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CLINICAL REPERCUSSIONS OF PITUITARY ADENOMAS AND POSSIBLE MANAGEMENTS: A LITERATURE REVIEW

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Abstract: Goal: Discuss the prognosis of pituitary adenomas considering their clinical consequences and resulting systemic changes, in addition to possible therapeutic measures for management. **Method:** Literature review carried out from October to November 2022, through searches in the Scielo and Pubmed databases with the descriptors "pituitary adenoma", "symptoms", "treatment" and "diagnosis". 2925 articles were found and, after the inclusion criteria, 13 studies were selected. **Review:** Pituitary adenoma (HA) is the second most common intracranial tumor in the population. HAs can be asymptomatic, oligosymptomatic or cause clinical repercussions for the patient, ranging from visual disturbances to infertility. In this context, the diagnosis of HAs can be complex and must be performed by interdisciplinary professionals, with magnetic resonance imaging being the gold standard exam for imaging diagnosis. **Final Considerations**: There are variants regarding the tumor - extension, pace of evolution and degree of impact on surrounding structures - that must be taken into account in order to shape an individualized and effective planning for each patient.

Keywords: Pituitary adenoma; Diagnosis; Treatment and Symptoms.

INTRODUCTION

The pituitary gland, anatomically divided into two parts, comprising the adenohypophysis and neurohypophysis, is of great clinical interest, since it presents functional impairment when some pathologies are present. Pituitary adenomas (HA) are benign tumors detected by typical signs and symptoms or insidiously by accidental imaging findings, with indication due to atypical symptoms, including headache. It is believed that its pathophysiology is related to the clonal expansion of abnormal cell lineages, having

two possible origins: genetically established mutations or chromosomal abnormalities (DALY A F.; BECKERS A., 2020).

Epidemiologically, HA accounts for 15 to 20% of the prevalence of intracranial tumors, with a reported incidence of approximately 3.9/100,000. Its manifestations are significant, bearing in mind that they may be due to changes in hormone production, such as hypogonadotropic hypogonadism, acromegaly, Cushing's syndrome and pituitary apoplexy from clinically relevant adenomas, with diagnoses confirmed by imaging tests or hormonal tests. However, incidentalomas can bring asymptomatic or oligosymptomatic conditions (MORTEN WINKLE M. et al., 2019).

Choosing the most appropriate treatment is a challenge for the patient's quality of life and prognosis. Without going into detail, treatments for adenomas consist of surgeries, such as transsphenoidal adenomectomy, control with dopamine agonists, glucocorticoid antagonists and/or hormone blockers, and radiotherapy, in an attempt to restore hormonal balance and maintain hormone-dependent physiological mechanisms (MELMED S., 2020). In this context, the objective of the present study is to discuss the prognosis of pituitary adenomas, considering their clinical consequences and resulting systemic changes, in addition to possible therapeutic measures for the management of such conditions in adult carriers.

METHODOLOGY

The present study is a Bibliographic Review, carried out from October to November 2022. The results were approached in a descriptive way before the following theme: "What is the prognosis of pituitary adenomas considering their clinical consequences and resulting systemic changes, in addition to of possible therapeutic measures for managing such conditions in adult carriers?" In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients who presented pituitary adenoma, investigating physiological alterations in the systems related to the condition, in addition to seeking the methods of diagnosis and treatment of better prognosis.

For the literature search, the PubMed and SciELO databases were used using the following descriptors in combination with the Boolean term "AND": Pituitary adenoma, Symptoms, Treatment and Diagnosis. Inclusion criteria include studies in Spanish, English and Portuguese; published over a five-year period. Exclusion criteria rely on studies that did not directly address the subject studied, not available in full, in addition to not meeting the inclusion criteria.

From this search, 2925 articles were found, of which 2917 articles belonged to the PubMed database and 8 articles to SciELO. After applying the inclusion and exclusion criteria, 12 articles were selected from the PubMed database and 1 article from Scielo, totaling 13 studies to compose the collection, which were published between 2019 and 2021 and are of the systematic review and review type. original.

DISCUSSION

HA is the second most common intracranial tumor in the population, whose clinical manifestations can be at the level of the central nervous system and/or systemic due to the physiological function of the affected gland (LIU X. et al., 2021). It is subdivided into microadenoma (<10mm) or macroadenoma (<10mm), and can be clinically classified as hypersecretive or hyposecretive depending on their behavior (MELMED S., 2020; MORTEN WINKLE M. et al., 2019; JAURSCH-

HANCKE C. et al., 2021). Hypersecretory syndromes are associated with the cell lineage of origin, which arises from clinical characteristics related to the hormone secretion pattern, such as growth hormone (GH)-secreting somatotrophs resulting in acromegaly, prolactin-secreting lactotrophs, which result in hyperprolactinemia, and thyrotropin-secreting thyrotrophs that result in hyperthyroidism. Hyposecretory syndromes, on the other hand, originate in gonadotrophic cells and are often manifested through hypogonadism and masses in the sella turcica (MELMED S., 2020; JAURSCH-HANCKE C. et al., 2021).

Prolactinoma is the most common secretory tumor, representing 60% of all HA, with a significant prevalence in females with an appearance ratio of 20:1. In women, elevated serum prolactin levels are higher than gonadotropins, resulting in gynecological changes, such as amenorrhea, oligomenorrhea, infertility and decreased libido. In men, however, impotence, oligospermia or azoospermia are observed, which also result in secondary infertility events. Both can present galactorrhea, reduced bone density and increased risk of vertebral fracture (MELMED S., 2020; MORTEN WINKLE M. et al., 2019).

GH-secreting somatotrophic tumors are responsible for causing acromegaly, which leads to significant metabolic and somatic dysfunction. The clinical features of such patients include deepening of the voice, hyperhidrosis, frontal cranial protuberance, carpal tunnel syndrome, arthropathies, vertebral fractures, increased risk of hypertension, arrhythmias, hypertrophic heart diseases, increased risk of diabetes due to insulin resistance and glucose intolerance, fluid retention, and ultimately sleep apnea. In 30% of cases, hyperprolactinemia is found, with manifestation of galactorrhea (MELMED S., 2020; MORTEN WINKLE M. et al., 2019).

Corticotrophic adenomas secrete corticotropin and represent around 15% of pituitary tumors, being more common in women (MELMED S., 2020). They are characterized by healthy but hypoactive adrenocorticotrophic cells (MORTEN WINKLE M. et al., 2019). Comorbidities such as the central obesity, hypertension, osteoporosis and diabetes can also be related to this condition (MELMED S., 2020). Hypersecretion of thyroid-stimulating hormone (TSH) is very rare, and when present, it has clinical symptoms related to thyrotoxicosis and, as laboratory findings, elevation of thyroxine and TSH levels (MORTEN WINKLE M. et al., 2019).

Silent-type AH are tumors that synthesize one or more anterior pituitary hormones, but do not result in signs and symptoms of hormonal hypersecretion. They can be truly silent, without clinical changes or serum hormone secretion corresponding to excessive hormone secretion, as well as symptomatological changes, or "whispering" silent, which generate only subtle clinical signs. Silent corticotrophic adenomas are characterized by the absence of Cushing's syndrome features and either a normal (completely silent) serum cortisol level or a mildly elevated ("whispering") serum cortisol level. Thyrotrophic adenomas are rare, and the vast majority are clinically silent, with 0.50% presenting with extrasellar extension, such as the visual disturbance and headache, but without hyperthyroidism (DRUMMOND J. et al, 2018).

However, it is possible to find positive plurihormonal adenomas for P1T1. These tumors tend to occur in a younger age group, have an aggressive behavior and are often not silent with symptoms related to hormonal excess (DRUMMOND J. et al, 2018).

Although most AH have a good prognosis and benign involvement, a small number can be aggressive, with uncontrolled tumor growth and poor prognosis (LIU X. et al., 2021).

The diagnosis of HA is complex and must be performed by interdisciplinary professionals, such as neurologists, neurosurgeons, endocrinologists, radiologists, ophthalmologists and otorhinolaryngologists (HLAVÁČ M. et al., 2019). They can usually be diagnosed by symptoms generated by compression of the optic chiasm, which leads to severe and progressive deficits in vision, resulting in vision loss, headache and cranial nerve dysfunction (MORTEN WINKLE M. et al., 2019; DRUMMOND J. et al., 2018).

The suspicion of HA is based on symptoms, laboratory and imaging tests, with a definitive diagnosis being possible only by histology and immunohistochemistry (MALDANER N. et al., 2018). HA are often incidental findings, called "incidentalomas", a consequence of the increase in imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) for the investigation of other diseases or complaints (MAHAJAN A. et al, 2020). The patient with HA, regardless of the way it was diagnosed, either by the symptoms presented or by an incidental finding, must be evaluated regarding its clinical history and physical examination before any laboratory and/or functional examination (JAURSCH-HANCKE C. et al, 2021). Neurological examination, visual acuity and oculomotor function are part of this assessment (HLAVÁČ M. et al. 2019).

The gold standard for the imaging diagnosis of HA is MRI, which has a higher sensitivity compared to CT. When HA is first discovered by CT or inefficiently visualized by it, MRI must be requested, including dynamic contrast (JAURSCH-HANCKE C. et al., 2021). The use of CT is indicated only in cases that require better preoperative elucidation, differential diagnoses and MRI contraindications (MALDANER N. et al., 2018). The indicated MRI must perform thin slices, in the coronal and sagittal planes, with and without contrast, in order to visualize the sella turcica (HLAVÁČ M. et al. 2019). Other methods, such as magnetic resonance image reconstruction by Deep Learning, have been studied to improve sensitivity in the detection of pituitary adenomas (LEE D.H. et al., 2021). In addition to MRI contributing to the diagnosis, it can also be used preoperatively to predict response to treatment of invasive pituitary adenomas, using analysis of MRI radiomic signatures (FAN Y. et al., 2019).

According to Jaursch-Hancke C. et al. (2021), investigations with endocrine therapeutic tests are used as a way to evidence or rule out secretory alterations in the hormonal flow, mainly because, even with small sizes, HA can be hormonally operative, as previously mentioned in this study. Effective laboratory tests for the diagnosis in the incipient context of any pituitary tumor are: 1 mg dexamethasone suppression test, IGF-1, cortisol prolactin TSH, free T4, free T3, luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the case of premenopausal women, estradiol must also be evaluated and, in men, total testosterone (JAURSCH-HANCKE C. et al., 2021). With regard to the differential diagnosis, it is necessary to consider that, despite of the higher prevalence of HA as intrasellar tumors, other possibilities must be considered, such as essentially intrasellar cystic lesions (HLAVÁČ M. et al. 2019), and also benign cysts - such as arachnoids, epidermoid and Rathke's pouch cysts (MALDANER N. et al., 2018).

According to Maldaner N. et al. (2018), it is also necessary to evaluate, in specific cases of pregnant or lactating patients, physiological pituitary hyperplasia, which has symptomatic similarities and also can

be confused with severe psychoses and prolonged severe primary hypothyroidism, allowing incorrect diagnoses of AH. In addition, the evaluation of parasellar growths such as gliomas, meningiomas, lymphomas and metastases is essential, as they may have similar manifestations, causing headache, visual field problems, and also, less commonly, hyper or hypoactive pituitary gland. Finally, it is substantial to rule out inflammatory-granulomatous processes such as histiocytosis, sarcoidosis and tuberculosis, infectious evolutions such as abscesses and autoimmune conditions consonant with hypophysitis, such as arteriovenous fistulas, which, as a result of their entangled relationship with the cavernous sinus, fortuitously generate enlargement of the pituitary gland.

The treatment of HA is considered difficult and sometimes controversial. Surgery plays an important role in the management of the patient's pathology, however, in order to obtain a better prognosis, it is necessary to take into account some items, such as which types and conditions of adenomas need to be operated on and, if there is any intercurrence and the surgery does not is successful, which would be the and other possible therapeutic options. For this reason, it is necessary to know the different possibilities of therapeutic management, which are divided into: clinical, radiotherapy and surgical treatment (PÉREZ-LÓPEZ C. et al., 2021).

Clinical treatment is most often used as a way to prevent the growth of adenomas that have already been submitted to radiotherapy and surgery, and still suffer recurrence. Because they have a low response rate, such treatments are considered a last option (PÉREZ-LÓPEZ C. et al., 2021). According to Maldaner N. et al. (2018), prolactinomas are an exception among pituitary adenomas, because when they are clinically treated with medications, a better success rate is obtained. Such treatment is carried out using dopaminergic agonists, which help regulate blood levels of prolactin in 90% of cases, acting by inhibiting prolactin secretion. Thus, such a therapeutic approach leads to tumor reduction and improves the patient's quality of life, with a consequent improvement in fertility and a decrease in visual disturbances.

Radiotherapy is a form of auxiliary treatment when there is a failure in the surgical procedure or when the tumor is partially resected, and also in cases where clinical treatment has not been effective. A distinction is made between stereotactic radiosurgery, performed with high-dose irradiation only once, being the most used technique currently according to the literature; and fractionated radiotherapy, which is applied for a few weeks and uses a low dose. In a general context, the rates of evolution or recurrence, especially in those patients who underwent surgical approaches, decrease with the use of radiotherapy (PÉREZ-LÓPEZ C. et al., 2021).

Surgery is the management of choice for those who have a large volume generating mass effect and repercussions on adjacent structures. Currently, the transcranial approach, through craniotomy, is restricted to adenomas that have suprasellar or parasellar growth. Thus, the vast majority of surgically treated HA are resected by a route known as the transnasal transsphenoidal route, which allows more direct access to the pituitary gland and provides an aesthetically attractive result, without visible scars. (FLESERIU M.; POPOVIC V., 2020).

FINAL CONSIDERATIONS

The most frequent tumors of the pituitary gland occur in the anterior portion and functionally interfere with the synthesis and secretion of hormones such as prolactin,

FSH, LH, TSH and GH, resulting in varied etiologies. Due to its diversity of types and manifestations of such pathology, the possible therapeutic approaches vary between surgery, radiotherapy and clinical treatment. There are variants regarding the tumor, considering the intracranial location, size, pace of evolution and degree of severity/impact on the surrounding structures, to be taken into account, in order to shape an adequate and personalized treatment, which provide quality of life and effective symptomatic reduction.

REFERENCES

1. DALY, Adrian F.; BECKERS, Albert. The epidemiology of pituitary adenomas. **Endocrinology and Metabolism Clinics**, v. 49, n. 3, p. 347-355, 2020.

2. DRUMMOND, Juliana et al. Clinical and Pathological Aspects of Silent Pituitary Adenomas. **J Clin Endocrinol Metab.** v.104, n. 7, p. 2473–2489, 2018.

3. FAN, Yanghua et al. Development and validation of an MRI-based radiomic signature for the preoperative prediction of treatment response in patients with invasive functional pituitary adenoma. **European journal of radiology**, v. 121, p. 108647, 2019.

4. FLESERIU, Maria; POPOVIC, Vera. The journey in diagnosis and treatment, from pituitary adenoma to aggressive pituitary tumors. **In Reviews in Endocrine and Metabolic Disorders**, v. 21, n. 2 p. 201-202, 2020.

5. HLAVÁČ, Michael et al. Differential diagnosis and treatment of pituitary adenomas. **HNO: Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie**, v. 67, n. 4, p. 307-318, 2019.

6. JAURSCH-HANCKE, Cornelia et al. The interdisciplinary management of newly diagnosed pituitary tumors. **Deutsches Arzteblatt International**, v. 118, n. 14, p. 237-243, 2021.

7. LEE, Da Hyun et al. Deep learning-based thin-section MRI reconstruction improves tumour detection and delineation in pre-and post-treatment pituitary adenoma. **Scientific Reports**, v. 11, n. 1, p. 1-10, 2021.

8. LIU, Xiaohai et al. Pituitary adenoma or pituitary neuroendocrine tumor: a narrative review of controversy and perspective. **Translational Cancer Research**, v. 10, n. 4, p. 1916, 2021.

9. MAHAJAN, Amit et al. Diagnosis and Management of pituitary disease with focus on the role of Magnetic Resonance Imaging. **Endocrine**, v. 68, n. 3, p. 489-501, 2020.

10. MALDANER, Nicolai et al. Modern management of pituitary adenomas-current state of diagnosis, treatment and follow-up. **Praxis**, v. 107, n. 15, p. 825-835, 2018.

11. MELMED, Shlomo. Pituitary-tumor endocrinopathies. **New England Journal of Medicine**, v. 382, n. 10, p. 937-950, 2020.

12. MORTEN WINKLE, Møller et al. Hypofyseadenom. **Ugeskr Læger**, v. 05180331, n. 181, 2019.

13. PÉREZ-LÓPEZ, Carlos; ÁLVAREZ-ESCOLÁ, Cristina; GUERRERO, Alberto Isla. Therapeutic approach to non-functioning pituitary adenomas. **Medicina Clínica (English Edition)**, v. 156, n. 6, p. 284-289, 2021.