Influence of Variables on Hormone Profile in Endoscopic Transsphenoidal Surgery for Pituitary Adenomas

Fernando Simões Nazareno¹
Rodrigo Alves de Carvalho Cavalcante²
Tiago Vinicius Silva Fernandes³
Osvaldo Vilela Garcia Filho⁴

OBJECTIVE: to evaluate the hormone profiles of patients with pituitary adenomas operated on in Hospital das Clínicas, Universidade Federal de Goiás (HC-UFG), correlating them with the variables age, sex, and Knosp grade. METHOD: This is a retrospective quantitative study of medical records, including a total population of 20 patients diagnosed with pituitary adenomas operated on using the pure endoscopic endonasal transsphenoidal approach. The hormone profiles of the three types of pituitary adenoma prevalent in this institution were analyzed: nonfunctioning macroadenoma, growth hormone-secreting pituitary adenoma (acromegaly), and adrenocorticotropic hormone-secreting pituitary adenoma (Cushing’s disease). Pre and postoperative hormone values were statistically paired with the variables selected. RESULTS: The global levels of the specific hormones of each disease decreased after surgery. However, no statistical significance was found between the variables selected in this study and the pre and postoperative hormone values. CONCLUSION: The main surgical goal, the specific hormones decrease, was achieved in all the surgeries performed. Analyzing the relationship between the variables and the hormone profiles, we conclude that age, sex, and Knosp grade did not influence the results obtained.

Keywords: Adenoma; Endoscopy; Pituitary; Hormones

RESUMO

Objetivo: Avaliar os perfis hormonais dos pacientes com adenoma hipofisário operados no Hospital das Clínicas, Universidade Federal de Goiás (HC-UFG), correlacionando-os com as variáveis idade, sexo e grau de Knosp. Método: Trata-se de um estudo retrospectivo de prontuários, com a inclusão de 20 pacientes com diagnóstico de adenoma hipofisário operados por via transesfenoidal endoscópica endonasal pura. Foram analisados os perfis hormonais dos três tipos de adenoma hipofisário prevalentes: macroadenoma não secretor, adenoma produtor de hormônio do crescimento (acromegalia) e adenoma produtor de hormônio adrenocorticotrófico (doença de Cushing). Foi realizado pareamento estatístico entre os valores hormonais pré e pós-operatórios e as variáveis selecionadas. Resultados: Observou-se redução global dos níveis hormonais específicos de cada doença após a cirurgia. Porém, não houve significância estatística entre as variáveis selecionadas neste estudo e o perfil hormonal pré e pós-operatório. Conclusão: O objetivo cirúrgico principal, que é a redução hormonal específica, foi alcançado em todas as cirurgias realizadas. Analisando a relação entre as variáveis e os perfis hormonais, conclui-se que idade, sexo e grau de Knosp não influenciaram os resultados obtidos.

Palavras-chave: Adenoma; Endoscopy; Hipófise; Hormônios
Endoscopic transsphenoidal surgery using an external light source was first performed by Guiot in 1962. In the 1990s, a surgical procedure to remove pituitary adenoma carried out only with the use of an endoscope, without the aid of a surgical microscope, was described for three patients. Posteriorly, endoscopic transsphenoidal access to the sella turcica was systematized.

Over time, Neuroendoscopy had great technical evolution. New tools have been developed to make the access to the skull base easier, more specifically to the sellar region. Several studies were published showing favorable results of surgical procedures employing endoscopic access to remove pituitary adenomas.

The wider vision of the sellar region offered by the endoscope allows the surgeon to perform resection, most of the times, of the whole tumor. However, some factors may interfere with the success of this procedure such as lateral growth of the tumor, with invasion of the cavernous sinus and adherence to the intracavernous carotid artery. Therefore, preoperative assessment of tumor characteristics (size and lateral growth) and Knosp grade are considered of paramount importance to predict the success of surgery.

Great volume and invasion of lateral structures make total excision of these lesions a significant challenge, interfering in the major objectives of the surgery, namely hormonal remission and decompression of nervous structures such as the optic nerve. In a recent study, 55 patients with giant pituitary adenoma, who underwent endoscopic endonasal surgery, were analyzed and the clinical outcomes were considered good, since gross total resection (GTR) was possible in 44% of them, and near-total resection in 47% (over 90% of the tumor). Medical records of 331 patients diagnosed with pituitary adenoma, operated on using the endoscopic endonasal transsphenoidal approach in a single institution, over a 15-year period, were revised. Extrasellar invasion and higher Knosp grade directly influenced the success of surgery.

In a retrospective study of therapeutic strategies for nonfunctioning pituitary adenomas in 275 patients, based on the modified Knosp grading system proposed by Micko et al., GTR was achieved in 82.6%, 76.7%, 73.5%, 50.0%, 44.4%, and 5.9% of the tumors with Knosp grades 0, 1, 2, 3A, 3B, and 4, respectively. Recently, a case series of 50 patients presenting with functioning and nonfunctioning pituitary adenomas, with invasion of the medial wall of the cavernous sinus (Knosp grades 1, 2, and 3) and who underwent endoscopic endonasal approach was analyzed. GTR was reported for all the patients, and complete biochemical remission was achieved in 34 cases (97%) of functioning adenoma.

After a comprehensive literature review, no studies showing specific correlations between age and/or sex of the patient and the surgical outcome of pituitary adenomas, based on the analysis of hormone profile, were found. Due to this lack of data, these variables are of particular interest to the present study. The correlation between Knosp grade and surgical success is already well known, as demonstrated in the aforementioned studies. Thus, this study aimed to evaluate the hormone profiles of patients diagnosed with pituitary adenoma operated on in Hospital das Clínicas, Universidade Federal de Goiás (HC-UFG), using the pure endoscopic endonasal transsphenoidal approach, correlating them with the variables age, sex, and Knosp grade.

Methods

This is a retrospective quantitative study of medical records of patients diagnosed with pituitary adenoma operated on in HC-UFG using the pure endoscopic endonasal transsphenoidal approach, from August 2017 to September 2018, totaling 20 cases, with follow-ups ranging from one month to one year.

Specific diseases – nonfunctioning macroadenoma, growth hormone (GH)-secreting pituitary adenoma (acromegaly), and adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (Cushing’s disease) – were analyzed separately, and the statistical pairing was performed with the
variables age, sex, and Knosp grade (Box 1).

**Box 1. Knosp grading system.**

| Grade | Description |
|-------|-------------|
| 0     | Adenoma does not extend the medial carotid line. |
| 1     | Adenoma extends the medial line, but does not reach the median line, so-called “intercarotid” line. |
| 2     | Tumor extends beyond the median line, but it does not extend beyond or tangent to the lateral line. |
| 3     | Tumor extends beyond the lateral line. |
| 4     | Tumor totally wraps around the intracavernous carotid artery. |

Source: Knosp et al.16

The specific hormones analyzed were GH, insulin-like growth factor 1 (IGF-1), prolactin, ACTH, and cortisol. The hormones of the pituitary axis analyzed were luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), circulating free thyroxine (free T4), estradiol, and testosterone.

In the demographics, percentage of males and females, and mean and standard deviation (SD) of the patients’ age were evaluated. Knosp grade was also obtained in the medical records.

Pre and postoperative hormone levels were registered in specific medical records kept by the Neuroendocrinology team of HC-UFG. Postoperative levels were analyzed 3 months after the surgical procedure. Both pre and postoperative levels of specific hormones of each disease analyzed were registered in the medical records of the three specific populations. Nonetheless, since not all the medical records had data on non-specific hormones and the hormones of the pituitary axis, they were not statistically analyzed.

Data were analyzed using measures of central tendency and dispersion. Comparisons were performed using the Student’s t-test with paired variable (pre and postoperative hormone levels). Pearson's correlation analysis was used to check possible correlations between the variables tested and the hormone profile per specific disease.

**RESULTS**

The analysis was carried out per specific disease. Of the 20 patients included in this study, 10 (50%) had nonfunctioning macroadenomas, 7 (35%) GH-secreting pituitary adenomas, and 3 (15%) ACTH-secreting pituitary adenomas.

**Nonfunctioning macroadenomas**

In the group of patients with nonfunctioning macroadenomas, the age ranged from 38 to 69 years, with a mean age of 56.5 years (SD = 9.18). Primary intervention was performed in 60% of these patients, whereas the others were reoperations. The results regarding sex and Knosp grade for this group of patients are shown in Table 1.

**Table 1. Variables evaluated in medical records of patients with nonfunctioning macroadenomas (n = 10).**

| Variable    | n | %  |
|-------------|---|----|
| Male        | 4 | 40 |
| Female      | 6 | 60 |
| Knosp grade 2 | 5 | 50 |
| Knosp grade 3 | 5 | 50 |
Pre and postoperative hormone levels of patients with nonfunctioning macroadenomas are listed in Table 2. Given that the only hormone level recorded for all the patients was prolactin. This was the only one statistically evaluated, and its mean decrease was 59.1% ($p = 0.059$) in the postoperative period.

After statistical pairing, no statistically significant correlation was found between the variables analyzed (sex, age, and Knosp grade) and prolactin levels. Pearson’s correlation analysis revealed that the correlation between sex and prolactin levels was 0.505 ($p = 0.166$), between Knosp grade and prolactin levels was 0.527 ($p = 0.145$), and between age and prolactin levels was -0.607 ($p = 0.063$).

### Table 2. Hormone levels in patients with nonfunctioning macroadenomas (n = 10).

| Hormone       | Medical record with register (n) | Mean   | SD     |
|---------------|---------------------------------|--------|--------|
| GH pre (ng/mL)| 5                               | 0.078  | 0.04604|
| IGF-1 pre (ng/mL) | 8                           | 99.788 | 34.1374|
| Prolactin pre (ng/mL) | 10                          | 22.933 | 21.07513|
| Prolactin post (ng/mL)   | 10                           | 9.387  | 6.83328|
| ACTH pre (µg/mL) | 8                             | 24.125 | 21.301 |
| Cortisol pre (µg/mL) | 6                            | 8.1333 | 3.97725|
| TSH pre (µUI/mL) | 8                            | 2.3838 | 1.77113|
| TSH post (µUI/mL) | 6                            | 2.7025 | 1.5796 |
| Free T4 pre (ng/mL)   | 7                             | 0.7957 | 0.19407|
| Free T4 post (ng/mL)  | 6                             | 0.7567 | 0.2103 |
| FSH pre (µUI/mL) | 7                             | 17.2471| 30.24527|
| FSH post (µUI/mL)  | 6                             | 5.015  | 5.92458|
| LH pre (µUI/mL)   | 7                             | 7.8857 | 10.3817|
| LH post (µUI/mL)   | 4                             | 15.5125| 22.94546|
| Testosterone pre (ng/dL) | 2                        | 243.965| 304.10541|
| Testosterone post (ng/dL) | 3                        | 152.7733| 106.72313|
| Estradiol pre (pg/dL) | 4                           | 16.9   | 8.4562 |
| Estradiol post (pg/dL) | 2                           | 16     | 11.314 |

SD: standard deviation; GH: growth hormone; IGF-1: insulin-like growth factor 1; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; free T4: circulating free thyroxine; FSH: follicle-stimulating hormone; LH: luteinizing hormone.
GH-secreting pituitary adenomas

In the group of patients with GH-secreting pituitary adenomas, the age ranged from 42 to 59 years, with a mean age of 49.71 years (SD = 6.47). Primary surgery was performed in six patients (85.7%), and one case was a reoperation (14%). The results of sex and Knosp grade of the patients in this group are shown in Table 3.

The hormone levels of patients in the group with GH-secreting pituitary adenomas registered in their medical records in pre and postoperative phases are presented in Table 4.

In the postoperative period, the mean decrease in GH and IGF-1 levels were 94.89% ($p = 0.029$) and 63.23% ($p = 0.013$), respectively. No statistically significant correlation was found between the variables studied and the pre and postoperative specific hormone profile. The correlation between Knosp grade and GH levels was 0.290 ($p = 0.578$) and between Knosp grade and IGF-1 levels was -0.264 ($p = 0.613$). The correlation between sex and GH levels was 0.271 ($p = 0.603$) and between sex and IGF-1 levels was 0.342 ($p = 0.507$). The correlation between age and GH levels was 0.612 ($p = 0.145$) and between age and IGF-1 levels was 0.395 ($p = 0.472$).

### Table 3. Variables evaluated in medical records of patients with GH-secreting pituitary adenomas (acromegaly) (n = 7).

| Variable      | n | %  |
|---------------|---|----|
| Male          | 4 | 57.1 |
| Female        | 3 | 42.9 |
| Knosp grade 1 | 1 | 14.3 |
| Knosp grade 2 | 3 | 42.9 |
| Knosp grade 3 | 2 | 28.6 |
| Knosp grade 4 | 1 | 14.3 |

ACTH-secreting pituitary adenomas

In the group of patients with ACTH-secreting pituitary adenomas, the mean age was 36.33 years (SD = 22.6). All cases (100%) occurred in female patients and were Knosp grade 1. Primary intervention was performed in two patients and reoperation in one. Hormone levels of patients in this group in pre and postoperative phases are listed in Table 5.

The mean decrease in ACTH and cortisol levels in the postoperative period were 96.5% ($p = 0.083$) and 99.15% ($p = 0.064$), respectively. No significant statistical correlation was found for these outcomes, probably reflecting the minute sample (n = 3).
Table 4. Hormone levels in patients with GH-secreting pituitary adenomas (acromegaly) (n = 7).

| Hormone       | Medical record with register (n) | Mean    | SD     |
|---------------|---------------------------------|---------|--------|
| GH pre (ng/mL)| 7                               | 21.33   | 19.04  |
| GH post (ng/mL)| 7                             | 1.09    | 0.89   |
| IGF-1 pre (ng/mL) | 7                          | 533.29  | 215.22 |
| IGF-1 post (ng/mL) | 7                         | 180.14  | 113.13 |
| Prolactin pre (ng/mL) | 7                      | 19.59   | 13.24  |
| ACTH pre (µg/mL) | 4                        | 90.85   | 126.81 |
| Cortisol pre (µg/mL) | 5                    | 10.13   | 7.97   |
| TSH pre (µU/mL) | 6                                | 1.58    | 0.93   |
| TSH post (µU/mL) | 6                              | 1.25    | 0.88   |
| Free T4 pre (ng/mL) | 6                         | 1.10    | 0.55   |
| Free T4 post (ng/mL) | 6                          | 1.38    | 0.34   |
| FSH pre (µU/mL) | 5                                | 7.23    | 4.61   |
| FSH post (µU/mL) | 6                                | 13.70   | 14.74  |
| LH pre (µU/mL) | 5                                | 2.33    | 1.66   |
| LH post (µU/mL) | 6                                | 5.62    | 5.25   |
| Testosterone pre (ng/dL) | 4                   | 265.50  | 231.00 |
| Testosterone post (ng/dL) | 5                 | 305.88  | 183.85 |
| Estradiol pre (pg/dL) | 2                          | 38.25   | 6.01   |
| Estradiol post (pg/dL) | 2                        | 56.35   | 6.15   |

SD: standard deviation; GH: growth hormone; IGF-1: insulin-like growth factor 1; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; free T4: circulating free thyroxine; FSH: follicle-stimulating hormone; LH: luteinizing hormone.
Table 5. Hormone levels in patients with ACTH-secreting pituitary adenomas (Cushing’s disease) (n = 3).

| Hormone                          | Medical record with register (n) | Mean   | SD      |
|----------------------------------|----------------------------------|--------|---------|
| GH pre (ng/mL)                   | 1                                | 0.0800 |         |
| IGF-1 pre (ng/mL)                | 1                                | 200.400|         |
| Prolactin pre (ng/mL)            | 1                                | 38.100 |         |
| ACTH pre (µg/mL)                 | 3                                | 155.00 | 78.307  |
| ACTH post (µg/mL)                | 3                                | 5.433  | 1.5567  |
| Cortisol pre (µg/mL)             | 3                                | 203.067| 93.0036 |
| Cortisol post (µg/mL)            | 3                                | 1.7400 | 0.63151 |
| TSH pre (µUI/mL)                 | 1                                | 1.100  |         |
| TSH post (µUI/mL)                | 2                                | 4.3200 | 0.70711 |
| Free T4 pre (ng/mL)              | 1                                | 1.800  |         |
| Free T4 post (ng/mL)             | 2                                | 1.1450 | 0.03536 |
| FSH pre (µUI/mL)                 | 1                                | 3.300  |         |
| FSH post (µUI/mL)                | 2                                | 22.200 | 23.1931 |
| LH pre (µUI/mL)                  | 1                                | 0.700  |         |
| LH post (µUI/mL)                 | 2                                | 18.2550| 16.35538|
| Testosterone pre (ng/dL)         | 1                                | 40.00  |         |
| Testosterone post (ng/dL)        | 2                                | 53.00  | 46.669  |
| Estradiol pre (pg/dL)            | 0                                |        |         |
| Estradiol post (pg/dL)           | 0                                |        |         |

SD: standard deviation; GH: growth hormone; IGF-1: insulin-like growth factor 1; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; free T4: circulating free thyroxine; FSH: follicle-stimulating hormone; LH: luteinizing hormone.
DISCUSSION

Based on our findings, pure endoscopic endonasal transsphenoidal surgeries performed in HC-UFG for the treatment of pituitary adenomas have been efficient. The major goals of the procedure, i.e. decrease and control of specific hormone levels, were achieved in the three groups analyzed. In a retrospective assessment of medical records of 160 patients with nonfunctioning pituitary adenomas, the most common ones in the pituitary region, also operated on using pure endoscopic endonasal transsphenoidal approach, 50% of them had improvement in hormone levels. Over a 10-year period the review of medical records of 228 consecutive patients submitted to endonasal transsphenoidal adenoma removal revealed significant improvement in both their hormone levels and symptoms. In 2016, 331 patients with pituitary adenoma (174 functioning) underwent endoscopic endonasal transsphenoidal surgery, and successful hormone control was achieved in 86.8% of them. In a study including 134 patients with acromegaly, operated on using the same technique, hormone remission was observed in 73.1% of them. In another study carried out with 130 patients presenting with acromegaly and operated on using the endoscopic endonasal transsphenoidal approach, 56.9% of them exhibited normal levels of GH and IGF-1 in the postoperative period.

No statistically significant correlations were found between the variables analyzed in this study (sex, age, and Knosp grade) and the specific hormone profile of the patients with nonfunctioning macroadenomas and GH-secreting pituitary adenomas. Regarding Knosp grade, this might be explained by the small size of our sample.

Due to the small number of patients with ACTH-secreting pituitary adenomas operated on in our service, no statistical correlation was possible. Therefore, further analyses, including a higher and representative number of cases, will be necessary.

Overall, female patients, nonfunctioning macroadenomas, and Knosp grade 2 prevailed in this study. All tumors in the population under study had cavernous sinus invasion. Even not finding statistical correlation between the variables analyzed and the hormone profile in this study, the extension of cavernous sinus invasion may influence the surgery outcomes, as described by other authors.

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CORRESPONDING AUTHOR

Fernando Simões Nazareno, MD
Instituto Integrado de Neurociências
Neurosurgeon
Avenida T-15, 106, Setor Bueno
74230-010, Goiânia, GO, Brazil
E-mail: fsneurocirurgia@hotmail.com