JNS

CLINICAL ARTICLE

J Neurosurg 124:589–595, 2016

Improved versus worsened endocrine function after transsphenoidal surgery for nonfunctional pituitary adenomas: rate, time course, and radiological analysis

***Arman Jahangiri, BS, Jeffrey R. Wagner, BS, Sung Won Han, BS, Mai T. Tran, MD, MPH, Liane M. Miller, BS, Rebecca Chen, BS, Maxwell W. Tom, BS, Lauren R. Ostling, MD, Sandeep Kunwar, MD, Lewis Blevins, MD, and Manish K. Aghi, MD, PhD**

Department of Neurosurgery and The California Center for Pituitary Disorders, University of California, San Francisco, California

OBJECTIVE The impact of transsphenoidal surgery for nonfunctional pituitary adenomas (NFAs) on preoperative hypopituitarism relative to the incidence of new postoperative endocrine deficits remains unclear. The authors investigated rates of hypopituitarism resolution and development after transsphenoidal surgery.

METHODS Over a 5-year period, 305 transsphenoidal surgeries for NFAs performed at The California Center for Pituitary Disorders were retrospectively reviewed.

RESULTS Patients with preoperative endocrine deficits (n = 153, 50%) were significantly older (mean age 60 vs 54 years; $p = 0.004$), more frequently male (65% vs 44%; $p = 0.0005$), and had larger adenomas (2.4 cm vs 2.1 cm; $p = 0.02$) than patients without preoperative deficits (n = 152, 50%). Of patients with preoperative endocrine deficits, 53% exhibited symptoms. Preoperative deficit rates were 26% for the thyroid axis; 20% and 16% for the male and female reproductive axes, respectively; 13% for the adrenocorticotropic hormone (ACTH)/cortisol axis, and 19% for the growth hormone (GH)/ insulin-like growth factor-1 (IGF-1) axis. Laboratory normalization rates 6 weeks and 6 months after surgery without hormone replacement were 26% and 36% for male and 13% and 13% for female reproductive axes, respectively; 30% and 49% for the thyroid axis; 3% and 3% for the cortisol axis; and 9% and 22% for the IGF-1 axis ($p < 0.05$). New postoperative endocrine deficits occurred in 42 patients (13.7%). Rates of new deficits by axes were: male reproductive 3% (n = 9), female reproductive 1% (n = 4), thyroid axis 3% (n = 10), cortisol axis 6% (n = 19), and GH/IGF-1 axis 4% (n = 12). Patients who failed to exhibit any endocrine normalization had lower preoperative gland volumes than those who did not ($0.24\ cm^3$ vs $0.43\ cm^3$, respectively; $p < 0.05$). Multivariate analyses revealed that no variables predicted new postoperative deficits or normalization of the female reproductive, cortisol, and IGF-1 axes. However, increased preoperative gland volume and younger age predicted the chances of a patient with any preoperative deficit experiencing normalization of at least 1 axis. Younger age and less severe preoperative hormonal deficit predicted normalization of the thyroid and male reproductive axes ($p < 0.05$).

CONCLUSIONS After NFA resection, endocrine normalization rates in this study varied with the hormonal axis and were greater than the incidence of new endocrine deficits. Low preoperative gland volume precluded recovery. Patient age and the severity of the deficiency influenced the recovery of the thyroid and male reproductive axes, the most commonly impaired axes and most likely to normalize postoperatively. This information can be of use in counseling patients with hypopituitarism who undergo NFA surgery.

http://thejns.org/doi/abs/10.3171/2015.1.JNS141543

KEY WORDS hypopituitarism; pituitary surgery; endocrine deficits; nonfunctional adenoma

ABBREVIATIONS ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GnRH = gonadotropin-releasing hormone; IGF-1= insulin-like growth factor-1; LH = luteinizing hormone; NFA = nonfunctional adenoma; T4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

SUBMITTED October 10, 2014. **ACCEPTED** January 13, 2015.

INCLUDE WHEN CITING Published online August 7, 2015; DOI: 10.3171/2015.1.JNS141543.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

* Mr. Jahangiri and Mr. Wagner contributed equally to this work.

Nonfunctional pituitary adenomas occur quite commonly in the general population, with a prevalence ranging from 10% to 20% based on both autopsy and healthy volunteer MRI studies.[8,14,15] Patients with nonfunctional adenomas (NFAs) large enough to cause symptoms present with a variety of complaints, one of which is hypopituitarism, but asymptomatic endocrine deficits may also be found on the laboratory workup of patients presenting with other indicators like headache or visual deficits. The incidence of hypopituitarism in any 1 axis in patients with NFAs has been reported to range from 69% to 85%.[13,16] This hypopituitarism is believed to result from compression and destruction of the pituitary gland by the expanding lesion, while focal necrosis resulting from compression of the portal vessels and pituitary stalk may also play a role.[1] The few studies that have investigated individual axes have suggested that the incidence of deficits caused by NFAs varies by axis,[5,17] with some authors theorizing that differential robustness of cells in the normal pituitary gland leads to a growing adenoma, which results in the following sequence of endocrine deficits: 1) growth hormone (GH), 2) luteinizing hormone (LH)/follicle-stimulating hormone (FSH), 3) thyroid, and 4) cortisol.[12]

The true incidence of endocrine recovery following the resection of an adenoma is challenging to assess, because many patients receive hormonal replacement therapy when an adenoma diagnosis is made but without an attempt to assess postoperative endocrine function in the absence of hormone replacement. Studies investigating whether pituitary function improves at all after transsphenoidal surgery for NFAs without specifying individual axes have reported considerably variable rates, ranging from at most 20% of patients[16,18] to up to 50% of patients.[3,6] Studies that have examined endocrine recovery by a specific axis after NFA surgery[1,5,13,17] have suggested that recovery varies by axis from 13% to 57%. These studies have identified factors associated with improvement in general (smaller adenomas, normal or slightly elevated prolactin, gross-total resection, and lack of tumor invasion) and improvement in individual axes (preoperative rise in serum thyroid-stimulating hormone [TSH] in response to thyrotropin-releasing hormone [TRH] stimulation; rise in serum LH after gonadotropin-releasing hormone [GnRH] stimulation). However, these studies were performed using smaller cohorts of 35–126 patients without a multivariate analysis to rule out interactions between analyzed variables.[1,13,17]

To address the normalization in endocrine deficits by individual axes after transsphenoidal surgery for a large cohort of NFAs, and to identify risk factors independently associated with normalization, the authors of the current study analyzed endocrine function before and after more than 300 consecutive transsphenoidal surgeries for NFAs conducted since the establishment of a dedicated pituitary center 5 years ago.

Methods

Study Design, Setting, and Participants

A retrospective review was conducted of 305 consecutive endonasal pituitary operations for NFAs on the first 282 patients treated in the 5 years since the California Center for Pituitary Disorders, a dedicated multidisciplinary center of pituitary expertise, was established. NFA was defined as tumor specimens staining negative for GH, prolactin, and adrenocorticotropic hormone (ACTH), with each of these stains performed on all adenomas resected at the center. The Institutional Committee on Human Research at the University of California, San Francisco, reviewed and approved this study.

Preoperative Variables Recorded

The parameters collected after review of the medical records included age, sex, lesion size, number of prior pituitary surgeries, confirmed endocrinological inactive pathology, endonasal surgical approach (295 microscopic vs 10 endoscopic operations), lesion location (sellar, suprasellar, or sellar with suprasellar extension), and preoperative laboratory values (LH/FH/testosterone available for 100 males, ACTH/cortisol available for 248 patients, GH/IGF-1 available for 162 patients, FSH/estradiol available for 71 females, and TSH/free thyroxine [T4] available for 239 patients). Preoperative MR images that could be uploaded and had paired 6-month postoperative MR images that could also be uploaded (25 patients without preoperative endocrine deficits, 41 patients with endocrine deficits who improved postoperatively, and 20 patients with endocrine deficits who failed to improve postoperatively) were used to assess the volume of normal pituitary gland and pituitary adenoma. These images were measured by 2 independent observers (J.R.W. and M.K.A.) using AWServer software (GE Healthcare) to outline areas of normal gland and adenoma on sequential coronal images. Preoperative hypopituitarism was defined based on normal reference ranges by axis from the University of California at San Francisco Department of Laboratory Medicine: 1) low free T4 (< 10 pmol/L) with normal or low TSH (< 4.12 mIU/L); 2) low estradiol (< 30 pg/ml) with low FSH (< 20 IU/L) in premenopausal females or FSH < 26 IU/L in postmenopausal females; 3) low testosterone (< 141 ng/dl) with normal or low FSH and LH (< 12 mIU/L); 4) cortisol < 4 μg/dl; and 5) IGF-1 < 217 μg/L (16–20 year-old females), < 281 μg/L (16–20 year-old males), < 87 μg/L (21–30 year-old females), < 155 (21–30 year-old males), < 106 μg/L (31–40 year-old females), < 132 μg/L (31–40 year-old males), < 118 μg/L (41–50 year-old females), < 121 μg/L (41–50 year-old males), < 53 μg/L (51–60 year-old females), < 68 μg/L (51–60 year-old males), < 75 μg/L (61–70 year-old females), < 60 μg/L (61–70 year-old males), < 54 μg/L (> 70 year-old females), or < 36 μg/L (> 70 year-old males). Patients lacking laboratory values for a particular axis were excluded from the analysis of whether that particular axis improved.

Postoperative Variables Recorded

Per institutional protocol, all patients regardless of preoperative endocrine function were discharged on dexamethasone steroid replacement, which was then discontinued for 48 hours prior to testing at 6-week and (if needed) 6-month follow-up visits. Postoperative assessment of resolution of a hormone deficit that was observed preoperatively involved checking (in the absence of hormone replacement) for: 1) normalization of free T4 and TSH (> 0.45 mIU/L) (assessable in 158 of 199 patients with preoperative central hypothyroidism); 2) normalization of FSH/estradiol (assessable in 22 of 71 females with a preoperative deficit); 3) normalization of FSH/LH/testosterone (assessable in 72 of 100 males with a preoperative deficit); 4) 8:00 AM cortisol > 10 μg/dl or ACTH-stimulated cortisol > 20 μg/dl (assessable in all 178 patients with preoperative deficits); and 5) normalization of GH/IGF-1 (assessable in 110 of 162 patients with preoperative deficits). Patients lacking laboratory values for a particular axis were excluded from the analysis of whether that particular axis improved. Postoperative MR images that could be uploaded were used to assess normal gland volume as described above.

Statistical Methods

Analysis of variance was used for parametric comparisons of more than 2 variables when the dependent variable was continuous. A chi-square test was used to compare more than 2 proportions. Parametric comparison between 2 variables was performed using the Student t-test. The Fisher's exact test was used to compare 2 proportions. Spearman's correlation coefficient was used to assess the correlation between gland volume and tumor volume. Binary logistic regression was used to correlate preoperative variables with the presence of an endocrine deficit or normalization of individual endocrine axes. All 2-way interaction terms were included to assess whether any pairs of these predictor variables interacted, but they did not, allowing the multivariate logistic regression to be used without concern for confounding interactions. All p values were 2-tailed, and those p values < 0.05 were considered statistically significant.

Results

Study Cohort

Over a 5-year period, 305 transsphenoidal operations were conducted on 282 patients with NFAs with a mean patient age of 57 years (range 16–93 years). There were 170 male patients (60%). Mean lesion size was 2.2 cm (range 3 mm to 7.1 cm).

Characterization of Preoperative Endocrine Deficits

In analyzing the 305 operations, it was found that all patients had some recorded assessment of anterior pituitary function, with 153 patients (50%) having a preoperative endocrine deficit of some kind. Patients with preoperative endocrine deficits were more likely to be older (mean age 60 vs 54 years; p = 0.004), male (64% male vs 36% female; p = 0.0005), and have larger NFAs (mean diameter 2.4 cm vs 2.1 cm, p = 0.02; mean volume 7.3 cm^3 vs 4.9 cm^3, p = 0.009) than patients without any preoperative endocrine deficits. Normal pituitary gland volume did not significantly differ between patients with (0.31 cm^3) or without (0.36 cm^3) preoperative endocrine deficits (p = 0.6). Also, normal pituitary gland volume did not correlate with tumor volume (p = 0.7). After confirming no interaction between the variables age, sex, and mean tumor diameter in pairs (p = 0.1–0.2), each was confirmed to affect the presence of preoperative endocrine deficits in multivariate analysis (p < 0.05; Table 1). Of those patients with a preoperative endocrine deficit, 81 (53%) of 153 exhibited symptoms, most commonly amenorrhea (20 of 363 premenopausal females), fatigue (n = 32), and decreased libido (n = 18). Rates of preoperative deficits by individual axes were 26% for the thyroid axis; 20% and 16% for male and female reproductive axes, respectively; 13% for the cortisol axis; and 19% for the GH/IGF-1 axis (p < 0.05; Fig. 1).

Rate of Postoperative Hormonal Recovery

In terms of laboratory values, endocrine normalization rates 6 weeks after surgery without hormone replacement were 26% and 13% for the male and female reproductive axes, respectively; 30% for the thyroid axis; 3% for the cortisol axis ; and 9% for the GH/IGF-1 axis (p < 0.05; Fig. 2). Laboratory normalization rates 6 months after surgery without hormone replacement were 36% and 13% for male and female reproductive axes, respectively; 49% for the thyroid axis; 3% for the cortisol axis; and 22% for the GH/IGF-1 axis (p < 0.05; Fig. 2). These data indicate that for 3 of the 5 axes additional patients experienced normalization between 6 weeks and 6 months. None of the patients who attained endocrine normalization between 6 weeks and 6 months exhibited improvement in the deficient laboratory values at 6 weeks. The rate of normalization of gonadal function at 6 months was comparable in patients with and without preoperative hyperprolactinemia (males: 36% and 34%, respectively, p = 0.9; females: 8% and 5%, respectively, p = 0.8), suggesting that resolution of the stalk effect was not contributing to gonadal normalization in either sex.

Factors Predicting any Endocrine Normalization

Mean tumor diameters did not differ between the 73 (66%) of 111 patients exhibiting normalization of any impaired endocrine axis after surgery and the remaining 34% of patients who did not exhibit any postoperative normalization (2.3 cm vs 2.4 cm; p = 0.6). Patients with preoperative endocrine deficits experienced 6-month postoperative expansion of the normal gland (p < 0.001), and patients without preoperative endocrine deficits did not experience 6-month postoperative expansion of the normal gland (p > 0.05). However, patients who did not exhibit any postoperative normalization of any deficient axes after 6 months had smaller preoperative gland volumes (mean 0.24 cm^3)

TABLE 1. Results of binary logistic regression correlating preoperative variables with the preoperative presence of any endocrine deficit

Variable	p Value*	OR
Age at op	**0.01**	1.3
Male sex	**0.01**	1.4
Size (mean diameter)	**0.02**	1.1

OR = odds ratio.
* Variables meeting criteria for statistical significance (p < 0.5) are indicated in bold.

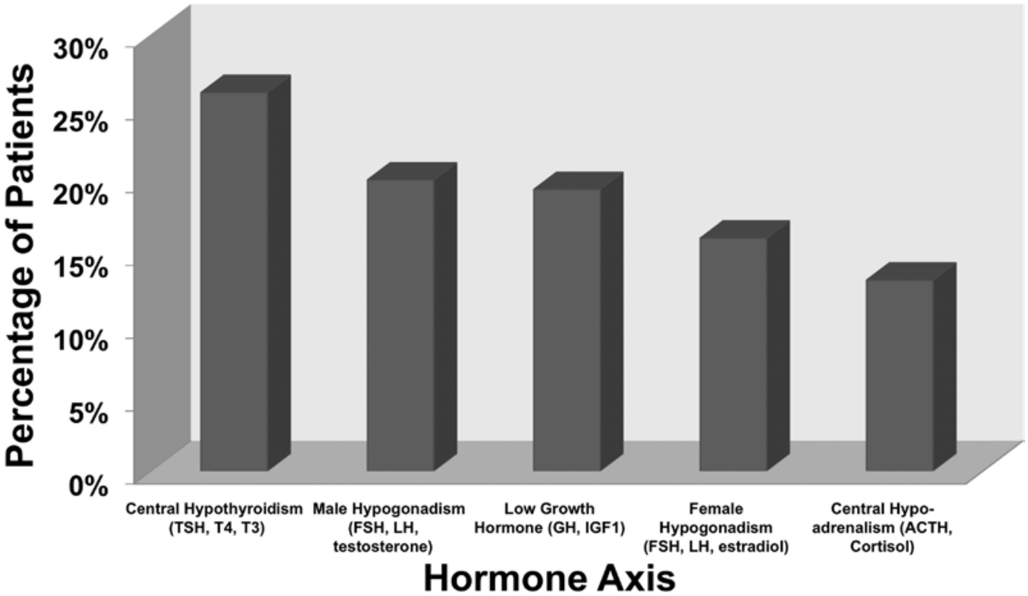

FIG. 1. Bar graph showing the percentage of patients with preoperative hormonal deficits, indicating the incidences of the deficits in NFAs for each of the 5 individual axes assessed. T3 = triiodothyronine.

than either patients who had experienced 6-month postoperative normalization of any impaired endocrine axis (mean 0.43 cm^3) or patients without preoperative endocrine deficits (mean 0.39 cm^3; $p < 0.05$; Fig. 3). In a multivariate analysis, increased preoperative gland volume ($p = 0.02$) and younger patient age ($p = 0.04$) increased the chances of a patient with any preoperative deficit experiencing normalization of at least 1 endocrine axis (Table 2).

Factors Predicting Normalization by Endocrine Axis

In terms of anterior pituitary hormone levels, preoperative FSH < 0.08 IU/L, TSH < 0.05 μIU/ml, or GH < 0.3 μg/L were not corrected with surgery. In terms of downstream hormones, preoperative testosterone < 2.0 ng/dl, estradiol < 9.0 pg/ml, free T4 < 0.3 pmol/L, cortisol < 1 μg/dl, or IGF-1 < 25 μg/L were not corrected with surgery. Multivariate analysis revealed that no variables predicted normalization of the female reproductive, cortisol, and GH/IGF-1 axes, whereas younger patient age at surgery and less severe preoperative hormonal deficit predicted normalization of the thyroid or male reproductive axes ($p < 0.05$; Table 2).

Worsened Endocrine Function After Surgery

New postoperative endocrine deficits occurred in 42 (14%) of 305 cases. New deficits occurred in the following

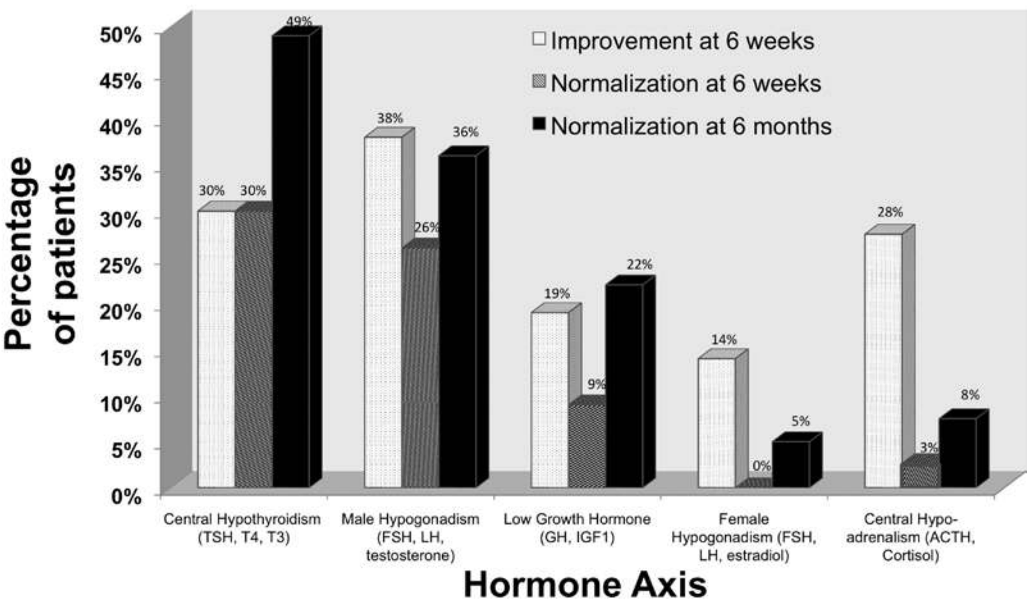

FIG. 2. Bar graph comparing the 6-week and 6-month postoperative endocrine normalization rates for each of the 5 individual axes assessed.

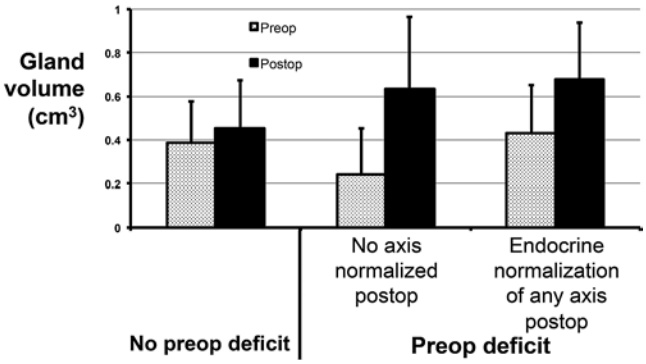

FIG. 3. Bar graph indicating the pituitary gland volumes before and after transsphenoidal surgery for NFAs. These are the normal pituitary gland volumes before and after transsphenoidal surgery for patients who had no preoperative endocrine deficit, patients who experienced improvement of an endocrine deficiency, and patients who did not experience improvement of an endocrine deficiency. Although patients with preoperative endocrine deficits experienced significant postoperative expansion of the normal gland ($p < 0.001$) and patients without preoperative endocrine deficits did not experience significant postoperative expansion of the normal gland ($p > 0.05$), patients who experienced no endocrine improvement had smaller preoperative gland volumes than patients who experienced endocrine improvement in any axis or patients without preoperative endocrine deficits ($p < 0.05$). *Error bars* represent standard deviations.

axes: male reproductive (n = 9, 3%), female reproductive (n = 4, 1%), thyroid (n = 10, 3%), cortisol (n = 19, 6%), and GH/IGF-1 (n = 12, 4%; Fig. 4). Of these new deficits, 36 were noted at the 6-week follow-up evaluation and 6 at the 6-month follow-up evaluation. Multivariate binary logistic regression analysis revealed that age, sex, tumor size, and extent of resection ($p > 0.05$) did not predict an increased risk of developing new postoperative endocrine deficits.

Discussion

Symptoms of NFAs are typically those of mass effect on the pituitary gland, causing hypopituitarism; on the dura, causing headaches; and on the optic apparatus, causing visual deficits. We and others have previously reported rates of improvement of visual symptoms[2,9] and headaches after transsphenoidal surgery for NFAs.[7] This report describes the rate of preoperative deficits by endocrine axis in a large cohort of more than 300 endonasal operations for NFA, the rate at which these deficits improve after surgery, and factors influencing endocrine normalization after surgery.

Although transsphenoidal surgery will invariably be recommended for patients with NFAs, and associated vision loss and headaches can improve in some patients after transsphenoidal resection of NFAs,[7] uncertainty remains as to whether transsphenoidal surgery should be offered to patients with adenomas causing asymptomatic laboratory evidence of hypopituitarism. In this study, variables associated with the possibility of endocrine normalization were younger age at surgery and less severe preoperative hormonal deficits for thyroid or male reproductive axes, which are the most likely axes to exhibit preoperative deficits and to improve postoperatively. These variables will be more favorable when asymptomatic hypopituitarism is identified rather than after a period of observation, an argument in support of offering elective resection for adenoma patients with asymptomatic hypopituitarism in the axes that were found during surgery to be particularly capable of improving (hypothyroidism, hyposomatotropism, and male hypogonadism) before the deficits became symptomatic and patients incurred the inconvenience and cost of hormone replacement. Another endocrinological argument in favor of considering elective surgery for NFAs with asymptomatic hypopituitarism is that the rate of new postoperative endocrine deficits was found to be less than the rate of postoperative resolution of preoperative endocrine deficits, consistent with the surgical technique of resecting an adenoma by developing an interface with the normal gland that can then be preserved and allowed to re-expand.

While this issue was not specifically investigated in this study, other studies have found a high rate of identification of asymptomatic hypopituitarism in patients with smaller lesions such as microadenomas.[13,16] Further studies will be needed to deduce the cost-benefit breakdown of comprehensive preoperative laboratory evaluation regardless of symptoms in patients with NFA. One such study suggested that a single serum prolactin check may be the most cost-effective management strategy for incidentally found pituitary microadenomas,[11] but laboratory costs have changed considerably since that 1997 study.

In terms of expectations when managing patients after NFA surgery, this study also found that deficits in 3 of the 5 anterior pituitary axes (male hypogonadism, hypothyroidism, and hyposomatotropism) experienced significant

TABLE 2. Results of binary logistic regression correlating preoperative variables with the postoperative normalization of endocrine function in each individual axis*

Variable	Any Axis		Thyroid		Cortisol		Female Reproductive		Testosterone		GH/IGF-1	
	p Value	OR	p Value	OR	p Value	OR	p Value	OR	p Value	OR	p Value	OR
Preop gland volume (cm^3)	**0.02**	**1.1**	Not assessable									
Age at op	**0.04**	**0.9**	**0.04**	**0.9**	0.5	0.9	0.3	0.949	**0.04**	**0.9**	0.2	1.1
Male sex	0.8	0.8	0.95	0.01	0.9	0.7	Not applicable		Not applicable		0.3	0.4
Tumor size (mean diameter)	0.3	0.8	0.1	0.3	0.3	0.4	0.4	0.3	0.3	0.6	0.9	0.9
Reoperation vs initial op	0.9	0.5	0.93	0.01	0.94	0.04	0.979	0.01	0.9	1.0	0.98	0.01
GTR relative to STR	0.5	1.3	0.5	0.5	0.6	0.9	0.6	2.3	0.5	0.6	0.4	2.4
Severity of hormonal deficit	Not applicable		**0.02**	**0.975**	0.4	0.91	0.6	0.94	**0.02**	**0.9**	0.1	1.03

* Variables meeting criteria for statistical significance ($p < 0.05$) are indicated in bold.

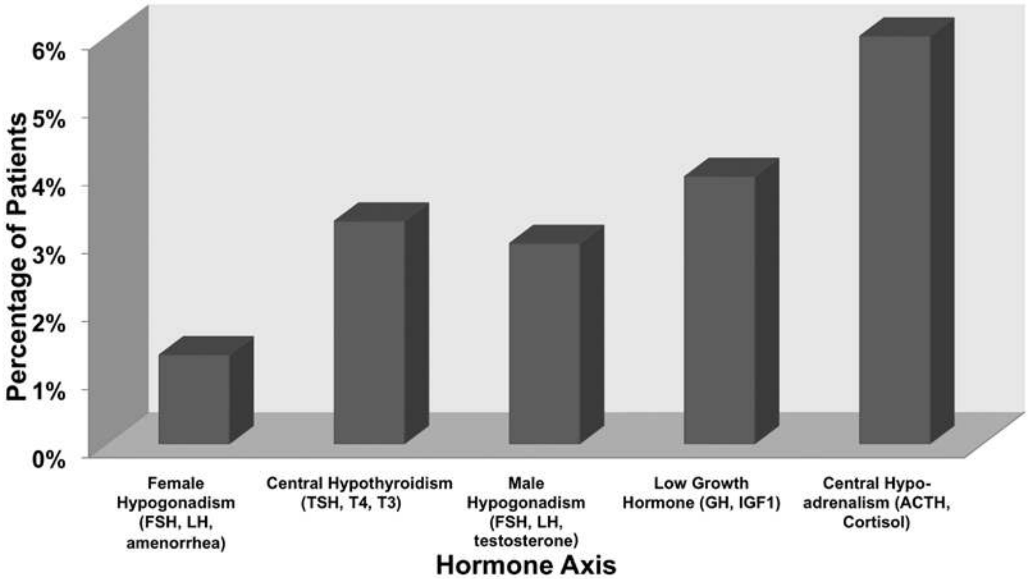

FIG. 4. Bar graph presenting the rates of new postoperative endocrine deficits 6 months after surgery for each of the 5 individual axes assessed.

additional delayed normalization at 6 months after surgery relative to that which was noted at the 6-week postoperative visit. This finding contrasts with previous findings from other sellar and parasellar pathologies, such as Rathke's cleft cysts and craniopharyngiomas, for which delayed normalization after 6 weeks was exceedingly rare.[10]

This study found that tumor, not gland, size predicted the presence of a deficit, while gland, not tumor, size predicted the ability of this deficit to improve, and tumor size and gland size did not correlate. Gland and tumor volume did not inversely correlate because the total space occupied by the gland and tumor is not fixed across patients due to factors such as variable baseline gland sizes in patients (e.g., young women will have larger gland volumes and therefore more residual gland with a 1-cm adenoma than older male and female patients) and differing adenoma growth patterns (e.g., an adenoma growing into the sphenoid sinus may leave more normal gland than a comparably sized adenoma confined to the sella). As to why tumor, but not gland, volume correlated with endocrine deficits, it is possible that the wider range of tumor volumes than gland volumes may allow the former variable to better serve as a marker of endocrine function. Endocrine normalization may reflect the amount of normal gland that the patient presented with regardless of tumor size because regenerative capacity improves with gland volume, perhaps due to more severe tumor-induced compression unable to be reversed or a greater preservation of stem cells[4] in a larger gland volume.

While the findings of the present study emerged from a large-enough cohort of patients with NFA to render them fairly generalizable, the study has limitations. The retrospective nature of this series means that not every endocrine laboratory value was checked preoperatively on every patient. This limitation explains why deficiency in growth hormone, a laboratory value that is not routinely checked among asymptomatic patients, was not one of the most common deficits we observed, even though growth hormone deficiency is conjectured to be the first laboratory deficiency expected from a growing adenoma. As stated above, the cost efficiency of checking a full laboratory panel on all patients with NFAs has yet to be well explored and may be best pursued in a funded prospective clinical trial, which would likely need to be smaller than this large retrospective series. While limiting this study to a single center created homogeneous ranges for normal laboratory values, it is possible that the assays performed at this center may over- or underestimate the incidences of deficits or their normalization relative to findings at other centers.

Conclusions

In this study, postoperative endocrine normalization varied with the hormonal axis with risk factors identified that were specific to each axis. This information from a large cohort with NFA can be used to counsel patients regarding their chances of postoperative endocrine normalization.

References

1. Arafah BM: Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. **J Clin Endocrinol Metab 62:**1173–1179, 1986
2. Berkmann S, Fandino J, Müller B, Kothbauer KF, Henzen C, Landolt H: Pituitary surgery: experience from a large network in Central Switzerland. **Swiss Med Wkly 142:**w13680, 2012
3. Berkmann S, Fandino J, Müller B, Remonda L, Landolt H: Intraoperative MRI and endocrinological outcome of transsphenoidal surgery for non-functioning pituitary adenoma. **Acta Neurochir (Wien) 154:**639–647, 2012
4. Chen J, Hersmus N, Van Duppen V, Caesens P, Denef C, Vankelecom H: The adult pituitary contains a cell population displaying stem/progenitor cell and early embryonic characteristics. **Endocrinology 146:**3985–3998, 2005
5. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J: The clinical and endocrine outcome to trans-

sphenoidal microsurgery of nonsecreting pituitary adenomas. **Cancer 68:**860–866, 1991
6. Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, et al: Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. **Neurosurgery 63:**709–719, 2008
7. Fleseriu M, Yedinak C, Campbell C, Delashaw JB: Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions. **J Neurosurg 110:**354–358, 2009
8. Hardy J: The transsphenoidal surgical approach to the pituitary. **Hosp Pract 14:**81–89, 1979
9. Jahangiri A, Lamborn KR, Blevins L, Kunwar S, Aghi MK: Factors associated with delay to pituitary adenoma diagnosis in patients with visual loss. **J Neurosurg 116:**283–289, 2012
10. Jahangiri A, Wagner J, Han SW, Tran MT, Miller LM, Tom MW, et al: Rate and time course of improvement in endocrine function after more than 1000 pituitary operations. **Neurosurgery 61 (Suppl 1):**163–166, 2014
11. King JT Jr, Justice AC, Aron DC: Management of incidental pituitary microadenomas: a cost-effectiveness analysis. **J Clin Endocrinol Metab 82:**3625–3632, 1997
12. Kravarusic J, Molitch ME: Lymphocytic hypophysitis and other inflammatory conditions of the pituitary, in **Oxford Textbook of Endocrinology and Diabetes.** New York: Oxford University Press, 2011, pp 259–266
13. Marazuela M, Astigarraga B, Vicente A, Estrada J, Cuerda C, García-Uría J, et al: Recovery of visual and endocrine function following transsphenoidal surgery of large nonfunctioning pituitary adenomas. **J Endocrinol Invest 17:**703–707, 1994
14. Molitch ME, Russell EJ: The pituitary "incidentaloma". **Ann Intern Med 112:**925–931, 1990
15. Naidich MJ, Russell EJ: Current approaches to imaging of the sellar region and pituitary. **Endocrinol Metab Clin North Am 28:**45–79, vi, 1999
16. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M: Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas—a study on 721 patients. **Acta Neurochir (Wien) 146:**27–35, 2004
17. Webb SM, Rigla M, Wägner A, Oliver B, Bartumeus F: Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. **J Clin Endocrinol Metab 84:**3696–3700, 1999
18. Wichers-Rother M, Hoven S, Kristof RA, Bliesener N, Stoffel-Wagner B: Non-functioning pituitary adenomas: endocrinological and clinical outcome after transsphenoidal and transcranial surgery. **Exp Clin Endocrinol Diabetes 112:**323–327, 2004

Author Contributions

Conception and design: Jahangiri, Wagner, Blevins, Kunwar, Aghi. Acquisition of data: Jahangiri, Wagner, Han, Tran, Miller, Tom, Chen, Ostling, Kunwar. Analysis and interpretation of data: Aghi. Drafting the article: Aghi, Tran. Critically revising the article: Aghi. Reviewed submitted version of manuscript: Aghi, Blevins.

Correspondence

Manish K. Aghi, The California Center for Pituitary Disorders, University of California, San Francisco, 505 Parnassus Ave., Rm. M779, San Francisco, CA 94143-0112. email: aghim@neurosurg.ucsf.edu.