings of the TRANSSPER Study, in which there were fewer new cases of DI among patients treated with an endoscopic rather than a microscopic resection approach. We agree with the letter writers that this difference in DI rates is likely due to the fact that the endoscopic approach was commonly used in our more complex resection cases, especially so in the early years of our dataset when the technique was first introduced to our center.

We again thank the authors for their insights and questions, and we thank the Journal of Neurosurgery for the opportunity to respond.

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Remission of acromegaly after transsphenoidal surgery

TO THE EDITOR: We read with interest the article by Guo et al.1 (Guo X, Zhang R, Zhang D, et al. Determinants of immediate and long-term remission after initial transsphenoidal surgery for acromegaly and outcome patterns during follow-up: a longitudinal study on 659 patients. J Neurosurg Published online January 14, 2022. doi:10.3171/2021.11.JNS212137). While the article has elaborated all the important factors, we are curious about their experience regarding the value of presurgical medical treatment in immediate and long-term remission. Presurgical medical treatment has been considered an important prognosticator.2 Its efficacy needs to be evaluated for its benefits versus costs. In fact, there are studies that have advocated the cost-effectiveness of presurgical medical treatment especially in centers lacking optimal surgical results.3 In our experience, remission without adjuvant therapy has rarely been noted. Since we work under limited resources, presurgical medical therapy is not affordable for most of our patients and is usually prescribed only after surgery, so we do not have much experience with its value in acromegaly as a determinant of short-term and long-term remission. We really want the authors to share their experience with presurgical medical treatment as well as their view regarding postoperative medical therapy.

We also want to inquire into the authors’ experience and view regarding the value of growth hormone (GH) nadir after an oral glucose tolerance test (OGTT) versus insulin-like growth factor 1 (IGF-1) levels in predicting remission. Researchers believe that IGF-1 levels may fluctuate and settle late as compared to GH levels. In the postoperative evaluation of patients with acromegaly 1 week after resection, it has been shown that an OGTT using 0.5 μg as the GH nadir cutoff value has a high predictive value, whereas early IGF-1 levels show varying patterns toward stabilization. This makes IGF-1 levels unsuitable as an early predictive parameter within 3 months postresection, so the free IGF-1 level may only have additional value in the postoperative assessment of disease activity.4

Another study has indicated that postoperative day 1 GH and short-term postoperative IGF-1 levels can be used to successfully predict immediate and long-term hormonal remission, respectively. A cutoff GH level on postoperative day 1 can help to identify patients who are likely to require adjuvant therapy, with GH levels ≥ 1.55 ng/ml indicating a failure of remission from resection alone (59% specificity, 75% sensitivity).5 Our experience is similar. We want to know the authors’ recommendation for a predictive scoring system.

Their article is really well written and informative, thus leading to more queries and ideas. While the authors have mentioned cavernous sinus invasion, we believe that specifying the Knosp grades of the tumors would enhance the value of the paper for the readers. The publication is excellent and interesting on the whole. Congratulations again.

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Disclosures
The authors report no conflict of interest.

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Response
We thank Dr. Maria and colleagues for their interest and comments regarding our article.

Transsphenoidal surgery (TSS) is the primary and first-line treatment option in most acromegaly patients.1 Resection of the GH-secreting pituitary adenoma relieves tumor burden, reduces hormone levels, improves quality of life, and extends patient survival.1,2 For a patient with...
residual intrasellar tumor following initial TSS, repeat surgery is the first consideration. Medical treatment using somatostatin analogs (SSAs) or dopamine agonists and radiotherapy is applied to patients who have a low chance of surgical remission or those who refuse repeat surgery. In this study, SSAs were given for at least half a year after adjuvant radiotherapy following initial TSS to control hormone levels before the radiation started to take effect. Many patients with recurrent acromegaly undertake lifelong medical treatment. Generally, about one-third of patients cannot attain endocrine remission despite all kinds of traditional treatments.

Whether presurgical treatment with SSAs improves postoperative remission in acromegaly is controversial. Studies have suggested that presurgical medical treatment predicts improvement in postoperative remission and has advocated its high cost-effectiveness. However, data are conflicting, and in many instances results were not sustained during long-term follow-up. The 2014 Endocrine Society guideline recommends against the routine use of presurgical medical therapy to improve biochemical control after surgery. Peking Union Medical College Hospital (PUMCH) is the China Pituitary Disease Registry Center and the founder of the China Pituitary Adenoma Specialist Council. We stuck to the Endocrine Society guideline and did not routinely apply presurgical medical treatment. The 659 acromegaly patients enrolled in this cohort from PUMCH neurosurgery were all untreated before surgery. However, the comments from Maria and colleagues were interesting, and we hope to design and conduct a randomized clinical trial soon, taking advantage of the large number of annual surgical cases at our institute and further verifying this point.

Criteria for biochemical control of acromegaly have changed during the past 2 decades thanks to the popularization of ultrasensitive GH assays. A GH nadir < 1 ng/ml after an OGTT was initially defined as the marker of postoperative remission in 2000; subsequently, in 2010, this recommendation was revised to 0.4 ng/ml. We agree with Maria and colleagues that circulating IGF-1 has a relatively long half-life period and that its concentration may fluctuate especially during the early postoperative months. Therefore, IGF-1 is not an ideal parameter within the first 3 postoperative months to indicate long-term remission. On the contrary, GH, which has a short half-life of about 20–30 minutes, can reflect the real-time endocrine changes after surgery. There have been some articles, as indicated by Maria and colleagues, focusing on the prediction of long-term remission using the hormone values from days after surgery, in which the authors have explored and verified hormone cutoff values to predict long-term prognosis. However, most of these studies were based on retrospective or small cohorts and could not provide high-level evidence into clinical practice.

In addition to the postoperative hormone levels, tumor invasiveness in the cavernous sinus, age at diagnosis, sex, and surgical technique, as demonstrated in this study, are also significant determinants of long-term remission after initial TSS in acromegaly. Since some of the determinants, including age, sex, and tumor invasiveness, are unchangeable, more importance should be attached to improving the modifiable factor, that is, the TSS. Improving our surgical skills and applying endoscopy to appropriate patients, instead of paying excessive attention to the postoperative hormone levels, are the most important tips to improve the long-term prognosis of acromegaly patients.

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Latin American collaboration in international neurotrauma registries: a strategy from the academy

TO THE EDITOR: We read with great interest the article published by Mediratta et al. in which the authors investigated the barriers to access to neurotrauma care services in low- to middle-income countries, showing alarming indicators on the risk of expense and impoverishment due to the cost of services, delays in timely care, and long distances to reach specialized centers, among others (Mediratta S, Lepard JR, Barthélémy EJ, et al. Barriers to neurotrauma care in low- to middle-income countries: an international survey of neurotrauma providers. J Neurosurg. Published online December 24, 2021. doi:10.3171/2021.9.JNS21916). These data are interesting and important under the new goals of global neurosurgery and the Lancet Commission on Global Surgery, both in the short term and the long term. They also demonstrate...
the need to develop rapid and effective strategies for calculating the real incidence, prevalence, and burden of disease generated by neurotrauma in these countries and to prioritize the design of academic, policy, and healthcare solutions for the population, targeting the barriers and conditions that need it most. For this, we propose a strategy that comes from the institution: the inclusion of neurosurgery student interest groups in the international registry of neurotrauma.

In Latin America, neurotrauma registries are scarce and contain underreporting. Some of the difficulties identified in designing an adequate registry are the presence of incomplete clinical data, limited resources, lack of support in technology and data processing software, lack of time, lack of motivation of human resources, and delays in ethics committee approval. However, these projects may be planned in hospitals but not in association with academic collaboration with universities. A solution would be to include potential personnel trained in neurotrauma research and theory; such personnel could be undergraduate students involved in neurosurgery student interest groups at universities.

Medical interest groups consist of academic collectives composed primarily of medical students with an interest in a particular discipline, which arise from the idea of promoting theoretical, practical, professional, and research training in a student’s specialty of interest. These groups have gained visibility for the output and impact they have had on emerging evidence and postgraduation student outcomes, with neurosurgery being one of the fields with the best results. Agarwal et al. evaluated the impact that the American Association of Neurological Surgeons Medical Student Chapters have had on the productivity and professional development of these students, noting a marked increase in the number of groups between 2014 and 2019 (from 12 to 121). Students involved in these groups increased their participation in peer-reviewed scientific publications in medical journals, participated more in scientific events (p = 0.02), submitted more abstracts (p = 0.06), had a higher number of accepted abstracts (p = 0.09), and had a higher success rate for admission to residency. In general, participation in student interest groups in neurosurgery and in research projects is a double gain for both students and research neurosurgeons, since it facilitates the execution and completion of studies. These results are similar to those published in other areas of medicine, which have attempted to replicate this model in Latin America, supporting its usefulness and maintenance.

Considering that more and more new registries and studies are proposed to improve the quality of neurotrauma information, the challenges to guarantee quality results are even greater. Solutions to these challenges are as follows. 1) Medical students have more time available, so they would be the researchers responsible for complete and adequate collection of primary data. 2) Students are motivated to integrate into neurosurgery departments and in the production of evidence in their field of interest. 3) Students have access to academic and research tools provided by universities, which facilitates access for other professionals as well. 4) Within the interest groups, mentoring and participation as authors in original studies is a common objective, which would be an excellent opportunity to achieve this goal. In these cases, professors and specialists would be primarily responsible for managing patient flow and identifying potential cases to include.

The constitution of an academic research network between medical student interest groups, universities, and hospitals in Latin America would be a solution to have an adequate number of motivated researchers in charge of data collection and processing, in addition to having the support of bibliographic and scientometric resources offered by universities on access to academic databases and technological tools. Funding can also be provided for the dissemination of results at national and international scientific events, increasing the likelihood of strengthening the interinstitutional participation of other researchers who are not familiar with the registry. This—not to mention that students belonging to a particular interest group, in this case, future neurosurgeons—would improve their skills and research interests and contribute to the production of new knowledge and engage with global neurosurgery. Already relying on the evidence reported by Agarwal et al. and Anampa-Guzmán et al., even better results are expected to be obtained, as there is an ongoing competition from undergraduate medical schools in Latin America. This is a low-cost, easy-to-replicate strategy from academia that would support the integral development of future neurosurgeon researchers.

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**Response**
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