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Journal of Neurosurgery and Clinical Neurology

Research article

Volume 4 Issue 01

Endocrine outcomes after Endoscopic Transsphenoidal Surgery for Non- Functioning Pituitary Adenomas

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Received date: 05 June 2023; **Accepted date:** 12 June 2023; **Published date:** 20 June 2023

Citation: Dinesh N, Shilin W, Colin TKA, Kwang OY, Lwin S (2022) Endocrine outcomes after Endoscopic Transsphenoidal Surgery for Non-Functioning Pituitary Adenomas. J Neurosurg Clin Neurol 4(1): https://doi.org/10.38207/JNCN/2023/JUN040101

Abstract

Introduction: Non-functioning pituitary adenomas (NFPAs) are common benign tumors that can cause endocrine dysfunction and neurovascular complications. Surgical resection using endoscopic transsphenoidal surgery (ETSS) is a standard treatment for NFPAs, but the rates of postoperative endocrine recovery and new-onset deficits remain uncertain. This study aimed to investigate the rates of preoperative endocrine deficits, postoperative endocrine recovery, and new-onset deficits in patients undergoing ETSS for NFPAs.

Methods: A retrospective review of records was conducted on adult patients who underwent ETSS for NFPAs between 2011 and 2018 at a tertiary neurosurgical institution in Singapore. Preoperative imaging and endocrine assessments were performed, and postoperative endocrine recovery was defined as normalizing biochemical values within six months after surgery. Statistical analysis was performed to identify factors associated with endocrine recovery.

Results: Of the 108 cases, 77.8 % of patients presented with preoperative endocrine deficits. The most common deficiencies were male hypogonadism (64.3 %) and adrenal insufficiency (45.5 %). Rates of recovery varied across axes, with the female gonadal axis showing the highest recovery rate (63.6 %). New-onset postoperative endocrine deficits were observed in various axes, with the cortisol axis being the most affected (53.7 %). Diabetes insipidus occurred in 55.6 % of patients, with larger tumor size and preoperative panhypopituitarism predicting permanent diabetes insipidus.

Conclusion: Patients with NFPAs undergoing ETSS frequently present with preoperative endocrine deficits, and the rates of endocrine recovery vary across axes. New-onset postoperative endocrine deficits are expected, with limited rates of recovery observed. Understanding these factors can help in patient selection and counseling for surgical intervention. Further research is needed to characterize endocrine outcomes better and optimize treatment strategies for NFPAs.

Introduction

Non-functioning pituitary adenomas (NFPAs) are among adulthood's most common benign central nervous system neoplasms, accounting for 15 % of all intracranial tumors, behind meningiomas and gliomas **[1]**. Although NFPAs are hormonally inactive and relatively benign, they have a propensity for growth and expansion and may directly compromise neurovascular structures closely associated with the pituitary gland. In addition, hypopituitarism may also result from direct mechanical compression and ischemia of the pituitary gland or disruption of the adenohypophyseal portal system. Although endocrine deficits are known to be expected in patients with NFPAs **[2]**, the incidence of hypopituitarism by individual endocrine axes varies significantly, and a wide range of rates of anterior hypopituitarism has been reported by previous studies **[3-6]**.

Endoscopic transsphenoidal surgery (ETSS) **[7]** is a standard surgical procedure performed for the resection of NFPAs **[8-10]**. Visual field deficits and compression of the optic chiasm are relatively uncontroversial indications for surgery; however, it is unclear if surgical treatment is indicated for patients presenting solely with endocrine dysfunction **[11]**, as hormonal recovery is uncertain **[12]**, and there is a significant risk of the development of new endocrine deficits. The rates of postoperative endocrine recovery of patients who underwent ETSS are poorly characterized, and the factors associated with recovery are poorly understood.

This study aims to investigate the rates of preoperative endocrine deficits, postoperative endocrine recovery, and new-onset deficits in patients with NFPAs who underwent ETSS to treat NFPAs and to identify factors associated with endocrine recovery.

Methods

This study is a retrospective review of records. Adult patients (aged 21 years and above) who underwent ETSS to treat NFPAs in 2011-2018 at National University Hospital, a tertiary neurosurgical institution in Singapore, were included in our study.

All patients with NFPAs presenting at our institution are managed by a multidisciplinary team, which includes a neurosurgeon, endocrinologist, otorhinolaryngologist, and ophthalmologist.

Preoperative magnetic resonance imaging (MRI) of the pituitary gland is routinely performed for all patients for surgical planning; imaging variables collected for this study are orthogonal tumor dimensions, maximum tumor diameter, presence of radiological hemorrhage, optic chiasm compression, and presence of para sellar or sphenoid sinus invasion.

The preoperative anterior pituitary function is assessed by evaluating the cortisol, thyroid, male gonadal, female gonadal, and growth hormone axes. Data on preoperative prolactin levels were also recorded, if available.

Preoperative adrenal insufficiency was defined as low 8 a.m. cortisol; secondary hypothyroidism as low T4 with low or normal TSH; secondary male hypogonadism as low testosterone with normal or low FSH and LH; and secondary female hypogonadism as low oestradiol with normal or low FSH and LH in premenopausal women, or low FSH in postmenopausal women. Insufficiency of the GH axis was defined as low IGF-1.

Patients who were missing laboratory values for pituitary axes were excluded from the analysis of the recovery of those axes, while patients who were lost to follow-up were excluded from our study entirely.

Postoperative endocrine recovery is normalizing biochemical values within 6 months after surgery.

Neuro-ophthalmologic assessment is also routinely performed for all patients with NFPAs at the study institution and includes visual acuity tests and Humphreys visual fields analysis.

The Domain Specific Review Board, Singapore's national medical research ethics board, has approved this study.

Standard statistical methods were used for analysis, such as the chi-squared test, Fisher's exact test (for categorical variables), and t-test (for continuous variables). Univariable analysis was first used to identify factors significantly associated with the postoperative recovery of each endocrine axis; identified variables were then included in a multivariable logistic regression model as a further test of significance. Two-tailed significance is set at 5 %, and all data were analyzed with SPSS v22.0.

Results

There were a total of 108 cases of NFPAs treated with ETSS; 9 patients had incomplete clinical and biochemical follow-up data and were thus excluded entirely from the study. 99 instances of NFPAs were included in the final analysis.

Preoperative clinical characteristics

Preoperative patient characteristics are shown in Table 1. The mean patient age is 54.3 years (interquartile range 44.9y – 62.6y); 57 % of all patients are male. 95 % of all patients in the study cohort were symptomatic at presentation, and only 5 % of cases were asymptomatic incidentalomas. Typical clinical symptoms are headache (37.4 %), visual field deficits (73.7 %; bitemporal hemianopsia – 45.4 %), and unilateral cranial nerve palsies (9.1 %). A small proportion of patients presented with pituitary apoplexy (8 %). 20 % of all cases were recurrent tumors that had undergone previous surgery, and one-fifth of these cases (4 % of all cases) had undergone previous Gamma Knife surgery.

Preoperative imaging characteristics

The mean maximum tumor diameter is 28.4mm (interquartile range 22.0 – 34.0mm) **(Table 1)**. 16.2 % of the NFPAs in this study cohort had radiological evidence of hemorrhage. 84 % of all tumors were invasive, and 87 % were compressing on the optic chiasm.

Table 1. Pre-operative clinical and imaging characteristics of patients in the study cohort (n=99); continuous data is presented as mean (standard deviation) and interquartile range; categorical data, as n and %.

Patient demographics		
Age	54.3(13.2)	44.9 – 62.6
Sex		
Male	56/99	56.6 %
Female	43/99	43.4 %
Body mass index	26.4(4.9)	22.8 – 29.4
Clinical presentation		
Symptomatic	94/99	94.9 %
Headache	37/99	37.4 %
Visual field deficits	73/99	73.7 %
Cranial nerve palsies	9/99	9.1 %
Incidentalomas	5/99	5.1 %
Pituitary apoplexy	8/99	8.1 %

Recurrent tumours	20/99	20.2 %
Previous pituitary surgery	20/99	20.2 %
Previous Gamma Knife	4/99	4.0 %
Imaging characteristics		
Maximum tumour diameter, mm	28.4(10.0)	22.0 – 34.0
Radiological haemorrhage	16/99	16.2 %
Optic chiasm compression	86/99	86.9 %
Invasion	83/99	83.8 %

Rates and predictors of preoperative anterior hypopituitarism

77.8 % of the patients in the study cohort presented with deficits in at least one endocrine axis. Rates of anterior hypopituitarism by individual axes **(Figure. 1)** are 45.5 % for the adrenal/cortisol axis; 64.3 % for the male gonadal axis; 25.6 % for the female gonadal axis; 27.3 % for the thyroid axis; and 25.3 % for the somatotropic (growth hormone) axis. The growth hormone axis is only routinely assessed in some patients. Hence available data may underestimate the actual rate of deficits of this axis. Rates of anterior panhypopituitarism (defined as involvement of the three principal axes – cortisol, male/female gonadal, and thyroid axes) were 17.2 % in this study cohort. The rate of elevated prolactin (from the stalk effect) was found to be 24.2 %; however, prolactin levels were not routinely measured in all patients.

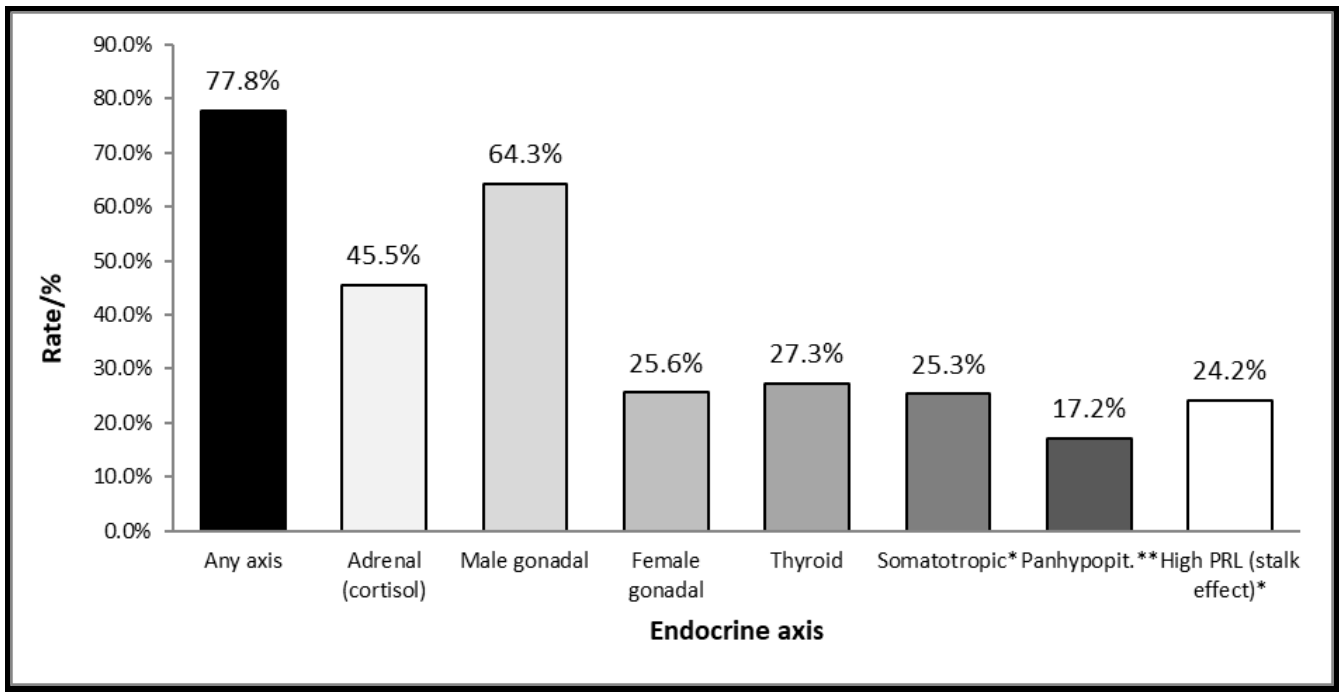

Figure. 1. Rates of preoperative anterior hypopituitarism – endocrine deficits by individual axes. Abbreviations: panhypopit. – panhypopituitarism; PRL – prolactin. Footnotes: *not routinely assessed in all patients, **defined as involvement of the adrenal, gonadal and thyroid axes.

Factors that are predictive of the presence of preoperative deficits in any anterior pituitary axis, as identified on univariable analysis, are **(Table 2)**: male sex (OR 2.90, 95 % CI 1.08 - 7.74, p=0.030), BMI > 23.5 (OR 5.28, 95% CI 1.86 - 15.00, p=0.002) and larger tumor size (maximum tumor diameter ⩾ 23mm; OR 2.74, 95 % CI 1.02 - 7.34, p=0.046). However, after adjusting for possible confounding effects on a multivariable logistic regression model, only BMI > 23.5 remains significant as a predictive variable (adj. OR 4.43, 95 % CI 1.45 – 13.53, p=0.009).

Table 2. Predictors of pre-operative anterior hypopituitarism, as identified on univariable and multivariable (logistic regression) analysis. Abbreviations: 95% CI – 95% confidence interval, adj. OR - adjusted odds ratio; BMI - body mass index; OR - odds ratio.

Variable	OR (95% CI)	p-value	Adj. OR (95% CI)	p-value
Male sex	2.90 (1.08 –7.74)	0.030	2.48 (0.83 – 7.40)	0.105
BMI > 23.5	5.28 (1.86 – 15.00)	0.002	4.43 (1.45 – 13.53)	0.009
Maximum tumour diameter ⩾ 23mm	2.74 (1.02 – 7.34)	0.046	1.32 (0.42 – 4.13)	0.638

Rates of recovery of anterior pituitary function – pre-existing, preoperative endocrine deficits

Rates of resolution of pre-existing preoperative endocrine deficits by individual axes **(Table 3)** are 24.4 % for the cortisol axis, 7.4 % for the thyroid axis, 16.7% for the male gonadal axis, and 63.6% for the female gonadal axis. Prolactin and the growth hormone axis are excluded from analysis as data for these axes is incomplete. Variables significantly predictive of recovery of the cortisol axis are gross total resection (OR 8.25, 95% CI 1.53 - 44.5, p = 0.007) and absence of postoperative diabetes insipidus (OR 6.40, 95 % CI 1.40 - 29.21, p = 0.011), as identified on univariable analysis. Both factors remained significant even after adjusting for confounding effects in a logistic regression model.

Other factors predictive of endocrine recovery include.

- the absence of preoperative visual loss ($p < 0.001$) and lack of chiasmal compression ($p=0.017$) for the thyroid axis,
- incidentalomas for the male gonadal axis ($p=0.023$),
- BMI≤29.0 and absence of postoperative panhypopituitarism for the female gonadal axis ($p=0.048$).

Although these factors are statistically significant, their effect sizes and odds ratios could not be accurately calculated due to zero-cell counts.

Table 3. Rates of recovery of anterior pituitary function – resolution of pre-existing preoperative endocrine deficits, by individual axes. Abbreviations: 95% CI – 95% confidence interval; adj. OR – adjusted odds ratio; DI – diabetes insipidus; GH – growth hormone; OR – odds ratio; panhypopit. – panhypopituitarism. PRL – prolactin. Footnotes: *ORs may not be accurately calculated due to zero cell counts.

Endocrine deficit (axis)	Preoperative incidence	Postoperative recovery rate	Predictive variables	OR (95% CI) p-value	Adj. OR (95% CI) p-value
Cortisol	45/99 (45.5 %)	11/45 (24.4 %)	Gross total resection	8.25 (1.53 - 44.5) p = 0.007	6.88 (1.19 - 39.96) p = 0.032
			Absence of postop. DI	6.40 (1.40 - 29.21) p = 0.011	5.24 (1.04 - 26.44) p = 0.045
Thyroid	27/99 (27.3 %)	2/27 (7.4 %)	Absence of preoperative visual deficits* Absence of chiasmal compression*	P < 0.001 p=0.017	
Male gonadal	36/56 (64.3 %)	6/36 (16.7 %)	Incidentaloma*	p=0.023	
Female gonadal	11/43 (25.6 %)	7/11 (63.6 %)	BMI≤29.0*	p=0.048	
			Absence of postoperative panhypopit.*	p=0.001	
Somatotropic (GH)	25/99 (25.3 %)	Not routinely assessed in all patients			
Elevated prolactin (stalk effect)	24/99 (24.2 %)				

New-onset postoperative endocrine deficits

Incidence of new-onset postoperative endocrine deficits by individual axes **(Table 4)** is 53.7 % for the cortisol axis; 16.7 % for the thyroid axis; 45.0 % for the male gonadal axis; and 6.3 % for the female gonadal axis. Data in this study suggest that the recovery rates for new-onset deficits are poor; only 34.5 % of patients with new-onset, postoperative hypocortisolism were able to achieve recovery of the cortisol axis. Smaller tumors may be associated with the resolution of new-onset deficits of the cortisol axis (maximum tumor diameter < 23mm; OR 12.44, 95 % CI 2.00 - 77.60, p=0.007). It was also noted that tumors with preoperative radiological evidence of hemorrhage had a 0 % recovery rate, which approached significance (p=0.068) at the α=5% level. No patients in this study who developed new postoperative deficits in other axes could recover the respective axes.

Table 4. New-onset postoperative endocrine deficits – incidence and resolution, by individual axes. Abbreviations: 95% CI – 95% confidence interval, OR – odds ratio, panhypopit. – panhypopituitarism.

Endocrine deficit (axis)	Postoperative incidence	Recovery rate	Predictive variables	OR (95 % CI), p-value
Cortisol	29/54 (53.7 %)	10/29 (34.5 %)	Maximum tumour diameter < 23mm	12.44 (2.00-77.60), p=0.007
			No radiological evidence of bleeding	p=0.068
Thyroid	12/72 (16.7 %)	0/12 (0 %)		
Male gonadal	9/20 (45.0 %)	0/9 (0 %)		
Female gonadal	2/32 (6.3 %)	0/2 (0 %)		

Postoperative diabetes insipidus

55.6 % of all patients in this study who underwent ETSS to treat NFPAs developed diabetes insipidus as a postoperative complication **(Table 5).** In 16.2 % of these patients, the condition did not resolve. Factors that are predictive of permanent diabetes insipidus include larger tumor size (maximum tumor diameter >= 28mm; OR 9.97, 95 % CI 1.96 - 50.60, p=0.006) and the presence of preoperative panhypopituitarism (OR 5.25, 95 % CI 1.23 - 22.32, p=0.017). Tumor size remained a significant predictive factor even after multivariable analysis (adj. OR 8.28, 95 % CI 1.56 - 43.85, p=0.013).

The mean duration of transient diabetes insipidus is 1.9 days (standard deviation 1.0 days; interquartile range 1.0 – 2.0 days).

The extent of resection (gross total resection vs. subtotal resection) was not significantly associated with the development of permanent diabetes insipidus.

Table 5. Incidence of postoperative diabetes insipidus (DI) and variables predictive of permanent postoperative DI. Abbreviations: 95% CI – 95% confidence interval; adj. OR – adjusted odds ratio; OR – odds ratio.

	Incidence	Rate of permanent DI	Predictive variables	OR (95 % CI) p-value	Adj. OR (95 % CI) p-value
Diabetes insipidus	55/99 (55.6%)	16/99 (16.2%)	Maximum tumour diameter >= 28mm	9.97 (1.96 - 50.60) p=0.006	8.28 (1.56 - 43.85) p=0.013
			Presence of preoperative panhypopituitarism	5.25 (1.23 - 22.32) p=0.017	2.23 (0.45 – 11.09) p=0.328

Other non-endocrine outcomes are shown in **(Table 6)**. The rate of tumor recurrence was 14.1 %. The strongest predictor of recurrence was subtotal resection **(Table 7),** significant on both univariable and multivariable analysis (adj. OR 9.75, 95 % CI 1.18 – 80.56, p=0.035).

Larger tumor size was significantly associated with recurrence on univariable analysis (maximum tumor diameter ≥ 40mm; OR 5.48, 95 % CI 1.30 - 23.18, p=0.0207) but not on multivariable analysis.

Table 6. Other postoperative outcomes of patients with NFPAs treated with TSS in this study cohort (n=99). Continuous data is presented as mean(standard deviation) and interquartile range; categorical data, as *n* and *%*. Abbreviations: CN – cranial nerves; CSF – cerebrospinal fluid; ICA – internal carotid artery; SIADH – syndrome of inappropriate diuretic hormone secretion.

Recurrence/progression of residual		
Incidence	14/99	14.1 %
Time to recurrence/progression (months)	26.4 (26.8)	3.0 – 54.0
Perioperative outcomes		
Death/mortality	0/99	0 %
SIADH	12/99	12.1 %
Post-operative CSF leak	14/99	14.1 %
Meningitis	5/99	5.1 %

ICA injury	0/99	0 %
Post-operative haematoma	2/99	2.0 %
Sinonasal complications		
Hyposmia/anosmia/dysosmia	33/99	33.3 %
Epistaxis	10/99	10.1 %
Vision and CN deficits		
Vision improved	57/99	57.6 %
Vision stable	37/99	37.4 %
Vision deteriorated	2/99	2.0 %
CN deficits improved	3/99	3.0 %

Table 7. Predictors of recurrence, as identified on univariable and multivariable (logistic regression) analysis. Abbreviations: 95% CI – 95% confidence interval; adj. OR – adjusted odds ratio; OR – odds ratio.

Variable	OR (95 % CI)	p-value	Adj. OR (95 % CI)	p-value
Subtotal resection	12.70 (1.59 to 101.43)	0.0165	9.75 (1.18 – 80.56)	0.035
Maximum tumour diameter >= 40mm	5.48 (1.30 to 23.18)	0.0207	3.35 (0.75 – 14.93)	0.113

Discussion

Rates of preoperative endocrinopathy

The overall rate of endocrine deficits (in any axis) found in this cohort of patients falls within the range reported in the literature (37 % to 85 %, according to various studies) **[5,13,14]**. Male hypogonadism was this study cohort's most common endocrine deficit, followed by secondary adrenal insufficiency (hypocortisolism). The relative incidence of individual endocrine deficits observed in this study cohort was mainly consistent with that reported in the literature, where GH deficiency, central hypogonadism, and adrenal insufficiency were the most common endocrinopathies found in patients with NFPAs. The lack of routine assessment of the GH axis in all patients at our center prevents an accurate estimation of the actual rate of GH deficits in this study cohort. Rates of central hypogonadism, secondary adrenal insufficiency, central hypothyroidism, and panhypopituitarism range from 36 % to 96 %, 17 % to 62 %, 8 % to 81 %, and 6 % to 29 % of all patients, respectively **[5,15-18]**, as reported in the literature.

Interesting to note is the differential rates of prevalence of male hypogonadism and female hypogonadism. While the reasons for this phenomenon are not entirely clear, other authors have observed it previously **[19]**.

Predictors of preoperative endocrinopathy

Tumor size has been shown in this study and by other authors **[20]** as a significant predictor of preoperative hypopituitarism. Elevated body mass index and obesity (21-24) likely are physical manifestations of hypopituitarism rather than causal factors *per se* of endocrine deficits.

Rates of postoperative endocrine recovery and Predictive Factors

Within published literature, there is a significant variation in the reported rates of endocrine recovery **[14,17,18,25]** and an absence of a consensus about the factors most predictive of endocrine recovery.

Such significant variation in rates of endocrine recovery is not adequately explained by current evidence and may, in part, result from wide-ranging physiological differences between individuals **[26]**. The need for definite clarity about predictive factors of endocrine recovery also increases the difficulty of identifying patients likely to achieve healing and who are thus most likely to benefit from surgery.

The existing evidence in the literature suggests a weak, inverse relationship between tumor size and the likelihood of endocrine recovery **[27]**. However, this relationship is observed inconsistently across studies **[20,28,29]**, implying that a complex interplay between anatomical and disease factors influences endocrine recovery.

Indeed, the results of this study suggest that total tumor size is neither the sole determinant nor the most important predictor of recovery. The univariable and multivariable analysis did not reveal full tumor size as a statistically significant predictor of recovery of pre-existing, preoperative endocrine deficits in any axis. Instead, the extent of damage sustained by the residual pituitary gland is a more critical determinant of the likelihood of recovery. Incidentolamas, the absence of postoperative panhypopituitarism or diabetes insipidus, or the lack of radiological evidence of hemorrhage, suggest a relatively intact gland that has preserved its capacity for regeneration and recovery.

The hypothesis that endocrine recovery is dependent on the regenerative capacity of the residual pituitary gland is supported by evidence from the few case series published in the literature. Jahangiri and co-workers **[20]**, by performing volumetric, quantitative measurements of the residual pituitary gland, found that patients who achieved postoperative endocrine normalization had larger preoperative gland volumes. A study by Arafah **[27]** found that the

patients who had a rise in serum TSH level in response to preoperative thyrotropin-releasing hormone (TRH) stimulation achieved some endocrine improvement postoperatively, suggesting that such a biochemical response was indicative of the presence of remnant viable pituitary tissue. Similarly, Marazuela and co-workers **[30]** found that a rise in TSH after TRH and in LH after GnRH stimulation was of value in predicting possible recovery of pituitary function after surgery.

In particular, the low recovery rates of the thyroid axis suggest that the thyrotropic cells of the anterior pituitary are highly susceptible to injury. An ischaemic mechanism of damage to the thyrotropic cells may be more likely than pure mechanical compression; prolonged ischemia causes cell death that may not be reversed with surgical decompression. As predictive factors of recovery, the absence of visual deficits and chiasmal reduction are surrogate markers of the severity of mass effect and ischemia. Finally, it must be noted that the rates of recovery of the thyrotropic axis reported in the literature are inconsistent across studies and vary considerably.

New onset, postoperative endocrine deficits

Rates of new-onset, postoperative endocrine deficits are broadly consistent with those reported in other case series **[14,28]**. Sample size limitations in this study prevent the accurate estimation of actual recovery rates and identifying factors associated with recovery. However, these preliminary results broadly suggest that new-onset endocrine deficits in any axis after surgery may be permanent and irreversible. The non-negligible risk of new, permanent postoperative endocrine deficits is an essential factor that should be considered when deciding on surgical treatment of an NFPA.

Extent of resection

Of note is that gross total resection was associated with the recovery of preoperative deficits of the cortisol axis on both univariable and multivariable analysis and was not associated with the development of new obligations or diabetes insipidus after surgery. A study by Webb and co-workers (28) also found that the absence of tumor rests on postoperative pituitary imaging was predictive of endocrine recovery. Thus, it may be reasonable to strive for the complete removal of tumor tissue during surgery; proper surgical technique, and careful identification of the plane between the tumor and normal pituitary tissue, will reduce the risk of iatrogenic injury to the normal pituitary gland.

Surgical management of NFPAs – endocrinological considerations

While visual loss and chiasm compression are relatively uncontroversial indications for surgical resection of an NFPA, the endocrinological indications for surgery remain unclear, as the postoperative recovery of pituitary function is not guaranteed.

Surgery may be beneficial in improving endocrine function in patients with pre-existing deficits, but its benefits must be adequately weighed against its risks, such as the development of new obligations, perioperative morbidity, and diabetes insipidus. Further studies are required to assess the burden of care of preoperative endocrinopathy and its impact on the patient's quality of life and to determine if surgery has an unquestionable benefit in alleviating either. In addition, due consideration should also be given to the potential burden of lifelong hormonal replacement for patients who developed permanent, new endocrine deficits after surgery. While the results presented in this study are inconclusive, the authors feel that the benefits of surgical intervention may not necessarily outweigh its risks and wish to caution against excessive zeal to perform surgery for endocrinological indications alone. Furthermore, the necessity of surgery is debatable in clinically asymptomatic individuals with only laboratory or biochemical evidence of pituitary dysfunction.

As not all patients may benefit from surgery, proper patient selection is crucial. Patients most likely to recover pituitary function and thus most likely to benefit from surgery should be carefully identified. It is unclear which factors are definitively associated with recovery. However, based on current evidence, it is likely that multiple anatomical and disease factors influence recovery. Patients with relatively uncomplicated tumors – more diminutive size, no invasion, no radiological evidence of hemorrhage - may benefit from surgery; other authors have also found that younger patients with less severe preoperative deficits may have better chances of recovery **[20]**. Ancillary investigations such as quantitative, volumetric measurements of the residual pituitary gland **[20]** and hormone stimulation tests **[27,30]** to determine regenerative potential may also be appropriate.

Finally, as recovery is uncertain and there is an indeterminate risk of developing new deficits after surgery, regular postoperative assessment of each significant endocrine axis is necessary. Further studies may help assess the burden of lifelong hormonal replacement and its impact on a patient's quality of life.

Limitations

The authors acknowledge that the retrospective nature of this study is a limitation, and that inherent bias may exist. Several patients were also lost to follow-up and needed complete clinical and biochemical follow-up data; they were excluded from the final analysis.

Conclusion

Pituitary dysfunction alone is not a strong indication for surgery for NFPAs, as preliminary evidence shows that the benefits of surgery may not necessarily outweigh its risks. Proper patient selection is crucial – evidence from this and other studies, while inconclusive, suggests that younger patients who have less complicated tumors and less severe preoperative deficits may benefit most from surgery. Ancillary investigations such as volumetric measurements of residual pituitary gland volume and hormone stimulation tests may also be

appropriate. It is reasonable to strive for complete tumor removal during surgery, as gross total resection increases the chances of endocrine recovery and is not associated with an increased risk of developing new postoperative deficits. Regular postoperative assessment of the significant endocrine axes is essential.

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