MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 7944-7951
DOI: 10.12659/MSM.909925

Received: 2018.03.12
Accepted: 2018.06.01
Published: 2018.11.06

Evaluation of a Novel General Pituitary Hormone Score to Evaluate the Function of the Residual Anterior Pituitary (Adenohypophysis) in Patients Following Surgery for Pituitary Adenoma

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Source of support: This study was supported by the Nanjing Military Medical Science and Technology Innovation Key Fund Project (Grant number: 11Z034) and the Fuzhou General Hospital Innovation Team Fund Project (Grant number: 2014CXTD07)

Background: The aim was to develop and assess a general pituitary hormone score to evaluate the function of the anterior pituitary (adenohypophysis) in patients following resection of pituitary adenomas.

Material/Methods: Sixty-six patients with pituitary null cell macroadenoma (1–3 cm diameter) (N=38) and pituitary null cell giant adenoma (≥3 cm diameter) (N=28) had preoperative and postoperative data including magnetic resonance imaging (MRI) and measurement of six pituitary hormones levels, adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The postoperative general pituitary hormone score, for 57 patients who underwent subtotal resection (>60%) and nine patients who underwent partial resection (≤60%), was 1–5 for each hormone level (score range, 6–30).

Results: ACTH, GH, TSH, PRL, FSH, and LH levels in 38 patients with pituitary null cell macroadenoma were not statistically different from the 28 patients with pituitary null cell giant adenoma; the general pituitary hormone score in the former group was significantly increased compared with the latter group ($P<0.05$). ACTH, GH, TSH, PRL, FSH, and LH levels in the 57 patients with subtotal tumor resection were not significantly different from the nine patients with partial tumor resection; the general pituitary hormone score in the former group was significantly reduced compared with the latter group ($P<0.05$).

Conclusions: A general pituitary hormone score was developed that might be relevant to the evaluation of pituitary function following surgical resection of pituitary null cell macroadenoma and giant adenoma.

MeSH Keywords: Hypothyroidism • Pituitary Adenomas • Pituitary Hormones

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909925

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Background

The anterior pituitary gland (adenohypophysis) secretes six main hormones that include adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Approximately 20% of pituitary adenomas are null cell tumors, of which almost half are nonfunctioning tumors that present as macroadenomas that cause a mass effect and hypopituitarism. The degree of pituitary endocrine dysfunction in patients with pituitary adenoma directly affects the surgical approach, the outcome of surgery, the postoperative requirement for hormone replacement, and the long-term quality of life for patients [1–3].

Therefore, it is important to evaluate not only pre-operative endocrine function but also postoperative endocrine function of the residual pituitary in patients with pituitary adenoma. In previous studies on pituitary endocrine function in patients with pituitary adenoma, the measurement of the individual levels of the six main pituitary hormones has been studied in patients with pituitary adenoma [4–8]. For example, Ishii et al. have used standard methods to measure individual pituitary hormone levels in patients with pituitary adenoma, which did not evaluate the overall function of the pituitary gland in patients with different types of pituitary adenoma [8]. The findings from the evaluation of individual pituitary hormone levels in patients with pituitary adenoma do not evaluate the overall function of the pituitary gland. Therefore, there remains a need to develop and assess suitable methods to assess the overall function of the pituitary gland in terms of hormonal function in this patient population.

Histopathology and immunohistochemistry have shown that the distribution of endocrine cells of the pituitary gland in pituitary adenoma can vary and may depend on the type of adenoma and the growth pattern of the adenoma with varied expression levels of the six main pituitary hormones [9]. Therefore, evaluation of hormonal dysfunction of the anterior pituitary cannot be made by measuring the level of any one of the six anterior pituitary hormones.

The aim of this study was to develop and assess a general pituitary hormone score, which included all six anterior pituitary hormones, to evaluate the function of the anterior pituitary (adenohypophysis) in patients following resection of pituitary macroadenoma, and to determine the potential clinical value of a general pituitary hormone score.

Material and Methods

Patient inclusion and exclusion criteria

A total of 66 patients with null cell pituitary adenoma who were admitted to our hospital between January 2009 and April 2013 were enrolled in the present study. The inclusion criteria included: a diagnosis of primary pituitary adenoma, confirmed by histopathological examination; negative hormone expression of the adenoma shown by immunohistochemical staining, confirming the null cell or nonfunctioning status of the adenoma. The exclusion criteria included: incomplete data from magnetic resonance imaging (MRI) or pituitary hormone testing; unreliable or unavailable medical records of menstrual history for female patients; incomplete histopathology and immunohistochemistry results; patient age <18 years or >80 years; a history of glucocorticoid replacement treatment, or recent intake of drugs affecting the level of pituitary hormones, including dopamine receptor agonists, antipsychotics, opioids, proton pump inhibitors, estrogen and calcium antagonists; and the presence of other diseases that might affect the synthesis and release of pituitary hormones.

All procedures included in the study were approved by the Ethics Committee of Fujian Medical University, China. Written informed consent was obtained from all patients or their families for the clinical procedures used and for inclusion in the study.

Patient characteristics and surgery

The 66 patients who met the inclusion criteria of the study included 27 men and 39 women, with a mean age of 49.3 years (age range, 26–79 years). The average tumor diameter was 29.60±9.97 cm. All patients underwent trans-sphenoidal resection of the pituitary adenoma performed by the same surgeon. Indications for surgery included: patients with a headache, decreased visual acuity, or visual field defects caused by pituitary adenoma; patients and their families who were motivated to undergo surgical treatment. Immediately after surgery, patients received hormone replacement treatment. On the first, second, and third day after surgery, the pituitary hormone levels were re-tested. Within 48 hours following surgery, the extent of the surgical resection (subtotal or partial) was confirmed by MRI.

Patient groups: macroadenoma and giant adenoma; subtotal resection and partial resection

Because the size of the pituitary adenoma has been shown to affect pituitary function [10], all cases were divided into either the macroadenoma group (diameter between 1–3 cm) [11], and the giant adenoma group (diameter ≥3 cm) [12]. The evaluation of preoperative pituitary function had been performed for each patient by measuring the levels of the six anterior

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pituitary hormones separately, including adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid stimulating hormone (TSH), prolactin (PRL), follicle stimulating hormone (FSH), and luteinizing hormone (LH), and these six hormones were also measured postoperatively.

It has previously been shown that pituitary function might be more severely reduced in patients with non-functioning pituitary adenoma when a larger portion of the tumor has been resected during surgery, and when partial surgery has been performed the remaining pituitary gland is protected in terms of function [13]. Therefore, all cases were divided into either the subtotal resection group (tumor resection >60%) and the partial resection group (resection ≤60%).

Preoperative pituitary function and postoperative pituitary function was evaluated by separate measurement of the six anterior pituitary hormones ACTH, GH, TSH, PRL, FSH, and LH. The extent of tumor resection was calculated by the residual tumor volume on postoperative MRI/the tumor volume on the preoperative MRI.

Chemiluminescence method for measurement of the six anterior pituitary hormones

Venous blood was drawn from all patients on the second day after admission to hospital and before breakfast on the first day after surgery. The levels of the six pituitary hormones, ACTH, GH, TSH, PRL, FSH, and LH, were measured using the ADVIA Centaur XP chemiluminescence system (Siemens, Berlin, Germany) at Department of Clinical Laboratory, Fuzhou General Hospital, China.

Normal reference ranges for the six hormones were: GH, 0–1 μg/L (men) and 0–10 μg/L (women); ACTH, 4.7–48.8 ng/L; TSH, 0.35–5.5 mU/L; PRL, 2.1–17.7 μg/L (men), 2.8–29.2 μg/L (nonpregnant women), 9.7–208 μg/L (pregnant women) and 1.8–20.3 μg/L (menopausal women); FSH, 1.4–18.1 mU/L (men), 2.5–10.2 mU/L (women in the follicular phase), 3.4–33.4 mU/L (women in the ovulatory period), 1.5–9.1 mU/L (women in the luteal phase), and 23–116 mU/L (menopausal women); LH, 1.5–9.3 mU/L (men), 1.9–12.5 mU/L (women in the follicular phase), 8.7–76.3 mU/L (women in the ovulatory period), 0.5–16.9 mU/L (women in the luteal phase), and 15.9–54 mU/L (menopausal women). If the serum level of any of the six hormones was below the lower reference limit, pituitary hormone axis dysfunction was diagnosed.

The general pituitary hormone score

Following anterior pituitary surgery, the function of the pituitary gland usually changes, the serum level of one or more pituitary hormones declines, and the serum level of some hormones can increase slightly. Conventionally, when judging the decline in the function of the anterior pituitary gland, when the index of any one hormonal axis falls below the normal range, the anterior pituitary is judged to be hypofunctional, but when hormone levels are lower than those before onset or before surgery, but not lower than normal ranges, this is not usually considered to reflect hypofunction of the anterior pituitary (adenohypophysis). Traditional individual hormonal evaluation methods are qualitative but not quantitative and are not appropriate for the dynamic monitoring of decreasing or increasing anterior pituitary function.

Because of the lack of a numerical index to measure the overall decline in the total endocrine levels of the pituitary gland, the development of a numerical index in the form of the general pituitary hormone score provided a quantitative grading method that classified each pituitary hormone according to the normal range, and added the levels of the six hormones in the patient to provide a general score. The total hormone levels were obtained at each test, to reflect the state of pituitary endocrine activity in different time periods for the patient, and to reflect whether the total functional level of the pituitary gland was decreased or increased.

Four reference points were used for the scoring of the six pituitary hormones: the upper limit of the normal reference range; half of the lower limit of the normal reference range; the lower limit of the normal reference range; and the mean value of the two limits. The four reference points divided the concentration of each pituitary hormone into five levels, which were scored from 1 to 5, representing the lower hormonal concentration to the higher hormonal concentration.

In the general pituitary hormone score, the five points were as follows: 1 point=<50% of the lower limit of the normal reference range; 2 points=lower than the lower limit of the normal reference range; 3 points=between the lower limit of the normal reference range to the mean value of the two limits; 4 points=from the mean value of the two limits to the upper limit of normal reference range; 5 points=a value above the upper limit of the normal reference range. Summation of the five scores of all six pituitary hormones was used to obtain the general pituitary hormone score, which ranged from a score of 6 to a score of 30.

Statistical analysis

The results were analyzed using SPSS version 19.0 software (IBM, Armonk, NY, USA). Differences in tumor diameter between two groups were compared using the t-test. Differences in hormones levels between two groups were compared using one-way analysis of variance (ANOVA). $P<0.05$ was considered to be statistically significant.

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Results

Clinical characteristics and anterior pituitary hormone levels for patients with macroadenomas and giant adenomas of the anterior pituitary gland

The 66 cases of pituitary adenoma were divided into the macroadenoma group and giant adenoma group. The macroadenoma group (mean diameter, 23.05±4.79 mm) included 38 cases (17 men and 21 women) with an average age of 47.0 years (range, 28–72 years). The giant adenoma group (mean diameter, 38.72±7.89 mm) included 28 cases (10 men and 18 women) with an average age of 52.6 years (range, 26–79 years). The diameters of the two groups were significantly different from each other (P<0.01). The gender and age of the two groups were not significantly different from each other (P>0.05).

The individual levels of the six anterior pituitary hormones, adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) showed no significant differences between the macroadenoma group and giant adenoma group (P>0.05). However, the general pituitary hormone score of the macroadenoma group (19.59±2.71) was significantly higher when compared with the giant adenoma group (18.07±2.00) (P<0.05) (Table 1). These results indicated that the hormonal function of pituitary macroadenomas was less impaired than that of giant adenomas.

Hormone function of the residual pituitary gland following subtotal adenoma resection group compared with partial adenoma resection

Postoperative pituitary hormone levels were evaluated in 57 patients who underwent subtotal resection (>60%) of the pituitary adenoma (22 men and 35 women) (mean age, 49.1 years; range, 26–79 years) with 34 macroadenomas and 23 giant adenomas (mean preoperative diameter, 29.77 ± 9.91 mm). Postoperative pituitary hormone levels were evaluated in nine patients who underwent partial adenoma resection (≤60%) (5 men and 4 women) (mean age, 51.0 years; range, 33–72 years), with 4 macroadenomas and 5 giant adenomas (mean preoperative diameter, 28.63±10.77 mm).

The diameters of the tumors between the subtotal resection group and the partial resection group were significantly different from each other (P<0.01). The preoperative gender and age of the two groups were not significantly different from each other (P>0.05). The individual levels of each of the anterior pituitary hormones ACTH, GH, TSH, PRL, FSH, and LH were not significantly different between the subtotal resection group and partial resection group (P>0.05). However, the general pituitary hormone score of the subtotal resection group (17.32±2.20) was significantly lower than that of the partial resection group (19.40±1.26) (P<0.05) (Table 2). These results indicated that the hormonal function of the residual anterior pituitary gland tissue in the partial resection group was less impaired than that of the subtotal resection group.

The general pituitary hormone score was more accurate than measurement of individual pituitary hormone levels in evaluating the effect of surgery on pituitary function

Evaluation of preoperative hormone levels showed that 13 out of 38 patients in the macroadenoma group had one or more pituitary hormone levels that were lower than the normal reference values (13/38); 17 out of 28 patients in giant adenoma group had one or more pituitary hormone levels that were lower than the normal reference values (17/28) (P=0.046).

The general pituitary hormone scores for the macroadenoma group and giant adenoma group were 19.59±2.71 and 18.07±2.00, respectively (P=0.015). Evaluation of the postoperative hormone levels showed that 34 out of 57 patients in subtotal resection group had one or more pituitary hormone levels that were lower than the normal reference values (34/57), while 2 out of 9 patients in the partial resection group had one or more pituitary hormone levels that were lower than the normal reference values (2/9), but these differences were not statistically significant (P=0.068). However, the general pituitary hormone scores for the subtotal resection group and partial resection group were 17.32±2.20 and 19.40±1.26, respectively (P=0.003). These results supported that the general pituitary hormone scoring system was a potentially more accurate method than the measurement of individual pituitary hormone levels in evaluating the effect of surgery on pituitary function following resection of pituitary macroadenomas.

Discussion

The aim of this study was to develop and assess a general pituitary hormone score to evaluate the function of the anterior pituitary (adenohypophysis) in patients following resection of pituitary macroadenoma, using pre-operative and postoperative measurement of levels of the six anterior pituitary hormones adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). A general pituitary hormone score was developed that might be relevant to the evaluation of pituitary function following surgical resection of anterior pituitary null cell macroadenoma and giant adenoma.

In some functional pituitary adenomas, the levels of the most important hormones may be meaningful. For example, the PRL

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Table 1. Preoperative levels of the six pituitary hormones and "general pituitary hormone" scores of large adenomas and giant adenomas.

	Macroadenomas (n=38)	Giant adenomas (n=28)	Homogeneity test of variance		Rank-sum test	
			Levene statistics	*P*	F	*P*
ACTH (ng/L)	20.65±16.22	16.57±10.85	3.870	0.053	1.336	0.252
GH (μg/L)	0.50±0.51	0.49±0.88	1.128	0.292	0.004	0.950
PRL (μg/L)	20.16±21.11	23.49±25.16	0.847	0.361	0.345	0.559
TSH (mU/L)	2.15±1.87	2.55±2.53	3.077	0.084	0.555	0.459
FSH (mU/L)	15.70±21.83	12.40±16.95	0.455	0.502	0.448	0.506
LH (mU/L)	7.45±1.31	4.23±8.19	1.748	0.191	1.877	0.175
General pituitary hormone scores	19.59±2.71	18.07±2.00	3.136	0.081	6.306	0.015

Table 2. Postoperative levels of the six pituitary hormones and "general pituitary hormone" scores of subtotal resection group and partial resection group.

	Subtotal resection group (n=57)	Partial resection group (n=9)	Homogeneity test of variance		Rank-sum test	
			Levene statistics	*P*	Z	*P*
ACTH (ng/L)	14.14±9.11	20.09±18.86	11.827	0.001*	–0.282	0.778
GH (μg/L)	0.44±0.49	0.70±0.79	2.836	0.097	–0.968	0.333
PRL (μg/L)	9.78±7.23	7.78±6.09	0.414	0.522	–0.853	0.393
TSH (mU/L)	0.86±0.87	0.95±0.70	0.668	0.417	–0.757	0.449
FSH (mU/L)	8.73±10.61	15.14±18.17	5.373	0.024*	–1.249	0.212
LH (mU/L)	4.88±7.47	9.80±10.84	5.114	0.027*	–1.795	0.073
General pituitary hormone scores	17.32±2.20	19.40±1.26	3.792	0.056	–3.022	0.003

* Homogeneity test of variance of multiple groups showed heterogeneity of variance. As a result, nonparametric test was performed instead.

level in prolactinoma determined using immunohistochemistry before surgical resection may be of predictive value for postoperative hormonal remission and for tumor recurrence [14]. However, for most types of pituitary adenomas, the measurement of individual hormone levels do not represent the endocrine function of the whole anterior pituitary gland, and inaccurate evaluation of hormone levels result in further postoperative hormone deficiency or unnecessary hormone replacement treatment. Therefore, accurate evaluation of endocrine function can be helpful when planning surgery and postoperative patient management, as well as the timing of hormone replacement therapy after surgery.

To improve the limitations of individual measurement of anterior pituitary hormones levels, a general pituitary hormone scoring system was developed and evaluated in this study that included evaluation of the six anterior pituitary hormones together to represent the overall endocrine function of the anterior pituitary gland. The general pituitary hormone scoring system used normal hormone reference ranges, which can be assumed to be the 95% reference value ranges for the healthy population. The average values of the upper and lower limits of individual reference ranges can be considered as the mean values for the healthy population.

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Table 3. Preoperative "general pituitary hormone" scoring and the examinations of pituitary hormone levels in predicting the prognosis after surgery.

	Case one			Case two		
	Results	Scoring	Hormone dysfunction	Results	Scoring	Hormone dysfunction
Gender	Male			Male		
Age	56			59		
Before surgery						
Maximal diameter	47.08 mm			33.31 mm		
ACTH	2.71 ng/L	2	Y	3.75 ng/L	2	Y
GH	0.064 μg/L	3	N	0.148 μg/L	3	N
TSH	0.173 mU/L	3	N	1.141 mU/L	3	N
PRL	21.07 μg/L	5	N	4.82 μg/L	3	N
FSH	10.92 mU/L	4	N	2.67 mU/L	3	N
LH	4.26 mU/L	3	N	1.65 mU/L	3	N
"General pituitary hormone" scores		20			17	
Day 2 after surgery						
Resection extent	93.40%			95.20%		
ACTH	13.89 ng/L	3	N	5.57 ng/L	3	N
GH	0.162 μg/L	3	N	0.295 μg/L	3	N
TSH	0.245 mU/L	3	N	0.596 mU/L	3	N
PRL	14.41 μg/L	4	N	1.69 μg/L	2	Y
FSH	8.56 mU/L	3	N	2.22 mU/L	3	N
LH	2.58 mU/L	3	N	1.10 mU/L	2	Y
"General pituitary hormone" scores		19			16	

In this study, the subjects were chosen who had histologically confirmed null cell pituitary adenomas, to exclude interference in the evaluation by hormonal secretion of functional pituitary adenomas. Null cell pituitary adenomas have no endocrine function. However, PRL levels in null cell pituitary adenomas may be elevated by secretion from the pituitary stalk or due to peritumoral pituitary effects and could have affected the results of the present study [15,16]. However, previous studies have shown that the diameter of nonfunctional pituitary adenomas is not correlated with the levels of PRL [17,18] Therefore, interference by PRL can be ignored when grouping the study participants by adenoma diameter, as was done in the present study. The findings of the present study supported this assumption, as between-group PRL levels were not significantly different when grouping either by adenoma diameter ($P>0.559$) or by the extent of tumor resection (subtotal or partial) ($P>0.393$).

The findings of this study showed that the general pituitary hormone score in the macroadenoma group was significantly different compared with the giant adenoma group, while individual hormone levels were not significantly different between groups. This observation confirms that the risk for pituitary dysfunction increases with the increasing size of the pituitary adenoma [10], and that general pituitary hormone scoring is more accurate than the evaluation of individual hormone levels in confirming this. Also, the general pituitary hormone score in the subtotal resection group was significantly different from that in partial resection group, while individual hormone levels were not significantly different between these groups. Therefore, the general pituitary hormone score was more accurate than the evaluation of individual hormone levels in reflecting the damage to pituitary tissues caused by surgery. Based on these results, it is possible that the general pituitary hormone scoring system could be used for preoperative patients evaluation, as if a patient has relatively low preoperative general pituitary hormone score, protective measures should be taken for the pituitary gland during the surgical procedure for anterior pituitary tumor resection.

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To highlight the value of the use of the general pituitary hormone score, two cases can be used as illustrative examples from the study population, who were the same age and gender and who both had abnormal levels of ACTH on individual hormone testing. The general pituitary hormone scoring system showed that, after surgery, one of the two patients had two dysfunctional hormones, a finding that was relevant to their postoperative management (Table 3).

This study had several limitations. When calculating the general pituitary hormone scores, higher scores usually suggested intact pituitary function while low scores usually indicated impaired pituitary function. However, this assumption should be made with caution with respect to PRL levels. Arafah et al. report that the PRL level of 33 cases with pituitary dysfunction was 25.9±8 μg/L, while that of 16 cases without pituitary dysfunction was 16.6±8.1 μg/L [17], suggesting that reduced pituitary function may lead to increased PRL levels. In the present study, the PRL levels in the macroadenoma group and giant adenoma group were 20.16±21.11 μg/L and 23.49±25.16 μg/L, respectively. In contrast, the general pituitary hormone score in the macroadenoma group and giant adenoma group were 19.59±2.71 μg/L and 18.07±2.00 μg/L, respectively. These results might indicate that the general pituitary hormone score for the giant adenoma group obtained in the present study might have been higher than its actual value (lower than 18.07±2.00 μg/L). There are also abundant factors that may affect the release of PRL, including the function of pituitary gland secretion, the pituitary stalk interruption effect, hypothyroidism, pregnancy, lactation, and drug treatment. However, in this preliminary study, the evaluation of PRL was undertaken in the same way as with other pituitary hormones in the general pituitary hormone scoring. The second main limitation of the study was the large age range of the study population (26–79 years), which may have had an impact on endocrine function of the patients. Because this preliminary study showed that overall hormone levels could partially reflect the reserve of patient's pituitary-endocrine function, limitations on age were not included and the age of patients in different groups was comparable with no significant difference in the age of patients between the macroadenoma group and giant adenoma group, or between the subtotal resection group and the partial resection group. Further analysis of the overall hormone levels in patients of different ages should be performed with larger sample sizes. The third main limitation of the study was that only null cell pituitary adenomas were studied. In future evaluation studies, the general pituitary hormone scoring method should be applied and evaluated in patients with functional anterior pituitary adenomas. A factor that was not specifically addressed in this study, but which should be studied further is that in adolescent patients, the use of the general pituitary hormone score might also overcome the general changes in levels of systemic endocrine function, and provide guidance for assessing the growth and development of younger patients.

Conclusions

In patients with pituitary adenomas who undergo partial or subtotal tumor resection, measurement of individual anterior pituitary hormone levels might not represent the endocrine function of the whole anterior pituitary gland. The general pituitary hormone score, described and evaluated in this study, might be helpful in the assessment of remnant pituitary function in pituitary adenoma patients, with a more accurate evaluation of endocrine function allowing for improvement in planning and performing surgery, and the timing and selection of appropriate hormonal replacement treatment after surgery.

Conflict of interests

None.

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