Cushing’s disease arises from functioning adrenocorticotropic hormone (ACTH)–secreting adenomas. These tumors can be very small and evade detection by MRI. Empty sella syndrome is a phenomenon by which an arachnoid outpouching of CSF into the sella leads to compression of the pituitary, likely due to intracranial hypertension (a common issue in Cushing’s disease), further leading to difficulty in visualizing the pituitary gland that may contribute to difficulty in finding a tumor on MRI, so-called MRI-negative Cushing’s disease. The authors sought to examine the association between empty sella syndrome and MRI-negative Cushing’s disease.

METHODS A single-institution database of Cushing’s disease cases from 2000 to 2017 was reviewed, and 197 cases were included in the analysis. One hundred eighty patients had a tissue diagnosis of Cushing’s disease and 17 had remission with surgery, but no definitive tissue diagnosis was obtained. Macroadenomas (tumors > 1 cm) were excluded. The degree of empty sella syndrome was graded on the degree of CSF visualized in the sella on midline sagittal T1-weighted MRI.

RESULTS Of the 197 cases identified, 40 (20%) presented with MRI-negative disease, and empty sella syndrome was present in 49 cases (25%). MRI-negative disease was found in 18 (37%) of 49 empty sella cases versus 22 (15%) of 148 cases without empty sella syndrome present. Empty sella syndrome was significantly associated with MRI-negative disease (OR 3.32, 95% CI 1.61–6.74, p = 0.0018). Decreased thickness of the pituitary gland was also associated with MRI-negative disease (mean thickness 5.6 vs 6.8 mm, p = 0.0002).

CONCLUSIONS Empty sella syndrome is associated with an increased rate of MRI-negative Cushing’s disease. Pituitary compression causing a relative reduction in the volume of the pituitary for imaging is a plausible cause for not detecting the tumor mass with MRI.

https://thejns.org/doi/abs/10.3171/2020.3.FOCUS2084

KEYWORDS Cushing’s disease; empty sella syndrome; pituitary compression

ABBREVIATIONS ACTH = adrenocorticotropic hormone; CI = confidence interval; OR = odds ratio.

SUBMITTED January 31, 2020. ACCEPTED March 3, 2020.

INCLUDE WHEN CITING DOI: 10.3171/2020.3.FOCUS2084.
surgery in the case of MRI-negative disease, this approach leads to an obvious degree of uncertainty, as manipulation of the pituitary gland may lead to a temporary correction in cortisol levels with a subsequent return to disease, and leads to increased disruption of the normal gland when compared to a focused excision of a visualized tumor.15,17 Inferior petrosal sinus sampling can be used to assess the laterality of an occult adenoma, but does not allow for definitive visualization of the lesion, and may be more useful for confirming a pituitary origin of disease rather than confirming lesion laterality.15,23

Empty sella syndrome, the appearance of a CSF-filled sella, is fundamentally a misnomer. It, in fact, results from an outpouching of arachnoid membrane compressing the pituitary gland and creating the impression of a CSF-filled space on MRI.10 The compression of the gland impairs the ability to visualize potential abnormalities on MRI, and may mask the presence of an otherwise discernable microadenoma. Indeed, primary empty sella syndrome (not resulting from postsurgical changes to the sella) can cause derangements in pituitary function in and of itself.5,14 Previous studies have attempted to codify the extent of CSF protrusion into the sella and grade the degree of empty sella syndrome.13,20,24 Empty sella syndrome has been correlated with increased intracranial pressure and spontaneous CSF leakage.14 Empty sella syndrome is frequently an incidental finding on MRI, but has been implicated in pathologic compression of the pituitary gland.7,8,22 We sought to determine whether the presence and degree of empty sella syndrome was associated with MRI-negative disease in patients with Cushing’s disease, which may account for difficulty in viewing a tumor on MRI when it is secondarily compressed.

**Methods**

**Study Population**

IRB approval was obtained from the Mayo Clinic Rochester for collection and review of patient data. An institutional database and tissue bank was reviewed for cases of Cushing’s disease from 2000 to 2017. Cases in which a tissue diagnosis of Cushing’s disease was obtained or in which transsphenoidal surgery resulted in disease remission were included. Cases in which disease recurred following surgery or in which no preoperative MRI was available for review were excluded. Patients with refractory disease ultimately requiring adrenalectomy were also excluded. Demographic data including patient age, sex, and tumor size (micro- or macroadenoma with a cutoff of 1 cm), were also collected, with macroadenomas excluded from subsequent analysis.

**Data Collection**

Empty sella cases were identified by independent review of preoperative MRI scans by two of the authors (B.T.H., A.G.B.), and cases included by consensus. An empty sella was defined as CSF protrusion into the sella across a line drawn across the diaphragm sella, and the grade of empty sella was measured by the length of a plumb line from this diaphragmatic line to the edge of the CSF protrusion divided by a second plumb line drawn to the edge of the sella, as described by Saindane and colleagues.13 Sample measurements are illustrated in Fig. 1. Empty sella grades were determined based on the percentage of CSF by these measurements as follows: grade I (normal, no CSF), grade II (1%–33% CSF), grade III (34%–66%), grade IV (67%–99%), and grade V (100% CSF, no detectable pituitary tissue). Pituitary thickness was measured on these same midsagittal sections.

**Statistical Analysis**

Statistical analysis was performed in Microsoft Excel 2016 and Prism 8 (GraphPad Software), with odds ratios (ORs) and 95% confidence intervals (CIs) used to report associations with MRI-negative disease and empty sella syndrome. A p value < 0.05 was considered significant. For comparison of categorical variables, chi-square analysis was performed. A Student t-test was used to compare continuous variables involving two groups, and for three or more groups a 1-way ANOVA was performed.

**Results**

Review of a single-institution database and tissue bank records of Cushing’s disease cases identified 197 unique cases meeting inclusion criteria during the review period (2000–2017). One hundred sixty (81%) of 197 patients were female, with a median age of 40 years at the time of diagnosis (range 7–82 years). Demographic data are summarized in Table 1. One hundred eighty patients had
a tissue diagnosis of Cushing’s disease based on review of pathology reports and tissue bank records. The remaining 17 included patients demonstrating long-term disease remission following transsphenoidal surgery. Forty cases (20%) were read as negative for adenoma on preoperative MRI. Empty sella syndrome was present in 49 cases (25%), while the remaining 148 cases had detectable microadenomas (tumor size <1 cm). MRI-negative disease was present in 18 (37%) of 49 empty sella cases, whereas only 22 (15%) of 151 cases without evidence of empty sella syndrome failed to demonstrate a lesion on MRI. Cases with evidence of CSF extension into the sella were graded I–V as described above. Representative images of grades I–IV are presented in Fig. 2. No grade V cases, in which the pituitary gland was completely obscured by CSF, were identified in this series. The grading breakdown is summarized in Table 1.

An empty sella of any grade was associated with a negative preoperative MR image (OR 3.32, 95% CI 1.61–6.74, p = 0.0018, Fisher’s exact test; Table 2). MRI-negative disease was also associated with reduced pituitary gland thickness, with MRI-negative cases averaging 5.6 mm in thickness versus 6.8 mm in MRI-positive cases (p = 0.0002, Student t-test). This effect persisted when we restricted our analysis to include only cases of empty sella syndrome (mean 4.2 mm in MRI-negative cases vs 6.8 mm in MRI-positive cases, p < 0.0001, Student t-test). Higher grades of empty sella (III and IV, 43 cases) were not associated with a higher likelihood of a negative preoperative MR image when compared to lower-grade (grade II) empty sella (OR 1.18, 95% CI 0.25–6.76, p = 0.99, Fisher’s exact test). Furthermore, the presence of empty sella syndrome alone, without accounting for MRI findings, was not associated with failure to obtain a tissue diagnosis (OR 1.74, 95% CI 0.6–5.16, p = 0.377, Fisher’s exact test). These findings are summarized in Table 2. We also failed to note any association between empty sella grade and the severity of Cushing’s disease as determined by preoperative BMI (p = 0.6302, 1-way ANOVA). However, there was a clear and significant trend toward a higher proportion of MRI-negative cases in those with higher grades of empty sella syndrome. MRI-negative disease was present in only 15% (22/148) of cases with no empty sella, but this proportion increased to 33% (2/6) with grade II empty sella, 35% (13/37) with grade III empty sella, and 50% (3/6) with grade IV empty sella (p = 0.0008, chi-square test for trend; Table 3).

**Discussion**

Effective surgical management of Cushing’s disease presents an unusual challenge in neurosurgery. Definitive surgery is typically curative; however, the frequency of ectopic sources of ACTH secretion and the often-small size of these tumors creates uncertainty when the tumor cannot be adequately visualized on MRI prior to surgical exploration of the gland. These cases require a thorough exploration of the gland, damaging healthy tissue without assurance of finding the pathologic lesion. Frequently, a successful surgical exploration will not yield sufficient tissue for a definitive diagnosis, as adenoma tissue can be quite soft and aspirated at the time of surgery. This creates obvious uncertainty in preoperative planning, but also in the postoperative course, in which manipulation and trauma to the gland may cause a transient improvement in cortisol levels, only with disease to return shortly thereafter. Resection of a portion of the pituitary may yield improvement in hypercortisolism, but cure is not certain. Pituitary surgery is also not without risks and complications, particularly the risks of CSF leaks, hypopituitarism, and diabetes insipidus, as well as more rare complications including damage to the carotid artery. After unsuccessful surgery, whether due to an inability to identify a small adenoma or an extrapituitary source of ACTH secretion, patients will frequently proceed to adrenalectomy, requiring lifelong endocrinological management. For these reasons, it is essential to be as certain as possible as to the

**TABLE 1. Demographic data**

| Variable                          | Value |
|----------------------------------|-------|
| No. of patients                  | 197   |
| Female, n (%)                    | 160 (81) |
| Median age in yrs (range)        | 40 (7–82) |
| MRI-negative disease, n (%)      | 40 (20) |
| Empty sella, any grade, n (%)    | 49 (25) |
| Grade II                         | 6 (3)  |
| Grade III                        | 37 (19) |
| Grade IV                         | 6 (3)  |
| Confirmed tissue diagnosis, n (%)| 180 (91) |

**FIG. 2.** MRI-negative Cushing’s disease. Representative sagittal T1-weighted MR images of empty sella grades included in this series. A: Grade I, normal pituitary, not empty sella. B: Grade II, 1%–33% CSF. C: Grade III, 34%–66% CSF. D: Grade IV, 67%–99% CSF. No cases of grade V (no detectable pituitary tissue) were found in our series.
presence of a pituitary adenoma prior to proceeding with surgery.

Frequently, empty sella syndrome is an incidental finding, an anatomical variant wherein the arachnoid membrane pushes into the sella, allowing CSF pulsations to compress the gland. However, this compression may potentially obscure the presence of a small adenoma within the gland by reducing the overall volume of the gland to visualize on standard sellar imaging. This could potentially be due to either direct compression of a small adenoma or sufficient compression of the surrounding pituitary tissue to obscure contrast with the tumor. Furthermore, compression of the gland may lead to a change in blood flow dynamics losing the ability to detect an adenoma due to differential contrast uptake. If one could decompress the gland prior to preoperative MRI, this could potentially improve visualization of subtle abnormalities within the gland prior to surgical exploration, although this is speculative. Interestingly, reports examining empty sella syndrome in the context of idiopathic intracranial hypertension have demonstrated reversal of the empty sella appearance with interventions such as acetazolamide therapy, lumboperitoneal shunting, and lumbar puncture. In these cases, restoration of normal sellar appearance was believed to be due to alteration of intracranial pressure, which suggests that this could also be feasible in the setting of pituitary adenomas.

Although the etiology of empty sella syndrome continues to be debated, it is clear that CSF dynamics and elevated intracranial pressure play a role in this phenomenon. One study reported that a significant proportion of patients with symptomatic empty sella syndrome exhibit CSF circulation impairment or blockage. Unsurprisingly, the presence of an empty sella has been correlated with conditions marked by increased intracranial pressure, such as benign intracranial hypertension. Obesity has also been linked to empty sella syndrome in benign intracranial hypertension due to increased intraabdominal pressure, leading to increased cardiac filling pressures and subsequent impaired venous return from the brain. Given that obesity is often a characteristic feature of patients with Cushing’s disease, it would be important to consider whether similar mechanisms (i.e., increased abdominal pressure) could contribute to empty sella syndrome in this patient population as well. It is worth noting that despite the association between empty sella syndrome and obesity, weight reduction does not always lead to resolution of the empty sella, suggesting that direct approaches to CSF diversion may be of greater utility. Understanding potential contributors such as obesity leading to increased intracranial pressure may offer additional guidance regarding specific interventions that may improve visualization of sellar contents in patients with concomitant empty sella syndrome, Cushing’s disease, and pituitary adenomas, which continues to be a challenge despite new imaging approaches.

### Conclusions

In our series we demonstrated a significant association between any degree of empty sella syndrome and the presence of MRI-negative Cushing’s disease, and a significant trend associating increased empty sella grade with MRI-negative disease. All cases included in our series demonstrated either tissue diagnosis of Cushing’s disease or postoperative remission, indicating an occult microadenoma as the source of disease despite a negative preoperative MR image. There are limitations to this study that are worthy of note, including its retrospective design and small sample size, which limits analysis of empty sella grades at a granular level. While empty sella measurements were performed separately by two authors based on stringent guidelines, the potential for bias in grading emp-
ty sella cases remains as the reviewers had knowledge of which cases represented MRI-negative disease based on the original radiology report. Our findings, however, may indicate an opportunity for intervention in cases of Cushing’s disease in which a concomitant empty sella may obscure an underlying adenoma. We believe it may be worth exploring the value of interventions such as pre-imaging lumbar puncture or a lumbar drain as a means to reduce the CSF compression of the gland to improve visualization on MRI in cases of MR-negative Cushing’s disease.

References

1. Brismar K, Bergstrand G: CSF circulation in subjects with the empty sella syndrome. *Neuroradiology* 21:167–175, 1981
2. Carr SB, Kleinschmidt-DeMasters BK, Kerr JM, Kiseljak-Vassiliades K, Wierman ME, Lillehei KO: Negative surgical exploration in patients with Cushing’s disease: benefit of two-thirds gland resection on remission rate and a review of the literature. *J Neurosurg* 129:1260–1267, 2018
3. Chatan GP, Patronas N, Smirniotopoulos JG, Piazza M, Benzo S, Ray-Chaudhury A, et al: Potential utility of FLAIR MRI in Cushing’s disease. *J Neurosurg* 129:620–628, 2018
4. D’Alessandris QG, Montano N, Bianchi F, Doglietto F, Fernandez E, Pallini R, et al: Persistence of primary empty sella syndrome despite obesity surgery: report of two unusual cases. *Br J Neurosurg* 26:875–876, 2012
5. De Marinis L, Bonadonna S, Bianchi A, Maira G, Giustina A: Primary empty sella. *J Clin Endocrinol Metab* 90:5471–5477, 2005
6. Etxabe J, Vazquez JA: Morbidity and mortality in Cushing’s disease: an epidemiological approach. *Clin Endocrinol* (Oxf) 40:479–484, 1994
7. Evans RW: Incidental findings and normal anatomical variants on MRI of the brain in adults for primary headaches. *Headache* 57:780–791, 2017
8. Guitelman M, Garcia Basavilbaso N, Vitale M, Chervin A, Katz D, Miragaya K, et al: Power of inferior petrosal sinus catheterization in Cushing’s disease. A single-center experience. *Clin Endocrinol* 83:260–267, 2015
9. Herman V, Fagin J, Gonsky R, Kovacs K, Melmed S: Clonal origin of pituitary adenomas. *J Clin Endocrinol Metab* 71:1427–1433, 1990
10. Kistler M, Chereda D, Vazquez JA, et al: MRI investigation of the brains of healthy young men. *J Neurol Sci* 218:144–146, 2004
11. Liotta M, Fagin J, Kerschner KE, et al: Pituitary adenomas: a clinicopathologic analysis. *Clin Neuropathol* 23:175–179, 2004
12. Liu T, Ma L, Zhao H, et al: FLAIR imaging of pituitary morphology in idiopathic intracranial hypertension. *J Magn Reson Imaging* 47:1033–1039, 2018
13. Liu H, Li J, Liang J, et al: MR imaging of pituitary morphology in idiopathic intracranial hypertension. *J Magn Reson Imaging* 47:1033–1039, 2018
14. Liu T, Ma L, Zhao H, et al: FLAIR imaging of pituitary morphology in idiopathic intracranial hypertension. *J Magn Reson Imaging* 47:1033–1039, 2018
15. Liu H, Li J, Liang J, et al: MR imaging of pituitary morphology in idiopathic intracranial hypertension. *J Magn Reson Imaging* 47:1033–1039, 2018
16. Sugerman HJ, DeMaria EJ, Felton WL, III, Nakatsuka M, Sismanis A: Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. *Neurology* 49:507–511, 1997
17. Sun Y, Sun Q, Fan C, Shen J, Zhao W, Guo Y, et al: Diagnosis and therapy for Cushing’s disease with negative dynamic MRI finding: a single-centre experience. *Clin Endocrinol (Oxf)* 76:868–876, 2012
18. Triggiani V, Giagulli VA, Moschetta M, Guastamacchia E: An unusual case of reversible empty sella. *Endocr Metab Immune Disord Drug Targets* 16:154–156, 2016
19. Tritos NA, Biller BM, Swearengen B: Management of Cushing disease. *Nat Rev Endocrinol* 7:279–289, 2011
20. Wang Q, Guo X, Gao L, Wang Z, Deng K, Lian W, et al: Surgical outcome of growth hormone-secreting pituitary adenoma with empty sella using a new classification. *World Neurosurg* 105:651–658, 2017
21. Wang Z, Xing B: Detection of MRI-negative Cushing’s disease by FLAIR imaging: is it reliable? *J Neurosurg* 129:839–841, 2018 (Letter)
22. Weber F, Knoefler H: Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 240:51–84, 2006
23. Wind JJ, Lonser RR, Nieman LD, DeVroom HL, Chang R, Oldfield EH: The localization accuracy of inferior petrosal sinus sampling in 501 patients with Cushing’s disease. *J Clin Endocrinol Metab* 98:2285–2293, 2013
24. Yuh WT, Zhu M, Taoka T, Quets JP, Maley JE, Muhonen MG, et al: MR imaging of pituitary morphology in idiopathic intracranial hypertension. *J Magn Reson Imaging* 12:808–813, 2000
25. Zagardo MT, Cail WS, Kelman SE, Rothman MI: Reversible empty sella in idiopathic intracranial hypertension: an indicator of successful therapy? *AJNR Am J Neuroradiol* 17:1953–1956, 1996

Disclosures

Dr. Bancos reports being a consultant to CLinCor, HRA Pharma, and Corcept.

Author Contributions

Conception and design: Van Gompel, Himes. Acquisition of data: Himes, Bancos. Analysis and interpretation of data: Van Gompel, Himes, Bancos. Statistical analysis: Himes, Study supervision: Van Gompel. Manuscript preparation: Van Gompel. Manuscript review: All authors. Approved the final version of the manuscript on behalf of all authors: Van Gompel.

Supplemental Information

Previous Presentations

Portions of this work were presented as an e-poster at the 2019 AANS Annual Scientific Meeting in San Diego, California, April 13–17, 2019.

Correspondence

Jamie J. Van Gompel: Mayo Clinic, Rochester, MN. vangompel.jamie@mayo.edu.