Cranioopharyngioma: same dangers, different age...

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Cranioopharyngiomas are rare epithelial tumors arising from Rathke’s pouch remnants, originally described by Zunke in the late 19th century. They constitute approximately 3% of all intracranial neoplasms and 10% in pediatric population. They are the most common pediatric brain tumor of nonglial origin, representing 54% of all sellar and suprasellar tumors. Its developmental path extends from the pharynx to the floor of the sella turcica, and tumors may be completely intrasellar (5-6%), extrasellar (20-41%), or a combination of both. Although typical locations are sellar and suprasellar, craniopharyngiomas have frequently been identified in several other locations.

In spite of benign histological characteristics and slow growth, these tumors frequently exhibit malignant behaviour, with locally infiltrative and recurring potential, even after apparently curative therapy. Anecdotal cases of malignant transformation and of ectopic and metastatic recurrence have been described after surgical treatment.

Data from the US reveal an overall incidence of 0.11 per 100,000 person-years, with no significant gender variance. The tumor may be diagnosed at any age, but a bimodal distribution occurs, with peak incidences in children between 5 and 14 years, and adults between 55 and 74. Almost half the cases occur in the adult population, and it has been suggested that these tumors bear significant clinical, biological and pathological differences among age groups.

Histologically, cranioopharyngiomas are predominantly cystic or mixed lesions, the solid ones accounting for less than 20% of cases. About 80-87% of craniopharyngiomas are calcified, and calcifications are more common in children (90%) than in adults (50%).

Two distinct types have been identified, with important age-distribution differences:

1. The adamantinomatous type is the most common, and predominantly affects children and adolescents. These are commonly cystic tumors, usually with a solid component, and a wide size variation at the time of diagnosis. Extensive fibrosis and inflammation are observed, resulting in dense adhesion to adjacent structures and contributing to the difficulties in complete resection of these tumors.

2. The papillary variant is almost exclusive of adults and usually involves only a solid component, typically with no calcifications. In contrast to the adamantinomatous type, these tumors are generally well circumscribed, with less infiltration of adjacent brain tissue, and therefore more amenable to surgical resection.

The clinical features associated with craniopharyngioma, consist of a broad spectrum of signs and symptoms, reflecting the pressure effects of the tumor on the surrounding brain structures (hypothalamo-hypophyseal axis, visual pathways, brain parenchyma, blood vessels and ventricular system). Symptoms frequently develop insidiously, and become apparent only after the tumor has reached significant dimensions. Thus, clinical presentation ranges from asymptomatic to endocrine, visual, intracranial hypertension-related or psychological abnormalities, some of which evolve largely unnoticed by patients, especially those of pediatric age.

The severity of the clinical manifestations relates to the location, dimensions and growth of the tumor, and 3 major syndromes have been described according:

- Prechiasmal localization –visual symptoms predominate.
- Retrochiasmal location –signs of raised intracranial pressure (ICP).
- Intrasellar cranioopharyngioma –headache and endocrinopathy.

Age-related clinical differences have also been postulated, with raised ICP predominating in children, sexual development abnormalities in adolescents, visual defects and hypopituitarism in adults and cognitive impairment in the elderly.

In the pediatric population, the most frequent presenting manifestations include signs of increased ICP: growth failure and visual disturbances. Headache is present in 60-80% of patients, vomiting (frequently without nausea) in 35-70% and papilledema in 25-
40%. Visual disturbances occur in 20-60% of cases, and most commonly consist of a bitemporal hemianopia. As previously mentioned, children seldom become aware of the vision deficit, until serious damage to the visual pathways has occurred.

Presenting endocrine symptoms are common in this age group, and up to 80% of patients show evidence of endocrine dysfunction at diagnosis, with deficiencies more frequently involving anterior pituitary hormones (GH in up to 75% of patients, gonadotropins in 40%, ACTH and TSH in 25%). Growth retardation is reported among 20-95% of patients, and precocious or delayed puberty or symptoms of adrenal insufficiency are also common. Hypothyroidism, growth hormone deficiency, and direct hypothalamic injury contribute to the obesity and weight gain observed in 25% of children and adolescents. Diabetes insipidus is present in 9-17% of patients.

Intellectual or emotional disturbance and somnolence can occur. These signs most likely are the result of thyroid dysfunction. Poor school performance is also common, as are psychological problems.

Diencephalic syndrome (an emaciated hyperactive child) result from extrinsic compression of the hypothalamus. The clinical features of craniopharyngiomas in adults are more varied, and depend on the location of the tumor. Endocrine symptoms similar to those in patients with non-functioning pituitary adenomas predominate in intrasellar locations. Invasive suprasellar tumors produce endocrine and visual abnormalities, as well as neurological defects such as ataxia and convulsions. Eighty-eight percent of children with experience decreased sexual drive and 82% of women complain of amenorrhea. Large tumors in adults can cause cognitive defects (memory loss, apathy, confusion) and psychiatric symptoms. Symptoms related to increased ICP are much less common than in children.

A recent literature analysis involving almost 1,000 patients, apart from a higher frequency of headache, nausea and vomiting, papilledema and cranial nerve palsies in children, revealed no other clinical differences between age groups.

Recent advances in endocrinology, neuroradiology, radiation oncology and neurosurgical techniques have contributed to an improvement in overall survival rates for craniopharyngioma, with more than 90% of patients surviving at 10 years.

Mortality is not only related to the tumor (local and endocrinological effects), but also to treatment complications and, particularly in adults, to a marked increase in cardiovascular and cerebrovascular mortality.

Data from different series are not consistent regarding the effects of age, histological type, or even treatment modality. Differences between pediatric and adult patients are suggested in some studies (with better prognosis for either age groups), but not in others. However, in some subgroups, such as neonates and children under 5 years at the time of diagnosis, a worse outcome has consistently been demonstrated.

Histological type or the location of the tumor have not been associated with significant differences in survival, in spite of some studies suggesting a better prognosis for the squamous papillary variant, while others did not support this opinion. Tumor type or location apparently has no effect on patient survival.

Disease recurrence is one of the most important factors influencing the outcome of these patients. Recurrence rates differ according to the treatment modality, varying from 0-62% at 10 years with complete resections, and from 25-100% in series with partial removal of the tumor. No other prognostic factors or criteria have emerged, that consistently predict the risk of recurrence. Age at diagnosis apparently has no effect on recurrence, although age less than 5 years has been found a significant predictive factor for the reappearance of the disease. Most, if not all the imaging features associated in some reports, with increased recurrence risk (tumor dimensions, location, calcification), appear related to resectability, and may influence recurrence only indirectly, by influencing surgical results. Finally, no data have convincingly established differences in prognosis between the 2 major histological types, although the squamous papillary type has been associated to a better outcome in most series.

Long-term morbidity is frequent, and is caused by the disease (either primary or recurrent) or by its treatment. Manifestations broadly involve endocrine, visual and neuropsychiatric deficits, and, once again, no differences between pediatric and adult populations have consistently been established in the literature.

Endocrine dysfunction is common, with at least 3 pituitary hormone deficiencies reported in 50-100% of patients. Particular hormonal deficits vary between 88-100% for GH, 80-95% for FSH/LH, 55-88% for ACTH, 39-95% for TSH and 25-85% for ADH. Diabetes insipidus is found in 25%-86% of survivors. Eighty percent of patients in one series were receiving hormonal replacement at follow-up.

Major visual deficits are found in 10-50% of patients and again, are not significantly associated with age at diagnosis.

Hypothalamic involvement produces a disruption in hunger, satiety and energy balance control, with obesity as one of the prominent features. This manifestation is reported in 25-75% of surgically treated patients, and is related to hypothalamic invasion by the tumor and/or surgical or radiation sequela.

The degree of obesity can be profound, leading to metabolic syndrome, and at present, there is no effective treatment available.
Patients treated for craniopharyngioma can also present memory, cognitive and emotional and behavioral deficits, that contribute to the poor academic and work performance and may compromise familial and social functioning \(^5,13,14\).

In conclusion, craniopharyngiomas remain a puzzling and challenging disease, in spite of all the advances in diagnosis and treatment modalities.

This clinical entity merges a spectrum of different epidemiological, clinical and pathological processes that share a common histological benignity, the same mechanisms of injury and the potential of recurrence.

Significant clinical and prognostic differences between children and adults, the two peak-incidence populations, have not consistently been found. However, the disease rarity and the wide variability and heterogeneity of the results found in most series, do not contribute to the consistency of these conclusions. Even in the absence of such differences, and with the good survival results, it appears that this disease and the therapeutic sequelae, must have a different and more profound impact in a developing organism than in an adult one.

Efforts must address not only the development of better and less harmful therapies to achieve tumor and recurrence control, but also the preservation of life quality and normal development. Metuculous attention to issues such as hormone deficiencies, visual loss, cognitive and emotional disorders, is essential to a good outcome, especially in children. This lifelong management process must be assured by a multidisciplinary and committed team of healthcare providers in order to achieve satisfactory long term results.

REFERENCES