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TUMOR PITUITARY APOPLEXIA IN EMERGENCY – LITERATURE REVIEW

Elizandra Hertel Lenhardt
Universidade de Cuiabá, medicine course
Cuiabá-MT
http://lattes.cnpq.br/7247953917565088

Aline Fávero da Silva
Universidade de Cuiabá, medicine course
Cuiabá-MT
http://lattes.cnpq.br/8909201598543513

Évellin do Espirito Santo
Universidade de São Paulo, faculdade de farmácia
São Paulo-SP
http://lattes.cnpq.br/1139455112493437

Andreia Tomborelli Teixeira
Escola de saúde pública do estado do Mato Grosso
Cuiabá-MT
http://lattes.cnpq.br/1583522586420003

Pedro Alberto Muffato
Universidade de Cuiabá, medicine course
Cuiabá-MT
http://lattes.cnpq.br/7961291434608301

Abstract: Pituitary apoplexy is a neuroendocrine emergency characterized by ischemia or more commonly sudden pituitary hemorrhage. Its occurrence is greater in those cases with previous pituitary adenoma. It has a variable clinical picture, involving sudden or insidious headaches, visual changes associated with compression of the optic tract or cranial nerves, focal neurological deficits, hypopituitarism, adrenocortical insufficiency and even coma and death. In view of the above, the present study aims to identify tumoral pituitary apoplexy as a neuroendocrine emergency that must be promptly recognized, aiming for its rapid management in urgent and emergency services. This is a literature review carried out in the months of August and September 2023. The treatment of choice is controversial and depends, mainly, on the level of consciousness, the degree of visual impairment and the level of hypopituitarism, and may involve the use of glucocorticoids., hormone replacement and neurosurgical intervention. Adequate and immediate therapeutic intervention contributes to a more favorable outcome, reducing the occurrence of sequelae.
Keywords: Pituitary apoplexy; neuroendocrine urgency; pituitary adenoma.

INTRODUCTION

Pituitary apoplexy is a neuroendocrine emergency characterized by an acute vascular event in the pituitary gland, in the form of ischemia or more commonly sudden pituitary hemorrhage (MAYOL DEL VALLE; DE JESUS, 2023). Although it can occur in structurally normal glands, its occurrence is greater in cases with previous pituitary adenoma, especially macroadenoma, a condition in which the tumor measures more than 10 mm in diameter (MORENO et al., 2015).

It is a rare condition, caused by progressive expansion in the glandular site, with a variable clinical picture, involving sudden or insidious headaches, visual changes associated with compression of the optic tract or cranial nerves, focal neurological deficits, hypopituitarism, adrenal insufficiency and even coma and death (MORENO et al., 2015).

Articles in the literature on pituitary apoplexy often lack detailed information on the prevalence of the condition in specific populations, risk factors, most effective treatment approaches, long-term outcomes, and large-scale prospective studies. Furthermore, they may be limited in terms of data on patients' quality of life after treatment and prevention strategies.

In view of the above, the present study aims to describe and point out, in the form of a literature review, tumoral pituitary apoplexy as a neuroendocrine emergency that must be promptly recognized, aiming for its rapid management in urgent and emergency services.

METHODOLOGY

This is a literature review in the form of a bibliographic search, carried out in the months of August and September 2023. After choosing the central theme, a bibliographic survey of scientific articles was carried out, using the descriptor "*pituitary apoplexy*" in the indexers PubMed/ MEDLINE (international literature in health sciences) and Scielo (online scientific electronic library).

The inclusion criteria were the following: articles published between 2010 and 2023, in Portuguese and English. This way, original articles, guidelines, retrospective studies, reviews on the topic and case reports were selected. Theses, dissertations, letters to the editor and incomplete texts were excluded. After analyzing the results, 22 articles were selected for the preparation of the present study.

THEORETICAL FOUNDATION

Initially described by Pearce Bailey in 1898 (MAYOL DEL VALLE; DE JESUS, 2023), tumoral pituitary apoplexy is a rare vascular event on the pituitary gland, with neuroendocrine manifestation, generating a potentially serious syndrome that requires emergency management. Its pathophysiological mechanism is not yet well understood; however, several pieces of evidence indicate that the blood vessels present in pituitary adenoma present incomplete maturation, little fenestration and a fragmented basement membrane, which may increase the risk of hemorrhagic events (ROCHA RAINHA et al., 2012).

The reported occurrence rate of pituitary apoplexy demonstrates a wide range from 1.5% to 27.7% in cases of pituitary adenoma. It is important to highlight that many of these reports do not distinguish between symptomatic and asymptomatic patients (MAYOL DEL VALLE; DE JESUS, 2023).

Tumor pituitary apoplexy, which is associated with adenoma, occurs in 60 to 80% of cases in previously asymptomatic patients without a previous diagnosis of the neoplasm. It frequently occurs between the fifth and seventh decades of life and is slightly more prevalent in men, within a male:female ratio of 1.6:1 (MORENO et al., 2015). In only 30% of cases, however, precipitating and risk factors can be listed: traumatic brain injury, systemic arterial hypertension, hypotension, diabetes mellitus, hypercoagulable state, use of antiplatelet agents and anticoagulants, dopaminergic blockers and previous heart surgeries (ROCHA RAINHA et al., 2012), in addition to thrombocytopenia (THOMAS, 2019), use of bromocriptine and cabergoline (GHADIRIAN, 2018), drugs for the treatment of erectile dysfunction (UNEDA, 2019) and local radiation (YU, 2020).

The clinical picture is variable and, in most patients, the apoplectic event is the initial manifestation of pituitary adenoma. It arises as a result of the progressive growth of the intrasellar content, causing an increase in its pressure and compressive effects (ROCHA RAINHA et al., 2012). The most common and early symptom is headache, which in most cases presents as sudden, intense, retro-orbital, bifrontal or suboccipital, associated or not with vomiting (MUTHUKUMAR, 2020; BRIET, 2015; GRZYWOTZ, 2017). There are numerous theories to explain the mechanisms involved in pituitary apoplexy headache, among which the following stand out: involvement of the superior branch of cranial nerve V (trigeminal) within the cavernous sinus, meningeal irritation, compressive effect on the dura mater or sellar enlargement (MAYOL, 2023). Headache lasting more than seven days and refractory to conventional treatments must also be considered.

The progressive increase in intrasellar pressure results in compression of glandular tissue and local ischemic events, leading to hypopituitarism and consequent acute adrenal insufficiency. Compressive phenomena can occur in up to 70% of patients, including: ocular motility disorders, diplopia, eyelid ptosis and strabismus, due to lateral compression of the cranial nerves associated with ocular motility, especially cranial nerve III (oculomotor), which is the most affected in this condition (RICCIUTI, 2018); lethargy and hemiplegia due to narrowing of the cavernous portion of the carotid artery; reduction in visual acuity or field and changes in the level of consciousness due to superior compression of the optic tract or chiasm and hypothalamus (ROCHA RAINHA et al., 2012; ZOLI, 2017; BARKHOUDARIAN, 2019).

Hypopituitarism is the complication most associated with morbidity and mortality. Around 80% of patients develop deficiency in one or more pituitary sectors. It occurs

mainly in the form of partial hypopituitarism, and the most prevalent deficiency is that of adrenocorticotropic hormone (ACTH), which causes adrenal insufficiency (BRIET, 2015). ACTH, thyroid-stimulating hormone (TSH) and gonadotropin deficiency occur, respectively, in 40 to 100%, 25 to 80% and 60 to 100% of cases (ROCHA RAINHA et al., 2012).

Differential diagnoses involve benign and malignant conditions, such as: meningitis, meningoencephalitis, stroke, subarachnoid hemorrhage, hypertensive encephalopathy, Rathke's pouch cyst, cavernous sinus thrombosis, temporal arteritis, optic neuritis, ophthalmoplegic migraine, Sheehan's syndrome and other sellar and parasellar tumors, such as craniopharyngioma (JUNG, 2020; LAW-YE, 2017; MARTINEZ, 2019; PEDRO, 2019; SHABAS, 2017). It is up to the clinician working in the emergency room to pay particular attention to headache complaints, which are shared by all these pathologies.

As a biochemical marker, hypoprolactinemia can be used as a predictor of poor prognosis. Regarding radiological findings, head computed tomography (CT) without contrast, which is the first-line examination in the acute phase of hemorrhage, may reveal intra or suprasellar hyperdensity in the first three days of hemorrhage evolution. Magnetic resonance imaging (MRI), in turn, is the most sensitive method, allows diagnostic confirmation in up to 90% of cases and can assist in the assessment of carotid artery involvement, in addition to being free of artifacts. (ROCHA RAINHA et al., 2012). MRI has the ability to identify the presence of sellar hemorrhage both in the hyperacute phase (less than 24 hours of evolution), with isointensity on T1 weighting and hyperintensity on T2, and in the acute phase (between one and three days of evolution), with hypointensity on T2 and T1, and in the late phase (over three days), with hyperintensity on T1 and T2 (WILIKIE; AL-MAHFOUDH, 2012).

There is a severity grading scale for pituitary apoplexy, which involves clinical and radiographic findings. This scale radiologically considers the pathology as a sellar mass presenting hemorrhage or ischemia and categorizes the patient into five grades: grade 1 – subclinical apoplexy, patient is asymptomatic; grade 2 – patient has symptoms associated only with hypopituitarism or adrenal insufficiency; grade 3 – patient has headache; grade 4 – presence of ocular motility dysfunction; grade 5 – patient with visual deficit and/or changes in the level of consciousness through a decrease in the Glasgow Coma Scale score (JHO, 2014).

The treatment of choice is controversial, since there are not a sufficient number of controlled and randomized trials on the pathology, and it depends mainly on three factors involved in the progression of the disease: level of consciousness, degree of visual impairment and the level of hypopituitarism (MUTHUKUMAR, 2020). This is an emergency management condition, generally involving fluid and electrolyte balance, ensuring hemodynamic stability and glucocorticoid replacement, which is the treatment of choice in adrenal crisis (MAYOL, 2023). The use of glucocorticoids is recommended even if there is no evidence of an adrenal crisis (MAYOL, 2023).

The most commonly used drugs are dexamethasone and hydrocortisone. The recommended dose of dexamethasone is 4 mg, intravenously, every six hours, during the first 48 hours (ROCHA RAINHA et al., 2012). Hydrocortisone, on the other hand, must be administered at a dose of 100 to 200 mg, intravenously *in bolus*, with additional doses

of 50 to 100 mg every 6 hours or continuous intravenous infusion of 2 to 4 mg/h (BRIET, 2015). The use of high-dose glucocorticoids in cases associated with chiasmal compression and visual changes aims to reduce edema and also prepare the patient for neurosurgical decompression, when indicated.

The decision between surgical treatment and conservative management still lacks evidence and current consensus, however, it is argued that emergency transsphenoidal neurosurgical decompression must be performed in those patients with a progressive decrease in the level of consciousness, involvement of the hypothalamus and visual deficit progressive (RICCIUTI, 2018). Surgical intervention must occur within seven days of the onset of visual deficit, however, if there is improvement with corticosteroid therapy, there is the option of following conservative therapy (ROCHA RAINHA et al., 2012). For those cases of very large pituitary macroadenoma, which involve extension beyond the optic chiasm or lateral to the temporal fossa, craniotomy may be the technique used, aiming for complete resection of the tumor (ZOLI, 2017).

Furthermore, when partial campimetric amputation occurs, without a significant decrease in visual acuity, clinical improvement can be expected in those patients treated pharmacologically. However, its monitoring must be intensive, with a neurological examination every two hours and daily campimetry (RAJASEKARANT et al, 2011). Complete recovery from oculomotor paralysis can occur, but it takes about three months (RICCIUTI, 2018). Furthermore, endocrinological follow-up is essential, since around 80% of patients require hormone replacement for a long period until the hypothalamic-pituitary-adrenal axis is reestablished (MUTHUKUMAR, 2020; RUTKOWSKI, 2018).

Although cases of tumoral pituitary apoplexy are treated in the emergency room, clinicians who work in primary health care must also pay attention to this condition, as the patient can seek care in basic health units, due to the ease of access and lack of knowledge of the severity of symptoms, and diagnosis is delayed. Given the risk factors identified for apoplexy, the management of apoplexy must also include health promotion and disease prevention measures, which must be implemented, such as the control of comorbidities such as systemic arterial hypertension and diabetes mellitus, physical activity and balanced diet.

FINAL CONSIDERATIONS

Pituitary tumor apoplexy is a potentially life-threatening clinical entity and can generate neuroendocrine and visual sequelae, if not managed in time, therefore, it must be recognized early by the doctor working in the emergency department. It must be considered in the emergency room as a differential diagnosis in patients with sudden headache and neuroendocrine and ophthalmological deficits, in addition to being added to headache protocols both in primary care services and in the urgency and emergency sector.

Also noteworthy is the lack of robust studies, such as meta-analyses and systematic reviews, on the topic, which raises the need for the pathology to be better investigated, especially on a national level. Furthermore, human, material and structural resources must be prepared to offer the most appropriate care to patients with this condition, aiming to reestablish neuroendocrine functions, visual recovery and prevention of sequelae.

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