Anatomic Variations in Pituitary Endocrinopathies: Implications for the Surgical Corridor

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Abstract

Objectives/Hypotheses Functioning pituitary adenomas may produce endocrinopathies such as acromegaly and Cushing syndrome. Both conditions lead to characteristic anatomic variations as a result of hormonally induced abnormal soft tissue deposition. We evaluate the anatomic differences between acromegalics and Cushing disease patients and compare these dimensions to controls.
Design Radiographic review of preoperative magnetic resonance images (MRI) of the pituitary gland.
Setting Tertiary academic medical center.
Participants Patients who underwent transnasal, transsphenoidal surgery for pituitary adenomas found to have acromegaly or pituitary Cushing between January 1, 2007 and September 1, 2015. A total of 15 patients with similar MRIs and no history of pituitary or sinonasal disease were selected as controls.
Main Outcome Measures Dimensions assessed were intercarotid distance; carotid canal width; piriform aperture width; distance from the piriform aperture to the anterior face of the sphenoid; sphenoid sinus height, width, and length; angle from anterior nasal spine to anteroinferior face of sphenoid sinus; choanal height; and nasal cavity height at the level of the vertical segment of the middle turbinate. Sphenoid sinus pneumatization patterns were recorded.
Results There were 30 acromegalics and 31 Cushing disease patients. When compared with controls, both acromegalics and Cushing disease patients had significantly wider piriform apertures and a longer distance from the piriform aperture to the anterior face of the sphenoid sinus ($p < 0.05$). Acromegalics had a significantly less acute angle (19 ± 3 degrees) from the anterior nasal spine to the sphenoid ($p < 0.05$). Cushing disease patients had significantly lower sphenoid sinus length and shorter nasal cavity height ($p < 0.05$). There were no differences in intercarotid distance or carotid canal width.

Keywords
- pituitary endocrinopathy
- anatomy
- radiology

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Conclusions As acromegalics and Cushing disease patients have known anatomic variations, the skull base surgeon should be aware of these differences and adapt their techniques and approaches as needed.

Introduction

Since the advent and widespread adoption of endoscopic techniques in skull base surgery, the transnasal, transsphenoidal surgical (TNTS) approach has become prominent in the surgical management of pituitary tumors. For this reason, an intense area of research interest has been in defining the limits and boundaries of the endoscopic surgical corridor; namely, the reach of the endoscope and instrumentation with special care to protect critical structures within a confined space (e.g., carotid artery, cranial nerves).[1–5] Particularly of interest is the relationship of these anatomic structures to the surgical field. For instance, numerous anatomic and radiographic studies have attempted to quantify the intercarotid artery distance at the clivus as a means to establish the safe boundaries for pituitary surgery.[6–8]

The majority of pituitary adenomas are "functioning," with acromegaly (growth hormone excess) and Cushing disease (adrenocorticotropic hormone excess) representing two unique pathologies for hormonal excess that lead to significant endocrinopathies.[9] Both conditions lead to characteristic anatomic variations of the head and neck as a result of hormonally induced abnormal soft tissue deposition.[10,11] Especially in the case of acromegalics undergoing TNTS, anatomic variations, namely, a deeper surgical corridor and a reduced intercarotid artery distance, have been previously reported.[8,12–14] On the other hand, there is a paucity of data in the literature regarding anatomic variations in patients with Cushing disease. In any case, otolaryngologists and neurosurgeons who perform endoscopic skull base surgery should be aware of such anatomic variations and their implications for the surgical corridor, modifying their technique and approach as needed. In this study, we radiographically evaluate the sellar anatomic differences between acromegalics and Cushing disease patients, and compare these dimensions to patients without pituitary adenomas and/or sinus disease.

Methods

An institutional review board approval was obtained for this study. We performed a retrospective chart review of all patients who underwent TNTS at a tertiary academic medical center for functioning pituitary adenomas on clinical history and physical examination, then confirmed on histopathologic analysis, between January 1, 2007 and September 1, 2015. All patients with preoperative magnetic resonance imaging (MRI) of the pituitary performed for surgical planning were included in the study. Patients with concomitant nonseptal, nonturbinate, sinonasal disease as seen on imaging (e.g., chronic rhinosinusitis, encephalocele, sinonasal tumors) were excluded. All pituitary MRI studies included a volumetrically acquired three-dimensional spoiled gradient echo contrast-enhanced T1-weighted sequence, with 1 mm isotropic voxel size. This was performed as an axial acquisition parallel to the planum sphenoidale, with coronal and sagittal reformations. Controls consisted of patients with MRI studies performed for non-pituitary, nonsinonasal disease, which also included volumetric sequences reformatted into sagittal and coronal planes. Epidemiological data, including age, sex, height, weight, and body mass index, were collected.

Radiographic measurements were performed on the picture archiving and communication system (PACS) planning station utilizing the ruler tool. Those dimensions with possible bilateral measurements (indicated by asterisks below) were performed on both the left and right sides independently and averaged. In all cases, the widest dimension of each measurement on inspection of all cuts of the scan was chosen. Depending on the anatomic dimension of interest, measurements were performed on axial (►**Fig. 1**), sagittal (►**Fig. 2**), or coronal (►**Fig. 3**) views. Dimensions measured included the following:

- Intercarotid distance (ICD): measured on axial sections between the most medial extent of the clival carotids as they appear parallel in the sella
- Carotid canal width* (CCW): measured on axial sections spanning the transverse width of each clival carotid as they appear parallel in the sella
- Piriform aperture width (PAW): measured on axial sections between the most medial extent of the anterior maxillae at the base of the nose
- Distance from piriform aperture to anterior face of sphenoid* (PAS): measured on axial sections from the lateral wall of the piriform sinus to the ipsilateral anterior face of the sphenoid sinus
- Sphenoid sinus height (SH): measured on sagittal sections from the planum sphenoidale to the floor of the sphenoid sinus
- Sphenoid sinus width (SW): measured on axial sections between the most lateral extents of the sphenoid sinus; intersinus septa do not serve as dividing points
- Sphenoid sinus length (SL): measured on sagittal sections from the anterior face of the sphenoid sinus to the bony sellar face
- Angle from anterior nasal floor to anteroinferior face of sphenoid sinus (NFS angle): measured on sagittal sections from the anterior nasal spine to the anteroinferior face of the sphenoid sinus (as an approximation of the natural ostium of the sphenoid sinus); this angle has been traditionally reported as being 30 degrees[15]
- Choanal height (CH): measured on sagittal sections at the same cut as NFS angle as the vertical distance from the floor of the nose at the level of the choana to the anteroinferior face of the sphenoid sinus

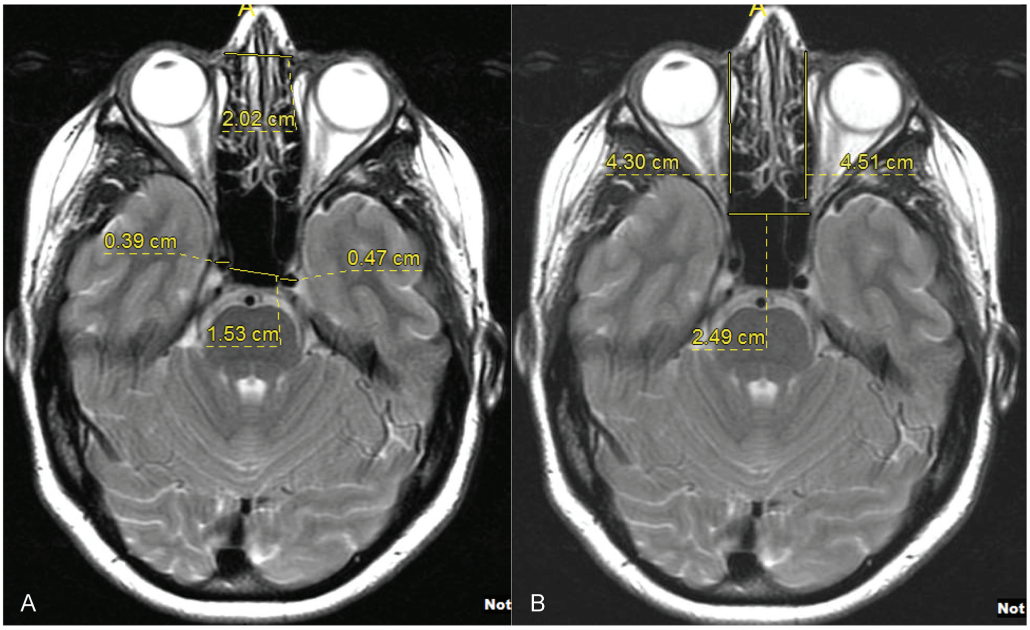

Fig. 1 Measured anatomic dimensions on axial view. These include, on the left side **(A)**, the intercarotid distance (1.53 cm), left carotid canal width (0.47 cm), right carotid canal width (0.39 cm), and piriform aperture width (2.02 cm); and on the right side **(B)**, the distance from piriform aperture to anterior face of left sphenoid sinus (4.51 cm); the distance from the piriform aperture to the anterior face of right sphenoid sinus (4.30 cm); and the sphenoid sinus width (2.49 cm).

- Nasal cavity height* (NCH): measured on coronal sections from skull base to the nasal floor at the level of the vertical segment of each middle turbinate
- Sphenoid sinus pneumatization patterns (conchal, presellar, sellar, and postsellar) were additionally recorded based on the system developed by Hamberger et al[16]
- The presence of Onodi cells, regardless of side, was also recorded

Each patient underwent a TNTS procedure with the senior authors (M. B. and M. B. W.). A previous study performed at our institution demonstrated that a modified approach to the sella, without routine maxillary antrostomy, nasoseptal flap elevation, and middle turbinectomy, improved postoperative sinonasal outcomes and recovery times.[17] Thus, the standard technique for TNTS utilized for all patients in this study is the transnasal approach, medial to the middle turbinates with

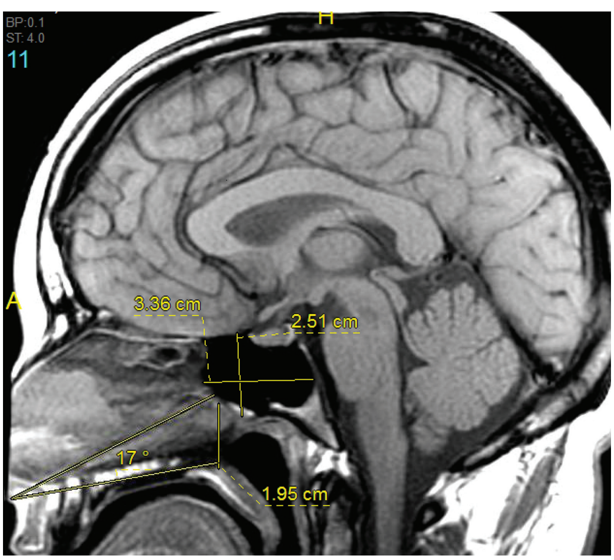

Fig. 2 Measured anatomic dimensions on sagittal view. These include sphenoid height (2.51 cm), sphenoid length (3.36 cm), choanal height (1.95 cm), and the angle from the anterior nasal spine to the anteroinferior face of the sphenoid sinus (17°). Sphenoid sinus pneumatization can also be determined from this view (in this case, sellar).

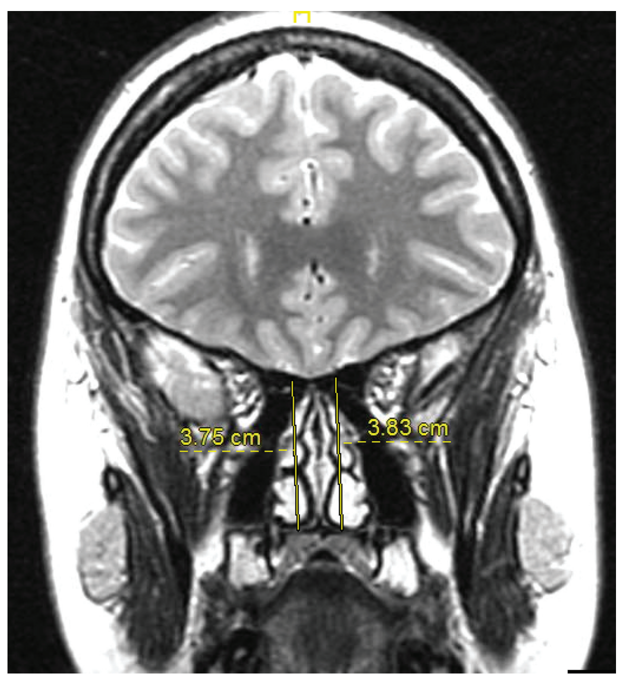

Fig. 3 Measured anatomic dimensions on coronal view. These include the left and right nasal cavity heights (3.83 and 3.75 cm, respectively).

turbinate preservation, followed by direct access to the natural sphenoid ostium. A posterior septectomy is performed to expose the sella widely and improve the surgical corridor.

To establish independent interrater reliability for review of the scans, each of the three scan reviewers (E. C. W., F. Y., K. W. B.) performed the full set of radiographic measurements using the PACS system on 10 patients (2 controls, 4 acromegalics, 4 Cushing disease patients). Intraclass correlation coefficients (ICC) were calculated for ICD, CCW, PAW, PAS, SL, NFS angle, CH, and NCH based on these measurements.

Statistical analysis for determining relationships between continuous variables was performed using two-tailed Student *t*-tests, while those involving categorical data were compared using chi-square tests. A significance level of 0.05 was used in all cases.

Results

A total of 15 controls, 30 acromegalics, and 31 Cushing disease patients were included in the study. The interrater agreement amongst the three independent reviewers was fair to substantial (ICC = 0.21–0.61). The summary statistics and comparisons between groups are denoted in ►**Table 1**. Acromegalics had a decreased intercarotid distance (1.50 cm) as compared with controls (1.63 cm) and Cushing disease patients (1.60 cm), but this difference was not significant. When compared with controls, both acromegalics and Cushing disease patients had wider piriform apertures and a longer distance from the piriform aperture to the anterior face of the sphenoid sinus. Acromegalics had a significantly less acute angle (19 $\pm$ 3 degrees) from the anterior nasal spine to the anterior sphenoid face. Cushing disease patients had decreased sphenoid sinus length and shorter nasal cavity height.

Discussion

In contrast to the microscope, the endoscope affords the skull base surgeon a dynamic view of the surgical corridor, with the ability to superiorly visualize structures around corners and advance deeper into the field. At the same time, utilizing a two-surgeon, four-handed approach permits fine dissection within this dynamic field. As in all cases of surgery, proper knowledge of the surrounding anatomy is critical for patient safety. Thus, endoscopic skull base surgeons must be well aware of anatomic variations as a result of the disease process that they are treating. Of these conditions, acromegaly and Cushing disease are of special significance due to their associated endocrinopathies. In this study, we present a comparison of anatomic dimensions important in endoscopic skull base surgery among acromegalics, Cushing disease patients, and controls.

Multiple previous studies have explored anatomic differences in acromegalics, most notably the association with medialized carotid canals at the clivus. In a case–control analysis of 45 patients, Ebner et al found that ICD was narrower (1.64 cm) and CCW was thicker (0.71 cm) when compared with controls.[6] Mascarella et al, in another radiographic study of 212 patients with sellar and parasellar lesions, determined that acromegalics were more likely to be associated with a narrower ICD (1.59 vs. 1.77 cm in controls).[7] Finally, Carrabra et al found a similar relationship that did not reach statistical significance (1.48 cm).[8] The current study found an ICD among acromegalics similar in measurement to the above (1.50 cm), but which was not significantly different from normal controls. A proposed mechanism for this medialization phenomenon (as well as widening of the carotid canals) is multifactorial, including alterations in vascular anatomy and chronic arterial hypertension.[6] Equally plausible is the chronic effects of excess growth hormone on soft tissue, where thickening of the soft tissue layers surrounding the clival and cavernous carotids push them closer to one another toward the midline. No previous reports attempting to characterize ICD and CCW in Cushing disease patients have been made, and the current study did not find any differences from controls. Regardless of cause and a standardized value, decreased ICD should be considered in all cases of TNTS intended for surgical management of acromegaly, as intraoperative carotid injury, though rare, is potentially devastating.[18] Aside from a careful review of preoperative imaging, one additional strategy is to dissect through the sellar face layer-by-layer and refer to intraoperative Doppler ultrasound to precisely map out the course of the carotid arteries relative to the surgical field. Depending on surgeon preference, the intraoperative image guidance may also be helpful in this endeavor. Of course, in cases of extremely medialized carotids ($<$ 1 cm ICD), consideration may be given to an open approach.

Carrabra et al additionally explored unique sphenoid pneumatization patterns in acromegalics.[8] They found that, among 23 acromegalics, the presellar or conchal pattern accounted for 26% of cases, whereas the sellar pattern was present in 74% of the cases (there were no postsellar cases).[8] In contrast, within our cohort of acromegalics, the presellar, sellar, and postsellar patterns accounted for 10, 23, and 67% of cases, while the Cushing cohort had prevalences of 7, 38, and 55%, respectively (there were no conchal cases). Furthermore, there has been conflicting evidence in the literature regarding what the most common pneumatization pattern is. In aggregating two radiographic studies and one cadaver study, among 530 patients evaluated, the most prevalent pneumatization pattern was sellar (49%), followed by postsellar (34%), presellar (15%), and conchal (2%).[4,19,20] Fortunately, sellar and postsellar patterns make up the majority of cases, providing direct access to the sellar face without the need for extensive drilling. There appears to be no association with less favorable sphenoid pneumatization patterns among acromegalics or Cushing disease patients.

Related to sphenoid pneumatization, fine sellar and parasellar dissection within the sphenoid sinus is partially limited by the anteroposterior diameter of the sphenoid sinus (sphenoid length). This dimension has been reported to be shorter in acromegalics, though the current study did not find a difference from controls.[8,14] On the other hand, sphenoid length seems to be decreased in Cushing disease patients (2.20 vs. 2.68 cm in controls). The more important technical

Table 1 Epidemiological data, descriptive statistics, and inferential comparisons for radiographic dimensions for controls, acromegalics, and Cushing disease patients

Variable	Subject groups			*p* Value		
	Control ($n = 15$)	Acromegaly ($n = 30$)	Cushing disease ($n = 31$)	Control vs. acromegaly	Control vs. Cushing disease	Acromegaly vs. Cushing disease
Age (y)	50.67 ± 17.15 (25–75)	45.57 ± 13.16 (16–68)	41.59 ± 14.20 (17–72)	0.27	0.06	0.26
Sex				0.75	0.09	0.008[a]
Male	5 (33%)	12 (40%)	3 (10%)			
Female	10 (67%)	18 (60%)	28 (90%)			
Height (in)	66.33 ± 4.29 (60–75)	68.95 ± 4.66 (61–78)	64.66 ± 2.82 (60–69)	0.08	0.12	< 0.001[a]
Weight (kg)	81.07 ± 16.16 (48–109)	91.45 ± 14.73 (63–126)	85.92 ± 19.38 (52–142)	0.04[a]	0.41	0.22
BMI (kg/m^2)	28.57 ± 5.92 (19–41)	29.91 ± 4.49 (21–40)	31.90 ± 7.23 (17–46)	0.40	0.13	0.20
ICD (cm)	1.63 ± 0.23 (1.19–1.98)	1.50 ± 0.41 (0.85–2.75)	1.60 ± 0.30 (0.94–2.34)	0.26	0.73	0.28
CCW (cm)	0.54 ± 0.16 (0.28–0.84)	0.52 ± 0.14 (0.30–1.00)	0.55 ± 0.10 (0.22–0.75)	0.67	0.80	0.34
PAW (cm)	1.72 ± 0.42 (1.22–2.62)	2.31 ± 0.25 (1.85–2.89)	1.98 ± 0.36 (1.22–2.88)	< 0.001[a]	0.04[a]	< 0.001[a]
PAS (cm)	4.47 ± 0.48 (3.68–5.53)	4.96 ± 0.52 (3.56–6.30)	4.82 ± 0.44 (3.80–5.80)	0.003[a]	0.02[a]	0.26
SH (cm)	2.26 ± 0.49 (1.64–3.50)	2.48 ± 0.50 (1.73–3.75)	2.41 ± 0.32 (1.87–3.11)	0.17	0.22	0.52
SW (cm)	3.21 ± 0.84 (2.30–5.28)	3.29 ± 0.93 (2.16–5.90)	3.07 ± 0.56 (2.25–4.77)	0.78	0.50	0.27
SL (cm)	2.68 ± 0.53 (1.70–3.44)	2.72 ± 0.73 (0.59–3.58)	2.20 ± 0.62 (1.17–3.25)	0.85	0.01[a]	0.004[a]
NFS angle (°)	24.33 ± 7.61 (17–45)	19.21 ± 2.74 (12–24)	22.03 ± 3.51 (15–29)	0.002[a]	0.17	0.001[a]
CH (cm)	2.20 ± 0.32 (1.54–2.69)	2.26 ± 0.24 (1.80–2.97)	2.08 ± 0.34 (1.45–2.81)	0.48	0.26	0.02[a]
NCH (cm)	4.92 ± 0.57 (3.90–6.09)	4.82 ± 0.51 (3.94–5.72)	4.58 ± 0.44 (3.75–5.51)	0.55	0.03[a]	0.05
Sphenoid pneumatization				0.28	0.58	0.47
Conchal	0	0	0			
Presellar	0	3 (10%)	2 (7%)			
Sellar	6 (40%)	7 (23%)	11 (38%)			
Postsellar	9 (60%)	20 (67%)	16 (55%)			
Onodi cells				0.09	0.04[a]	0.68
Yes	6 (40%)	5 (17%)	4 (13%)			
No	9 (60%)	25 (83%)	27 (87%)			

Abbreviations: BMI, body mass index; CCW, carotid canal width; CH, choanal height; ICD, intercarotid distance; NCH, nasal cavity height; NFS angle, angle from anterior nasal floor to anteroinferior face of sphenoid sinus; PAS, distance from the piriform aperture to the anterior face of sphenoid; PAW, piriform aperture width; SH, sphenoid sinus height; SL, sphenoid sinus length; SW, sphenoid sinus width
Note: Values, whenever possible, are listed in format of mean ± standard deviation (minimum–maximum).
[a]Statistical significance at the 0.05 level.

point in consideration of sphenoid length is limiting the early-step sphenoidotomies to only the anterior face of the sphenoid sinus bilaterally. Inadvertent "past-pointing" during the sphenoidotomy risks premature breaching of the sellar face and places lateral sellar structures (i.e., carotid artery, optic nerve) at risk.

We found that both acromegalics and Cushing disease had an increased distance from the piriform aperture to the anterior face of the sphenoid sinus. For acromegalics, these results are corroborated by Carrabra et al and Saeki et al.[8,13] The direct impact of this is a significantly deeper surgical cavity, requiring further insertion of the endoscope and instruments through the nasal cavity to adequately reach the anterior face of the sphenoid sinus. At the same time, there is an increased probability of "sword fighting" between instruments. One ameliorating factor for both acromegalics and Cushing disease patients, as previously noted by Saeki et al,[13] is that they both tend to have wider piriform apertures. With this in mind, some of these challenges with deep surgical access may be overcome with longer instrumentation, though there are certainly still limitations in maneuvering these instruments with ease proximally. Additionally, ease of instrument maneuvering may be improved in cases of deep surgical fields by further increasing the surgical corridor through modifications to the surgical approach, such as by middle turbinectomy or via an expanded transethmoid approach to the sella. Though these techniques may not be ideal due to possible associated worsened sinonasal outcomes,[17] they can be considered for these patients where gross total resection of the tumor may outweigh the risks of sinonasal morbidity.

Traditional teaching based on early anatomic studies resulted in the widely accepted canon of identifying the natural ostium of the sphenoid sinus at an angle 30 degrees from the anterior nasal spine.[15] More recent cadaver studies have reaffirmed this finding, deeming the angle to be both 5 degrees above and below 30 degrees in the majority of cases.[21] Practically, there is likely no exact way to navigate to the natural ostium strictly based on estimating this angle. In this study, controls demonstrated a similar NFS angle (24 ± 8 degrees) as quoted in the literature. Interestingly, in accordance with having a deeper surgical corridor, acromegalics appear to have a much less acute angle (19 ± 3 degrees). Although unlikely to affect the surgical approach, the realization of this variation and working toward the sphenoid sinus based on fixed landmarks remains the safe standard.

Given the rarity of both acromegaly and Cushing disease, we can only perform radiographic analysis on a small sample size despite our institution having completed more than 650 TNTS procedures during the study period. For the same reason, it was not possible to match cases with controls with respect to potential confounders (e.g., significantly more females in the Cushing group). Though this somewhat limits the precision of data, this study remains the first to systematically quantify anatomic variations in Cushing patients, and assess these differences as they compared with acromegalics and controls. Additionally, due to the rarity of these conditions within the general population, there naturally is a limitation to the strength of the conclusions made from this study. Further studies with a larger patient cohort to evaluate these findings are warranted. Finally, though slight deviations away from the standard plane may occur, they are generally no more than a few degrees of difference in the tilt. Measurements were taken in planes that were felt to be most reproducible, from scan to scan, and less affected by slight variations in scan angle. Controls, acromegalics, and Cushing disease patients were reviewed and measured using the same technique to reduce systematic bias.

Conclusion

As acromegalics and Cushing disease patients have distinct anatomic variations affecting the endonasal surgical corridor, the skull base surgeon should be aware of these differences and adapt their techniques and approaches as needed. In acromegalics, the presence of medialized carotid arteries, a deeper surgical field, and a less acute angle to the sphenoid ostium are common variations. Cushing disease patients tend to have a deeper surgical field and decreased sphenoid length, underscoring the importance of meticulous dissection along the anterior face of the sphenoid sinus.

Note
This study was presented as a Poster of Distinction at the 25th Annual Meeting of the North American Skull Base Society; February 13, 2016, Scottsdale, AZ.

Financial Disclosures
None.

Conflict of Interest
None.

Level of Evidence
Not applicable.

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