

## Craniopharyngioma: retrospective analysis of clinical manifestations, treatment, and outcome of patients at a university center

*Craniofaringioma: análise retrospectiva das manifestações clínicas, tratamento e evolução de pacientes em um centro universitário*

*Craneofaringioma: análisis retrospectivo de las manifestaciones clínicas, el tratamiento y la evolución de pacientes en un centro universitario*

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### Abstract:

**Objective:** to describe clinical, radiological, and endocrinological characteristics at diagnosis, as well as to evaluate therapeutic approaches, histopathological findings, the evolution of visual and hormonal abnormalities, and the occurrence of tumor recurrence or residual disease during follow-up. **Methods:** a retrospective descriptive study based on a review of medical records of patients diagnosed with craniopharyngioma who were followed at the Neuroendocrinology Outpatient Clinic of the Hospital de Clínicas at the Universidade Federal do Triângulo Mineiro in Uberaba/MG, Brazil, between January 2013 and October 2025. **Results:** twelve patients were included, with a predominance of diagnoses in the pediatric age group. The most frequent initial manifestations were headache, visual disturbances, and hormonal deficits. Most patients exhibited impairment of multiple pituitary axes at the time of diagnosis. All patients underwent surgical treatment, which resulted in increased hormonal deficiencies postoperatively. Residual lesions or tumor recurrence were observed in more than half of the cases. **Conclusion:** craniopharyngioma is associated with high morbidity from the time of diagnosis and is frequently linked to significant visual and endocrinological impairment. Surgical treatment is essential for tumor control but may exacerbate hormonal dysfunction. Management requires long-term follow-up and a multidisciplinary approach aimed at disease control and functional preservation.

**Keywords:** Craniopharyngioma; Pituitary neoplasms; Hypopituitarism.

### Resumo:

**Objetivo:** descrever as características clínicas, radiológicas e endocrinológicas ao diagnóstico, bem como avaliar as abordagens terapêuticas adotadas, os achados anatomopatológicos, a evolução das alterações visuais e hormonais e a ocorrência de recidiva ou remanescente tumoral durante o seguimento. **Método:** estudo descritivo retrospectivo baseado na revisão de prontuários de pacientes com diagnóstico de craniofaringioma acompanhados no ambulatório de Neuroendocrinologia do Hospital de Clínicas da Universidade Federal do Triângulo Mineiro de Uberaba, Minas Gerais, entre janeiro de 2013 e outubro de 2025. **Resultados:** foram incluídos 12 pacientes, com predomínio de diagnóstico na faixa etária pediátrica. As manifestações iniciais mais frequentes foram cefaleia, alterações visuais e déficits hormonais. A maioria dos pacientes apresentava comprometimento de múltiplos eixos hipofisários já ao diagnóstico. Todos foram submetidos a tratamento cirúrgico, com aumento das deficiências hormonais no pós-operatório. Lesão residual ou recidiva tumoral foi observada em mais da metade dos casos. **Conclusão:** o craniofaringioma apresenta alta morbidade desde o diagnóstico e está frequentemente associado a comprometimento visual e endocrinológico significativo. O tratamento cirúrgico é fundamental para o controle tumoral, porém pode agravar disfunções hormonais. O manejo exige seguimento prolongado e abordagem multidisciplinar voltada ao controle da doença e à preservação funcional.

**Palavras-chave:** Craniofaringioma; Neoplasias hipofisárias; Hipopituitarismo.

### Resumen:

**Objetivo:** describir las características clínicas, radiológicas y endocrinológicas en el momento del diagnóstico, así como evaluar los abordajes terapéuticos adoptados, los hallazgos anatomopatológicos, la evolución de las alteraciones visuales y hormonales y la aparición de recidiva o remanente tumoral durante el seguimiento. **Método:** estudio descriptivo retrospectivo basado en la revisión de historias clínicas de pacientes con diagnóstico de craneofaringioma atendidos en la consulta externa de Neuroendocrinología del Hospital de Clínicas de la Universidad Federal do Triângulo Mineiro de Uberaba, Minas Gerais, durante el período comprendido entre enero de 2013 y octubre de 2025. **Resultados:** se incluyeron 12 pacientes, con predominio del diagnóstico en el grupo de edad pediátrica. Las manifestaciones iniciales más frecuentes fueron cefalea, alteraciones visuales y déficits hormonales. La mayoría de los pacientes presentaba afectación de múltiples ejes hipofisarios ya en el momento del diagnóstico. Todos fueron sometidos a tratamiento quirúrgico, con aumento de las deficiencias hormonales en el posoperatorio. Se observó lesión residual o recidiva tumoral en más de la mitad de los casos. **Conclusión:** el craneofaringioma presenta una alta morbilidad desde el momento del diagnóstico y se asocia con frecuencia con una afectación visual y endocrinológica significativa. El tratamiento quirúrgico es fundamental para el control tumoral, pero puede agravar las disfunciones hormonales. El manejo requiere un seguimiento prolongado y un abordaje multidisciplinario orientado al control de la enfermedad y a la preservación funcional.

**Palabras clave:** Craneofaringioma; Neoplasias hipofisarias; Hipopituitarismo.

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## INTRODUCTION

**C**raniopharyngioma is a benign neoplasm related to remnants of the craniopharyngeal duct epithelium. It accounts for approximately 1.2–4.6% of intracranial tumors, with a global estimated incidence of 0.5 to 2.5 new cases per million inhabitants per year. It is the most common non-neuroepithelial intracranial neoplasm in children and adolescents, representing about 5–11% of intracranial tumors in this age group, with around 30–50% of all cases diagnosed during childhood and adolescence<sup>1</sup>.

Craniopharyngiomas most frequently occur in the sellar and suprasellar regions; they can develop along the hypothalamic-pituitary axis, extending from the sella turcica to the third ventricle, and originate from epithelial remnants of the craniopharyngeal duct (Rathke's pouch). Approximately half of these tumors arise from the floor of the third ventricle, often in close contact with hypothalamic structures.

Histopathologically, craniopharyngiomas are classified into two main subtypes: adamantinomatous and papillary. The adamantinomatous subtype is the most common and exhibits a bimodal age distribution, with peaks between the ages of 5–15 and 45–60. It is characterized by predominantly cystic lesions with frequent calcifications, squamous epithelium arranged in cords and nodules, and cholesterol-rich cystic fluid; it is associated with somatic mutations in the CTNNB1 gene, leading to activation of the WNT/ $\beta$ -catenin pathway. The papillary subtype occurs almost exclusively in adults, with a mean age at diagnosis between 40 and 55 years and no significant gender difference; it generally presents as a solid lesion with well-differentiated squamous epithelium, an absence of calcifications, and a distinct molecular profile, frequently associated with the BRAF V600E<sup>1</sup> mutation. Both subtypes are classified as Grade I tumors by the World Health Organization (WHO), reflecting their low histological grade, although they are associated with high morbidity due to their hypothalamic-pituitary location<sup>2</sup>.

There are various hypotheses regarding the origin of craniopharyngiomas, the most relevant being: ectodermal remnants of Rathke's pouch and an origin from residual embryonic epithelium of the anterior pituitary and the anterior infundibulum. The first hypothesis posits that adamantinomatous craniopharyngiomas arise from cell remnants forming the craniopharyngeal canal, which corresponds to the path taken by Rathke's pouch through the sphenoid bone to form the adenohypophysis. The second hypothesis suggests that the papillary subtype arises from the metaplasia of pituitary cells in the pars tuberalis of the adenohypophysis, resulting in the formation of squamous cell nests<sup>3-4</sup>.

Craniopharyngioma symptoms generally evolve slowly and progressively, often leading to a delay in diagnosis. Clinical manifestations stem primarily from tumor growth and the

compromise of adjacent structures, notably including headache, visual disturbances, nausea, and vomiting. Endocrine dysfunctions are common and linked to direct involvement or compression of the hypothalamic-pituitary axis; they can affect multiple hormonal axes, such as the somatotrophic, gonadotrophic, thyrotrophic, lactotrophic, and corticotrophic axes. The clinical impact of these alterations varies by age group, manifesting as growth deficiency in children and sexual dysfunction in adults. Involvement of the infundibulum is frequently associated with the development of arginine-vasopressin deficiency<sup>5</sup>.

Visual disturbances result primarily from tumor compression or extension into the optic pathways; visual field defects, particularly bitemporal hemianopsia, and reduced visual acuity are common. Tumors with parasellar extension may cause diplopia or strabismus due to cranial nerve involvement. Less frequent manifestations include motor deficits, seizures, psychiatric changes, and autonomic disorders. In cases of large lesions, the obstructive effect can lead to papilledema and optic nerve atrophy, further impacting visual function<sup>5-6</sup>.

The diagnosis of craniopharyngioma is established based on clinical-radiological correlation, with magnetic resonance imaging (MRI) serving as the imaging modality of choice. MRI allows for the precise characterization of tumor location (intraseellar and/or supraseellar), its extent along the hypothalamic-pituitary axis, and the involvement of critical adjacent structures such as the optic chiasm, hypothalamus, and third ventricle. T1 and T2-weighted sequences, combined with contrast-enhanced imaging, enable the identification of the lesion's solid and cystic components and the assessment of enhancement patterns. CT scan is recommended as a complementary study, particularly for detecting calcifications, a characteristic finding of the adamantinomatous subtype that is relevant for differential diagnosis and treatment planning. In addition to imaging, a systematic endocrinological workup is recommended at the time of diagnosis, assessing the corticotrophic, thyrotrophic, gonadotrophic, somatotrophic, and lactotrophic axes (including hyperprolactinemia due to pituitary stalk compression), given the high frequency of associated dysfunctions. A comprehensive ophthalmological evaluation, including visual acuity and visual field testing, is part of the diagnostic process even in the absence of visual complaints, due to the high prevalence of subclinical optic pathway impairment in patients with craniopharyngioma<sup>7</sup>.

Treatment for craniopharyngioma must be individualized and managed by a multidisciplinary team, taking into account the patient's age, tumor extent, and the risk of hypothalamic-pituitary impairment. Surgery is the cornerstone of therapeutic management, with the extent of resection carefully balanced between achieving tumor control and preserving function. In cases of incomplete resection or recurrence, adjuvant radiotherapy may be

recommended, preferably using modern conformal techniques. For predominantly cystic tumors, intracystic therapies, such as the administration of interferon-alpha or radioisotopes, may be considered in selected situations, particularly to reduce surgical morbidity. For the papillary subtype harboring the BRAF V600E mutation, targeted therapies using BRAF inhibitors have been described as an alternative in specific cases, although they are not yet standardized as first-line treatment. Endocrinological management and long-term clinical follow-up remain essential components of treatment<sup>7-9</sup>.

Given the rarity of craniopharyngioma, its high morbidity, and the need for long-term monitoring, reporting the experience of university centers helps expand knowledge regarding the clinical, endocrinological, radiological, therapeutic, and prognostic characteristics of these patients.

Thus, this study aims to describe the clinical, radiological, and endocrinological characteristics at diagnosis, as well as to evaluate the therapeutic approaches adopted, histopathological findings, the course of visual and hormonal abnormalities, and the occurrence of recurrence or residual tumor during follow-up.

## METHODS

This is a descriptive, retrospective study based on a review of medical records of patients diagnosed with craniopharyngioma. The patients included in this study were diagnosed and/or followed up at the Neuroendocrinology Outpatient Clinic of the Universidade Federal do Triângulo Mineiro (UFTM). Case selection was restricted to patients whose follow-up occurred between January 2013 and October 2025, aiming to reduce heterogeneity resulting from differences in diagnostic, therapeutic, and follow-up methods over time.

Clinical, laboratory, radiological, and therapeutic information was obtained retrospectively through a review of physical and electronic medical records. Data collection was conducted between October and December 2025. Physical records were analyzed at the institution's *Serviço de Arquivo Médico e Estatística* - SAME (Medical Records and Statistics Service), while electronic data were accessed via the *Aplicativo de Gestão para Hospitais Universitários* - AGHU (University Hospital Management Application). The collected information was organized into a dedicated electronic database within a secure institutional environment.

Data analysis in this study was descriptive, featuring a narrative presentation of clinical findings. Quantitative data, such as absolute values and frequencies, were included to interpret the results. Information extraction was performed using a standardized data collection form

covering demographic, clinical, endocrinological, radiological, anatomopathological, therapeutic, and follow-up variables.

The study was submitted to the Research Ethics Committee of the UFTM Clinical Hospital and received approval (opinion no. 8.025.762).

## RESULTS

This study reports on 12 patients diagnosed with craniopharyngioma. Age at diagnosis varied widely, ranging from childhood to adulthood. The majority of diagnoses occurred before the age of 18 (66.7%), indicating a predominance in the pediatric and adolescent age groups. The youngest patient was 2 years old at diagnosis, while the oldest was 64.

Signs and symptoms at diagnosis were described for 11 of the 12 patients; upon initial evaluation, they exhibited a broad spectrum of clinical manifestations, predominantly visual symptoms and alterations related to endocrine dysfunction. Headache was the most frequent symptom, reported by nine patients (81.8%), followed by visual complaints (63.6%) and short stature (54.5%). Other clinical manifestations included low weight (18.2%) and delayed puberty (18.2%), as well as neurological symptoms, such as gait ataxia, incoordination, nuchal rigidity, and nystagmus, observed in only one patient (9.1%). Primary amenorrhea was identified in one female patient (9.1%).

Ophthalmological manifestations included reduced visual acuity and visual field defects. Four patients (36.4%) reported no visual symptoms; however, visual field abnormalities were identified in two of these cases. Postoperatively, visual complaints persisted in patients who were already symptomatic and emerged in one patient who had previously been asymptomatic.

Hormonal deficiencies at diagnosis were assessed in 11 patients in this series and were present in 90.9% of these cases, involving one or more hormonal axes (Table 1). The axes most frequently affected were the corticotrophic and somatotrophic (63.6%), followed by the thyrotrophic (45.4%) and gonadotrophic (36.3%) axes. Somatotrophic deficiency was frequently accompanied by complaints of short stature. Less frequent abnormalities included antidiuretic hormone (AVP) deficiency in one patient (9.1%) and hyperprolactinemia in another (9.1%). The majority presented with panhypopituitarism.

In the postoperative period, an increase in the frequency of hormone deficiencies was observed compared to the preoperative period. Thyrotrophic axis deficiency affected all patients, while corticotrophic and gonadotrophic axis deficiencies were identified in 90.9% of cases. The frequency of somatotrophic axis deficiency remained unchanged (63.6%), as did that

of hyperprolactinemia (9.0%). Also notable was the increase in the frequency of AVP deficiency, rising from 9.0% preoperatively to 81.8% postoperatively (Table 1).

**Table 1.** Deficiencies of the hypothalamic-pituitary hormonal axes in patients with craniopharyngioma before and after surgical treatment. Uberaba, MG, Brazil, 2025.

| Hormonal Axis  | Preoperative (n = 11) | Postoperative (n = 11) |
|----------------|-----------------------|------------------------|
| Corticotropic  | 07 (63.3%)            | 10 (90.9%)             |
| Gonadotropic   | 04 (36.3%)            | 10 (90.9%)             |
| Lactotropic*   | 01 (9.0%)             | 01 (9.0%)              |
| Somatotropic   | 07 (63.6%)            | 07 (63.6%)             |
| Thyrotropic    | 05 (45.4%)            | 11 (100.0%)            |
| AVP Deficiency | 01 (9.0%)             | 09 (81.8%)             |
| No change      | 01 (9.0%)             | 00 (0.0%)              |

**Note:** Due to the unavailability of complete hormonal data for the preoperative period, one patient was excluded from the pre and postoperative analyses to avoid bias in the comparison between the periods. \* Hyperprolactinemia

Preoperative radiological evaluation revealed lesions predominantly located in the sellar and suprasellar regions, with varying degrees of extension along the hypothalamic-pituitary axis. Tumor size ranged from approximately 1.5 to 4.9 cm in greatest diameter, with a predominance of lesions between 2 and 3 cm. The lesions exhibited predominantly cystic or mixed solid-cystic characteristics, with lobulated contours and relatively well-defined margins.

Coarse or peripheral calcifications were described in 58.3% of patients. Signal characteristics were heterogeneous, predominantly showing T2 hyperintensity and variable T1 intensity; findings included hyperintense areas consistent with cystic, proteinaceous, or hemorrhagic content, as well as hypointense focuses suggestive of calcification or hemosiderin deposition. Post-contrast enhancement patterns varied, with a predominance of ring or heterogeneous enhancement of the solid component, whereas some predominantly cystic lesions showed no significant enhancement.

Dilation of, extension into, or contact with the third ventricle was observed in 33.3% of patients, while invasion or bulging of the cavernous sinuses was noted in 16.6%. Relationships with the optic pathways were described in 58.3% of cases, involving displacement, stretching, or compression of the optic chiasm, including in patients without visual complaints, some of whom nonetheless exhibited visual field defects. The appearance of the pituitary gland and pituitary stalk varied, with descriptions ranging from compression and displacement to the absence of mass effect, depending on the specific case.

The initial therapeutic approach was surgical for all patients, consisting of transcranial craniotomy in 83.3% of cases and a transsphenoidal approach in 8.3%. In one case (8.3%), the surgical approach was not specified. Re-operation was required in two cases (16.4%). Regarding adjuvant therapies, radiotherapy alone was used in two cases (16.7%), while another patient (8.3%) received a combination of chemotherapy and radiotherapy. Despite all

interventions, 58.3% of patients showed residual lesions on follow-up imaging. During the follow-up period, one patient (8.3%) died due to postoperative neurological complications, specifically cerebral edema and diffuse ischemia.

Anatomopathological examination confirmed a diagnosis of craniopharyngioma in nine patients (75.0%). Of these, 66.6% had the adamantinomatous subtype and 11.1% the papillary subtype; the specific subtype was not specified in 22.2% of cases. In two other patients (16.6%), the examination was suggestive of craniopharyngioma. In one case (8.3%), the anatomopathological report was unavailable; however, the diagnosis was supported in all cases by clinical and radiological findings.

Bone Mineral Density (BMD) assessment was performed in nine patients (75.0%); four (44.4%) showed no abnormalities, while the remaining five (55.6%) exhibited low bone mass or osteoporosis.

## DISCUSSION

In this series, the majority of patients were diagnosed before the age of 18, a finding consistent with the epidemiology of craniopharyngioma described in the literature, which shows a higher frequency during childhood and adolescence, alongside a bimodal age distribution featuring a second peak in adulthood<sup>1,5,6</sup>. The occurrence of diagnoses across various age groups in this cohort reinforces the need to consider craniopharyngioma in the differential diagnosis of sellar and suprasellar lesions, regardless of the patient's age.

The most frequent initial manifestations were headache, visual disturbances, and signs of pituitary insufficiency. This pattern aligns with the expansive nature of craniopharyngioma, which compromises the hypothalamic-pituitary axis, the source of most symptoms present at diagnosis<sup>1,6</sup>. The frequency of abnormalities related to growth and pubertal development highlights the early impact of endocrine dysfunction on young patients, a phenomenon widely documented in pediatric series<sup>8,10</sup>. Among children and adolescents, it is also crucial to pay close attention to headaches and visual disturbances; these are more common at diagnosis in this age group and are associated with intracranial hypertension, which can present in various ways and lead to long-term sequelae<sup>7</sup>. Focal neurological manifestations were rare in this cohort, a finding consistent with previous descriptions<sup>5</sup> that attribute such symptoms primarily to the tumor's compressive effect. Ophthalmological abnormalities ranged from reduced visual acuity to subclinical visual field deficits; their detection in asymptomatic patients underscores the importance of systematic ophthalmological evaluation. The persistence or onset of postoperative visual complaints highlights the complexity of surgical treatment and the

anatomical proximity to the optic chiasm, an aspect emphasized in recent consensus statements<sup>1,7</sup>.

All patients, except one, exhibited hormonal deficiencies affecting one or more hormonal axes. Alterations predominantly involved the corticotrophic and somatotrophic axes, followed by the thyrotrophic and gonadotrophic axes, alongside isolated cases of antidiuretic hormone deficiency and hyperprolactinemia. The majority of patients presented with panhypopituitarism, underscoring the severity of the impairment of the hypothalamic-pituitary axis. These findings are consistent with previous studies<sup>1,6,11</sup>, which describe a high prevalence of hormonal dysfunctions at the time of clinical presentation and highlight panhypopituitarism as a common feature of craniopharyngioma in both adults and children.

Following surgical treatment, there was a marked increase in the frequency and extent of hormonal deficiencies, particularly involving the thyrotrophic, corticotrophic, gonadotrophic, and AVP axes. This highlights the impact of treatment on pituitary function and the balance between tumor control and functional preservation<sup>1,5,7,10</sup>. Consequently, multimodal management — combining conservative surgery, precision radiotherapy, and continuous endocrinological follow-up — is currently considered the most appropriate strategy; this aligns with international consensus guidelines<sup>7,8,12</sup>, which emphasize the need for individualized approaches aimed at both tumor control and functional preservation.

Radiological evaluation revealed that the lesions occur primarily in the sellar and suprasellar regions, presenting cystic or solid-cystic characteristics, a pattern described in recent studies<sup>1,6,10</sup>. Imaging showed heterogeneous T1 and T2 signals, with areas suggesting proteinaceous, hemorrhagic, or calcified content and variable post-contrast enhancement, features typical of craniopharyngiomas<sup>5,13</sup>. Compressive symptoms were frequent, involving the third ventricle and optic pathways, even in patients without visual symptoms, demonstrating an association between radiological findings and ophthalmological sequelae<sup>7,8,12</sup>. There is a correlation between hypothalamic involvement identified via imaging and a higher likelihood of endocrine dysfunction in patients with craniopharyngioma, supporting the link between anatomical alterations and the patients' hormonal profiles<sup>13</sup>.

In this series, transcranial craniotomy was the predominant surgical route, likely due to the suprasellar extension of the lesions and their frequent contact with the hypothalamus, optic chiasm, and third ventricle. Current guidelines recommend the transcranial approach for tumors with non-cystic lateral extension or an intraventricular component, whereas the endonasal approach is preferred for confined midline lesions; the choice depends on tumor anatomy and the team's experience<sup>6,7</sup>. A recent meta-analysis shows no consistent differences

in complete resection or recurrence rates between the surgical routes, indicating that tumor topography carries more weight in the therapeutic decision than the technique alone<sup>5</sup>.

The presence of residual disease or recurrence in more than half of the patients highlights the difficulty of achieving surgical tumor control in craniopharyngioma, particularly for tumors located close to adjacent structures such as the optic pathways and the hypothalamic-pituitary axis. In such cases, fractionated conformal radiotherapy is used as an adjuvant therapy for tumor control, offering efficacy comparable to total resection but with lower surgical morbidity<sup>7,8,10</sup>. Current management of craniopharyngioma involves integrated strategies combining surgery, radiotherapy, and, in selected cases, targeted therapies, requiring multidisciplinary longitudinal follow-up<sup>1,5,10</sup>.

Pathological examination revealed a predominance of the adamantinomatous subtype, as it is more common in children and adolescents, in contrast to the papillary subtype, which occurs exclusively in adults<sup>5</sup>. The morphological differences between the histological subtypes are of practical relevance, given that the adamantinomatous subtype typically exhibits greater local infiltration, calcifications, and firm adhesions, whereas the papillary subtype tends to behave as a solid lesion with more defined cleavage planes<sup>6</sup>.

Although histological confirmation is preferable prior to definitive treatment, research indicates that in typical clinical-radiological scenarios or neurosurgical emergencies, the management approach can be determined even without complete tissue characterization<sup>8</sup>. Current classification relies primarily on morphology, with immunohistochemistry and molecular analysis serving as complementary tools reserved mainly for cases of diagnostic uncertainty or when targeted therapy is being considered<sup>7</sup>.

## CONCLUSION

This series demonstrates that, despite being classified as a benign tumor, craniopharyngioma is associated with significant morbidity from the time of diagnosis. Most patients already presented with major visual and hormonal issues at diagnosis, illustrating the disease's early impact on the hypothalamic-pituitary axis.

Surgery remained a central component of treatment and was crucial for tumor control. However, it was frequently associated with the worsening of hormonal deficiencies, highlighting the delicate balance between tumor resection and the preservation of function. The high rate of residual disease and the need for adjuvant therapies indicate that definitive disease control is not always achievable.

Craniopharyngioma requires long-term follow-up and multidisciplinary care; treatment should not focus solely on tumor control via imaging but must also include hormonal monitoring, ophthalmological evaluations, and clinical support for rehabilitation. In the long term, the patient's quality of life depends as much on disease control as on the proper management of complications.

The results of this series underscore the importance of systematic clinical, ophthalmological, and endocrinological assessment from the time of diagnosis, as well as multidisciplinary follow-up after surgery, involving psychologists, educational psychologists, and occupational therapists. Furthermore, these data aid in characterizing the clinical profile and progression of craniopharyngioma patients treated at a Brazilian university center, serving as a foundation for future research involving larger patient cohorts and extended follow-up.

Study limitations include the retrospective design, the small number of patients, an inherent consequence of the disease's rarity, and reliance on medical record data; these factors may have resulted in incomplete data for certain variables and limit the generalizability of the findings. Nevertheless, the case series presented expands knowledge regarding the clinical, hormonal, and therapeutic course of these patients at a referral center.

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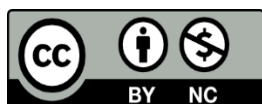
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