Anorexia–cachexia syndrome-like hypothalamic neuroendocrine dysfunction in a patient with a papillary craniopharyngioma

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Summary

The craniopharyngiomas are solid cystic suprasellar tumors that can present extension to adjacent structures, conditioning pituitary and hypothalamic dysfunction. Within hypothalamic neuroendocrine dysfunction, we can find obesity, behavioral changes, disturbed circadian rhythm and sleep irregularities, imbalances in the regulation of body temperature, thirst, heart rate and/or blood pressure and alterations in dietary intake (like anorexia). We present a rare case of anorexia–cachexia syndrome like a manifestation of neuroendocrine dysfunction in a patient with a papillary craniopharyngioma. Anorexia–cachexia syndrome is a complex metabolic process associated with underlying illness and characterized by loss of muscle with or without loss of fat mass and can occur in a number of diseases like cancer neoplasm, non-cancer neoplasm, chronic disease or immunodeficiency states like HIV/AIDS. The role of cytokines and anorexigenic and orexigenic peptides are important in the etiology. The anorexia–cachexia syndrome is a clinical entity rarely described in the literature and it leads to important function limitation, comorbidities and worsening prognosis.

Learning points:

• Suprasellar lesions can result in pituitary and hypothalamic dysfunction.
• The hypothalamic neuroendocrine dysfunction is commonly related with obesity, behavioral changes, disturbed circadian rhythm and sleep irregularities, but rarely with anorexia–cachexia.
• Anorexia–cachexia syndrome is a metabolic process associated with loss of muscle, with or without loss of fat mass, in a patient with neoplasm, chronic disease or immunodeficiency states.
• Anorexia–cachexia syndrome results in important function limitation, comorbidities that influence negatively on treatment, progressive clinical deterioration and bad prognosis that can lead the patient to death.
• Anorexia–cachexia syndrome should be suspected in patients with emaciation and hypothalamic lesions.

Background

Craniopharyngioma (CP) is a rare solid cystic tumor, with epithelial-squamous tissue and extra-axial localization, arising along the path of the craniopharyngeal duct, with slow-growing characteristic (1, 2). The age distribution is bimodal with a peak in childhood and a second peak among middle-aged and older adults (3). The incidence of craniopharyngioma is approximately 0.5–2 per 100 000 per year (4). According to the World Health Organization, craniopharyngioma comprises 2–5% of all central nervous system tumors (5). The craniopharyngiomas can be classified into 2 histologic subtypes: adamantinomatous and papillary
craniopharyngiomas. The adamantinomatous type may be encountered at any age but predominantly in the first 2 decades of life, and the papillary variety has been primarily reported in adults (6). Clinical presentation of craniopharyngioma varies with size, location and tumor extension. The spectrum of clinical manifestations ranges from mild headache, visual impairment (i.e. visual acuity disorder and visual field defect) to severely increased intracranial pressure and papilledema (7, 8). The extension of craniopharyngioma to adjacent structures is related with pituitary and hypothalamic dysfunction, conditioning hypopituitarism and hypothalamic syndromes (9).

Case presentation
A 48-year-old man was admitted for evaluation and management of acute adrenal insufficiency, myxedema and diabetes insipidus. His family history reveals type 2 diabetes and hypertension; his father had pulmonary tuberculosis. There was no familial case of endocrine tumors or any other disease. The patient had a history of type 2 diabetes mellitus, systemic arterial hypertension and secondary dyslipidemia. Eight months ago, he presented polyuria, polydipsia, fatigue, weakness and hyporexia; unexplained weight loss of 27 kg (59.52 lb) was evidenced in approximately 4 months (basal: weight 80 kg/176 lb, height 1.85 cm and BMI 23.3). There was no visual impairment. Subsequently, nausea, vomiting, daily nocturnal fever and impaired alertness were added. Patient was evaluated in emergency room due to sudden stupor. Physical examination revealed stupor, emaciation, mild dehydration, hypotension, sinus bradycardia, pretibial myxedema and diminution of deep tendon reflexes. The rest had no alterations.

Investigation
During the initial approach, neuroinfection and hemorrhagic/ischemic lesion were excluded. There was biochemical evidence of hypernatremia (Na+ 153 mEq/L), hypotonic polyuria, central hypocortisolism, central hypothyroidism and hypogonadotropic hypogonadism (Table 1). Magnetic resonance image of brain (MRI) evidenced a heterogeneous solid cystic suprasellar lesion, without cerebral edema but a mild ventricular dilatation (Fig. 1). The diagnosis of hypopituitarism and central diabetes insipidus was established. We initiated the approach of suprasellar lesion.

Treatment
Due to the evidence of acute adrenal insufficiency, myxedema and diabetes insipidus, the ABCDE approach, hydration and acute replacement of hydrocortisone, levothyroxine and desmopressin was initiated. Patient had partial clinical improvement and continued hormonal replacement (levothyroxine, prednisone and desmopressin, a testosterone enantate), with an adequate substitution for his hypopituitarism at 6 weeks. Specialized nutritional assessment, with proper caloric intake, was established.

Outcome and follow-up
During the next 5 months, the patient had severe fatigue, progressive generalized weakness, muscle atrophy, hyporexia, abulia, anhedonia, cognitive decline, short-term memory loss, limitations of activities of daily living, unexplained weight loss despite an adequate diet (35 kg/77.16 lb at these moments, with a loss of 43.75% respect basal weight) and loss of bowel and bladder control.

Figure 1
Magnetic resonance image of brain with coronal and sagittal T1 fat saturation post-gadolinium weighting, showing a heterogeneous solid-cystic suprasellar lesion, with 17 × 17 × 21 mm dimensions in transverse, anteroposterior and longitudinal axis respectively.
At 6 months, patient was again admitted for stupor in the health center. Adequate hypopituitarism substitution was corroborated. Exploration revealed a severe emaciation. Biochemically, there was hypoalbuminemia (serum albumin concentrations between 1.9 and 2.2 mg/dL), with data of chronic protein-energy malnutrition. Renal and hepatic functions were normal (Table 1). At that moment, he lost 42 kg/92.50 lb of weight (52.5% respect basal weight). The diagnosis of neuroinfection, tuberculosis (MTB/RIF assay and mycobacterium culture were negative), bacterial, viral or fungal systemic infections, immunological disease, immunodeficiency, gastrointestinal disease (normal endoscopy and colonoscopy) and extracranial neoplasia was discarded. Neurology team discarded depression, dementia or autonomic dysfunction in sphincters control. In the approach of suprasellar lesion, the clinical and imaging data suggested the presence of craniopharyngioma; however, the neurosurgery intervention was delayed due to a high risk of perioperative morbidity and mortality according to preoperative assessment. A specialized nutritional team re-evaluated the patient, adjusting the calorie intake. During hospitalization, patient showed marked anorexia, requiring even enteral nutrition and strict nutritional supervision. Clinical conditions improved, and serum albumin concentrations were normalized; however, the patient persisted with hyporexia and low weight. After hospital discharge, nutritional supervision was continued; however, loss of weight, anorexia, limitations of activities of daily living, weakness, muscle atrophy, anhedonia and abulia persisted. Multiple strategies were developed for enteral feeding. The diagnosis of anorexia–cachexia syndrome was established. Five months later, patient presented hydrocephalus and intracranial hypertension (Fig. 2), requiring ventriculoperitoneal shunt. Clinical evaluation was unsatisfactory, with progressive deterioration until death.

### Histopathology report

Autopsy was performed followed by an identification of a solid and papillary tumor with cystic degeneration, suprasellar localization and extension to optic chiasm (Fig. 3). Microscopically, pathologist found fibrovascular lining formations by well-differentiated squamous epithelium without surface maturation, with scattered chronic inflammation. The brain tissue around the tumor had reactive changes. The cystic wall had no...
lining epithelium. The histopathology report concluded the diagnosis of a papillary craniopharyngioma with suprasellar extension and important contact with hypothalamus, likewise, optic chiasmatic region extension (Fig. 4). Rest of the organs had no alterations. Ziehl–Neelsen stain in diverse tissues was negative. There was no histopathology evidence of extracranial neoplasm, infectious, inflammatory or infiltrative disease.

Discussion

This is a rare case of anorexia–cachexia syndrome like a manifestation of neuroendocrine dysfunction in a patient with a papillary craniopharyngioma. According to the literature, the extension of craniopharyngioma (CP) to adjacent structures is related with neuroendocrine affection. Pituitary hormone deficiencies are common in CP. At the time of diagnosis, 40–87% of patients present at least one hormonal deficit and, 17–27%, central diabetes insipidus (like in our patient) (10). A hypothalamic neuroendocrine dysfunction has been found in 35% of patients at diagnosis and includes obesity, behavioral changes, disturbed circadian rhythm and sleep irregularities, imbalances in regulation of body temperature, thirst mechanism impairment, heart rate and/or blood pressure imbalance and feeding alterations (11). The rate of neuroendocrine hypothalamic dysfunction dramatically increases after radical surgical treatment up to 65–80% (12).

Hypothalamic involvement of CP and treatment-related hypothalamic lesions, resulting in pathological patterns of eating behavior with hyperphagia and obesity, or weight loss and emaciation, conditioning an important impact on prognosis and quality of life in surviving patients. Obesity is commonly reported in CP with neuroendocrine dysfunction; however, diencephalic syndrome and anorexia–cachexia syndrome are uncommon but relevant conditions. Diencephalic syndrome (DS) was first described by Russell in 1951 and is defined by profound emaciation with the absence of cutaneous adipose tissue, locomotor hyperactivity, euphoria and alertness. Hoffmann et al. reported 11 cases of DS in patients with childhood CP included in HIT-Endo and KRANIOPHARYNGEOM study. These patients were mostly related to signs of intracranial pressure, failure to thrive and low weight. After diagnosis and treatment, all patients increased in their BMI SDS and, after 2 years of follow-up, DS patients still had a significantly lower weight compared to patients who were obese at the time of diagnosis; during later follow-up, this difference was no longer of statistical significance (13, 14).
Anorexia–cachexia syndrome (ACS) is a complex metabolic process experienced by patients in advanced stages of chronic illness. ‘Anorexia’ is defined as ‘the uncontrolled lack or loss of the appetite for food’ and ‘cachexia’ is defined as ‘anorexia, involuntary weight loss, tissue wasting and poor performance’ (15, 16). In 2007, the universal definition of ‘cachexia’ as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass was established. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity (17). Actually, the definition continues in discussion of clinical trial endpoints. ACS can occur in a number of diseases like cancer neoplasm, non-cancer neoplasm, chronic disease or immunodeficiency states like HIV/AIDS. The literature reports very few cases of anorexia in patients with CP. ACS is a condition of advanced protein calorie malnutrition related to a poorly understood and complex process involving multiple interactions with components of the tumor and host defenses. Current understanding of the mechanisms leading to cachexia can be categorized as: (1) human relationship with food (e.g., psychological, social/environmental and others), (2) nutritional deficiency (e.g., essential fatty acids and amino acids, antioxidants and others), (3) anabolic deficit (e.g., insulin and insulin-like growth factors, gonadal steroids and others) and (4) catabolic drivers (e.g., inflammatory, tumor derived and others) (18, 19). A characteristic of chronic diseases associated with the development of cachexia is increased production of pro-inflammatory cytokines. The elevations in interleukin-1 beta (IL-1β), leukemia inhibitory factor (LIF), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) have been implicated in the physiologic and behavioral responses to inflammation, including anorexia, HPA axis activation, fever, increased non-REM sleep and anhedonia (20, 21, 22, 23, 24). The intracerebroventricular administration of several pro-inflammatory cytokines in rodents is effective in recapitulating the cardinal features of cachexia including: anorexia, weight loss, increased energy expenditure and catabolism of fat and lean body mass (25, 26). These findings suggest that there are systems within the brain that are sufficient to promote the cachectic state in response to cytokines.

TNF-α, IL-1 and IL-6 play a crucial role in the ATP–ubiquitin-dependent proteolytic pathways activation, and thus, in the development of hypotrophy. The ubiquitin–proteasome-dependent proteolysis is the most important mechanism of muscle protein loss in cachexia derived from several diseases (27).

The behavioral and metabolic responses that occur in the clinical syndrome of cachexia involve the synergistic effects of combinations of cytokines acting in both the brain and the periphery. The central expression of pro-inflammatory cytokines stimulates their own production and is strongly induced by peripheral inflammation, providing a mechanism for inflammatory response amplification. Several lines of evidence strongly implicate the hypothalamus as a critical site of action for inflammatory cytokines (28). Inflammation within neuronal tissue, represented by markers for NF-κB activation, is localized exclusively to the hypothalamus and brainstem, responding to inflammatory stimuli by initiating the local production of cytokines in nuclei involved in the regulation of ingestive behavior. Feeding centers in the hypothalamus, including the paraventricular (PVN) and arcuate nuclei (ARC), express receptors for these cytokines. The cytokines may exert their cachexigenic effects by directly influencing the activity of hypothalamic centers controlling energy balance via c-fos induction. In the presence of the anorexia–cachexia syndrome, leptin levels are decreased, whereas ghrelin is normal or elevated (29). Nevertheless, energy intake is not increased as expected. The hypothalamic inappropriate response to these peripheral signals appears to be mediated by the persistent activation.

Figure 4

Microscopic picture. (A) and (B) papillary formations lining squamous epithelium without atypical features. (C) Cystic wall without lining epithelium, with scattered inflammation.
of POMC neurons. The expression of alpha-melanocyte-stimulating hormone (α-MSH), an anorexigenic peptide, cleavage product of the pro-opiomelanocortin (POMC) precursor, increases in anorexia–cachexia syndrome. The increase of melanocortin signaling results in anorexia, a increase of metabolic rate and alterations in tissue mass, with a potential role for the MC4-R in mediating some aspects of sickness behavior. Studies have also shown that orexigenic neuropeptides, agouti-related protein (AgRP) and neuro-peptide-Y (NPY) mRNA expressions are diminished during inflammatory states, providing an alternative mechanism for inflammation-induced negative energy balance. All conduce to decreased appetite and increased energy expenditure perpetuated by a chronic state of inflammation (30, 31, 32, 33, 34, 35). Diverse factors such as insulin resistance, anhedonia, lethargy and reproductive axis failure in the anorexia–cachexia syndrome are also related with alteration of melanocortin signaling. The changes in melanocortin tone alter glucose utilization and lipolysis via sympathetic nervous system (36, 37).

Therefore, it is plausible that altered melanocortin signaling secondary to cytokine influence may directly impact insulin sensitivity and energy partitioning. One possible mechanism may involve cytokine induction of SOCS-3, which could inhibit leptin signaling (38). Because insulin resistance in cachexia has been directly linked to increased mortality, further research on this mechanism is warranted. Elevation in IL-6 and acute phase protein concentrations have been observed in plasma from depressed patients, same that exacerbated the inflammatory state (39, 40, 41). The lethargy may be complicated by debilitation and weakness resulting from extended inflammatory response and negative energy balance. Recently, intact leptin signaling in both POMC and AgRP neurons has been associated with controlling locomotor activity to the extent that it can significantly alter total energy homeostasis. These findings indicate that pro-inflammatory cytokines may have similar actions on these neurons (42, 43, 44).

We present a rare case of anorexia–cachexia syndrome in a patient with a papillary craniopharyngioma that resulted in pituitary and hypothalamic neuroendocrine dysfunction, a clinical entity rarely described in the literature that is related with an important function limitation, comorbidities that influence negatively on treatment, progressive clinical deterioration and bad prognosis that can lead the patient to death. It is therefore important to suspect ACS in patients with emaciation in the context of hypothalamic lesions that can condition hypothalamic affection.

Consent/ethical consideration

The autopsy was performed according to the legal and ethical issues with respect to the disposal of organs, tissues and human corpses in Mexico (Current General Law of Health).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

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