UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

CAROLINA JOANA NUNES DA VEIGA E MOURA

Craniopharyngioma and Hypothalamic Obesity

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE ENDOCRINOLOGIA

Trabalho realizado sobre a orientação de:

DRª ISABEL MARIA MONNEY DE SÁ PAIVA

PROFESSORA DOUTORA MARIA LEONOR VIEGAS GOMES

ABRIL 2019

Craniopharyngioma and Hypothalamic Obesity

Carolina Joana Nunes da Veiga e Moura[1]

Dr[a] Isabel Maria Monney de Sá Paiva[2]

Professora Doutora Maria Leonor Viegas Gomes[1.2]

[1]Faculty of Medicine of University of Coimbra

[2]Department of Endocrinology of Centro Hospitalar e Universitário de Coimbra

Carolina Joana Nunes da Veiga e Moura

cveigamoura@gmail.com

Indíce

Abbreviations

ANS: Autonomic nervous system

BMI: Body mass index

BMR: Basal metabolic rate

CH: Congenital hypopituitarism

CP: Craniopharyngioma patients

DHA: Dorsal hypothalamic area

DI: Diabetes Insipidus

DMN: Dorsomedial nucleus

EI: Energy intake

ESS: Epworth Sleep Scale

FSIGT: Frequent Sampled Intravenous Glucose Tolerance Test

GH: Growth hormone

GTR: Gross total resection

HI: Hypothalamic involvement

HO: Hypothalamic obesity

HSS: Hypothalamus sparing-surgery

HVA: Homovanillic Acid

IEG: Eating behavior and weight problems inventory

IGT: Impaired glucose tolerance

IHT: Insulin hypoglycemia test

MRI: Magnetic Resonance Imaging

NFPA: Non-functioning pituitary adenoma

OGTT: Oral Glucose Tolerance Test

PR: Partial resection

PYY: Peptide YY

Sds: Standard deviation score

SO: Simple obese

TGTV: Tumor growing to the third ventricle

VMA: Vanillylmandelic acid

Abstract

Craniopharyngioma is a sellar and/or parasellar tumor affecting children and adults, with high survival rate at the moment. Nevertheless, its long-term impact on quality of life is substantial, leaving behind lifelong sequelae, such as an intractable hypothalamic obesity. The aim of this systematic review is to ascertain the etiological mechanisms behind the emergence of obesity and what predisposes these patients to it. A literature search was conducted on PubMed database, with restrictions for English language and publication date since 2008. Afterwards, a manual review of the retrieved articles' references was performed. A two-stepped analysis allowed the obtention of 33 articles from which data were extracted and inserted into a standardized document. From the 33 articles retrieved, only 28 were included in the systematic review itself. Most of the studies comprised childhood-onset patients (n=22), whereas only 6 included both adult and childhood-onset patients. The great majority of the articles referred to hypothalamic obesity as resulting from hypothalamic involvement and disfunction. In this line, main thematic focus was put on: the role of tumor location; therapeutic approach and post-operative lesion; appetite hormonal dysregulation; autonomic nervous system's imbalance; or physical activity, basal metabolic rate and energy intake's changes. Only 2 articles went beyond the scope of the previous categories. The results obtained for each proposed mechanism were disparate. Consensus was met regarding the cruciality of the post-operative lesion location in the emergence of obesity. However, the disturbances verified on the appetite-hormonal feedback as well as on the autonomic nervous system's regulation were difficult to interpret. Additionally, while strengthening the idea that both BMR and physical activity are reduced in CP patients, our results weren't consensual regarding the impact of tumor location and different therapeutic approaches on the patients' body mass Index. As we observed a great number of sources of heterogeneity, we stress the need for future investigators to reduce them, to get a clear view on what really triggers this weight gain. In conclusion, this review provides a summary of the up-to-date knowledge on the triggers of hypothalamic obesity in CP patients.

Keywords: Craniopharyngioma, obesity, hypothalamus, body mass index.

Introduction

Craniopharyngioma (CP) is a rare sellar and/or parasselar tumor, histologically benign, with high survival rate at the moment. Although it can virtually arise from anywhere along the craniopharyngeal canal, it is most frequently located on both intra and suprasellar regions (53-75%) as well as solely on the suprasellar region (94-95%).This tumor shows a bimodal age distribution: childhood-onset type typically between ages 5 and 14, representing 30 to 50% of all craniopharyngiomas; and adult-onset type, with peak incidence rates between 50 and 74 years (50-70% of all CP). It is divided in two subtypes: adamantinous, more common in children; and papillary, affecting mostly adults. Its location in the surroundings of the optic chiasm and hypothalamic pituitary-axe give rise to clinical manifestations such as visual impairment and endocrine deficits, which result in impaired psychosocial functionality. These symptoms can be present at diagnosis, due to the tumor's location and/or arise post-operatively, as a consequence of the proposed treatment. At diagnosis, 35% of children CP patients show symptoms of hypothalamic disfunction, with an increasing percentage, up to 65-80%, after treatment. Furthermore, also at presentation, 40-87% of all CP patients have at least one hormonal deficit, this being more pronounced among the adult-onset type (1-3).Thus, despite its good prognosis, craniopharyngioma's sequelae have a huge impact on quality of life in surviving patients.

In the past few years, the suggestion that obesity is linked to defective hypothalamic control of adiposity signaling peptides arose. Indeed, hypothalamus is known to contain key regions thought to be responsible for the body weight's regulation. At the same time, it is connected to the limbic system, playing a major role in motivation to eat. It is known that hypothalamic impairment typically leads to the emergence of circadian rhythm regulation abnormalities, behavioral changes and hormonal deficits, among others. Nevertheless, in this scope, hypothalamic impairment can give rise to an imbalance between anorexigens and orexigens as well as promote the blockade of important adiposity mediators (1, 4).

The prevalence of obesity at long-term follow-up of CP patients has been assessed (around 38-58%), but is highly variable and difficult to interpret due to different study designs and limitations among them (5). Its etiology comprises several mechanisms and remains subject of controversy, with different authors proposing different explanations and, simultaneously, similar studies giving contrary results. Even though hypothalamic damage was on the basis of most theories, mechanisms such as food-intake regulating hormones disturbance (6),

reduced basal metabolism rate (BMR) and physical activity (7) and autonomic nervous system (ANS) imbalance (8) have been discussed, amid others (5).

Both childhood and adulthood obesity play a major role in the development of cardiovascular disease, one of the leading causes of death in the western world. Despite CP's rarity and high rate of survival, the estimated prevalence of hypothalamic obesity (HO) in CP survivors and its unresponsiveness to conventional treatment (including lifestyle modifications) demands for better insight on its etiological mechanisms. Indeed, so far, "(...) no generally accepted (pharmacological or bariatric) therapy for hypothalamic obesity in childhood has been shown to be effective in randomized studies."(1).

The goal of this work is to gather and systematize information on: i) which mechanisms underlie the emergence of hypothalamic obesity in craniopharyngioma patients, so that better knowledge on how to treat it emerges ii) to identify the features that increase the individual predisposition to a higher amount of weight gain.

Methods

Literature search

A literature search was conducted using PubMed as database. The applied search terms were (“craniopharyngioma” AND “obesity”) and the search was restricted to language (English-written publications only) and publication date (previous ten years). The latter restriction was imposed considering PubMed’s results by year (Figure 1) yielding an increased number of publications on the theme in the past ten years. Furthermore, in order to search for additional relevant articles, a manual review of the literary references of previously obtained articles was performed, allowing the obtention of articles dated as far as 1996.

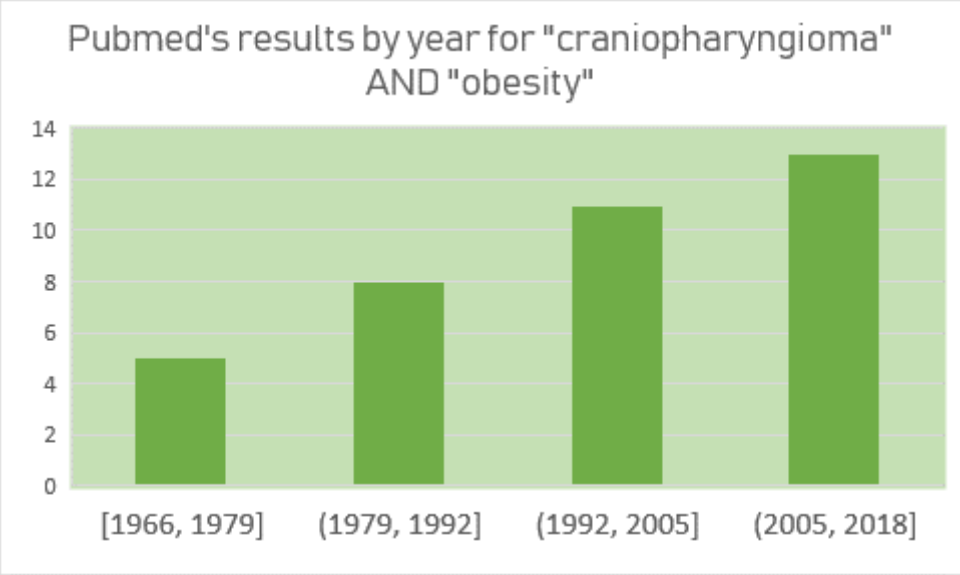

Figure 1. Results by year for "craniopharyngioma" AND "obesity. Data extracted from PubMed into a Microsoft Excel file.

Data Analysis and Study Selection

A two-stepped analysis was conducted by the author. The electronic search allowed the acquirement of 152 articles. The first approach was based on the reading of both the title and abstract of each article. The articles proceeded to the second-step if the following inclusion criteria were present: i) original articles or narrative reviews; ii) studies presenting an explicit or implicit correlation between all-ages craniopharyngioma patients and hypothalamic obesity. A total of 32 articles was retrieved from step one and submitted to a full-text reading. Thus, nine articles were excluded from the present study due to: i) lack of availability of free full text; ii) center of attention not being the correlation of CP and obesity. The manual review

of the articles' references allowed the obtention of 10 articles which were included in the study. Therefore, this review was based upon a total of 33 articles (Figure 2).

Data Collection

The collected information was introduced in a document template in order to compare and group studies accordingly to their: year, context/location, sample's size and characteristics, confounding variables, main measurements/variables, main results and limitations.

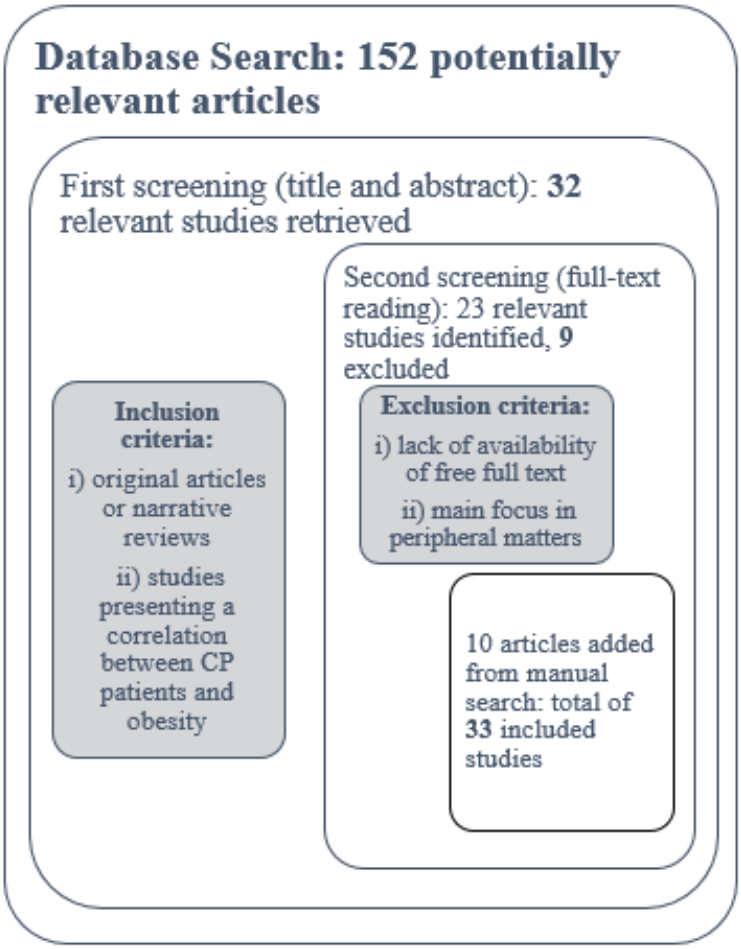

Figure 2. Chart of the process of review

Results

Study selection

The 33 publications selected at the end of the database and manual searches included two sorts of articles, as previously defined: narrative reviews and original articles. Narrative reviews were crucial on gaining a general knowledge on the tumor. Original articles were exhaustively examined, and their results and conclusions were taken into account for the systematic review.

Study characteristics

Of the 28 original articles included in this study, 12 had a longitudinal design (n=9 retrospective; n=1 prospective; n=1 both) and 16 were cross-sectional. The methodology employed was quantitative in 15 studies, whereas 13 studies adopted both quantitative and qualitative methods, in a mixed-methodology approach. The latter consisted mainly in questionnaires conducted during interviews to the participants. The great majority of the studies were carried out in Europe (1 in the Netherlands, 1 in Switzerland, 1 in Sweden, 3 in France, 3 in the United Kingdom, with the highest number in Germany, where 7 studies were conducted). Two particular studies were conducted simultaneously in two European countries: Italy and Germany (9); and Netherlands and Germany (10). Remaining studies were conducted in North America (n=5); South America (n=2), China (n=1) and Australia (n=1). Although the electronic database covered articles from 2008 to 2018, the manual search allowed the obtention of equally relevant articles dated as far as 1996. Therefore, 2 studies were led between 1996 and 2000; 6 between 2001 and 2005; 6 between 2006 and 2010; 12 between 2011 and 2016; and 2 between 2017 and 2018.

When it comes to participants, most studies (n=22) included only childhood-onset CP patients. In these studies, mean age during the study was 16.9 years old and mean age at diagnosis was 8.8 years old. On the other hand, 6 studies comprised both childhood-onset and adult-onset CP patients, although in different proportions (most frequently more adults than children). Therefore, mean age during the study was 44 years old and mean age at diagnosis was 31 years old. In terms of gender, 8 studies comprised opposite-sex individuals in similar proportions, whereas 13 studies were predominantly composed by men and 7 other studies by women. Only 1 study didn't mention the gender of the participants (11).

As mentioned above, 16 studies were cross-sectional. Controls consisted of healthy individuals with variable body mass indexes (BMI) in 12 studies; NFPA patients in 1 study (9); and individuals with exogenous obesity in 2 studies (12,13). In one study, despite being cross-sectional, no control group existed – 3 different pathological groups were compared (7). Six studies had their participants matched with controls for age, sex and BMI; 4 studies were only age and sex matched; the remaining 5 studies didn't match their participants neither for age, sex nor BMI. The main characteristics are summarized in Table 1. Three cross-sectional studies regarded participants other than CP patients, such as patients with Non Functioning Pituitary Adenoma (9,14), hypopituitarism (7,15) and hypothalamic pilocytic astrocytoma (16). Similarly, 2 longitudinal studies also included patients with Rathke's cleft cysts (3) and a panoply of other cerebral tumors (11). Sample sizes ranged from 18 individuals (17) to 1054 participants (15).

Table 1. Major characteristics of the selected studies

Author(s), year	Context	Study design	Main thematic focus	Age of onset of participants
De Vile *et al.*, 1996 (18)	UK	LGT	Location of tumor	Children
Roth *et al.*, 1998 (6)	Germany	CS	Hormonal dysregulation	Children
Muller *et al.*, 2002 (16)	Germany	CS	BMR and EI variations	Children
Schofl *et al.*, 2002 (15)	Germany	CS	ANS dysregulation	Children and adults
Coutant *et al.,* 2003 (19)	France	CS	ANS dysregulation	Children
Lustig *et al.*, 2003 (11)	USA	LGT	Location of tumor and treatment-related damage	Children
Harz *et al.*, 2003 (17)	Germany	CS	BMR and EI variations	Children
Srinivasan *et al.*, 2004 (20)	Australia	CS	Hormonal dysregulation	Children
Roth *et al.*, 2007 (8)	Germany	CS	ANS dysregulation	Children
Shaikh *et al.*, 2008 (7)	UK	CS	BMR and EI variations	Children
Trivin *et al.*, 2009 (21)	France	LGT	Hormonal dysregulation	Children
Holmer *et al.,* 2010 (23)	Sweden	CS	BMR and EI variations	Children
Simoneau-Roy *et al.*, 2010 (13)	Canada	CS	Hormonal dysregulation	Children
Roth *et al.*, 2011 (22)	Germany	CS	Hormonal dysregulation	Children
Cohen *et al.,* 2013 (16)	Canada	CS	ANS dysregulation	Children

Elowe-Grau *et al.,* 2013 (22)	France	LGT	Treatment-related damage	Children
Qi *et al.*, 2013 (23)	China	LGT	Location of the tumor	Children
Khan *et al.,* 2014 (24)	UK	LGT	Obesity at presentation	Children
Roemmler-Zehrer *et al.*, 2014 (9)	Germany and Italy	CS	Hormonal dysregulation	Children and adults
Rosenfeld *et al.*, 2014 (24)	USA	LGT	Treatment-related damage	Children
Hoffman *et al.,* 2015 (10)	Germany and Netherlands	CS	BMR and EI variations	Children
Nogueira *et al.*, 2015 (25)	Brazil	CS	BMR and EI variations	Children and adults
Roemmler-Zehrer *et al.*, 2015 (14)	Germany	CS	Behavior and personality influences'	Children and adults
Roth *et al.*, 2015 (3)	USA	LGT	Location of tumor	Children
Sterkenburg *et al.*, 2015 (26)	Germany	LGT	Location of tumor	Children
Caminiti *et al.,* 2017 (19)	Argentina	LGT	BMR and EI variations	Children
Andereggen *et al.,* 2018 (18)	Switzerland	LGT	Treatment-related damage	Children and adults
Van Iersel *et al.*, 2018 (27)	Netherlands	LGT	Treatment-related damage	Children and adults

ANS: Autonomic Nervous System; BMR: Basal Metabolic Index; CS: cross-sectional; EI: Energy Intake; LGT: longitudinal

Outcomes

The results retrieved from each publication can be grouped according to their main proposed mechanism for the development of obesity (Table 1). Nevertheless, we opted for a more practical approach and 3 main subsections will be presented next. Firstly, subsection (A) comprises articles regarding the role of craniopharyngioma's location in the emergence of hypothalamic obesity. Secondly, subsection (B) encompasses the information retrieved from articles that explore the impact of different surgical approaches and post-operative lesions in the arisal of obesity. Thirdly, subsection (C) comprises publications that focused on the functional mechanisms underlying the emergence of hypothalamic obesity (appetite-regulation hormones disruption, Autonomic Nervous System imbalance, Basal Metabolic Rate and Energy Intake (EI) changes). Lastly, section (D) comprises two articles that explore different mechanisms: behavior and personality influences on the development of obesity and the importance of obesity at presentation (14,28).

Section (A). *The impact of craniopharyngioma's location in the emergence of hypothalamic obesity*

In a longitudinal study, De Vile *et al.* (18) showed that among 63 CP patients, grouped according to the tumor location, no significant differences were found in BMI sds at diagnosis. Similar results were obtained by Sterkenburg *et al.* (26), who demonstrated no differences in BMI sds at diagnosis between patients with and without hypothalamic involvement (HI). Furthermore, Roth *et al.* (3), in a longitudinal study encompassing 41 CP patients and 4 children with Rathke's cleft cysts, concluded that no significant differences were seen between different tumor location groups regarding BMI sds before surgery. More recently, Andereggen *et al.* (29) studied 32 CP patients (with and without HI) and baseline weight characteristics weren't significantly different among the two groups.

Somewhat contrarily, Lustig *et al.* (11), in a sample of 148 children with different histological brain tumours, including CP, concluded that in comparison with other tumors, CP patients had a higher BMI at presentation. Additionally, the authors demonstrated that the existence of at least one endocrinopathy pre-operatively played a significant role in the BMI increase post operatively.

Later on, Qi *et al*. (23) evidenced that all CP location groups increased their weight during a 5 year follow-up. Nevertheless, patients with tumoral extension to the third ventricle had greater weight at diagnosis in comparison to the group with infradiaphragmatic extension. Similarly, Nogueira *et al.* (25), in a cross-sectional study, showed that obesity was more frequent in tumors encompassing the anterior and posterior hypothalamic areas with extension to and beyond mamillary bodies when in comparison to tumors limited to the anterior hypothalamus.

Section (B). *The therapeutic approach and the consequent post-operative lesions as triggers of hypothalamic obesity*

B1) Therapeutic approaches

Some authors point towards the idea that surgical extension plays a role on the development of obesity post-treatment. Lustig *et al.* (11) showed that in a group of children with different brain tumors, including CP, extent of surgery was considered an important factor in the post-operative development of obesity. Furthermore, patients submitted to hypothalamic

dosimetry superior to 51 Gy presented with higher abnormal BMI sds rates. Similarly, Elowe-Grau *et al.* (30) showed that after surgery, BMI sds was lower in patients submitted to hypothalamus-sparing surgery (HSS) than in patients who had undergone extensive resection surgery. Besides, HSS was associated with an inferior prevalence of corticotropic and gonadotrophin deficiency as well as Diabetes Insipidus. More recently, Van Iersel *et al.* (27), in a longitudinal study, concluded that 4 out of 35 CP patients were obese at diagnosis. From a totality of 35, 21 patients underwent Gross Total Resection (GTR), 11 were submitted to Partial Resection (PR) and biopsy was performed in 3 patients. From the patients who weren't obese at diagnosis, 3 developed obesity after being submitted to PR and 13 after GTR. The authors concluded that GTR was markedly associated with higher BMI sds at follow-up, as well as higher rates of Diabetes Insipidus and panhypopituitarism.

Rosenfeld *et al.* (24) showed that patients submitted to both surgical resection and radiation displayed a significantly greater increase in BMI in comparison to the patients treated with surgery or radiotherapy alone. No differences regarding BMI were observed between patients submitted exclusively to radiation or surgery. This study included patients from diverse ethnical origins. Native American individuals revealed a greater obesity prevalence at diagnosis and an increased mortality in comparison to the other groups, representing 50% of the fatalities at the last follow-up. The study conducted by Anderreggen *et al.* (29) demonstrated that being submitted to Gross Total Resection or Partial Resection played no difference regarding BMI sds. However, adjuvant radiotherapy led to a considerably higher BMI sds in patients who were submitted to it.

B2) Post-surgical lesions

De Vile *et al.* (18) showed that all CP location groups showed an increment in their original BMI, particularly during the first 6 months post-operatively. In patients with no damage to the hypothalamus (group 1), BMI sds rate of increase declined throughout time, allowing the stabilization of their weight. In patients with damage to the third ventricular floor (groups 2 and 3), BMI sds rate of increase diminished with time, but never became null. One year after surgery, the group with extensive destruction of the floor of the third ventricle (group 3) had, by far, the greatest increment in BMI sds, when in compared to the other groups (group 1 and 2). Corroborantly, Roth *et al.* (3) discovered that both obese and nonobese patients increased their BMI sds during the first year post-operatively, but beyond that, no additional gains were recorded. When assessing postsurgical brain imaging, lesions of the medial and/or posterior hypothalamus, third ventricular floor and mamillary bodies were more

prevalent in obese patients than in non-obese ones. Lesions in these areas could lead to disfunction of the hypothalamic nuclei contained among them: dorsomedial nucleus (DMN) and dorsal hypothalamic area (DHA), located in the posterior hypothalamus, may be damaged and linked to the emergence of obesity. Additionally, the authors demonstrated that 17 out of 45 patients developed Diabetes Insipidus, and those 17 patients displayed greater BMI sds than the ones who didn't develop DI. Roth *et al.* (3) concluded that patients with the highest BMI sds most frequently presented with post-operative lesions of the posterior hypothalamus and, at the same time, represented most of the Diabetes Insipidus' cases. These results pointed towards the existence of a common trunk for the development of Diabetes Insipidus and Obesity: hypothalamic disfunction.

In the same line, Qi *et al.* (23) demonstrated that, at last follow-up, patients with tumoral extension to the third ventricle displayed greater BMI sds than the group with infradiaphragmatic location. However, the authors showed no correlation between different tumor locations and post-operative hormonal levels. Similarly, Nogueira *et al.* (25) found that tumors located to the anterior and posterior hypothalamic areas with extension to and beyond mamillary bodies had the greatest increase in BMI sds. In agreement to the previously cited studies, the study conducted by Sterkenburg *et al.* (26) found that in the 8 to 12 years following surgery, HI led to a significant rise in BMI sds (median BMI change of +4.27 in HI vs +0.32 SD without HI). Afterwards, the weight gain ended up reaching a plateau. Later on, Andereggen *et al.* (29) verified that at long term follow-up, a significant increase was registered in BMI, particularly in CP patients with hypothalamic involvement.

All the above cited studies strengthen the hypothesis that post-operative lesion and its location contribute to a greater predisposition towards obesity. However, evidence isn't clear about whether there is a correlation between post-operative lesion location, BMI and the emergence of endocrinopathies.

Section (C). *Functional mechanisms underlying the emergence of obesity*

C1. Appetite-regulating hormones' dysregulation after treatment

The great majority of authors with publications regarding appetite-hormones and their impact on HO evaluate CP patients years after surgery. Roth *et al.* (6), in a cross-sectional study, demonstrated that 11 out of 14 CP patients had elevated leptin levels. These higher levels were found exclusively in patients with suprasellar disease (n=11), as none of the patients

with intrasellar tumor had them. Besides, leptin values were found to increase in accordance with the size of the tumor. In the healthy control group, BMI was found to be positively correlated with leptin values. Post-operatively, in CP patients with suprasellar disease, leptin values were above the expected considering the patients' BMI, leading the authors to the conclusion that, in CP patients, leptin regulation is somehow affected. Later on, Holmer *et al.* (31) demonstrated that leptin and leptin per kg of fat mass were higher in CP patients in comparison to control group, suggesting a disruption in the regulation of this hormone, possibly a peripheral resistance to it. Furthermore, the authors showed that ghrelin levels were negatively correlated with weight and were significantly lower in the CP group in comparison to healthy age-sex matched controls. Contrarily, Nogueira *et al.* (25) demonstrated that ghrelin levels were higher in CP children than in control children.

Another study conducted by Roth *et al.* (22) showed that baseline values of insulin were increased and insulin sensitivity was decreased in obese CP patients when in comparison to normal weight CP patients, normal weight and obese controls. No differences were found in insulin and insulin sensitivity values between normal weight CP patients and normal weight controls, excluding craniopharyngioma *per se* as the main responsible for these variations. In obese CP patients, a significant post-prandial insulin increase was registered when in comparison to the remaining groups. Furthermore, when comparing obese CP patients with obese controls, baseline ghrelin and post-prandial ghrelin levels were lower in the former, thereby excluding obesity itself as the main cause for these changes. Ghrelin values decreased significantly after meal in all groups except for the obese CP patients. The authors attributed this relative hypoghrelinemia in obese CP patients to its upregulated inhibition by insulin. Besides, CP patients with hypothalamic involvement displayed higher leptin baseline values and lesser post-prandial ghrelin values' reduction. Baseline Peptide YY (PYY) levels were lower in obese controls than in normal weight controls. PYY levels increased after meal in all groups. Nevertheless, PYY post-prandial values were lower in normal weight CP patients vs normal weight controls; in obese CP patients vs obese controls; in obese CP patients vs normal weight controls; and in obese controls vs normal weight controls. The rate of post-meal PYY increase was lower in CP patients when in comparison to controls, which was attributed to an ANS dysregulation. To sum up, the authors concluded that obese CP patients showed baseline and post-meal hyperinsulinemia, decreased insulin sensitivity and increased insulin resistance alongside reduced postmeal responses to ghrelin and PYY, in comparison to the remaining groups. Even though there were similarities in some parameters between normal weight CP patients and normal weight controls, the significant differences found among hormonal levels between obese CP patients and obese controls couldn't be

solely explained by obesity. Neither craniopharyngioma *per se* nor solely obesity could explain these hormonal variations, leading to the conclusion that the association of both might be the most plausible trigger of such changes.

The study led by Roeemler-Zehrer *et al.* (9) demonstrated that weight, fat mass and baseline glucose levels were greater in CP patients in comparison to Non-Functioning Pituitary Adenoma patients. After Oral Glucose Tolerance Test (OGTT), there was no difference between the two groups regarding glucose values. Furthermore, baseline and after glucose load insulin values weren't significantly different between groups. Baseline and post-OGTT leptin levels, when corrected for fat mass percentage, were higher in CP patients than in NFPA patients. Following OGTT, leptin values decreased significantly in the 60 minutes in CP patients when in comparison to the NFPA group. These differences strengthened the authors' speculation that this hormonal dysregulation cannot be attributed to a pituitary lesion, but to hypothalamic one. Baseline ghrelin levels were similar among the two groups. After age and sex adjustment, post-OGTT ghrelin response and recovery levels were lower in CP group than in the NFPA group. A greater number of CP patients showed growth hormone deficiency. However, the quantity of patients with GH deficiency not being supplemented with it didn't differ between the groups and IGF-1 levels were similar among the groups. Hence, pituitary insufficiencies became unlikely as the source of the previously cited metabolic differences.

Schofl *et al*. (15), in a cross-sectional study, addressed the integrity of glycemic regulation, demonstrating that baseline glucose levels were lower in CP patients with hypothalamic involvement (A) and in patients with hypopituitarism (B) than in control group (C). After insulin hypoglycemia test (IHT), the decrease in glucose levels was similar among groups, but the glucose recovery to the original values was slower in A and B and ended at lower levels than in C – even lower than the baseline ones. Similarly, Coutant *et al.* (19) showed that the baseline glucose level was lower in CP patients than in their age-sex matched healthy controls. After insulin IHT, glucose slope of increase to recovery point was lower in CP group. Peak plasma GH, ACTH and cortisol were decreased in CP patients when in comparison to the control group. Both the authors attributed this abnormal IHT response to a defect in ANS regulation.

Quite contrarily to the previous studies, Srinivasan *et al.* (20) showed no significative anthropometric differences between overweight or obese CP patients and age-sex-BMI

matched controls, with exception for fat abdominal mass, clearly higher in the former. Baseline glucose and insulin levels were similar in both groups. Regarding insulin sensitivity, CP patients showed better glucose tolerance than controls – the authors postulated that this group showed a "more efficient insulin independent glucose uptake". The authors attributed this higher glucose disposal to an upregulated insulin-independent glucose uptake in face of a decreased insulin sensitivity; as well as to a GH deficiency in these patients. Moreover, leptin levels were elevated in both groups and weren't correlated with BMI. Simoneau-Roy *et al*. (13) showed that anthropometric measures didn't differ between CP patients and age-sex-BMI matched controls. GTT demonstrated that 40% of CP patients had Impaired Glucose Tolerance (IGT) whereas in the control group, none had IGT. 10 out of 15 CP patients had metabolic syndrome, but only 3 out of 15 controls suffered from it. Insulin secretion after OGTT and Frequent Sampled Intravenous Glucose Tolerance Test (FSIGT) was increased in CP patients, although a greater increase was found with OGTT. Insulin sensitivity was found reduced in CP patients after FSIGT, but not following OGTT, when in comparison to controls. Given their results, the authors proposed that vagal stimulation and consequent insulin liberation were more intensely triggered by enteric stimuli than by intravenous challenging. The authors suggested that more complex mechanisms due to hyperinsulinemia could be responsible for the differences observed in insulin sensitivity after oral and intravenous glucose load. Recently, Caminitii *et al.* (32), in a longitudinal study, showed that normal weight and obese CP patients had normal fasting glucose levels. However, 40% were insulin resistant.

Differently to the authors cited above, Trivin *et al.* (21) evaluated patients both pre-operatively and post-operatively. The authors demonstrated that, previously to surgery, patients with severe involvement of the hypothalamus had higher glucose and insulin values as well as greater insulin resistance when compared to patients without hypothalamic involvement, regardless of BMI. No significant correlation was found between BMI and HI. These findings suggested that insulin resistance was mainly attributed to hypothalamic damage, not obesity itself. Additionally, pre-operative insulin resistance levels were found to influence BMI sds one year post-operatively. Pre-operative levels of leptin were higher in the group with severe involvement of the hypothalamus. After surgery, BMI and leptin levels were found to increase and soluble leptin receptor (sOB-R) levels to decrease in all patients, in comparison to the pre-operative levels. The positive correlation between BMI sds and leptin values and the negative correlation of both the latter with sOB-R values (both pre and post-operatively) enhanced the idea that leptin's interaction with its receptor isn't altered in CP patients.

C2. Energy Expenditure and Energy Intake variations

Several studies have centered their attention on the energy intake and energy expenditure variations at long-term follow-up after craniopharyngioma treatment. The latter were assumed to be a consequence of either a lower basal metabolic rate or/and a reduced physical activity. The study conducted by Harz *et al.* (17) showed that caloric intake was the highest in the control group, followed by CP patients with HI and, lastly, by intrasellar CP patients, with the lowest energy intake of all. In all groups, age was inversely correlated with energy intake. Fat intake was the highest in the control group. Carbs intake was higher in CP patients with HI and was inversely correlated with BMI. In terms of physical activity, CP patients showed less movement counts than healthy controls (outpatient group) particularly during school or work time. In comparison to inpatients enrolled in a weight reduction programme, CP patients still showed less movement counts, but the greatest difference between groups occurred during leisure time. In both settings (outpatient and inpatient), age was negatively correlated to physical activity percentages. The authors concluded that reduced physical activity rather than hyperphagia accounted for the development of obesity in CP patients. A similar study with comparable results was led by Holmer *et al.* (31). The authors concluded that Basal Metabolic Rate percentage of expected was quite lower in CP patients when in comparison to their age-sex matched controls. Energy intake and EI/BMR rate were lower in CP patients than in controls. Furthermore, BMR and EI weren't significantly different between patients with tumors growing into the third ventricle (TGTV) and non-TGTV tumors. However, EI/BMR ratio was the lowest in patients with TGTV. Fat, carbs and protein intake was similar between groups. CP patients tendentially had lighter meals, particularly women, excluding hyperphagia as a determinant factor in the emergence of obesity in CP. Furthermore, the control group had greater levels of activity than CP patients. The degree of activity during leisure time was significantly lower in CP: they spent more time inactive and the number of steps was lower than the control group. No differences were observed between groups when it came to physical activity at work. Moreover, Roth *et al.* (8), in a cross-sectional study, verified that activity scores were inferior in CP patients with elevated BMI in comparison to normal weight CP patients, which could be explained by the obesity alone as a causative factor. Nevertheless, CP patients with HI had inferior activity scores in comparison to those without HI, suggesting other factors (visual impairment, for example) as potential causes.

Shaik *et al.* (7) studied 3 different groups of children: patients with hypothalamic obesity (HO), 5 of them suffering from a CP; patients with congenital hypopituitarism (CH) ; and simply obese patients (SO). Their results showed that simply obese individuals were

significantly heavier than CH patients (and non-significantly than the HO group). All groups had an abnormally low energy intake, highlighting the non-specificity of the correlation between Energy Intake and BMI in craniopharyngioma patients. The HO group displayed the highest carbs intake of all groups. After adjustment for thyroid hormone values and lean mass, Basal Metabolic Rate was lower in HO patients than in the CH and SO groups, which the authors associated with a dysregulation in Autonomic Nervous System. The degree of activity was the lowest in the HO group, even after adjustment for fat mass.

Some authors focused on the mechanisms underlying this alleged lack of physical activity in CP patients. Muller *et al.* (16) proposed that craniopharyngioma led to a potential damage to the hypothalamic suprachiasmatic nucleus, responsible for regulating circadian rhythm. Consequently, an altered melatonin secretion caused harmful effects on CP patients, compromising their quality of daily life. Indeed, CP patients with BMI sds higher than 4 (severely obese) showed higher Epsworth Sleep Scale (ESS) scores when compared to the remaining CP patients. 42% of the severely obese CP patients had a score above 10 points, which indicated severe somnolence. Additionally, 35% of CP patients scored higher than 10 points. When comparing CP patients with patients with hypothalamic pilocytic astrocytoma and controls, the authors demonstrated that matinal and nocturnal melatonin levels were correlated to BMI and tumor type. Obese craniopharyngioma patients showed lower nocturnal melatonin concentrations than the other groups. No differences were found regarding cortisol levels between groups, thereby excluding cortisol's confounding effect. No differences regarding melatonin levels were seen between normal weight controls and normal weight CP patients. Therefore, the authors concluded that increased daytime sleepiness in CP patients (predominant in obese patients) was related to reduced nocturnal melatonin concentrations. Consistently, Cohen *et al.* (12) demonstrated that CP patients were more prone to physical debility and somnolence. Furthermore, Sterkenburg *et al.* (26) showed that CP patients with hypothalamic involvement were more fatigued and less motivated than those without HI.

Nogueira *et al.* (25) conducted a cross-sectional study in which energy intake was found to be lower in adult CP patients than in age-sex matched healthy controls. However, no differences regarding Energy Intake in the children groups (CP patients and age-sex matched healthy controls) were observed. No correlation was found between EI and BMI. Lipid intake was higher in all CP patients than in controls – above the recommended daily intake level. HDL cholesterol levels were worse in CP adult patients in comparison to adult controls. Triglycerides and LDL-cholesterol were increased in CP children patients when

compared to the children control group. The authors regarded the prevalence of dyslipidemia as a consequence of the obesity patterns among the CP group. These results were corroborated by Srinivasan *et al.* (20), who identified CP patients as having the worst lipid profile: elevated triglycerides and reduced HDL-cholesterol in comparison to the control group. Consistently, Caminiti *et al.* (32), in a longitudinal study with CP children patients, showed that 32% had dyslipidemia. Even though no significant differences were found regarding BMI between patients with (35/39) and without Diabetes Insipidus (4/39), 64% of the DI patients were obese and the remaining 36% had a normal weight. These findings strengthened the idea of DI as an endocrine marker of risk for obesity and the possibility that other endocrinopathies, particularly growth hormone deficiency and/or supplementation, might play a role in the emergence of dyslipidemia in CP patients.

Finally, Hoffman *et al.* (10) focused on eating behavior and assessed it in a cross-sectional study. The authors verified that among a sample of 186 people, 108 had normal weight or were overweight (48 CP and 60 controls), 62 were obese (44 CP and 18 controls) and 16 were severely obese (9 CP patients and 7 controls). Using as a tool the Eating Behavior and Weight Problems Inventory (IEG), severely obese CP patients showed the most pathological scores, demonstrating "a strong attitude towards eating". Nevertheless, in an advanced comparison of CP patients according to their BMI sds, normal weight CP patients scored better than normal weight controls in some of the domains in the IEG. The authors didn't provide any explanation for this fact. When stratifying the control group according to their weight, severely obese controls were the ones with the worst scores. These findings suggested that pathological eating wasn't on the basis of the development of obesity in CP patients, but might contribute to its perpetuation, in severely obese patients.

C3. Autonomic Nervous System's imbalance

Assessment of imbalance between sympathetic and parasympathetic nervous system markers was performed post-surgically by the totality of the reviewed authors in this section. Schofl *et al.* (15) demonstrated that an insulin hypoglycemia test (IHT) induced a lower catecholaminergic response in CP patients with HI than in healthy controls. In 5 out of the 8 CP patients, the increase in epinephrine and norepinephrine levels was significantly low, almost undetectable, when in comparison to the remaining CP patients and controls. In these same 5 CP patients, the heart rate response to the IHT was lower than in the remaining 3 CP patients and controls. Neurogenic symptoms arose in all groups during the test: cholinergic symptoms were present in all groups; but CP patients with deficient counterregulatory

catecholaminergic response showed no change in adrenergic symptoms, contrarily to the control group. Furthermore, when submitted to an orthostasis test, all groups suffered changes in both catecholamines' plasmatic levels and heart rate, including the 5 CP patients, this time with unimpaired sympathetic response. However, no correlation was found between the sympathetic nervous system defect and post-operative BMI sds. All groups showed similar baseline glucagon levels. The apparent contradictory sympathetic responses to Insulin Hypoglycemic Test and orthostatic test in CP patients with HI reinforced the likelihood of a hypothalamic defect. In fact, whereas hypoglycemic insulin test required hypothalamic processing for the liberation of catecholamines, the orthostatic test required simply brainstem activity. The authors concluded that structural and functional damage to the hypothalamus, proportional to the extent of the tumor or surgery damage, was correlated with a selective and partial defect (circumscribed to the hypothalamic region) in the sympathetic nervous system. Moreover, Coutant *et al.* (19) showed that baseline epinephrine levels were similar among CP patients and controls, whereas epinephrine's response to IHT and urinary excretion were reduced in CP patients. Norepinephrine's baseline levels were increased in CP patients, but its response to IHT and urinary excretion were similar between CP patients and controls. No correlation was found between catecholaminergic metabolism and BMI sds post-operatively in CP patients. Urinary Dopamine and Vanillylmandelic Acid (VMA) levels were lower in CP patients than in controls. Even though all patients received clinically adequate substitutive hormonal therapy, peak plasma GH and ACTH and cortisol values were lower in CP patients than in the control group. A 4-fold increase in hydrocortisone substitutive dosage produced no effect on epinephrine synthesis. Indeed, whereas a correlation between peak epinephrine response to IHT and cortisol levels was found in controls, such correlation wasn't present in CP patients. Furthermore, CP patients presented unimpaired response to the orthostasis test. The authors' hypothesis of a defective adrenal medulla (with insufficient glucocorticoid replacement to alter epinephrine synthesis) was supported by epinephrine's lower response to IHT, given that acute hypoglycemic response is mainly mediated by the adrenal medulla. The unimpaired epinephrine's response to the orthostasis test corroborated this hypothesis, because epinephrine's positional response mostly reflects Sympathetic Nervous System activity. In this line, norepinephrine's upregulation would act as a compensatory increase in SNS activity to compensate for the adrenomedullary defect. Dopamine and VMA (resulting from norepinephrine and epinephrine catabolism) originate partially from the adrenal medulla, but also from widespread areas of the central and peripheral SNS. Their reduced levels in urine of CP patients didn't allow the authors to exclude the hypothesis of a concrete damage to a certain hypothalamic regulatory region as the main causative factor for these variations, even though the integrity of

response to the orthostasis test presented as a contradictory proof. Therefore, insufficient data didn't allow the authors to conclude where the damage came from.

Roth *et al.* (8), in a cross-sectional study, showed that 50% of CP patients displayed epinephrine and dopamine urinary values under the detection limit. Nevertheless, in 100 out of 109 patients, norepinephrine values were clearly above the detection limit. Urinary HVA and VMA levels were lower in obese CP than in normal weight CP patients. CP patients with HI showed higher BMI sds and lower urinary VMA and HVA levels than patients without HI. These findings suggested that a reduced sympathetic tone was present in CP patients, contributing and correlating with the development of obesity. Furthermore, the lowest levels of urinary VMA and HVA belonged to patients with lower Heart Rate responses. However, no differences regarding Arterial Pressure were seen between patients with different levels of urinary catecholaminergic metabolites. The authors' explanation for this fact was the potential equalization of an already elevated blood pressure (due to obesity itself) with a low blood pressure due to the sympathetic nervous system defect. Moreover, Cohen *et al.* (12) conducted a study in which no significant differences were observed regarding parasympathetic and sympathetic indices between CP patients with HO and their age-sex matched controls. However, unexpectedly, urine metanephrine-creatinine ratio was significantly higher in CP patients than in the control group. The authors recognized this as unexpected, given that similar levels of blood catecholamines existed in CP patients and controls. They proposed that catecholaminergic adrenal production might have been increased to compensate for the defective central secretion. Additionally, no correlation was found between BMI and sympathetic markers in controls, nor between BMI and parasympathetic markers in either CP patients' group or controls. Nevertheless, the CP group showed a positive correlation between their BMI and sympathetic markers, highlighting the role of sympathetic defect in BMI sds.

Section (D). *Other proposed mechanisms*

Khan *et al.* (28) proposed that obesity at presentation predicted whether CP patients would aggravate their obesity. In this study, at diagnosis, 10 out of 25 CP patients were obese and at 5 years follow-up, they remained obese. Their maximum weight gain period was during the first year post-operatively. From the 11 patients who weren't obese at diagnosis, 7 ended up developing obesity at 5 years follow-up and their maximal weight gain occurred on the second year post-operatively. Only 4 patients were lean at diagnosis: one developed obesity

at 5 years follow-up and maximal increase in weight was recorded between the 4th and 5th years post-operatively. The authors concluded that being obese at diagnosis increased the probabilities of remaining obese in long term. On the other hand, in non-obese patients at diagnosis, emergence of obesity was unpredictable and usually occurred 1 to 2 years after diagnosis.

Roemmler-Zehrer *et al.* (14) studied the hypothesis that personality traits might contribute to weight gain in CP patients by creating abnormalities in food intake process. In a cross-sectional study, 26 craniopharyngioma patients and 31 Non-Functioning Pituitary Adenoma patients being treated for their tumors and 114 controls were submitted to questionnaires and analytic measurements. BMI was higher in CP patients than in the remaining individuals. CP patients suffered from a non-significantly more intense conscious hunger perception when compared to NFPA and controls. CP and NFPA patients displayed higher scores in terms of depression, anxiety, harm avoidance, fatigability, asthenia and neuroticism than controls. CP patients also showed impaired food restraint and high concerns on body shape. Nevertheless, CP patients showed no alterations when it came to “control” over eating.

Discussion

Several results were withdrawn from this review, allowing a better insight on the etiological mechanisms underlying hypothalamic obesity settlement in CP patients. Regarding the impact of tumor location, some authors (18,21,30) stated that pre-operative assessment of the tumor's location played no role in BMI variations at diagnosis. On the other hand, Qi *et al.* (26) and Nogueira *et al.* (25) recognized that some tumor locations make the patient more prone towards gaining weight. Furthermore, Qi *et al*. (23), similarly to other authors (5), failed to demonstrate a direct correlation between craniopharyngioma's location and the presence of hormonal deficits, leading to the exclusion of an eventual endocrinopathy as the ultimate cause of obesity. Sample sizes didn't seem to differ between these contradicting studies. Whereas the great majority of the above studies contemplated childhood-onset CP, two studies comprised children and adults, in different proportions (more adults than children), among their samples (25,29). Age may have acted as a confounding factor, as natural weight gain during ageing might lead to higher BMI sds at diagnosis in adults. Taking into account the preponderance of adults in these two studies, this possible interference from age may strengthen Andereggen *et al.* (29)'s results – if, among their sample, children and adults were contemplated in the same proportions, chances are that the lack of correlation between tumor location and BMI sds would become even more significant. Furthermore, even though all studies evaluated tumor location by Magnetic Resonance Imaging (MRI), different classifications were implemented regarding hypothalamic involvement. Additionally, MRI scans were analyzed by more than one clinician blinded for clinical data in only 3 studies (3,18,25). The remaining articles retrieved imagiological data from the patients' clinical records.

The impact of different therapeutic approaches on the development of obesity has been controversial. Three studies (11,27,30) stated that Gross Total Resection is significantly associated with higher BMI sds and higher prevalence of endocrinopathies, when in comparison to Partial Resection. These studies, altogether, comprise data collected between 1965 and 2012, making unlikely that advances in surgical techniques and post-operative management could operate as a confounding factor. Two studies with relatively small sample sizes demonstrated that radiation therapy as an adjuvant to surgery seemed to predispose CP patients to obesity (24,29). For Lustig *et al.* (11), radiation dosages alone superior to 51 Gy increased the likelihood of weight gain. Contrarily to the previous authors, Andereggen *et al.* (29) found no differences in BMI sds according to surgical extension. In fact, most of the above cited studies focused on childhood-onset craniopharyngioma and only two studies

(27,29) assessed both children and adult-onset CP. Though combining different age ranges enhances the statistical power of these studies, doing so disproportionally (more adults than children or vice-versa) could have influenced the study, given the natural weight gain associated with ageing. Thereby, Andereggen *et al's* (29) negative correlation between surgical approach and BMI sds could be attributed to the preponderance of adults in the sample and their limited weight gain potential during a 10 year follow-up. Inversely, Van Iersel *et al.'s* (27) positive correlation between surgical approaches and BMI variations could result from the higher proportion of children among the sample and their full potential towards weight gaining throughout life. Furthermore, different follow-up periods between studies and between patients in the same study could also have acted as a confounding factor. As a matter of fact, Elowe Grau *et al.* (30) studied a cohort of patients submitted to Gross Total Resection retrospectively and a cohort of patients submitted to Hypothalamus Sparing Surgery prospectively. Patients that underwent GTR displayed a significantly longer follow-up time in comparison to the ones submitted to HSS. This could have influenced their results, favoring HSS instead of GTR.

Contrarily to pre-operative assessment of tumor location, the role of post-operative lesions is practically established. Consistently with what previous authors have stated (1,2,5), post-operative lesions' location is linked to a significant weight gain in the years to follow, particularly if affecting the medial and/or posterior hypothalamus; third ventricular floor; and mamillary bodies (3,10,18,25,29). The studies pointing towards an association between post-operative lesion and BMI sds showed follow-up periods ranging from 30 months to 10 years. The fact that the greatest weight gain seemed to occur during the first year post-operatively (3,18) strengthens the hypothesis that it is mostly attributable to the reminiscent hypothalamic lesion than to the weight gain associated with ageing. Furthermore, the emergence of obesity post-operatively could be partially attributed to the substitutive hormonal therapy (particularly GH and cortisol). However, most of the studies demonstrated that no correlation existed between hormonal replacement therapy and BMI sds (18,23). Nevertheless, some of the studies focusing on this theme fail to recognize the correlation between endocrinopathy and hypothalamic post-operative lesion.

The role of appetite-regulating hormones in the development of obesity is still open to discussion. Precise knowledge on the mechanisms underlying feedback signals' disruption remains to arise. Nevertheless, the glycemic regulatory hormones and hormonal hypothalamic afferences' impairment observed in obese CP patients suggests that these might be implicated in the emergence of Hypothalamic Obesity. Leptin levels are normally

correlated with adiposity in healthy subjects. Nevertheless, in CP patients, leptin levels adjusted for fat mass percentage (leptin/kg) were abnormally high, either in comparison to healthy individuals or NFPA patients (9). Furthermore, leptin per kg of fat mass was higher in CP patients with HI than in those without HI. Ghrelin levels are known to be lower in obese individuals rather than in lean ones. Therefore, the fact that ghrelin baseline and post-prandial levels were lower in childhood-onset CP patients in comparison to healthy controls isn't unexpected (31). However, Nogueira *et al.* (25) showed that ghrelin levels in adulthood-onset CP patients were similar to those of healthy controls. Given that the two latter studies assessed CP patients as adults, different follow-up times (longer in Holmer *et al's* study) could have influenced their disparate results. Moreover, Roth *et al.* (22) showed that baseline and post-prandial ghrelin levels were lower in obese childhood-onset CP patients than in obese controls, suggesting that these hormonal alterations cannot be explained solely by obesity itself. Similarly, Roemmler-Zehrer *et al.* (9) demonstrated that CP patients (with child and adult-onset) showed lower ghrelin levels than NFPA patients, making likely a specific mechanism through which CP triggers obesity. Nogueira *et al.* (25) demonstrated that children surviving CP had higher ghrelin levels than their healthy controls. The heterogeneity of results could be a consequence of different study methodologies: such diverse ages at diagnosis and follow-up periods between studies could have interfered in the authors' results, not allowing a consensus to be reached. As for the mechanism underlying these hormonal variations, several authors point towards the idea that CP patients with HI might show damage to the Ventromedial Nucleus (sometimes bilaterally), affecting its afferent arm and, consequently, the recognition of leptin and ghrelin (33). This could lead to an increase in leptin resistance and inadequate ghrelin post-prandial suppression, with consequent reflections on the mechanism of satiety. It is important to highlight that these studies were performed post-operatively. Thereby, damage to hormonal pathways should be attributed mostly to a post-operative lesion or to the treatment approach itself.

Glycemic regulation is also reported as dysregulated (1,33). Roth *et al.* (28) and Simoneau-Roy *et al.* (13) demonstrated that CP patients, particularly obese ones, showed hyperinsulinemia and decreased insulin sensitivity in comparison to normal weight and obese age-sex matched controls, demonstrating a preponderant role of craniopharyngioma, not simply obesity, in insulin dysregulation. On the other hand, Roemmler-Zehrer *et al.* (9) demonstrated no differences in glucose and insulin levels between CP and NFPA patients. These results could have suffered interference from the inability to match CP and NFPA patients for age and sex. Given that the latter were older than the former, the higher prevalence of natural insulin resistance in elderly patients might have attenuated the true

insulin sensitivity values in CP patients. Srinivasan *et al*. (20) compared glucose and insulin levels in CP patients with age-sex-BMI matched controls and found no differences between them. Besides, they reported better glucose tolerance in CP patients than in controls, attributed to a greater insulin-independent glucose uptake. Given that peripheral insulin sensitivity correlates with the degree of physical activity (13), and that CP patients typically present with reduced activity levels, these findings appear dubious. Their particularly short sample size (n=24) and inability to match in pairs all the CP patients with their controls, leaving unmatched 6 subjects, may have hampered their results. Lastly, Schofl *et al.* (15) and Coutant *et al.* (19) established that baseline glucose and its recovery to original levels after Oral Glucose Tolerance Test were respectively lower and slower in CP patients when compared to controls. This could fit into the hypothesis of a low sympathetic activity and response to hypoglycemia. Small sample sizes (13,15) and the fact that not all studies were age-sex matched could constitute a confounding factor, as ageing could be associated with metabolic variations in some parameters. Lastly, different protocols of glucose load challenges, with different numbers of measurements and time periods, could have given rise to contradictory results.

The degree of obesity of CP patients would point towards the idea that their physical activity is reduced, and their energy intake increased. However, major evidence retrieved from the studies, in accordance to what previous authors state (1,33), seems to suggest that although CP patients effectively show reduced movement counts, energy intake isn't actually increased, when in comparison to controls (7,8,17,25,31). The fact that different studies, with different control groups – healthy individuals (17), healthy individuals with variable BMI (31), patients with hypopituitarism and simply obese individuals (7) – all reached the same conclusions strengthens the hypothesis that craniopharyngioma, not simply obesity, is closely associated with the verified variations. In fact, Roth *et al.* (8) demonstrated that CP with HI and obese CP patients showed lower activity scores than CP without HI and normal weight CP patients, establishing a link between craniopharyngioma as a major influencer of activity and obesity as an adjunctive factor lessening it. Nevertheless, Harz *et al.* (17) demonstrated that, despite similar values of Energy Intake and Basal Metabolic Rate, EI:BMR ratio was lower in patients with hypothalamic involvement than in those without HI. This was attributed to a chronic substitutive therapy with Growth Hormone in these patients, leading to an increase in body lean mass. In fact, BMR is influenced by a number of factors such as sympathetic nervous system activity and hormonal deficiencies or excessive supplementation (7). Therefore, the fact that the studies above mentioned guaranteed adequate hormonal supplementation to their patients strengthens their results. According to

Harz. *et al*. (17), EI and physical activity were inversely correlated with age. Nevertheless, all studies comprised patients and controls in the same age range, excluding age as a confounding factor. Methodology was similar among studies. Physical activity was measured by accelerometry during 2 and 7 days, by Harz *et al.* (17) and Shaikh *et al.* (7), respectively. Considering their concordant results, different periods of measurement don't seem to have interfered in the studies. Holmer *et al.* (31) used both quantitative and qualitative methods (pedometry and questionnaire) while assessing physical activity, empowering their study's results. The subjectivity underlying EI measurement might constitute a source of bias. In fact, Harz *et al.* (17) measured EI through nutritional diaries during one week, having obtained a 48% percentage of compliance from CP patients, which could have influenced their results negatively. Questionnaires and interviews were also performed (31). The subjective nature of these methods allows CP patients to underreport their EI, which must be considered as a possible explanation for the authors' results, besides the true EI restriction. Lastly, despite the low energy intake, CP patients suffer from high levels of LDL-C and TG, alongside reduced HDL-C and an increased incidence of dyslipidemia and metabolic syndrome (20,25,32).

The greatest ambiguity arises when assessing the existence of an autonomic nervous system imbalance. Lustig *et al.* (33) theorized that hypothalamic damage led to the suppression of the sympathetic nervous system, leading to an increased vagal output that, among others, gave rise to increased lipogenesis, hyperinsulinemia and decreased BMR. Even though patients presented abnormalities in the catecholamine metabolism when in comparison to controls, it isn't clear whether these were correlated to changes in BMI. Schofl *et al*. (15) and Coutant *et al*. (19) defended that no correlation existed between a defective counterregulatory sympathetic activity and BMI sds post-operatively. None of these studies matched their patients according to BMI, which could have hampered their results, given that BMI interferes with catecholaminergic regulation. Despite their similar results, Schofl *et al.* (15) studied both child and adult-onset CP patients on adulthood, under their usual substitutive therapy; whereas Coutant *et al.* (19) assessed only children CP patients who were off their medication during the tests. The obtention of similar results under different circumstances strengthens the hypothesis that no correlation exists between BMI and a Sympathetic Nervous System defect. Additionally, the responsiveness of CP patients to the orthostasis test reflects the integrity of the SNS, complicating the recognition of a post-operative SNS defect as responsible for this weight gain. On the other hand, Roth *et al.*(8) and Cohen *et al*. (12) stated that a defect in the SNS was correlated to BMI sds post-operatively. Roth *et al.* (8) matched their CP patients according to age, which strengthened

the power of the study, given that different SNS activity varies with age. As no age-related reference values existed regarding urinary catecholamines, normalization of the obtained data couldn't be accomplished, which could represent a source of bias. Moreover, Cohen *et al*. (12) were the only authors to match their 32 CP patients for age, sex and BMI, allowing the recognition of the SNS defect as a consequence of the tumor itself, not of an obese state. Lastly, all the studies were performed around 6 months to years after surgery. This fact raises the question of whether they evaluate the defective SNS activity as a consequence of the tumor and/or surgery; or if this defect follows the emergence of obesity, being consequent to it.

Lastly, Khan *et al.* (24) suggested that obesity at presentation could be identified as a risk factor for the later development of obesity. Although it might be a contributive factor, several other parameters act as confounding variables: the existence of obesity at presentation might be a consequence of early hormonal variations, endocrinopathies, or hypothalamic involvement itself. Therefore, a more holistic approach is required.

Limitations, strengths and future research direction

Some limitations can be attributed to the present review. Firstly, electronic database search was restricted to PubMed, leaving aside potentially relevant information which could have been retrieved from other sources. Furthermore, selection of only English-written articles may have narrowed our results and, therefore, hindered further knowledge in this theme. Secondly, the manifest imbalance between childhood-onset and adulthood-onset studies might confound our results and conclusions. In fact, different age onset is associated with different histological types and possibly, with different tumoral behaviors. Thirdly, even though the samples' sizes were significantly different among the 28 studies included in this review, equal importance was given to them all. Additionally, the fact that some studies included participants other than CP patients (as a pathological group, not as controls) might have interfered in our results. Furthermore, in the section regarding functional mechanisms behind hypothalamic obesity (Section C), most of the articles focused exclusively on the post-operative status of the CP patients. Therefore, doubt remains as to whether these changes were already present at diagnosis or simply emerged because of a post-surgical hypothalamic lesion.

Nevertheless, this review provides a summarization of the up-to-date knowledge on the hypothalamic obesity's pathogenesis in CP patients. The manual retrieval of potentially

relevant sources in addition to the electronic research strengthened our results. Besides, the selection of studies implementing both qualitative and quantitative methods allowed a better understanding on the quality of life of these patients, which we wouldn't have if limitations upon quantitative methods had been posed. Finally, the choice of including studies in which comparison of CP patients was performed with both healthy and obese controls as well as with patients with other pituitary tumors or deficiencies reinforced the significance of this review.

Further research shall cover the limitations of the present study. The greatest challenge for studies to come is to gather in one single study comparisons between CP patients among themselves and, at the same time, between CP patients and healthy, obese and with other cerebral tumors controls. Additionally, future authors should try to stratify patients and controls according to their degree of obesity. Broadening sample sizes is also recommended.

Conclusion

“Craniopharyngioma is a paradigmatic disease comprising different risk factors for hypothalamic obesity” (2). This systematic review provides information retrieved from a set of articles regarding various aspects of hypothalamic obesity in craniopharyngioma patients. The results obtained weren’t always corroborating but allowed a better insight and consequent reflection on the difficult to decipher etiopathogenesis of CP patients’ obesity. Nevertheless, they provide a clear reinforcement to the role of the post-surgical lesion location as well as reduced physical activity and Basal Metabolic Rate in the emergence of obesity. However, the importance of treatment approach and appetite-regulating hormonal and autonomic nervous system’s dysregulation remains unclear. The reports of disturbances in hypothalamic functional mechanisms and their explanation gave rise to a few pharmaceutical treatment options, such as the use of octreotide in order to reduce insulin secretion and, consequently, its anabolic effects. In face of the mixed results regarding some pharmacological approaches, and the relative lack of efficient alternatives, attempts at bariatric surgery have been made, achieving moderate tolerability and short-term weight reduction (2,33).

Ultimately, by collecting data on several mechanisms underlying obesity in CP patients, this work’s main value resides in providing the possibility of a better targeting in what comes to treatment strategies. Further research on this theme, with wider sample sizes, might provide a full understanding of what triggers such a weight gain in craniopharyngioma patients and, consequently, allow better therapeutic approaches to emerge.

Acknowledgements

Agradeço à Dra. Isabel Paiva, pela orientação que me foi dada neste trabalho, pela paciência que teve naquilo que, para mim, foi uma autêntica introdução no mundo científico.

Agradeço à Professora Doutora Maria Leonor Gomes, pela orientação inicial que me deu, bem como pela sua disponibilidade ao longo do projeto.

Agradeço também a todos meus amigos. Um obrigada especial à Carolina Oliveira pela paciência em responder às minhas infindáveis questões iniciais e ao David Rodrigues, pela disponibilidade em ajudar na reta final.

Um agradecimento especial ao Bernardo, que vivenciou de perto as minhas falhas e o meu progresso, nunca duvidando de mim, sempre com a maior das paciências.

Por fim, um enorme agradecimento ao meu Pai e Mãe, a quem tudo devo, sem quem nada disto seria possível. Obrigada.

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