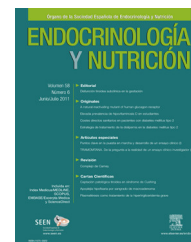




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REVIEW ARTICLE

Metabolic consequences of craniopharyngioma and their management[☆]

Cristina Lamas Oliveira

Sección de Endocrinología y Nutrición, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

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PALABRAS CLAVE

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Riesgo cardiovascular

Abstract Most patients diagnosed with craniopharyngioma survive long-term, but suffer many consequences of the disease and its treatment. Among the metabolic consequences, there is a high prevalence of panhypopituitarism and diabetes insipidus, mainly due to the surgical treatment. Obesity is also more prevalent in these patients than in the general population, and gets worse with time. It is a consequence of a diminished basal metabolic rate and a lower physical activity compared to that of matched controls, with a similar or lower caloric intake. Many different hormonal alterations that could be responsible for those changes in the energy balance have been found. Patients whose tumor involved the hypothalamus are more prone to develop obesity and its consequences. Cardiovascular risk factors are also more prevalent in these patients, leading to a high cardiovascular morbidity and mortality. Sleep disturbances, dysfunction in thermoregulation and thirst and a lower bone mineral density can also be found. Although randomized clinical trials comparing different treatments are lacking, it looks like therapeutic strategies have a minor influence on the risk of long-term sequelae.

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Consecuencias metabólicas del craneofaringioma y su tratamiento

Resumen La mayoría de los pacientes diagnosticados de craneofaringioma sobreviven a largo plazo pero lo hacen con importantes secuelas. Entre las secuelas endocrinometabólicas nos encontramos una prevalencia muy alta de panhipopituitarismo y diabetes insípida que se deben principalmente al tratamiento quirúrgico. También mayor obesidad que en la población general que tiende a empeorar con el paso del tiempo y que se debe a un menor metabolismo basal y a menor actividad física con una ingesta comparable o menor que la de los controles pareados. Se han detectado numerosas alteraciones hormonales que podrían ser las responsables de estos cambios en el balance energético. Los pacientes cuyo tumor afectaba al hipotálamo son especialmente susceptibles. En estrecha relación con la obesidad se aprecia un aumento de los factores de riesgo cardiovascular y de la morbimortalidad por enfermedad cardiovascular.

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E-mail address: clamaso@sescam.jccm.es

Otras secuelas son las alteraciones del sueño, de la termorregulación, de la sed y una menor masa ósea. Aunque apenas existen estudios randomizados que comparen distintos tratamientos en el manejo del craneofaringioma, no parece que la actitud terapéutica sea determinante en la aparición de estas secuelas.

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Introduction

Craniopharyngioma is a tumor derived from remnants of Rathke's pouch that develops in the sellar and parasellar regions, with a benign histology but an often locally aggressive behavior. Survival is only slightly lower as compared to the general population, with very long-term survival rates of 85–90% in most recent series.^{1–6} Disease-free survival is however lower due to the difficulty in achieving total resection and the high recurrence rate. In addition, most patients undergoing treatment for craniopharyngioma have permanent sequelae which affect different health spheres and impair their quality of life^{7–9}: visual, neurological, psychological, and endocrine sequelae, and the side effects of radiotherapy. This review will address the endocrine and metabolic consequences resulting from the damage caused by the tumor or its treatment to the hypothalamus and pituitary gland, their prevalence in patients who have received treatment for craniopharyngioma, and the factors leading to their occurrence in order to take them into account when making decisions related to the treatment of these patients.

Hypopituitarism

At disease diagnosis, approximately 60% of patients have a deficiency of some adenohypophysial hormone.^{1,3,10} However, the proportion reaches 87–95% after tumor surgery, regardless of whether a transsphenoidal or transcranial approach is used or whether total or partial tumor resection is performed. In addition, most patients have panhypopituitarism.^{1,3,10–14} The recovery of any deficient adenohypophysial hormone in the preoperative study, sometimes occurring after surgery for a pituitary macroadenoma, is exceptional in patients with craniopharyngioma, in which the involvement of the spared axes of the patient usually occurs.^{1,3,10,13,15,16}

Such a high incidence makes the study of predisposing factors difficult. Although a study reported a greater prevalence in patients with intrasellar versus purely suprasellar tumors,¹⁴ other authors found no difference.¹³ It has not been shown either that radiotherapy is a determinant factor (as occurs in other sellar tumors), as is demonstrated by the very high incidence of hypopituitarism after surgery, which is usually performed before radiotherapy.

Diabetes insipidus

The involvement of neurohypophysis may also be produced by the effect of the tumor itself (12–36%)^{1,13,16,17} or as a sequel after surgery, so that 70–90% of patients undergoing surgery for craniopharyngioma suffer from permanent diabetes insipidus.^{1–3,9,10,12,13,15,17–22} Radiotherapy plays a very limited role in the genesis of this complication. A small

proportion of patients also experience a loss of thirst sensation as a sequel of surgery. This is the so-called adipsic diabetes insipidus, which makes the maintenance of normal osmolality very difficult. Two reported series found this complication in 7.1% and 3.3% of patients undergoing surgery for craniopharyngioma respectively.^{3,12}

Obesity

Obesity is another common sequelae in the long-term follow-up of patients diagnosed with craniopharyngioma and, together with visual sequelae, represents one of the main factors conditioning the quality of life and functional capacity.^{8,23}

The prevalence of obesity, as assessed in large series of patients on long-term follow-up, is highly variable (38–58%)^{1,3,19,22,24–26} and difficult to interpret because the prevalence of obesity in the population of origin is not available, and has also increased in recent decades, although in all cases where comparisons were made with paired controls or with the general population, higher obesity prevalence rates with higher fat mass were found in both children and adults.^{11,27,28} Most studies did not stratify patients by different degrees of obesity or used disparate definitions for obesity degrees. This makes it even more difficult to estimate the prevalence of severe or morbid obesity, which has the greatest impact on patient quality of life and health. The body mass index (BMI) in adults does not usually differ from controls with pituitary adenoma before surgery,²⁹ but the situation changes after surgery, and both the prevalence of obesity and the BMI are higher the longer the period of time after surgery.²⁸ Other predictors of obesity include the preoperative BMI and hypothalamic involvement in MRI imaging or as a surgical finding.^{9,11,14,28–31} Different treatment approaches do not appear to significantly condition the subsequent occurrence of obesity.

Various hypotheses have been proposed to explain the increased risk of obesity in these patients: the loss of the feeling of satiety due to the involvement of the ventromedial nucleus, decreased basal metabolism, less physical activity, vagally mediated hyperinsulinemia, and decreased sympathetic activity. As will be seen below, many of these hypotheses are supported by the results of clinical studies. Hypopituitarism is also a known cause of weight increase and, particularly, of an increased fat mass proportion. Potential contributing factors include glucocorticoid over-dosage, low triiodothyronine levels found in patients treated with levothyroxine, sex steroid underdosing, and growth hormone deficiency. However, patients with craniopharyngioma are significantly more obese and have greater fat mass as compared to those with hypopituitarism of another origin despite the use of similar doses of replacement therapies and comparable hormone levels.^{32,33} Hypopituitarism does not therefore appear to be a determinant factor in the

genesis of the problem. In a study analyzing obesity predictors in children with suprasellar tumors with a 43% prevalence of obesity after a mean of four years after surgery, hormone deficiencies showed no association with the occurrence of obesity.²⁸

Some studies have examined the energy balance in these patients. The Hartz et al. study assessed 27 children and adolescents with a history of craniopharyngioma. Their daily calorie intake was recorded and their physical activity was measured using an accelerometer, and the results were compared to data on calorie intake data collected from more than 1000 controls and to the activity measured in 26 age- and BMI-matched controls. The patients had lower calorie intake (approximately 500 kcal less daily) and less physical activity, with greater differences being found in leisure periods as compared to working or study periods.³⁴ More recently, Holmer et al. studied 42 adult patients with craniopharyngioma and found lower weight-adjusted basal metabolism as estimated by indirect calorimetry (90 kcal/day less), a lower intake (300 kcal/day less, which increased to 430 kcal/day less if the comparison was made after adjusting for sex, age, and weight) with a similar proportion of macronutrients, and lower physical activity as compared to age-, sex-, and BMI-matched controls. Work-related physical activity was comparable, and the difference in total activity was again due to leisure-time physical activity. The authors suggested as potential causes of this lower physical activity a decreased exercise tolerance, visual and neurological sequelae, or hormonal dysregulation.²⁷ Other authors found greater daytime somnolence as compared to controls, particularly in more obese patients, probably related to decreased melatonin secretion or impaired circadian rhythm, which may also contribute to decreased physical activity.^{35–38} In addition, when assessed with a food attitudes questionnaire, the patients showed more restrictive attitudes than controls with similar BMIs. Other studies found similar results, including the reduction of both basal energy expenditure assessed by indirect calorimetry^{39,40} and physical activity as compared to controls^{30,39} measured using questionnaires about routine activities, records, or pedometers or accelerometers. Both parameters are affected to a greater extent when the tumor extends to the hypothalamus. It has also been confirmed that calorie intake is not higher as compared to controls with similar BMIs.³⁹

As regards the hormone regulation of body weight, patients who have experienced a craniopharyngioma show higher serum leptin levels as compared to BMI-matched healthy controls.^{11,24,27} This is attributed by the authors to a leptin resistance state and to inadequate ghrelin suppression after intake with no differences in peptide YY levels.²⁴ This same group found lower urinary levels of catecholamine metabolites in obese patients with a history of craniopharyngioma as compared to healthy controls³⁰ and suggested a decreased sympathetic activity as the mechanism contributing to the reduction in physical activity and weight increase in these patients. A more recent study analyzed hormone response to intake and found that obese patients with craniopharyngioma had higher basal and postprandial insulin levels than controls with similar BMIs and non-obese patients with craniopharyngioma; postprandial peptide YY levels were lower in patients, both obese and non-obese, as compared to controls; and the suppression of

postprandial ghrelin levels was also shown to be lower in patients irrespective of their BMI. The authors concluded that intake perception by the central nervous system is clearly attenuated in patients who have had a craniopharyngioma.⁴¹ O’Gorman et al. also found a delayed ghrelin response after an oral glucose tolerance test.⁴²

Cardiovascular risk

During long-term follow-up, patients with prior craniopharyngioma have a greater prevalence of classical cardiovascular risk factors as compared to both the control population and to patients with hypopituitarism of another origin.^{1,11,12} In a series of 70 patients with a history of craniopharyngioma with a median age of 27 years at diagnosis (age at evaluation was not provided), 66% of whom had a BMI higher than 30, 11.5% had diabetes mellitus, 46.9% dyslipidemia, and 15.3% arterial hypertension. This prevalence increases with age and BMI, irrespective of whether or not the patients have received growth hormone replacement therapy. Higher prevalence rates of metabolic syndrome and carbohydrate intolerance and decreased insulin sensitivity are already found in adolescence as compared to age-, sex- and BMI-matched controls,^{20,25,41,43,44} and similar data have been reported in adults.^{11,33} Females are affected to a greater extent, which is probably related to late puberty induction and to underdosing in their lifetime estrogen replacement therapy.^{1,11} As for obesity, the cardiovascular risk factors were more prevalent in patients with tumors involving the hypothalamus, and the authors suggested that this was due to hyperinsulinism secondary to the vagal stimulus generated by the hypothalamic lesion. In fact, insulin resistance, as assessed by the HOMA index, was already higher at diagnosis, before surgery, in patients with radiographic involvement of the hypothalamus despite their having BMIs similar to those of patients with tumors not involving the hypothalamus.³¹

One of the causes of this greater cardiovascular risk may be impaired body composition. O’Gorman et al. found greater abdominal obesity, as well as significantly lower insulin sensitivity, in 15 adolescents with craniopharyngioma as compared to 15 BMI-matched controls.²⁰ An additional small study of nine children and adolescents with craniopharyngioma and nine controls matched by age, sex, pubertal stage, and BMI found a higher percentage of intra-abdominal fat (measured by dual energy X-ray absorptiometry, DXA), as well as higher triglyceride levels and a lower HDL cholesterol/total cholesterol ratio. In contrast to other studies, no significant differences were found in insulin sensitivity.²⁵

This greater prevalence of risk factors also results in a high prevalence of cardiovascular and cerebrovascular disease. Thus, among a series of 54 patients diagnosed with craniopharyngioma at a mean age of 31 years and with a mean age of 49 years at the time of evaluation, 6% had experienced myocardial infarction, 14% stroke, and 2% a transient ischemic attack. In addition, 57% of patients had at least one classical cardiovascular risk factor. The risk was greater in premenopausal women with periods of untreated hypogonadism.¹ Radiotherapy probably increases the prevalence of cerebrovascular disease, but few studies

have considered this late side effect in patients with craniopharyngioma, and in the abovementioned study by Pereira et al.,¹ radiotherapy did not significantly increase the risk of cerebrovascular disease. As expected, increased vascular mortality has also been demonstrated. Thus, the Bülow et al. study found a standardized vascular mortality rate of 3.21 as compared to the general population, but it should be noted that most patients had never received growth hormone replacement therapy. The risk was again higher in females.⁴⁵ Similar data were reported in the Pereira et al. study, which also included a majority of patients with no growth hormone replacement therapy and with a standardized mortality rate of 2.88 (1.64 in males and 3.8 in females).¹

Hypothalamic dysfunction

Other clinical manifestations seen in patients with a history of craniopharyngioma and which are probably due to hypothalamic dysfunction include the abovementioned daytime drowsiness, severe insomnia, respiratory disorders during sleep associated with frequent micro-awakenings,²⁰ the involvement of the autonomic nervous system, the chronic syndrome of inappropriate antidiuretic hormone secretion (SIADH), and thermal regulation changes.³

Osteoporosis

Osteoporosis may be another more frequent disease in this population, as a recent study found that patients with a history of craniopharyngioma have less bone mass than age-matched controls. This may be due to late puberty induction which prevents the achievement of a good peak bone mass, which could be the result of androgen deficiency in females, GH deficiency, inadequate corticosteroid replacement therapy, or decreased physical activity.⁴⁶ However, few data are available about the prevalence of osteoporosis in adulthood and fracture incidence in this population. An analysis of patients with craniopharyngioma enrolled into the KIMS follow-up cohort of patients with growth hormone deficiency found fracture prevalence rates of 17.8% in cases diagnosed in childhood and 25.3% in those diagnosed at an adult age. The distal radius was the most common fracture site.¹⁸

Conclusion

Most patients diagnosed with craniopharyngioma have a long-term survival, but experience significant sequelae. Endocrine and metabolic sequelae include a very high prevalence of panhypopituitarism and diabetes insipidus, obesity, which tends to worsen over time and is due to decreased basal metabolism and less physical activity with a similar or lower intake as compared to matched controls, greater cardiovascular risk, and lower bone mass. Patients with tumors involving the hypothalamus have a greater risk of experiencing all these late complications. Although few randomized studies comparing different therapeutic approaches to the management of craniopharyngioma are available, the initial treatment approach does not appear to be determinant for the occurrence of these sequelae. Thus, the most reasonable approach in these cases continues to

be the performance of the widest possible surgical resection sparing the healthy tissue adjacent to the tumor and the administration of adjuvant radiotherapy for persistent or relapsing disease at centers which have experience in the treatment of craniopharyngioma. Long-term follow-up of these patients focusing on the prevention and treatment of obesity and its consequences and all cardiovascular risk factors is indispensable, as is the replacement of hormone deficiencies in an attempt to optimize the quality of life of these patients.

Conflict of interest

The author states that she has no conflict of interest.

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