Incidentalomas or Non-Incidentalomas: What is the Relevance of Pituitary Adenomas in the Adult?

Patricia Fainstein-Day

Servicio de Endocrinología, Metabolismo y Medicina Nuclear. Hospital Italiano de Buenos Aires. Buenos Aires, Argentina

ABSTRACT

Introduction: from the anatomical point of view, pituitary adenomas (HA) are observed in 10% of the population. They are mostly small and non-functioning. Most incidentalomas discovered in high-resolution imaging studies ordered in frequent clinical situations, such as head trauma, stroke and dementia, correspond to indolent HA. We wonder what is the clinical relevance of pituitary adenomas.

Development: clinically relevant HAs are mostly benign tumors that lead, in different degrees, to an increased morbidity and/or mortality in patients by mechanisms related to hormone hypersecretion, hormone insufficiency and/or occupying mass effects. The prevalence of clinically relevant HA is higher from what was assumed 20 years ago. It affects approximately 1/1000 of the population. The most prevalent are prolactinomas and non-functioning adenomas. Acromegaly, Cushing's disease and aggressive tumors make for complex patients with increased morbidity and mortality. Early diagnosis and multimodal treatment provide a reasonable improvement in survival. Epidemiological study of clinically relevant HAs is important for estimating the impact on health systems.

Conclusions: Higher-resolution imaging studies will continue to highlight pituitary incidentalomas. Careful evaluation of patients will identify clinically relevant HAs.

Key words: pituitary adenoma, pituitary tumor, pituitary incidentaloma, epidemiology, incidence, prevalence, prolactinoma, non-functioning pituitary adenoma, acromegaly, Cushing's disease.

INTRODUCTION

Pituitary adenomas (HAs) are monoclonal tumors resulting from somatic mutations that directly or indirectly drive cellular proliferation of anterior pituitary cells. Rarely do the mutations occur in germ cells, in which case, HAs are familial[1]. Well-differentiated HAs are also called pituitary neuroendocrine tumors (PitNETs), according to the latest World Health Organization (WHO)[2] classification.

HAs can be functioning or nonfunctioning. The most common functioning are prolactinomas, followed by tumors secreting growth hormone (GH) and adrenocorticotrophin (ACTH). Hyperthyroidism secondary to thyrotrophin (TSH) secretion is very rare. In turn, most nonfunctioning adenomas have positive

Autor for correspondence: patricia.fainstein@hospitalitaliano.org.ar, Fainstein Day P.

Received: 01/02/23 Accepted: 05/05/23 Online: 06/30/2023

DOI: http://doi.org/10.51987/revhospitalbaires.v43i2.350

How to cite: Fainstein-Day P. Incidentalomas or Non-Incidentalomas: What is the Relevance of Pituitary Adenomas in the Adult? Rev. Hosp. Ital. B.Aires. 2023;43(2):79-84.

ISSN (Online) 2314-3312

immunohistochemistry for luteinizing hormones (LH) and/or follicle-stimulating hormones (FSH); this results in hormonal hypersecretion in a few cases. The vast majority of these HAs called gonadotrophinomas are, in fact, functionless adenomas[3].

The WHO classification introduces new terminology and describes tumor subtypes according to the immunohistochemical presence or absence of transcription factors. But these are not yet available in many centers[2].

HA frequency in autopsies and imaging studies.

Data on HA prevalence can be confusing. On the one hand, anatomical, imaging, and autopsy studies of adult subjects indicate that 11 to 22.5% of the population are HA carriers. These tumors are typically small, less than 3 mm in maximum diameter, while macroadenomas, 10 mm or larger, account for less than 5% of the total. We can deduce then that progression from small microadenomas to macroadenomas is infrequent. Findings from autopsy and imaging studies do not relate to clinically relevant HAs but to asymptomatic HAs[4,5].

Pituitary incidentalomas

An increasing number of adult HA diagnoses are made from imaging studies, computed tomography (CT), or magnetic resonance imaging (MRI) of the brain, indicated by head trauma, stroke, dementia, and seizures. This class of previously unsuspected diagnosis is called "incidentaloma" in medical jargon. Only a proportion of them have clinical relevance and vary according to the resolution of the equipment used to perform the study. While most incidentalomas are HAs, other tumors, such as meningioma, craniopharyngioma, and metastases, are also detected. The proportion of clinically relevant HA diagnosed from incidentalomas is variable.

When establishing the relevance of pituitary incidentalomas, international guidelines suggest that, in all cases, patients should undergo an evaluation that includes biochemical data to detect hypersecretion and hormonal insufficiencies and a visual field in those incidentalomas that touch the optic chiasm. Unless the lesions indicate surgical or medical treatment, we suggest a repeat MRI at 12 months in micro-incidentalomas and at six months in macro-incidentalomas. Subsequent follow-up in both cases, if they have not grown, would be with MRI performed less frequently[6-8].

Clinically relevant pituitary adenomas in adults

This is the name given to HAs that produce signs and symptoms of an occupying mass, insufficiency, and/or autonomous hormonal hypersecretion.

Clinically relevant HAs are those that have an impact on the patient's life, as they are associated with increased morbidity and mortality, deterioration in the quality of life, and demand significant resources from the healthcare system[9-11].

Epidemiological studies of clinically relevant HA show that they represent 15% of all brain tumors and are the most frequent intracranial tumors in adults and adolescents. Although their prevalence is much lower than suggested by anatomical studies, they have been underestimated in oncologic registries up to 20 years ago because they are mostly benign tumors.

A non-functioning HA can grow and invade the normal pituitary producing different degrees of isolated or combined hypopituitarism: adrenal insufficiency, GH deficiency, hypothyroidism, and pituitary hypogonadism. It can also invade neighboring tissues. The dorsum of the sella turcica represents the site offering the least resistance to expansion, and the optic chiasm is a frequent victim (Fig. 1). The extension of the tumor to both sides can put pressure on the cranial nerves in the cavernous sinuses. Fortunately, diplopia, palpebral ptosis, and alterations of facial sensation are not frequent, but they occur in patients with aggressive tumors. Aggressive HA can also progress to the roof of the palate, invading the sphenoid sinus and producing infections and cerebrospinal fluid fistulas[12].

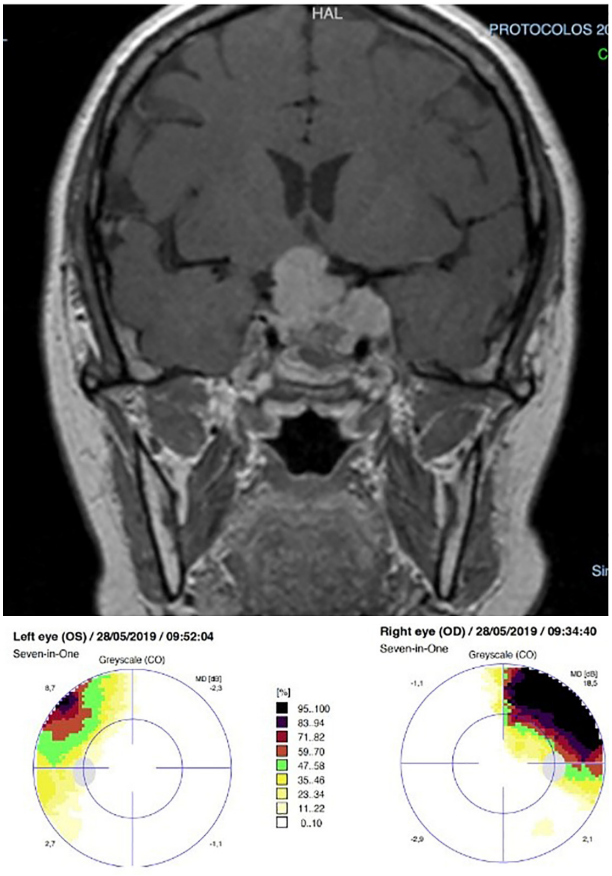


Figure 1. Non-functioning pituitary adenoma with mass effect. MRI of pituitary adenoma, showing suprasellar extension and left-sided cavernous sinus encompassing the left internal carotid artery without producing stenosis. The visual field shows bitemporal hemianopsia produced by compression of the optic chiasm.

Tumors that produce an increased and autonomous secretion of prolactin, GH, and ACTH secretion generate diseases known to most physicians, such as prolactinoma, acromegaly, and Cushing's disease, respectively.

Prolactinoma is the most frequent HA. Hyperprolactinemia leads to decreased secretion of sex steroids producing alterations of the menstrual cycle in women, sexual impotence in men, decreased libido, infertility, and osteopenia/osteoporosis in both sexes. Eighty percent of prolactinomas are microadenomas affecting young women. In males, they are usually macroadenomas with mass-occupying symptoms that sometimes have partial resistance to dopaminergic agonists (Fig. 2)[13-14].

GH hypersecretion produces gigantism in children and acromegaly in adults. The best-known signs of acromegaly correspond to acral growth and changes in the facies, which occur insidiously and imperceptibly for the patient and family members over the years. Thus, it is often diagnosed when the patient consults for orthopedic, dental, or rheumatologic complications. Other effects of GH hypersecretion are hyperglycemia and arterial hypertension, enlarged heart, thyroid, and other organs. Morbidity and mortality are related to cardiovascular disease, cerebrovascular disease, and respiratory disorders. Mortality associated with an increased prevalence of colon cancer is under discussion. Complications decrease with early diagnosis, and the prognosis for life is lower in patients unless the disease goes into complete remission, in the opinion of some authors. Eighty percent of growth hormone-secreting tumors are macroadenomas that affect men and women equally (Fig. 3)[15].

The most common manifestation of chronic hypercortisolism in adult Cushing's disease is centripetal or visceral obesity. But specific areas of adipose tissue deposition distinguish it, such as the face, supraclavicular hollows, and the dorsocervical region, forming the classic full-moon face and buffalo hump. However, specific physiognomic changes are related to protein loss expressed in thin and fragile skin, muscular hypotrophy in the shoulder and pelvic girdles, and osteoporosis (Fig. 4). Other known deleterious effects of hypercortisolism include arterial hypertension, diabetes mellitus, immunodeficiency, and psychiatric disturbances. Historically, Cushing's disease represents a severe disease with high morbidity and mortality related to cerebral and cardiac vascular disease and infections. Most ACTH-secreting tumors are microadenomas that are sometimes difficult to localize. Early diagnosis and control of cortisol levels have improved this picture, yet, long-term follow-up shows that, in these patients, the prognosis for life remains compromised even after remission of the disease. Therefore, Cushing's disease constitutes a challenge for physicians.[16]

It is relevant to mention that functioning tumors may have, in turn, with variable frequency, complications related to the mass effect.

Apart from prolactinomas, the preferred treatment for clinically relevant HAs is an endoscopic or transsphenoidal surgery. In non-functioning HAs, surgical treatment aims at reducing the mass effect. Endocrinologic replacement therapy for hormone deficiencies is of utmost importance to reduce morbidity and mortality and improve the quality of life of patients[13,14].

Prolactinomas require treatment with cabergoline or other dopaminergic agonists that normalize prolactin secretion and significantly decrease tumor size with a low frequency of adverse effects[16,17]. With acromegaly and Cushing's disease, the diseases are more severe, and the patients are also more complex. GH- and ACTH-secreting tumors are candidates for surgery, and should hormonal hypersecretion not be normalized, there are different drugs used, some of which are classic and well-known, such as somatostatinergic agonists (octreotide and lanreotide) in acromegaly, and ketoconazole and other enzymatic inhibitors of cortisol synthesis in Cushing's disease. In cases where biochemical control is impossible to obtain with drugs or the tumors are invasive, radiotherapy is used[13-17].

The new drugs are more effective, simpler to use, and have fewer adverse effects but are more expensive. They have developed from medical research and are in various stages of clinical investigation or use in some countries. Control of hormone hypersecretion in acromegaly and Cushing's disease is the only way to improve the high morbidity and mortality in these patients[3,15,16].

Although the frequency of pituitary cancer defined by the presence of metastases is less than 0.5% of all HA, 10-15% show a higher rate of growth, recurrence, and resistance to treatment. The treatment of these invasive and aggressive tumors is multimodal and includes radiotherapy in all its technical variants and cell proliferation inhibitor drugs[17].

It follows from the above that, except for most prolactinomas, optimal treatment of clinically relevant HAs requires a team effort of experts in endocrinology, neurosurgery, radiation therapy, neuropathology, imaging, and oncology.

Epidemiology of clinically relevant pituitary adenomas: our experience in the Plan de Salud del Hospital Italiano de Buenos Aires

In 2016, we published a study on the incidence and prevalence of clinically relevant HAs in the Plan de Salud del Hospital Italiano over 10 years conducted among 135 019 active members over 18 years of age[18].

The diagnosis of prolactinoma, acromegaly, and Cushing's disease was based on symptoms of hormonal hypersecretion, whereas in non-functioning tumors, on occupying mass symptoms, and pituitary hormone deficiency.

The overall prevalence of these tumors was 97.76/100,000, one pituitary tumor per thousand active associates (1/1030), with a higher incidence in women than in men (77.3%).

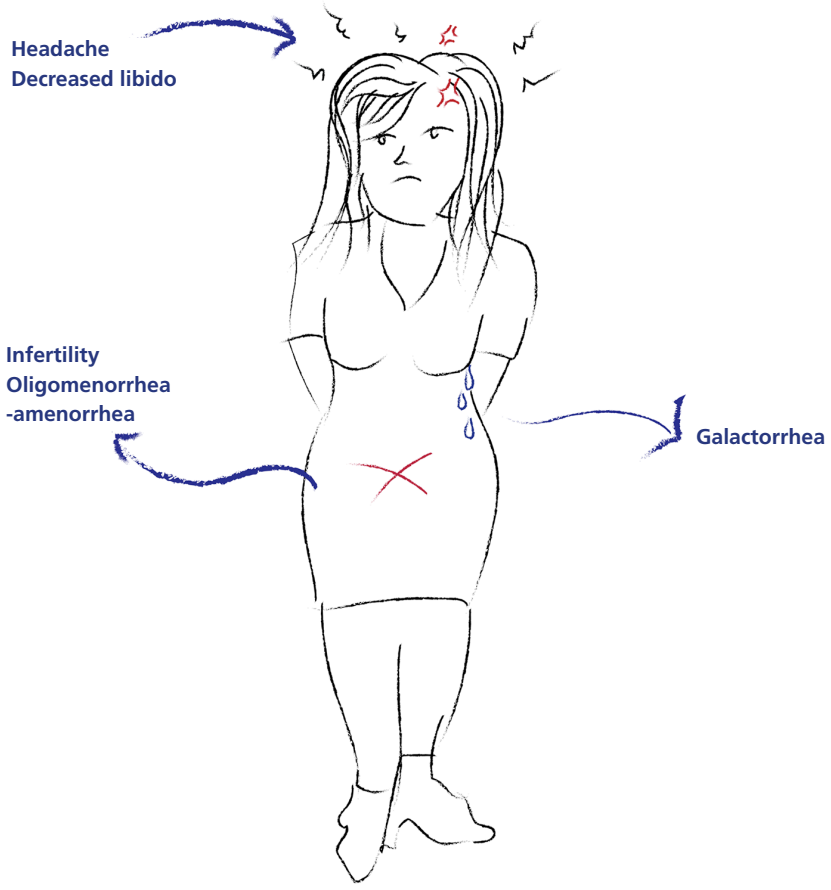
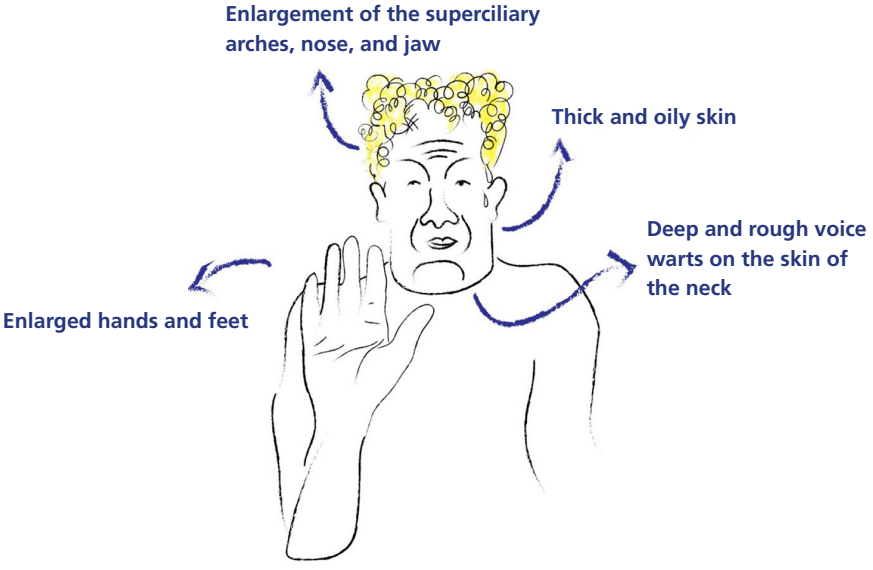


Figure 2. Prolactinoma. Typical symptoms and signs of prolactinoma in women.



Headaches / Excessive sweating / Arthralgias / Snoring / Sleep apnea / High blood pressure / Cardiovascular disease / Chronic obstructive pulmonary disease / Goiter / Cancer

Figure 3. Acromegaly. Typical symptoms and signs of acromegaly.

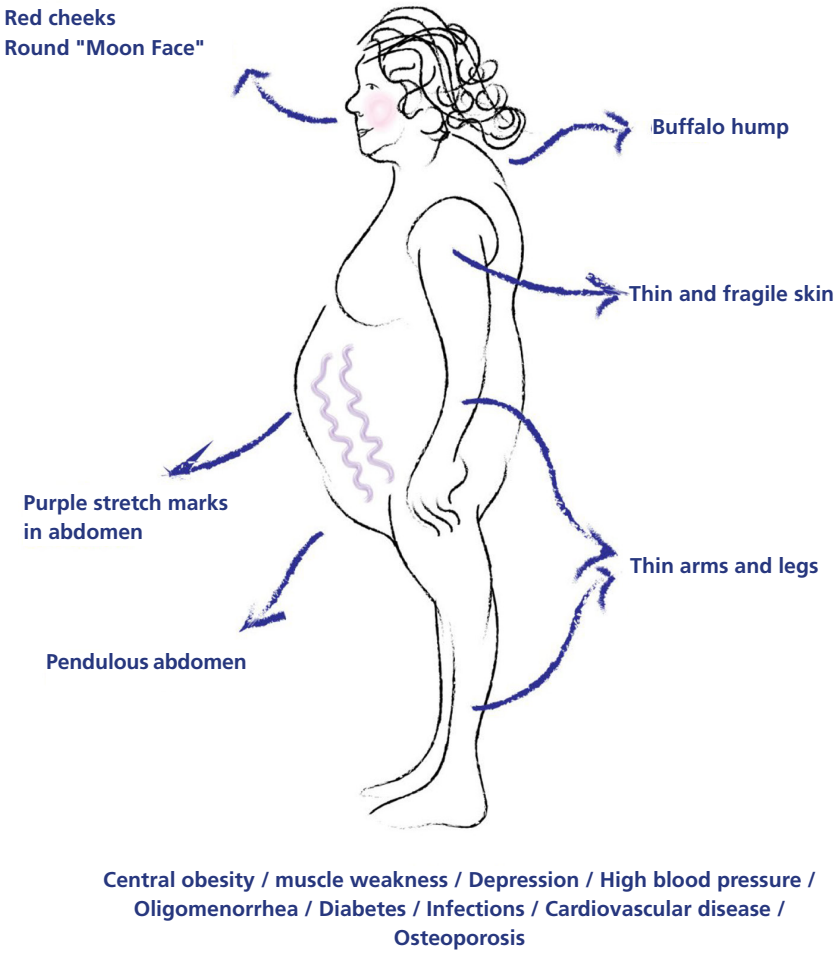


Figure 4. Cushing's disease. Symptoms and signs characteristic of Cushing's disease

The most frequent type of tumors were prolactinomas (57.6%), followed by non-functioning tumors (22%), acromegaly (14.2%), and Cushing's disease (6.1%). We did not detect any thyrotropinoma. Approximately half of the tumors were microadenomas (52.3%)[18].

These data are comparable to those found in similar epidemiological studies. The first was conducted in Liège (Belgium)[19]. It was followed by others in England, Malta, Iceland, and Canada19, between 2006 and 2016. A comparison of these epidemiological studies, including ours, is provided in a recent publication[20].

Higher-resolution imaging studies increasingly point to pituitary incidentalomas more frequently. An appropriate evaluation of patients will be able to discriminate those with clinically relevant HA from indolent tumors.

On the other hand, more effective treatments decrease morbidity and prolong patients' lives. The prevalence of patients with clinically relevant HA will likely increase, as will the demand for healthcare system resources.

CONCLUSIONS

From the anatomical point of view, AHs appear in 1 out of every ten inhabitants. They are small and non-functioning. Most incidentalomas correspond to this type of indolent tumor.

One out of every thousand inhabitants is affected by clinically relevant HA.

The clinical relevance of HAs, incidentalomas or not, is given by the increased morbidity and/or mortality due to mechanisms related to hormonal hypersecretion, hormonal insufficiency, and/or occupying mass effects. The most prevalent ones are prolactinomas and non-functioning adenomas.

The epidemiological study of clinically relevant HAs is essential for estimating their impact on health systems.

Except for most prolactinomas, clinically relevant HAs require the teamwork of endocrinologists, neurosurgeons, imaging specialists, neuropathologists, and radiation therapists.

Conflict de interests: the author declares no confict of interests.

REFERENCIAS

1. Vandeva S, Daly AF, Petrossians P, et al. Somatic and germline mutations in the pathogenesis of pituitary adenomas. Eur J Endocrinol. 2019;181(6):R235-R254. https://doi.org/10.1530/EJE-19-0602.
2. Asa SL, Mete O, Perry A, et al. Overview of the 2022 WHO Classification of Pituitary Tumors. Endocr Pathol. 2022;33(1):6-26. https://doi.org/10.1007/s12022-022-09703-7.
3. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382(10):937-950. https://doi.org/10.1056/NEJMra1810772.
4. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101(3):613-919. https://doi.org/10.1002/cncr.20412.
5. Buurman H, Saeger W. Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. Eur J Endocrinol. 2006;154(5):753-758. https://doi.org/10.1530/eje.1.02107.
6. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. Endocrinol Metab Clin North Am. 2008;37(1):151-171, xi. https://doi.org/10.1016/j.ecl.2007.10.011.
7. Fainstein Day P, Guitelman M, Artese R, et al. Retrospective multicentric study of pituitary incidentalomas. Pituitary. 2004;7(3):145-148. https://doi.org/10.1007/s11102-005-1757-1. Errata en: Pituitary. 2011;14(2):198. Susana, María [corrected to Mallea Gil, Maria Susana]; Gil, Mallea [removed].
8. Freda PU, Beckers AM, Katznelson L, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(4):894-904. https://doi.org/10.1210/jc.2010-1048.
9. Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, et al. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. J Clin Endocrinol Metab. 2000;85(4):1420-1425. https://doi.org/10.1210/jcem.85.4.6498.
10. Brue T, Castinetti F. The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis. 2016;11(1):135. https://doi.orf/10.1186/s13023-016-0516-x.
11. Karavitaki N, Collison K, Halliday J, et al. What is the natural history of nonoperated nonfunctioning pituitary adenomas? Clin Endocrinol (Oxf). 2007;67(6):938-943. https://doi.org/10.1111/j.1365-2265.2007.02990.x.
12. Chanson P, Raverot G, Castinetti F, et al. Management of clinically non-functioning pituitary adenoma. Ann Endocrinol (Paris). 2015;76(3):239-247. https://doi.org/10.1016/j.ando.2015.04.002.
13. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006;65(2):265-673. https://doi.org/10.1111/j.1365-2265.2006.02562.x.
14. Fainstein Day P, Glerean M, Lovazzano S et al. Gender differences in macroprolactinomas: study of clinical features, outcome of patients and ki-67 expression in tumor tissue. Front Horm Res. 2010;38:50-58. https://doi.org/10.1159/000318494.
15. Fleseriu M, Biller BMK, Freda PU, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021;24(1):1-13. https://doi.org/10.1007/s11102-020-01091-7.
16. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9(12):847-875. https://doi.org/10.1016/S2213-8587(21)00235-7.
17. Castinetti F. Radiation techniques in aggressive pituitary tumours and carcinomas. Rev Endocr Metab Disord. 2020;21(2):287-292. https://doi.org/10.1007/s11154-020-09543-y.
18. Fainstein Day P, Loto MG, Glerean M, et al. Incidence and prevalence of clinically relevant pituitary adenomas: retrospective cohort study in a health management organization in Buenos Aires, Argentina. Arch Endocrinol Metab. 2016;60(6):554-561. https://doi.org/10.1590/2359-3997000000195.
19. Daly AF, Rixhon M, Adam C, et al. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab. 2006;91(12):4769-4775. https://doi.org/10.1210/jc.2006-1668.
20. Daly AF, Beckers A. The epidemiology of pituitary adenomas. Endocrinol Metab Clin North Am. 2020;49(3):347-355. https://doi.org/10.1016/j.ecl.2020.04.002.