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Comparative analysis of hypothalamic damage caused by pediatric craniopharyngioma versus pediatric low grade gliomas

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Thesis

**COMPARATIVE ANALYSIS OF HYPOTHALAMIC DAMAGE CAUSED BY
PEDIATRIC CRANIOPHARYNGIOMA VERSUS PEDIATRIC LOW GRADE
GLIOMAS**

by

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ABSTRACT

Numerous studies have suggested rapid weight gain following diagnosis and initial treatment of childhood craniopharyngioma (CP) due to the damage sustained by the hypothalamus. Hypothalamic lesions formed by the treatment of the tumor and/or by invasiveness of the tumor itself are known to cause intractable weight gain, known as hypothalamic obesity. In contrast, hypothalamic obesity manifested in pediatric low-grade glioma (PLGG) patients is not as prominently addressed in literature; likely due to the expansive set of histological tumor subtypes that makes generalization challenging. Specifically, there is a lack of analysis that examines the difference in treatment, endocrinopathies, and weight gain between CP and PLGG patients.

The purpose of this study was to compare hypothalamic damage in subjects diagnosed with pediatric hypothalamic low-grade glioma versus subjects diagnosed with childhood craniopharyngioma. We hypothesized that CP patients will have a more rapid post diagnosis weight gain and a greater degree of obesity compared with PLGG patients due to the more invasive nature of the tumor and the aggressive surgical treatments involved.

We performed a retrospective review of the clinical records of patients who received a diagnosis of childhood craniopharyngioma or pediatric low-grade glioma at Dana-Farber Cancer Institute between 1980 and 2009. We identified 45 patients, who met criteria for evaluation, 28 were previously diagnosed with childhood craniopharyngioma and 17 were diagnosed with hypothalamic pediatric low-grade glioma. We analyzed the impact of treatment, the presence of endocrinopathies, and weight gain after diagnosis. We concluded that there was no statistically significant difference in the rate or magnitude of post diagnosis weight gain, disproving our initial hypotheses.

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LIST OF ABBREVIATIONS

11 β -HSD1.....	11 β -Hydroxysteroid Dehydrogenase 1
ACTH.....	Adrenocorticotropic Hormone
AgRP.....	Agouti-Related Protein
α -MSH.....	α -Melanocyte Stimulating Hormone
ApoA-I.....	Apolipoprotein A1
ApoB.....	Apolipoprotein B
ARC.....	Arcuate Nucleus
BDNF.....	Brain-Derived Neurotrophic Factor
BMI.....	Body Mass Index
CART.....	Cocaine- and Amphetamine-Related Transcript
CCK.....	Cholecystokinin
CNS.....	Central Nervous System
CP.....	Craniopharyngioma
CRH.....	Corticotrophin-Releasing Hormone
DNA.....	Deoxyribonucleic Acid
DS.....	Diencephalic Syndrome
GABA.....	Gamma-Aminobutyric Acid
GH.....	Growth Hormone
GTR.....	Gross Total Resection
HDL.....	High-Density Lipoprotein
hs-CRP.....	High-Sensitivity C-reactive protein

HyOb.....	Hypothalamic Obesity
IGF-1.....	Insulin-Like Growth Factor 1
IOTF.....	International Obesity Task Force
LDL.....	Low-Density Lipoprotein
LHA.....	Lateral Hypothalamic Area
MC3R.....	Melanocortin-3 Receptor
MC4R.....	Melanocortin-4 Receptor
MCH.....	Melanin-Concentrating Hormone
MRI.....	Magnetic Resonance Imaging
mRNA.....	Messenger Ribonucleic Acid
NF1.....	Neurofibromatosis Type 1
NPY.....	Neuropeptide Y
PLGG.....	Pediatric Low-grade Glioma
POMC.....	Pro-Opiomelanocortin
PR.....	Partial Resection
PVN.....	Paraventricular Nucleus
T3.....	Triiodothyronine
T4.....	Thyroxine
TRH.....	Thyrotropin-Releasing Hormone
TSH.....	Thyroid Stimulating Hormone
VMH.....	Ventromedial Nucleus of the Hypothalamus
XRT.....	Radiation Therapy

INTRODUCTION

Hypothalamus

The hypothalamus is a brain structure that is located below the thalamus and part of the diencephalon that functions to regulate autonomic, endocrine, and behavioral mechanisms (1). As part of the diencephalon, the hypothalamus is a part of the forebrain, along with the thalamus, subthalamus, and epithalamus (5). Anatomically, it makes up one percent of the total brain volume and has an approximate weight of 1 gram (6). The hypothalamus is the most ventral part of the diencephalon and lies along the walls of the third ventricle, just under the hypothalamic sulcus at its dorsal border, and continues along the floor of the ventricle (1-3). The ventral surface is exposed on the base of the brain and composed of three prominent features: the mammillary posterior region, the medial tuberal region that passes through the fornix, and the supraoptic anterior region that lies above the optic chiasm. It is the superior portion of the hypothalamus that borders the thalamus (2, 6).

The hypothalamus can be categorized anatomically into 3 generalized functional zones: the paraventricular, medial, and lateral (7). Neurons in the paraventricular zone behave functionally by controlling the release of pituitary hormones, regulating sympathetic nerve activity, and the control of food intake (8-10). Neurons of the medial zone are specialized to receive sensory information and establish adaptive behaviors (7). Lateral zone behaves as a relay station between the medial hypothalamus and cortical/limbic areas of the brain that control cognition and behavior. In addition, it acts

to relay signals to the somatic and autonomic systems that control stimulation associated with driven behaviors like food intake, sensorimotor coordination, and skeletal and autonomic motor functions (7, 11).

The main function of the hypothalamus is to maintain internal bodily homeostasis. This is carried out by a neuroendocrine function that utilizes the release and inhibition of eight key hormones from the anterior and posterior pituitary glands, respectively known as the adenohypophysis and neurohypophysis (6). In turn, hormones released by the hypophyses are used to regulate distal target organs and the peripheral hormones released by specific endocrine glands: the adrenal glands, thyroid gland, ovaries, and testes. The tropic hormones synthesized and released by the anterior pituitary are involved in the processes of endocrine and immune responses, metabolism, satiety regulation, cardiovascular regulation, sleep, stress, thermoregulation, and sexual behavior (3, 6). Hormones released by the posterior pituitary control water and electrolyte balance as well as uterine contraction during child birth and lactation in females (4). In turn, positive and negative feedback regulators send signals back to the hypothalamus, fine-tuning the activation and suppression of hormones released by the hypophyses and glands in order to preserve biological processes (6).

Adaptive responses by the hypothalamus to regulate body weight are accomplished by controlling appetite and satiety through the balance of 3 factors: food consumption, energy expenditure, and stored energy in the form of lipids. There are four main areas of the hypothalamus which control these three factors: the ventromedial nucleus of the hypothalamus (VMH), paraventricular nucleus (PVN), arcuate nucleus

(ARC), and the lateral hypothalamic area (LHA) (7, 12, 13). Distinct neuropeptides within these areas have positive and negative synergistic effects on appetite.

The PVN lies in the periventricular zone and secretes neuropeptides that have an indirect anorexigenic effect on food intake via absorption, digestion, response to stress, and the metabolism of fats. Neuropeptides in the PVN observed to produce anorexigenic responses include: corticotrophin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and oxytocin (12, 13). Secretion of oxytocin acts on the solitary tract nucleus in the medulla oblongata by modifying response to bordering satiety signals and inhibiting food intake (12). Secreted TRH regulate energy homeostasis and food intake through its influence on metabolic processes, thereby causing an anorexigenic response. These include increased lipolysis and fatty acid oxidation, an increase in core body temperature, modifications to the cephalic phase of digestion, and evidence of stress-induced anorexia through interactions with the limbic nervous system (13, 17). Similarly, CRH promote stress-induced anorexia by activating the hypothalamic-pituitary-adrenal axis, causing the suppression of neural food-motivated responses in response to stress-stimuli (14-16).

In the ARC, which lies in the periventricular zone, there are two distinct sets of neurons: one set of neurons that coexpress orexigenic responses via neuropeptide Y (NPY) and agouti-related protein (AgRP), and the other set of neurons that coexpress anorexigenic responses via pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) (7, 13). The α -melanocyte stimulating hormone (α -MSH) is produced by the precursor, POMC, which is post-transcriptionally altered and

released from the presynaptic terminals of POMC neurons. The α -MSH binds with high affinity to G protein-coupled receptors, melanocortin-3 and -4 receptor (MC3R, MC4R), activating catabolic processes that increase energy expenditure and reduce food intake (13, 18, 19). Studies have shown that there is a down regulation of POMC expression during periods of negative energy balance (20, 21). NPY promotes food intake by increasing appetite ingestive behavior as a response to food stimuli (26). AgRP is released from neurons of ARC NPY- and AgRP- producing neurons and mediate their physiological effects on body weight by blocking G protein-coupled receptor signaling. AgRP competes with α -MSH to bind to MC3R and MC4R with high affinity, acting as a competitive antagonist (22, 23). AgRP also acts as an inverse agonist because binding causes a basal decrease in MC3R and MC4R signaling, which is not dependent on the concentration of agonists (24). CART is found to promote lipolysis, increasing energy expenditure, and increasing satiety as a result of afferent central vagal signals once food is sensed in the gut (25).

The LHA lies in the lateral zone and has extensive behavioral and autonomic output connections to the limbic system, brainstem, and spinal cord, which include specific functions controlling feeding behavior and energy balance. It contains two neuronal populations that produce orexigenic neuropeptides: orexins, also known as hypocretin, and melanin-concentrating hormone (MCH) (7, 12, 13). Orexins promote food intake by increasing arousal to food stimuli, strengthening the motivational and reward responses (12, 27). MCH has also been shown to have a significant role in stimulating motivational aspects of feeding. Previous studies illustrated knockout rats

lacking MCH or MCH receptor produced lean rats with an altered metabolism and a reduced operant response to high sugar or fat food stimuli, compared with control rats with the hormone present (12, 28, 29).

Located in the medial zone of the hypothalamus, the VMH is known to generate satiety and maintain glucose homeostasis. The VMH receives signals primarily from the ARC and contain neurons which produce brain-derived neurotrophic factor (BDNF) (13). BDNF is a neuropeptide that stimulates an anorexigenic response that is sensitive to glucose levels and energy status (13, 30-32). Studies have shown that VMH neurons sensing an increase in glucose intake caused elevations in BDNF mRNA expressions (30). Conversely, extended fasting caused a decrease in BDNF expression, with elevation following refeeding (32).

Leptin is a cell signaling protein secreted by white adipose tissue, which plays a pivotal role in the regulation of food consumption and energy homeostasis. Serum concentrations of leptin signal body fat content to the hypothalamus via regions of the central nervous system (CNS), which regulate the main hypothalamic areas involved in energy homeostasis, primarily the ARC (33-35). Leptin is produced and secreted by white adipocytes, where the rate of leptin produced and the amount secreted is proportional to bodily adipose tissue mass, allowing the plasma leptin concentration to be used as a biomarker of adiposity (13, 34, 35).

During states of high body fat content, leptin produces a cascade, suppressing food intake and stimulating energy expenditure (13, 18, 33). Circulating leptin passes through the Blood Brain Barrier where it binds to ARC neuronal leptin receptors, causing

inhibition of neurons that express NPY and AgRP, while increasing mRNA levels of neurons that express POMC and CART, stimulating its release. Reducing NPY and AgRP potently decreases their food intake stimulation, thereby reducing appetite and ingestive behaviors to food stimuli (35, 36). Furthermore, increased CART stimulates increased lipid peroxidation, energy expenditure, and satiety signals as a result of afferent central vagal signals, amplifying central vagal signals sent to the brain by gut hormones like CCK (13, 25, 36) Increased POMC allows for increased α -MSH concentrations. With inhibition of AgRP as a competitive inhibitor, increased amounts of α -MSH is available to bind to MC3R and MC4R, causing a decrease in appetite and food intake, but also an increase in renal and lumbar sympathetic nerve activity (19, 35, 37). This increased sympathetic nerve activity promotes energy expenditure through fat oxidation, glycogenolysis, thermogenesis, and increased movement (47).

Conversely, reduced plasma leptin concentration, signifying low body fat content, promotes energy intake and limits energy expenditure. In the fasting state, the reduction of leptin concentration stimulates ARC neurons that express NPY and AgRP, and inhibit those that express POMC and CART. Increased NPY stimulates appetite and food ingesting behavior in response to food stimuli. Increased AgRP competitively inhibit the effects of α -MSH, causing increased food intake, decreased sympathetic nerve activity, and decreased energy expenditure (35, 36). Inhibition of POMC and CART further enhance these effects. Studies show that reduced leptin trigger the central nervous system's adaptive responses to starvation in order to reduce energy expenditure of the immune system, fertility, growth, and metabolic rate (33). This includes the suppression

of sex hormones, growth hormone (GH), thyroxine (T4) and triiodothyronine (T3) levels, and lymphocyte proliferation and differentiation (33, 38, 39). Further studies show that detection thresholds are altered in response to food-related sensory input signals. These include the increased transcription of leptin receptors in olfactory mucosa as pre-ingestive behavior, and the hyperpolarization of cells associated with taste behavioral responses to sweet compounds, making them less responsive to taste stimulation (40-43).

Insulin is another important adiposity signal with receptors in the ARC. It carries the same function as leptin, inhibiting the release of NPY and AgRP, while stimulating the release of POMC and CART (36, 57). Insulin concentrations in the cerebrospinal fluid are directly proportional to the level of concentration circulating in the plasma (36). Thus, during fasting states, the concentration of insulin is low, leading to the stimulation of the orexigenic pathway (NPY and AgRP) and the inhibition of the anorexigenic pathway (POMC and CART). This leads to increased feeding behavior and energy efficiency with reduced fat oxidation. During fed states, the concentration of insulin is high and the opposite takes place, resulting in decreased appetite and food intake, and increased sympathetic nerve activity leading to increased fat oxidation. (36, 47, 57).

In contrast to leptin and insulin, the stomach hormone, ghrelin, acts as an adiposity signal that produces opposing effects on the neurons of the ARC (47, 58). Ghrelin directly stimulates the neurons that express NPY and AgRP. Although Ghrelin doesn't directly affect the mRNA levels of the neurons expressing POMC and CART, it indirectly inhibits these neurons through the release of an inhibitory neurotransmitter, GABA, secreted by NPY (59, 60). This triggers food seeking behavior with increased

energy efficiency, reducing the oxidation of fat in order to store more energy in states of fasting (47, 58). During fed states, the stomach secretes less ghrelin, which prevents NPY and AgRP neuronal activation and NPY neurotransmission, inhibiting food intake and decreasing appetite (47).

Hypopituitarism and Hypothalamic Dysfunction

Due to their central midline position, the hypothalamus and the pituitary gland are susceptible to dysfunction via congenital abnormalities at the base of the skull or as secondary acquired dysfunction to pathological disease or treatment at the skull base (44-46). Damage to the hypothalamus, pituitary, or the infundibulum that connects the two glands can cause hypopituitarism, defined as the impaired secretion of one or more pituitary hormones from the anterior and posterior pituitary (44, 46). Panhypopituitarism indicates the impaired secretion of all pituitary hormones, but is often used clinically to describe patients who are deficient in growth hormone, gonadotropins, and corticotrophins, while the posterior pituitary still retains function (50). Hypothalamic dysfunction and hypopituitarism can cause long term morbidity, including debilitating obesity disorders, fatigue, problems with temperature regulation, and disrupted circadian rhythms (44-46).

In most cases, acquired hypopituitarism manifests due to skull base mass lesions or their corresponding treatment of surgery or radiotherapy. Brain tumors compress the pituitary stalk portal vessels due to its expansion in size or as a result to an increase in intrasellar pressure. Localized mass lesions causing hypopituitarism include gliomas,

craniopharyngiomas, arachnoid cysts, and Rathke cleft cysts (46). In patients with craniopharyngioma, 85 to 95 percent of patients suffer from endocrine deficits, with 80 to 93 percent manifesting irreversible diabetes following complete resection of the tumor, and 75 percent manifesting growth hormone deficiencies (49).

Radiation-induced hypopituitarism is a common consequence of radiation therapy that occurs when the hypothalamic-pituitary axis lies within the field of administered radiation (45, 46, 51). For treatment of sellar and parasellar tumors, hypothalamic damage is considered to be present in the early pathophysiology of radiation-induced toxicity, which differs from the atrophy of the pituitary gland, which is considered a “late-onset contributing factor” (45, 51). This occurs through the ionization of cell DNA that can lead to the degeneration of glial cells. Ionizing radiation may cause conformational changes in the DNA structure of the cell or lead to the destruction of the cell through the production of free radicals. The destruction of glial cells leads to neural demyelination and instability, causing neural damage in the hypothalamus-pituitary axis. Sub-acute damage involves vascular changes that may cause edema, or the accumulation of fluid. Chronic neural damage involves the vascular lining synthesizing more collagen and producing a thicker basement membrane, leading to the eradication of small blood vessels, necrosis of irradiated tissues, and atherogenesis, or the formation of plaques, in major brain arteries (51).

Anterior pituitary hormone deficits due to radiation treatments are more numerous and manifest at a greater rate as the radiation dose increases (46, 50, 51). Growth Hormone has been shown to be the most radiosensitive to the effects of radiation therapy

with doses as low as 18 Gy causing a deficiency (50, 51). Other anterior pituitary hormones, like Thyroid Stimulating Hormone (TSH), require greater radiation doses above 50 Gy to cause a deficiency (51).

Hypopituitarism has various effects depending on the age of onset, type of hormone that shows a deficit, and hormone replacement to normalize endocrine function. For instance, children who manifest GH deficiencies have a reduced growth velocity for their age, resulting in shorter stature and final height (51). Untreated GH deficient children attain an average final height of approximately 1 standard deviation below ethnically-, age-, and sex-matched controls (57). Adults face a greater risk of abnormalities in protein, fat, and carbohydrate metabolism, causing a decreased amount of lean body mass and higher fat mass. (50, 51). This results in muscle weakness, fatigue, and increased intra-abdominal or visceral fat deposition leading to central obesity. TSH is another pituitary hormone which carries a propensity towards central obesity as a consequence to its deficit. Patients manifest secondary hypothyroid symptoms, which include cold intolerance, weight gain, poor growth, delayed bone maturation, and fatigue (46, 50). Some of the symptoms caused by hormone deficits may be alleviated with hormone replacement therapy. For example, GH-deficient children who received adequately-dosed and timely GH replacements were shown on average to achieve a higher final height compared with those who were untreated or received a lower dose (51, 53).

Hypothalamic dysfunction has a similar pathogenesis akin to hypopituitarism, where direct infiltration by skull base neoplasms, trauma, inflammatory disease, surgical

resection, or irradiation may inflict damage to the hypothalamus (46). The difference is, unlike hypopituitarism, many of the symptoms associated with hypothalamic dysfunction persist despite adequate hormone replacement therapy. Studies on craniopharyngioma patients who exhibited symptoms of fatigue and excessive daytime sleepiness were not alleviated by hormone replacements of cortisol nor thyroxine (for ACTH or TSH deficiency). Thus, patients are faced with long-term morbidities that include disrupted circadian rhythms and hypothalamic obesity (46, 47, 49).

Damage to the suprachiasmatic nucleus of the hypothalamus has been shown to cause sleep disturbances and daytime hypersomnolence. Evidence has been observed in craniopharyngioma patients that show the tumor, or the treatments associated, can create dysfunction in the hypothalamic circadian pacemaker, which controls the timing of the sleep propensity rhythm. In addition, there is a deficiency in melatonin secreted into the bloodstream by the pineal gland (52). It is believed that the dysfunctional circadian pacemaker causes disturbance in the mechanisms controlling daytime circadian arousal, leaving the sleep drive unopposed, thus causing the daytime hypersomnolence. Self-reports of long term survivors of craniopharyngioma have shown persistent day time sleepiness, and difficulty falling asleep or staying asleep for the entire night (54). Hormone replacements of cortisol or thyroxine were shown to be ineffective at alleviating symptoms of daytime hypersomnolence, however there are self-reports of obese craniopharyngioma patients stating that there were some improvements with supplemental melatonin (55, 56).

Dr. Joseph Babinski in 1900 and subsequently, Dr. Alfred Fröhlich in 1901 were one of the first to document medical case studies describing a link between hypothalamic damage and obesity. A major complication that manifests due to hypothalamic dysfunction is intractable weight gain, known as hypothalamic obesity, which is shown to persist regardless of caloric restriction (47, 48). Hypothalamic obesity (HyOb) is caused by the impairment in hypothalamic regulatory centers controlling energy homeostasis, leading to significant polyphagia and weight gain (61, 62). Although, mechanisms of HyOb pathogenesis is not totally clear, known mechanisms include: the suppression of the sympathetic nervous system, resistance to insulin, and the loss of sensitivity to afferent peripheral humoral signals (47, 49, 61).

Damage to the some of the main areas of the hypothalamus that regulate energy homeostasis lead to HyOb. Previous studies show that destruction of the VMN, PVN, or ARC lead to the impairment of satiety signals (13, 49). Many of the neurons in these areas that normally produce anorexigenic neuropeptides in these areas are absent. These anorexigenic neuropeptides include: CRH, TRH, and Oxytocin in the PVN, POMC and CART in the ARC, and BDNF in the VMH (7, 12, 13). In addition, destruction of BDNF in the VMN causes hyperglycemia due to glucose levels no longer being monitored (13). In mice, injections of an inhibitor, colchicine, to each of the nuclei of the hypothalamus responsible for energy homeostasis, resulted in a substantial increase in fat mass, along with serum leptin and insensitivity to intracerebroventricular administration of leptin (63, 64).

Particularly, disruption of cortisol regulation by CRH and ACTH has been shown to lead to Hypothalamic Obesity. Surgical resection of craniopharyngioma in HyOb patients with ACTH deficiency caused a substantial elevation in the activity of 11 β -hydroxysteroid dehydrogenase 1 (11 β -HSD1), the enzyme that catalyzes the conversion to produce active cortisol (84, 85). Increased levels of 11 β -HSD1-derived corticosterone in children have led to increased adiposity, with an associated increase in waist circumference and waist-to-hip ratio. In addition, there is a rise in body mass and resistance to insulin (85, 86).

The death or absence of VMH neurons prevents the integration of afferent leptin signaling. Patients who manifested HyOb after surgical resection of craniopharyngioma were found to have remarkably higher levels of leptin for their body mass index (BMI), indicating a manifested leptin resistance (66). Further studies involving mice with hypothalamic lesions showed a 20-fold increase in the level of leptin mRNA in the adipose tissue. This hyperleptinaemia confirms the unresponsiveness of hypothalamic leptin receptors (61, 65). Disrupted leptin signaling leads to deregulation of adipocyte levels in the body, decreased metabolic rate, and increased food intake (33-35).

There is also evidence that HyOb causes decreased ghrelin suppression. A study involving 15 subjects with HyOb showed dampened and delayed ghrelin suppression when compared with 15 obese BMI-matched controls (67). This suggests an increase in ghrelin exposure, which may further contribute to the intractable weight gain, although further studies are needed to confirm this hypothesis.

Another mechanism of the HyOb pathogenesis is the suppression of the sympathetic nervous system due to unilateral denervation to white adipose tissue, causing impaired lipid mobilization and decreased sympathetic tone (61, 68). This is documented by patients exhibiting an impaired ability to generate an epinephrine response to insulin-induced hypoglycemia, lowered 24-hour epinephrine secretion, and lowered morning heart rates (47, 69, 71). There is also evidence of HyOb patients having a decreased basal metabolic rate. The oxidation rate of glycerol-3-phosphate by the mitochondria of adipose tissue was reduced, indicating a reduction in the rate of metabolism of adipose tissue, (61, 70).

Insulin hypersecretion is another symptom of Hypothalamic Obesity, defined by insulin resistance. Fasting insulin and insulin secreted after given a 75g oral glucose tolerance test were remarkably high in HyOb patients, with measured levels of fasting insulin being greater than weight-matched controls (70, 72). This hyperinsulinaemia was shown to be present in craniopharyngioma patients immediately following surgical resection treatment, prior to the onset of obesity, suggesting direct hypothalamic regulation of insulin release by beta cells of the pancreas (73).

Three mechanisms are attributed to the insulin hypersecretion: loss of POMC neurons, loss of central insulin signaling, and an increase in vagal stimulation (74-76). Insulin is directly regulated by α -MSH, thus loss of POMC neurons cause loss of insulin suppression, severely increasing insulin levels (75). Previous studies on knockout mice lacking neuronal insulin receptors show an elevation in peripheral insulin, food intake, and insulin resistance indicating signaling of insulin in the brain as a regulator of

peripheral plasma insulin levels (76). Another mechanism of HyOb hyperinsulinaemia is the increased stimulation of the parasympathetic nervous system due to loss of inhibition. Previous studies have shown that a subdiaphragmatic vagotomy, inhibiting vagal stimulation, on adult female HyOb rats prevented obesity, hyperinsulinaemia, and proliferation of pancreatic beta cells. However, it did not prevent from overeating (77-79).

Hypothalamic Obesity imposes the risk of developing further health complications, particularly those associated with Metabolic Syndrome. Metabolic Syndrome is defined by a number of adverse health outcomes: elevated blood pressure, insulin resistance with or without glucose intolerance, abdominal obesity, atherogenic dyslipidemia, leading to an increased risk of cardiovascular disease, stroke, and coronary heart disease (80, 81, 83). Atherogenic dyslipidemia pertains to an increase in triglycerides and low-density lipoprotein (LDL) cholesterol levels, with decreased levels of high-density lipoproteins (HDLs). Atherogenic dyslipidemia is directly associated with an increased risk of myocardial infarctions (82). Obesity may cause inflammation due to excess adipose tissue releasing inflammatory cytokines. This promotes the production and release of the clotting factor, fibrinogen, forming fibrin clots in the blood. This proinflammation and prothrombotic state is associated with an increased risk of cardiovascular disease (80, 83).

Management of HyOb morbidities remains suboptimal due to the numerous facets of the disorder, calling for further research on therapeutic drug protocols to improve the quality of life of HyOb patients. Rosenbaum *et al.* have conducted experiments restricting

caloric intake in obese patients to reduce weight by 10 percent in order to induce a starvation state, while exogenously administering leptin in dosing that reflected pre-starvation physiological levels. The result was a generated response to the administered leptin, with energy expenditure, skeletal muscle work efficiency, sympathetic nervous system tone, appetite control, and thyroid hormone concentrations returning to pre-weight loss levels (87, 88). This marks evidence of leptin sensitivity being improved through forced weight loss.

Another area of treatment for HyOb patients is through the activation of the sympathetic nervous system. There is evidence of ephedrine stimulating β -adrenergic receptors of the sympathetic nervous system, causing an increase in energy expenditure with a decrease in food intake (90). In a case study in 2008, administering caffeine (200 mg) and ephedrine hydrochloride (25 mg), to 3 HyOb patients that were gaining weight at initial assessment, acted to prevent further weight gain and maintained a significant weight loss in 2 of the 3 patients. It was believed that these “sympathomimetic drugs” were acting peripherally to increase sympathetic tone and metabolism (89).

Insulin hypersecretion may be suppressed with the use of somatostatins. Suppression of insulin secretion promoted a decrease in fatigue, hunger, and body weight. A double blind placebo-controlled study was conducted on 18 pediatric HyOb patients testing the effects of a particular somatostatin drug, octreotide. Results showed stabilization in weight and BMI, suppression in insulin, and improved quality of life, which was correlated with the amount of octreotide dose given (91).

An alternative to drug therapy to treat symptoms of hypothalamic obesity is gastric bypass surgery. Initial reports of bariatric surgery performed on craniopharyngioma patients with hypothalamic obesity seem promising, showing BMI decreasing or being stabilized in the years following surgery, along with an improved feeding behavior response. However, the scope of the studies have been limited, and long term follow-up studies on the safety and efficacy of bariatric surgery have yet to be examined.

Together, hypothalamic dysfunction and hypopituitarism causes intractable obesity, known as hypothalamic obesity, through impaired sensitivity to feeding signals in the hypothalamus, reduction in metabolic rate, and hypersomnolence. It is necessary to examine two types of invasive brain tumors that are known to affect the hypothalamus: Childhood craniopharyngiomas (CPs) and pediatric low-grade gliomas (PLGGs).

Childhood Craniopharyngiomas and Pediatric Low-Grade Gliomas

Craniopharyngiomas are rare, benign, epithelial tumors that arise from ectoblastic remnants of Rathke's pouch, and can be found anywhere along the path of the craniopharyngeal duct. They are usually found in the sellar/parasellar area in the hypothalamic and pituitary regions of the brain (94, 95). CPs are the most common intracranial tumors of nonglial origin in the pediatric population, with a high survival rate of approximately 92 percent. However, because of its tendency to infiltrate the hypothalamus, patients tend to experience significant morbidity, and in some cases

mortality more than 10 years after diagnosis, due to sequelae caused by hypothalamic obesity (49, 95).

Craniopharyngiomas are classified by the World Health Organization as a grade I tumor, which is considered to be histologically benign (92). They are classified histologically into two variants: an adamantinomatous subtype, normally found in childhood onset craniopharyngiomas, and squamous-papillary subtype, normally found in adults. Mixed forms of the two subtypes can also exist (92, 93, 94). Approximately 96 percent of childhood craniopharyngioma cases are of the adamantinomatous subtype versus up to 2 percent being of the squamous-papillary subtype (94, 96). The histology of the adamantinomatous subtype differs from the papillary by forming a more indistinct, and adherent interface with the surrounding brain tissue and vascular structures. In contrast, the papillary subtype is more circumscribed and infiltrates adjacent brain tissue less frequently (94, 96).

Incidence rates of CPs are very low with an overall incidence of 0.5 to 2.0 cases per million people each year (49). Craniopharyngiomas are the most common lesions to involve the hypothalamic-pituitary axis in children, accounting for 2 to 5 percent of all intracranial neoplasms, and 5.6 to 15 percent of intracranial tumors in children (94, 97). Peak incidence rates of CP occur at the age of 5 to 14 years, although it can be detected at any age, including pre- and neonatal periods (97).

Clinical manifestations initially presented at diagnosis are predominantly headaches, nausea and vomiting, and visual impairment. Other less common presenting symptoms include impaired motor functions, seizures, and psychiatric symptoms (49).

There are also endocrine deficits which, studies show, manifest at a time point far before initial diagnosis of CP is made. Many of the CP patients had a history of weight gain, reduced growth rate at the time of diagnosis, and one to three hormone deficits (95, 98). It has been postulated that particular clinical manifestations are based upon the age group of the patient. There are indications where the most commonly presented symptoms of increased intracranial pressure are reported in young children, sexual immaturity are reported in adolescents, and visual impairments are reported in young adults (99). The objectives of treatment are to relieve these clinical manifestations and to prevent further tumor progression and regrowth.

The primary therapeutic modality most widely used for CP is surgery and radiation, with attention to the preservation of visual and hypothalamic function. To prevent recurrence of disease, the preferred option is complete removal of the tumor by surgical resection, known as gross total resection (GTR) (49, 101, 102). For tumors with extensive hypothalamic involvement, GTR is not recommended due to the increased risk of hypothalamic damage. Rather, a partial removal (PR) or subtotal resection of the tumor is preferred followed by adjuvant external beam irradiation. Studies show that in cases with subtotal resection alone, chance of progression of the residual tumor is 71 to 90 percent. In contrast, PR followed by radiotherapy decreases the chance of progression to 21 percent (100, 102). Thus, radiation has been shown to prevent progression of the tumor, which is why it is utilized following subtotal resection for tumors extending into the hypothalamus.

Unfortunately, hypothalamic damage is a common, inevitable consequence of CP, regardless of the modality of treatment. An examination of the MRI's of 63 CP survivors indicated that excessive post-operative obesity primarily occurs in patients who have sustained "severe, bilateral hypothalamic damage". All of the subjects who were severely obese after surgery showed evidence of an impaired hypothalamus, with either a completely deficient or an extensively damaged third ventricle floor (106). Hypothalamic obesity is the most common manifestation of hypothalamic damage, reported in approximately 40 to 60 percent of CP patients treated surgically in conjunction with or without radiation (66, 94). This results, as previously mentioned, from the disruption of signaling to mechanisms of the hypothalamus that control energy homeostasis, satiety, and hunger, leading to reduced physical activity, leptin and ghrelin insensitivity, vagally induced insulin hypersecretion, and hypersomnolence.

CP increases the prevalence of risk factors for developing atherosclerotic cardiovascular disease (103). Adult subjects with childhood onset craniopharyngioma exhibited increased serum levels of high-sensitivity C-reactive protein (hs-CRP) and LDL concentrations, indicating a greater percent of subjects (48%) having at least a 1.7 times greater increased risk of cardiovascular disease compared with matched controls (29%). In addition, the ratio of the lipid-transporting proteins, apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA-I), was calculated to determine if there is an increased risk of myocardial infarction. Elevated cardiovascular disease risk was identified in 52 percent of patients compared with 33 percent in matched controls. Conventional hormone

replacement was insufficient to normalize cardiovascular disease risk, suggesting implications for irreversible hypothalamic damage (103-105).

Patients who presented with a high BMI at the time of diagnosis were at higher risk for developing hypothalamic obesity. Analysis on preoperative risk factors for postoperative obesity found that CP with hypothalamic involvement caused a mean increase in BMI compared with patients lacking hypothalamic involvement. In addition, endocrine deficiencies and hormonal substitution therapy did not seem to have a significant impact on the development of HyOb in CP patients (95). Other studies have shown that the degree of obesity is positively correlated with the degree and extent of hypothalamic damage, usually from surgical resection and/or irradiation (100).

Pediatric low-grade gliomas encompass a diverse set of uncommon, slow growing, neoplasms, which are estimated to account for 30 to 50 percent of pediatric CNS tumors. These tumors typically involve midline structures of the brain, like the cerebellum, brainstem, hypothalamus, and optic pathway (107, 108). Like CP patients, PLGG patients have a high survival rate, with a 5-year overall survival at 94.6 to 97 percent and a 15-year overall survival at 86 percent (107, 109, 110).

Low-grade gliomas are neuroectodermal tumors that originate from glial cells of the CNS that include oligodendrocytes and astrocytes. Three types of tumors are pure astrocytomas, pure oligodendrogliomas, or mixed glioneuronal tumors. Tumor subtypes are classified by the World Health Organization as Grade I and Grade II with the majority of PLGGs being histologically benign, and not undergoing malignant transformation. Grading is based on a number of histological factors that include: presence of necrosis,

giant cells, mitosis, proliferation, hyperchromatic nuclei, and pleomorphic cells. By definition, Grade I tumors have well circumscribed borders, while Grade II are “diffusely infiltrating with bizarre nuclei” (92, 108, 110).

PLGGs are difficult to categorize because they can occur anywhere in the CNS and comprise of multiple different tumor histologies. The most common location is the cerebellum, where cerebellar PLGGs make up approximately 15 to 25 percent of all pediatric CNS tumors, followed by gliomas in the cerebrum at 10 to 15 percent, gliomas of the midline structures, which account for hypothalamic gliomas, at 10 to 15 percent, optic pathway gliomas at 5 percent, and brain stem gliomas at 2 to 4 percent (108, 109). Neurofibromatosis type 1 (NF1), a benign soft tissue tumor, has been known to develop into 70% of the optic pathway gliomas and hypothalamic gliomas. Nearly a fifth of children diagnosed with NF1 will develop into an optic pathway or hypothalamic glioma (108).

The therapeutic modalities for pediatric low-grade gliomas are frequently less invasive than the procedures to treat childhood craniopharyngioma. Other than optic pathway/hypothalamic gliomas, the initial management of PLGGs is surgery. Gross total resection is considered the most consistent prognostic factor for progression-free overall survival, with associated 10-year overall survival rate of 90% with a low chance of recurrence (107, 109, 112). If a subtotal resection is performed, usually adjuvant therapy does not take place unless there are signs of tumor progression. Chemotherapy is considered the primary postoperative adjuvant therapy for progressive PLGGs versus irradiation, which have little evidence suggesting improved overall survival. In contrast,

optic pathway gliomas and hypothalamic gliomas do not utilize surgery or radiation as initial therapeutic measures. Surgical resection and irradiation therapy is typically avoided due to an increased risk of developing a stroke and endocrine dysfunction, including obesity and hypopituitarism. Therefore, chemotherapy is used as initial therapy for optic pathway/hypothalamic gliomas to preserve hypothalamic function and attain the best chances of progression-free survival (108, 113, 114).

PLGG survivors face long-term endocrinopathies based on tumor location and the extent of surgical resection. In a study examining long-term morbidities in PLGG patients, increases in cumulative incidence rates of obesity, hormone deficiencies, and insulin resistance were associated with tumor location in the diencephalon (107, 125). This is observed in posterior optic nerve gliomas, which tend to grow into larger masses that compress the hypothalamus or obstruct the anterior third ventricle, impinging on normal hypothalamic signaling and causing hypothalamic dysfunction (111).

Subtotal resections of tumors tend to cause tumor progression with decreased long-term overall survival rates. PLGG subjects with at least 90 percent of their tumor resected had an overall survival rate of 91 percent at 8-years post-diagnosis. In contrast, patients with partially resected tumors had an overall survival rate of only 60 percent (110). Out of all unresected/partially resected PLGG tumors, hypothalamic/chiasmatic gliomas carry the most sustained risk for tumor progression, which significantly increases the risk of long term morbidities. In a study examining long term PLGG survivors with progressive hypothalamic/chiasmatic gliomas, 75 percent were found to be

obese/overweight, more than half were GH deficient, ACTH deficient, and hypothyroid, and nearly 25 percent had insulin resistance (107).

In contrast to childhood craniopharyngiomas inducing hypothalamic obesity, pediatric low-grade gliomas are known to induce intractable weight loss, related to hypothalamic dysfunction, known as Diencephalic Syndrome (DS). DS is a rare, potentially lethal, multifaceted condition, marked with causing a failure to thrive in infants and young adults. DS patients are defined by the absence of subcutaneous adipose tissue, in spite of a normal or slightly diminished caloric intake, while maintaining an age-appropriate linear growth rate. Initial reports in 1951 described clinical characteristics of severe emaciation, hyper alertness, increased vigor and/or hyperkinesia, irritability, pallor, and normal or accelerated linear growth. Other symptoms that may be associated with DS include: involuntary eye movements (nystagmus), optic atrophy, and increased intracranial pressure (115-117).

Diencephalic Syndrome is described being almost exclusively associated with lesions of the hypothalamic-optic chiasm, being predominantly found in patients with juvenile pilocytic astrocytomas (116). In the first year of life, DS has been reported in 5 percent of intracranial tumors, 15 percent of optic pathway tumors, and 21 percent of hypothalamic glioma tumors (119-121). Although the general frequency of dissemination of low-grade gliomas is approximately 5 percent, it has been suggested that there is an association between DS and early dissemination of PLGGs. Therefore, despite being histologically low-grade, the tumors of DS patients are often aggressive in behavior (116, 117).

DS has a significant impact on the hypothalamic-pituitary axis, which has an effect on the mechanisms that modulate energy expenditure, appetite, and rate of growth. Vlachopapadopoulou *et al* found that total energy expenditure for DS patients was found to be 30 to 50 percent higher than matched controls and 13 percent higher than the patient's energy intake. This suggests that weight loss and emaciation is due to an excessive expenditure of energy (122). Although the specific mechanism of cachexia manifestation in PLGG patients is unknown, it is believed to be directly attributed to the LGG tumor itself. It has been postulated that the LGG tumor produces an excess of a lipolytic peptide, β -lipotropin, which is a fat mobilizing protein. This may account for the loss of subcutaneous adipose tissue and partial GH resistance. A decrease in tumor size following therapy was also followed by a rapid weight gain (123, 124).

Several reports confirm an elevation in basal GH concentrations, partial GH suppression after administration of a glucose load, and normal Insulin-like growth factor 1 (IGF-1) in DS patients before undergoing treatment of the tumor, which many studies suggest to be indicative of an acquired partial GH resistance. Elevated cortisol levels may contribute to the stimulation of GH secretion. Furthermore, some patients had ghrelin concentrations, before treatment, that were more than twice the level of normal weight controls, which may stimulate GH release (117, 118, 123).

According to previous studies, leptin regulation does not seem to be altered in DS patients; however, there are new implications that suggest otherwise. Brauner *et al* reports of measured plasma leptin concentrations in DS patients correlating with their BMI before and after treatment. Concentrations were similar to leptin levels in BMI-

matched controls (118). They hypothesized that this suggests the regulation of leptin is not altered. However, a new case report examined a patient with measured leptin concentrations that fell following weight gain in response to treatment that decreased tumor size. They attributed this paradoxical response as either leptin axis dysregulation in DS or the PLGG diencephalic tumor impacting leptin secretion (126).

SPECIFIC AIMS

The purpose of this study was to compare hypothalamic damage in subjects diagnosed with pediatric hypothalamic low-grade glioma versus subjects diagnosed with childhood craniopharyngioma. Numerous studies have suggested rapid weight gain following diagnosis and initial treatment of CP due to the damage sustained by the hypothalamus. Hypothalamic lesions formed by surgery/irradiation therapy, or by invasiveness of the tumor itself, are known to cause intractable weight gain. In contrast, hypothalamic obesity manifested in PLGGs is not as prominently addressed in literature; likely due to the expansive set of histological tumor subtypes that makes generalization challenging. Specifically, there is a lack of in-depth literature that examines the difference of treatment, endocrinopathies, and weight gain post diagnosis between CP versus PLGGs. PLGGs appear to have less of an impact on hypothalamic obesity and are even related, in some rare cases, to directly produce emaciation and intractable weight loss. We hypothesized that CP patients will have a more rapid post diagnosis weight gain and a greater degree of obesity compared with PLGG patients. This study was implemented to investigate whether a difference existed in post diagnosis weight gain of CP and PLGG patients.

This study utilized data from the brain tumor database at Dana-Farber Cancer Institute to examine the extent of obesity of pediatric low-grade glioma patients versus childhood craniopharyngioma patients at 6 months post-diagnosis, 5 years post-diagnosis, and at their most recent visit. Statistical analysis was performed to evaluate if a statistical

difference exists in post diagnosis BMI between diseases. Additional analyses were performed to identify endocrine dysfunctions that are present, the frontline treatments received, and the impact of treatment administered on the degree of obesity.

METHODS

Patient Population

We performed a retrospective review of the clinical records of patients who received a diagnosis of childhood craniopharyngioma or pediatric low-grade glioma at Dana-Farber Cancer Institute between 1980 and 2009. The brain tumor database includes over 900 patients. The Dana-Farber Cancer Institute Institutional Review Board approved data collection efforts for use in this study. Patients were included in the study if they met the following inclusion criteria: being younger than 18 years old at the date of diagnosis, having been evaluated for care at Dana-Farber Cancer Institute, receiving a biopsy-proven diagnosis of craniopharyngioma or a brain tumor classified as a low-grade glioma. Patients were excluded from the study if they met any of the following criteria: being lost to follow-up after initial diagnosis, at Dana-Farber Cancer Institute, and/or being over the age of 18 at the time of diagnosis. Patients seen for a second opinion but not followed primarily at Dana Farber Cancer Institute were also excluded.

Hypothalamic PLGGs were diagnosed by histopathologic confirmation of a grade 1 (pilocytic) astrocytoma or grade 2 astrocytoma. A grade 2 astrocytoma include: fibrillary astrocytoma, pilomyxoid, oligoastrocytoma, oligodendroglioma, or low-grade astrocytic growths not otherwise specified. Optic pathway tumors acknowledged to be a glioma by neuroimaging, but without biopsy as evidence, were included in the study.

We were able to identify 45 patients (30 males and 15 females) who fit the criteria for inclusion in the study. Of the 45 patients, 28 were previously diagnosed with

childhood craniopharyngioma and 17 were diagnosed with pediatric low-grade glioma. Details on age, sex, height, weight, frontline treatments, extent of resection, and cumulative radiation dose were extracted from patient medical records. Height and weight were acquired from patient health records to calculate the body mass index (BMI), used as a measure of obesity. BMI was calculated using the formula, [BMI = weight (kilograms) ÷ height² (square meters)]. Height and weight data were collected for each patient at the date of their cancer diagnosis, 6 months after diagnosis, 5 years after diagnosis, and at their latest follow-up visit.

Statistical Analyses

Statistical analysis was performed by our informatics team of the pediatric oncology department at Dana-Farber Cancer Institute using SPSS software.

To compare the weight status of pediatric patients, BMI standard deviation scores, also known as BMI z-scores, were used as a measure of relative weight, adjusted for child age and sex (Table 1). BMI z-scores were assigned to patients from age 2 to 20 years old, and are based on body mass index-for-age growth charts obtained from the Center for Disease Control website for reference (www.cdc.gov/growthcharts). Z-scores for infants less than 2 years old were based on age, sex, and weight, rather than BMI. The degree of obesity was based off of BMI reference standards produced by the International Obesity Task Force (IOTF).

Patients of ages 0 to 23.9 months were assigned a z-score based on weight. Patients age 24 months to 239.9 months were assigned a z-score based on BMI. For

patients age 0 to 239.9 months, the degree of obesity was based on z-score, with z less than -1 assigned as being “underweight”, equal to or greater than -1 but less than 1 being “normal”, equal to or greater than 1.5 but less than 2 being “obese”, and greater than or equal to 2 being “morbidly obese”. For patients age 20 years old or greater, the degree of obesity was based on the BMI: less than 18.5 being “underweight”, greater than or equal to 18.5 but less than 25 being “normal”, greater than or equal to 25 but less than 30 being “overweight”, greater than or equal to 30 but less than 40 being “obese”, and greater than or equal to 40 being considered “morbidly obese”.

Table 1. Degree of Obesity with Corresponding BMI/BMI Z-Scores

Degree of obesity	Age < 2 years old	Age 2 - 20 years old	Age > 20 years old
Underweight	$Z < -1$	$Z < -1$	$BMI < 18.5$
Normal	$-1 \leq Z < 1$	$-1 \leq Z < 1$	$18.5 \leq BMI < 25$
Overweight	$1 \leq Z < 1.5$	$1 \leq Z < 1.5$	$25 \leq BMI < 30$
Obese	$1.5 \leq Z < 2$	$1.5 \leq Z < 2$	$30 \leq BMI < 40$
Morbidly obese	$Z \geq 2$	$Z \geq 2$	$BMI \geq 40$

A Wilcoxon rank sum test is a non-parametric statistical hypothesis test that assesses whether the sum of ranks differ between two sample cohorts. A two-sided Wilcoxon test was used to compare the BMI of CP versus PLGG patients at 6 months post diagnosis, 5 years post diagnosis, and the overall change in BMI from diagnosis until the last date of contact.

The frontline treatments received by the proportion of patients were summarized. Results were categorized by disease type. The variables of this analysis included having: surgery alone, radiation therapy (XRT) alone, chemotherapy alone, surgery + XRT, surgery + chemotherapy, XRT + chemotherapy, or surgery + XRT + chemotherapy.

The proportion of patients was calculated, overall and by each tumor type, in terms of: the presence of endocrinopathies, whether the tumor impedes on the anterior or posterior pituitary, hormonal deficiencies, and the presence of diabetes insipidus. For each proportion, a 95% confidence interval was calculated. A Fisher's exact test was utilized to compare the proportions between the two tumor types. Tumor location was determined based on which particular hormones were deficient.

The extent of treatment administered was compared with the degree of obesity overall by utilizing a two-sided Wilcoxon test. We explored the degree of obesity in patients who received a gross total resection versus subtotal as frontline treatment. In addition, we examined the impact of cumulative radiation dose administered to all patients on the degree of obesity. Results were depicted graphically on a boxplot.

RESULTS

There was not a significant difference in BMIs and the rate of weight gain between low-grade glioma patients and craniopharyngioma patients 6 months after diagnosis, 5 years after diagnosis, and at their most recent visit. P-values and data are summarized in Table 2.

Table 2. Comparison of CP and LGG Patient BMI Over time

	Diagnosis	N	Mean	p-value*
BMI at 6 months post diagnosis	Low-grade glioma	14	22.5	0.3
	Craniopharyngioma	21	23.6	
BMI at 5 years post diagnosis	Low-grade glioma	14	30.4	0.9
	Craniopharyngioma	26	29.0	
Change in BMI from diagnosis until most recent visit	Low-grade glioma	15	10.0	0.1
	Craniopharyngioma	26	16.1	

*two-sided p-values of Wilcoxon tests

Proportions of each frontline treatment and combinations of the treatments received by the patients are summarized in Table 3. Out of the 28 craniopharyngioma patients, 14 (50%) underwent surgery alone, while the other 14 (50%) had a subtotal resection and radiation therapy. Similarly, 8 (48%) received radiation treatment either by itself or in combination with surgery and/or chemotherapy Only 3 (18%) out of the 17

PLGG patients had a gross total resection as primary treatment. 8 (48%) out of the 17 PLGG patients had a subtotal resection with either radiation, chemotherapy, or a combination of the two.

Table 3. Proportions of Frontline Treatments and Combinations of Treatments Received

	Overall N=45 N(%)	Craniopharyngioma N=28 N(%)	Low-grade glioma N=17 N(%)
None	1(2%)	0	1(6%)
Surgery Alone	17(38%)	14(50%)	3(18%)
Surgery + XRT	17(38%)	14(50%)	3(18%)
Surgery + Chemotherapy	4(9%)	0	4(24%)
XRT Alone	3(7%)	0	3(18%)
XRT + Chemotherapy	1(2%)	0	1(6%)
Chemotherapy Alone	1(2%)	0	1(6%)
Surgery + XRT+ Chemotherapy	1(2%)	0	1(6%)

XRT = Radiation Therapy

The proportions of patients in each disease outcomes are summarized in Table 4. Endocrinopathies were found to be manifested in 27/28 (96% with 95% confidence interval between 90-100%) of CP patients and 13/17 (76% with 95% confidence interval between 56-97%) of PLGG patients. Out of the 45 total patients, 40 have tumors that impede the anterior pituitary and 30 have tumors that impede the posterior pituitary. There was found to be no statistically significant difference in the presence of

endocrinopathies between CP and PLGG patients. However, there is a statistically significant difference in adrenal insufficiency ($p = 0.03$), being in 17/28 (61% with 95% confidence interval between 43-79%) of CP patients compared to 4/17 (24% with 95% confidence interval between 3-44%).

Table 4. Proportions of Selected Disease Outcomes

		Overall N=45 N(%, 95% CI)	Craniopharyngioma N=28 N(%, 95% CI)	Low-grade glioma N=17 N(%, 95% CI)	p- value*
Endocrinopathies (present)		40(89%, 80%-98%)	27(96%, 90%-100%)	13(76%, 56%-97%)	0.06
Tumor Location	Anterior	40	24	16	NA**
	Posterior	30	24	6	
Hypothyroidism		27(60%, 46%-74%)	18(64%, 47%-82%)	9(53%, 29%-77%)	0.5
Growth Hormone Deficiency		26(58%, 43%-72%)	18(64%, 47%-82%)	8(47%, 23%-71%)	0.4
Adrenal Insufficiency		21(47%, 32%-61%)	17(61%, 43%-79%)	4(24%, 3%-44%)	0.03
Sex steroid deficiency		17(38%, 24%-52%)	12(43%, 25%-61%)	5(29%, 8%-51%)	0.5
Hypo/Hypergonadism		18(40%, 26%-54%)	13(46%, 28%-65%)	5(29%, 8%-51%)	0.4
Diabetes Insipidus		17(38%, 24%-52%)	13(46%, 28%-65%)	4(24%, 3%-44%)	0.2

*Two-sided p-value of Fisher's exact test to compare the proportions between two disease groups.

**There are overlaps in tumor locations

Wilcoxon tests were performed to compare the BMI at different time points for each type of treatment administered. Data and p-values are summarized in Tables 5-7. There was no statistically significant difference in BMI between CP and PLGG who had surgery and PLGG patients who did not have surgery (Table 5). Furthermore, there was no statistically significant difference in BMI in patients that have undergone gross total resection versus those who had a subtotal resection.

CP and PLGG patients who received radiation treatment had a higher BMI at 5-years after their diagnosis compared to those without ($p = 0.04$). In addition, patients who received radiation treatment were found to have a higher BMI at their most recent visit ($p = 0.0055$) compared to patients lacking radiation treatment (Table 6).

PLGG patients who received chemotherapy had significantly higher BMI at 6-months post diagnosis ($p=0.02$) and at the most recent visit ($p=0.02$) compared to PLGG patients who did not receive treatment (Table 7). A comparison between PLGG and CP patients was not made since CP patients do not undergo chemotherapy.

Table 5. Comparing the Impact of Surgery on PLGG and CP BMI

	Surgery	N	Mean	p-value*
BMI at 6 months post diagnosis	Yes	33	3.5	0.7
	No	2	4.0	
BMI at 5 years post diagnosis	Yes	37	3.8	0.9
	No	3	4.0	
BMI at recent visit	Yes	41	4.6	0.6
	No	4	5.0	

*two-sided p-values of Wilcoxon tests

Table 6. Comparing the Impact of Radiation Treatment on PLGG and CP BMI

	Radiation	N	Mean	p-value*
BMI at 6 months post diagnosis	Yes	25	3.7	0.2
	No	10	2.9	
BMI at 5 years post diagnosis	Yes	30	4.1	0.04
	No	10	3.0	
BMI at recent visit	Yes	33	4.9	0.0055
	No	12	3.9	

*two-sided p-values of Wilcoxon tests

Table 7. Comparing Impact of Chemotherapy on PLGG BMI

	Chemotherapy	N	Mean	p-value*
BMI at 6 months post diagnosis	Yes	28	3.8	0.02
	No	7	2.3	
BMI at 5 years post diagnosis	Yes	34	4.0	0.1
	No	6	2.8	
BMI at recent visit	Yes	38	4.8	0.02
	No	7	3.7	

*two-sided p-values of Wilcoxon tests

Descriptive statistical analysis in Figure 1 shows the cumulative radiation dose on each degree of obesity of PLGG patients at their most recent visit. “Morbidly obese” patients were found to have a larger overall range, interquartile range, and associated with receiving a greater median cumulative radiation dose. This is in contrast with “Normal” and “Obese” patients, who were found to have a lower median cumulative radiation dose and narrower range of dosage.

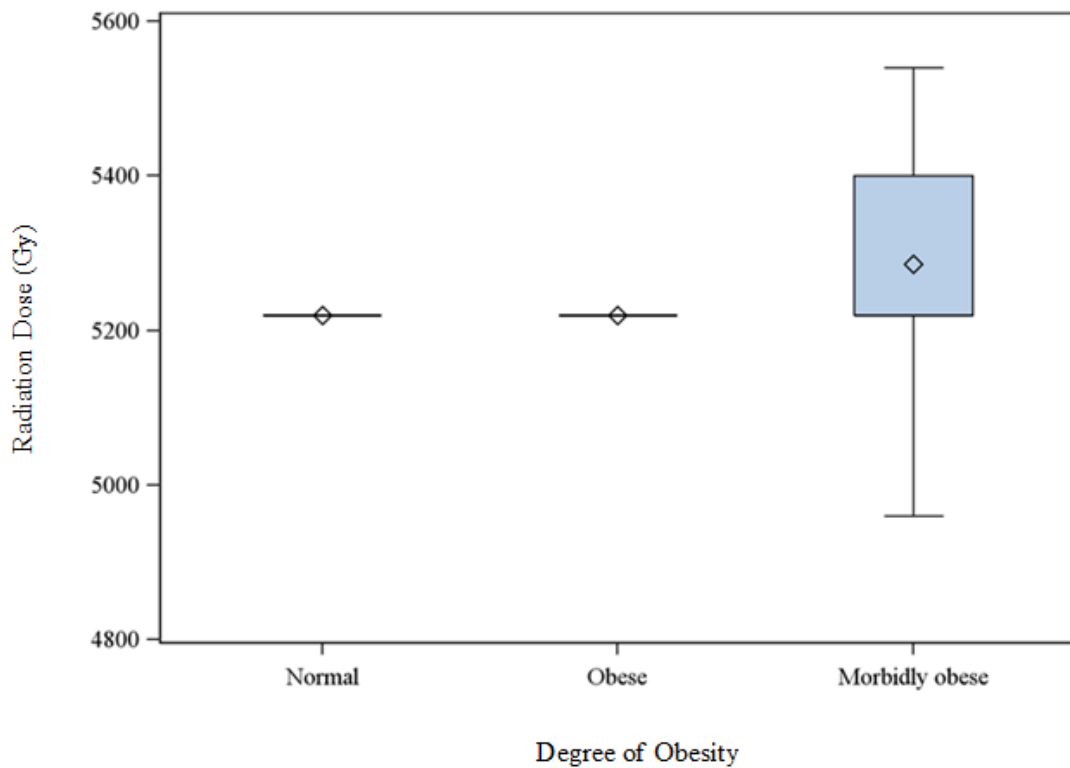


Figure 1: Boxplot of cumulative radiation dose on each degree of obesity of PLGG patients at their most recent visit.

DISCUSSION

The purpose of this study was to compare hypothalamic damage in subjects diagnosed with pediatric hypothalamic low-grade glioma versus subjects diagnosed with childhood craniopharyngioma. It was hypothesized that CP patients will have a more prominent display of hypothalamic obesity; having a more rapid post diagnosis weight gain and a greater degree of obesity compared with PLGG patients. It was further hypothesized that there would be a greater number of endocrine dysfunctions that manifest in CP patients due to the greater proportion of patients undergoing invasive frontline procedures of surgery and radiation; shown to have a great impact on hypothalamic functionality. Hypothalamic PLGG patients receive less invasive procedures of chemotherapy and surveillance monitoring, opting for a more wait-and-see approach. However, this study suggests that there is no difference in the rate or magnitude of post diagnosis weight gain, indicating the manifestation of hypothalamic obesity in both CP and PLGG patients, and disproving our initial hypotheses.

We found that histological tumor types of craniopharyngioma or pediatric low-grade glioma did not seem to have a relevant influence on the post diagnosis manifestation of hypothalamic obesity. Rather, it is hypothalamic involvement, regardless of the histological tumor type itself, which seems to have a major impact on the development of obesity. There was not a statistically significant difference in BMI and BMI z-scores between CP and hypothalamic PLGG patients from the time of their

diagnosis until 6 months after diagnosis, 5 years after diagnosis, and their most recent visit, which in most cases was over 10 years after their initial diagnosis.

In addition, with the exception of ACTH, there was no difference in the proportion of patients who manifested endocrine dysfunctions. There were a statistically significant proportion of CP patients who presented with ACTH deficiency compared with PLGG patients. Previous reports attribute ACTH deficiency, and subsequently the rise in 11 β -HSD1-derived corticosterone, as a mechanism for the cause of hypothalamic obesity in children, with an increase in adiposity, body mass, and insulin resistance. The fact that ACTH deficiency is less prevalent in PLGG patients appears to refute this claim and support the idea that endocrine deficiencies have less influence on the development of obesity. This is because PLGG patients still develop the same extent of obesity as CP patients, regardless of having normal pituitary ACTH secretion.

Gross total and subtotal resections, predominant frontline treatments of CP, were found to have little difference in BMI, when compared with the BMI of PLGG patients without surgery. This suggests the lack of influence invasive surgical procedures directly have on postoperative weight gain.

In contrast, the BMI in PLGG patients who received chemotherapy was higher 6 months after diagnosis and at the most recent clinical visit compared with CP and PLGG patients who did not receive chemotherapy. This may be a risk factor for hypothalamic obesity in PLGG patients since 7 out of 17 PLGG patients (36 %) had some form of chemotherapy either alone or in conjunction with surgery and/or radiation, however further research needs to be conducted to confirm this claim.

Patients who received radiation therapy had significantly higher BMI 5 years after initial tumor diagnosis and at their most recent clinical visit compared with those who didn't receive radiation treatment. Furthermore, higher doses of radiation were associated with patients who tended to be morbidly obese at their most recent clinical visit. Radiation treatment has been utilized as a common modality of treatment for both PLGG and CP; confirms previous reports on the increased risk that radiation treatment has on long term obesity and the call for lower radiation dosage if possible.

The results of our study are limited due to retrospective analysis and some observations are speculative at this point without further research. Although we had a small sample size, we needed to discriminate the role of tumor histology versus tumor location on the sequelae of obesity. This study suggests a greater role that tumor location plays in the manifestation of hypothalamic damage, subsequently causing hypothalamic obesity. The degree of hypothalamic involvement of the tumor, rather than the histology of the tumor itself, seems to have a more relevant influence on hypothalamic damage and subsequent weight gain.

An in-depth comparison of post diagnostic weight gain in childhood craniopharyngioma and pediatric low-grade glioma patients has not been examined in the literature prior to this study. Retrospective analysis was necessary to understand the implications of tumor histology on the sequelae of hypothalamic obesity after tumor diagnosis. Further analysis should be conducted on tumor location and the extent of hypothalamic tumor involvement in an attempt to better understand the pathogenesis of hypothalamic obesity and improve the modalities of treatment in the future.

REFERENCES

1. Kruk, M. R., Westphal, K. G. C., Van Erp, A. M. M., Judith van Asperen, Cave, B. J., Slater, E., ... Haller, J. (1998). The hypothalamus: cross-roads of endocrine and behavioural regulation in grooming and aggression. *Neuroscience & Biobehavioral Reviews*, 23(2), 163–177. doi:10.1016/S0149-7634(98)00018-9
2. Weyhenmeyer, A. J. & Gallman, A. E. (2006). *Rapid Review Neuroscience*, 1st Edition. Mosby.
3. Baroncini, M., Jissendi, P., Balland, E., Besson, P., Pruvo, J. P., Francke, J. P., ... & Prevot, V. (2012). MRI atlas of the human hypothalamus. *Neuroimage*, 59(1), 168-180.
4. Feher, J. (2012). 9.2 - Hypothalamus and Pituitary Gland. In *Quantitative Human Physiology* (pp. 777–786). Boston: Academic Press. Retrieved from <http://www.sciencedirect.com/science/article/pii/B9780123821638000852>
5. Jacobson & Marcus (2008). *Neuroanatomy for the Neuroscientist*. Springer. p. 147. ISBN 978-0-387-70970-3.
6. Melmed, S. (Ed.). (2010). *The pituitary*. Academic Press.
7. Berthoud, H.-R. (2002). Multiple neural systems controlling food intake and body weight. *Neuroscience and Biobehavioral Reviews*, 26(4), 393–428.
8. Lee, S. K., Ryu, P. D., & Lee, S. Y. (2013). Differential distributions of neuropeptides in hypothalamic paraventricular nucleus neurons projecting to the rostral ventrolateral medulla in the rat. *Neuroscience Letters*. doi:10.1016/j.neulet.2013.09.070
9. Chen, Q.-H., & Toney, G. M. (2010). In Vivo Discharge Properties of Hypothalamic Paraventricular Nucleus Neurons With Axonal Projections to the Rostral Ventrolateral Medulla. *Journal of Neurophysiology*, 103(1), 4–15. doi:10.1152/jn.00094.2009

10. Badoer, E. (2001). Proceedings of the Australian Physiological and Pharmacological Society Symposium: The Hypothalamus HYPOTHALAMIC PARAVENTRICULAR NUCLEUS AND CARDIOVASCULAR REGULATION. *Clinical and Experimental Pharmacology and Physiology*, 28(1-2), 95–99. doi:10.1046/j.1440-1681.2001.03413.x

11. Simerly, R. B. (2004). Chapter 14 - Anatomical Substrates of Hypothalamic Integration. In George Paxinos (Ed.), *The Rat Nervous System (Third Edition)* (pp. 335–368). Burlington: Academic Press. Retrieved from <http://www.sciencedirect.com/science/article/pii/B9780125476386500158>

12. Parker, J. A., & Bloom, S. R. (2012). Hypothalamic neuropeptides and the regulation of appetite. *Neuropharmacology*, 63(1), 18–30. doi:10.1016/j.neuropharm.2012.02.004

13. Yu, J. H., & Kim, M.-S. (2012). Molecular Mechanisms of Appetite Regulation. *Diabetes & Metabolism Journal*, 36(6), 391. doi:10.4093/dmj.2012.36.6.391

14. Krahn, D. D., Gosnell, B. A., & Majchrzak, M. J. (1990). The anorectic effects of CRH and restraint stress decrease with repeated exposures. *Biological Psychiatry*, 27(10), 1094–1102. doi:10.1016/0006-3223(90)90046-5

15. Florio, P., Zatelli, M. C., Reis, F. M., degli Uberti, E. C., & Petraglia, F. (2007). Corticotropin releasing hormone: a diagnostic marker for behavioral and reproductive disorders? *Frontiers in Bioscience: a Journal and Virtual Library*, 12, 551–560.

16. Lawson, E. A., Holsen, L. M., Desanti, R., Santin, M., Meenaghan, E., Herzog, D. B., ... Klibanski, A. (2013). Increased hypothalamic-pituitary-adrenal drive is associated with decreased appetite and hypoactivation of food-motivation neurocircuitry in anorexia nervosa. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 169(5), 639–647. doi:10.1530/EJE-13-0433

17. Lechan, R. M., & Fekete, C. (2006). The TRH neuron: a hypothalamic integrator of energy metabolism. *Progress in Brain Research*, 153, 209–235. doi:10.1016/S0079-6123(06)53012-2

18. Shi, J., Yan, J., Lei, Q., Zhao, J., Chen, K., Yang, D., ... Zhang, Y. (2009). Intra-gastric administration of evodiamine suppresses NPY and AgRP gene expression in the hypothalamus and decreases food intake in rats. *Brain Research*, 1247, 71–78. doi:10.1016/j.brainres.2008.09.091
19. Cone, R. D. (1999). The Central Melanocortin System and Energy Homeostasis. *Trends in Endocrinology & Metabolism*, 10(6), 211–216. doi:10.1016/S1043-2760(99)00153-8
20. Brady, L. S., Smith, M. A., Gold, P. W., & Herkenham, M. (1990). Altered expression of hypothalamic neuropeptide mRNAs in food-restricted and food-deprived rats. *Neuroendocrinology*, 52(5), 441–447.
21. Bergendahl, M., Wiemann, J. N., Clifton, D. K., Huhtaniemi, I., & Steiner, R. A. (1992). Short-term starvation decreases POMC mRNA but does not alter GnRH mRNA in the brain of adult male rats. *Neuroendocrinology*, 56(6), 913–920.
22. Breit, A., Wolff, K., Kalwa, H., Jarry, H., Buch, T., & Gudermann, T. (2006). The Natural Inverse Agonist Agouti-related Protein Induces Arrestin-mediated Endocytosis of Melanocortin-3 and -4 Receptors. *Journal of Biological Chemistry*, 281(49), 37447–37456. doi:10.1074/jbc.M605982200
23. Biebermann, H., Kühnen, P., Kleinau, G., & Krude, H. (2012). The neuroendocrine circuitry controlled by POMC, MSH, and AGRP. *Handbook of Experimental Pharmacology*, (209), 47–75. doi:10.1007/978-3-642-24716-3_3
24. Nijenhuis, W. A. J. (2001). AgRP(83-132) Acts as an Inverse Agonist on the Human-Melanocortin-4 Receptor. *Molecular Endocrinology*, 15(1), 164–171. doi:10.1210/me.15.1.164
25. Hunter, R. G., Philpot, K., Vicentic, A., Dominguez, G., Hubert, G. W., & Kuhar, M. J. (2004). CART in feeding and obesity. *Trends in Endocrinology & Metabolism*, 15(9), 454–459. doi:10.1016/j.tem.2004.09.010

26. Ammar, A. A., Nergårdh, R., Fredholm, B. B., Brodin, U., & Södersten, P. (2005). Intake inhibition by NPY and CCK-8: A challenge of the notion of NPY as an “Orexigen.” *Behavioural Brain Research*, 161(1), 82–87. doi:10.1016/j.bbr.2005.01.014
27. Aston-Jones, G., Smith, R. J., Moorman, D. E., & Richardson, K. A. (2009). Role of lateral hypothalamic orexin neurons in reward processing and addiction. *Neuropharmacology*, 56 Suppl 1, 112–121. doi:10.1016/j.neuropharm.2008.06.060
28. Mul, J. D., la Fleur, S. E., Toonen, P. W., Afrasiab-Middelmann, A., Binnekade, R., Schetters, D., ... Cuppen, E. (2011). Chronic loss of melanin-concentrating hormone affects motivational aspects of feeding in the rat. *Public Library of Science One*, 6(5), e19600. doi:10.1371/journal.pone.0019600
29. Marsh, D. J., Weingarh, D. T., Novi, D. E., Chen, H. Y., Trumbauer, M. E., Chen, A. S., ... Qian, S. (2002). Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. *Proceedings of the National Academy of Sciences of the United States of America*, 99(5), 3240–3245. doi:10.1073/pnas.052706899
30. Unger, T. J., Calderon, G. A., Bradley, L. C., Sena-Esteves, M., & Rios, M. (2007). Selective Deletion of Bdnf in the Ventromedial and Dorsomedial Hypothalamus of Adult Mice Results in Hyperphagic Behavior and Obesity. *Journal of Neuroscience*, 27(52), 14265–14274. doi:10.1523/JNEUROSCI.3308-07.2007
31. Rios, M. (2013). BDNF and the central control of feeding: accidental bystander or essential player? *Trends in Neurosciences*, 36(2), 83–90. doi:10.1016/j.tins.2012.12.009
32. Bariohay, B. (2005). Brain-Derived Neurotrophic Factor Plays a Role as an Anorexigenic Factor in the Dorsal Vagal Complex. *Endocrinology*, 146(12), 5612–5620. doi:10.1210/en.2005-0419
33. Ahima, R. S., & Osei, S. Y. (2004). Leptin signaling. *Physiology & Behavior*, 81(2), 223–241. doi:10.1016/j.physbeh.2004.02.014

34. Jéquier, E. (2002). Leptin Signaling, Adiposity, and Energy Balance. *Annals of the New York Academy of Sciences*, 967(1), 379–388. doi:10.1111/j.1749-6632.2002.tb04293.x
35. Brydon, L. (2011). Adiposity, leptin and stress reactivity in humans. *Biological Psychology*, 86(2), 114–120. doi:10.1016/j.biopsycho.2010.02.010
36. Baskin, D. G., Figlewicz Lattemann, D., Seeley, R. J., Woods, S. C., Porte Jr., D., & Schwartz, M. W. (1999). Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Research*, 848(1–2), 114–123. doi:10.1016/S0006-8993(99)01974-5
37. Haynes, W. G., Morgan, D. A., Djalali, A., Sivitz, W. I., & Mark, A. L. (1999). Interactions Between the Melanocortin System and Leptin in Control of Sympathetic Nerve Traffic. *Hypertension*, 33(1), 542–547. doi:10.1161/01.HYP.33.1.542
38. Flier, J. S. (1998). What's in a Name? In Search of Leptin's Physiologic Role. *Journal of Clinical Endocrinology & Metabolism*, 83(5), 1407–1413. doi:10.1210/jc.83.5.1407
39. Ahima, R. S., Prabakaran, D., Mantzoros, C., Qu, D., Lowell, B., Maratos-Flier, E., & Flier, J. S. (1996). Role of leptin in the neuroendocrine response to fasting. *Nature*, 382(6588), 250–252. doi:10.1038/382250a0
40. Baly, C., Aioun, J., Badonnel, K., Lacroix, M.-C., Durieux, D., Schlegel, C., ... Caillol, M. (2007). Leptin and its receptors are present in the rat olfactory mucosa and modulated by the nutritional status. *Brain Research*, 1129, 130–141. doi:10.1016/j.brainres.2006.10.030
41. Getchell, T. V., Kwong, K., Saunders, C. P., Stromberg, A. J., & Getchell, M. L. (2006). Leptin regulates olfactory-mediated behavior in ob/ob mice. *Physiology & Behavior*, 87(5), 848–856. doi:10.1016/j.physbeh.2005.11.016
42. Lu, B., Breza, J. M., Nikonov, A. A., Paedae, A. B., & Contreras, R. J. (2012). Leptin increases temperature-dependent chorda tympani nerve responses to sucrose in mice. *Physiology & Behavior*, 107(4), 533–539. doi:10.1016/j.physbeh.2012.04.018

43. Niki, M., Jyotaki, M., Ohkuri, T., Yoshida, R., & Ninomiya, Y. (2011). Modulation of sweet taste responses by antagonists for leptin and endocannabinoid receptors in normal lean and db/db mice. *Appetite*, 57, Supplement 1, S32. doi:10.1016/j.appet.2011.05.236
44. Webb, E. A., & Dattani, M. T. (2011). Understanding hypopituitarism. *Paediatrics and Child Health*, 21(7), 289–294. doi:10.1016/j.paed.2011.01.004
45. Darzy, K. H. (2013). Radiation-induced hypopituitarism: Current Opinion in *Endocrinology & Diabetes and Obesity*, 1. doi:10.1097/MED.0b013e3283631820
46. Lee, P., Ho, K. K. Y., & Greenfield, J. R. (2011). Hypothalamic/Pituitary Morbidity in Skull Base Pathology. *Otolaryngologic Clinics of North America*, 44(4), 1005–1021. doi:10.1016/j.otc.2011.06.010
47. Lustig, R. H. (2011). Hypothalamic Obesity after Craniopharyngioma: Mechanisms, Diagnosis, and Treatment. *Frontiers in Endocrinology*, 2. doi:10.3389/fendo.2011.00060
48. Bruch, H. (1993). The Fröhlich syndrome: report of the original case. 1939. *Obesity Research*, 1(4), 329–331.
49. Bereket, A., Kiess, W., Lustig, R. H., Muller, H. L., Goldstone, A. P., Weiss, R., ... Hochberg, Z. (2012). Hypothalamic obesity in children. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, 13(9), 780–798. doi:10.1111/j.1467-789X.2012.01004.x
50. Toogood, A. A., & Stewart, P. M. (2008). Hypopituitarism: Clinical Features, Diagnosis, and Management. *Endocrinology and Metabolism Clinics of North America*, 37(1), 235–261. doi:10.1016/j.ecl.2007.10.004
51. Fernandez, A., Brada, M., Zabuliene, L., Karavitaki, N., & Wass, J. A. H. (2009). Radiation-induced hypopituitarism. *Endocrine Related Cancer*, 16(3), 733–772. doi:10.1677/ERC-08-0231

52. Lipton, J., Megerian, J. T., Kothare, S. V., Cho, Y.-J., Shanahan, T., Chart, H., ... Pomeroy, S. L. (2009). Melatonin Deficiency and Disrupted Circadian Rhythms in Pediatric Survivors of Craniopharyngioma. *Neurology*, 73(4), 323–325. doi:10.1212/WNL.0b013e3181af78a5
53. Darzy, K. H., & Shalet, S. M. (2006). Pathophysiology of radiation-induced growth hormone deficiency: efficacy and safety of GH replacement. *Growth Hormone & Insulin Growth Factor Research: Official Journal of the Growth Hormone Research Society and the International Insulin Growth Factor Research Society*, 16 Suppl A, S30–40. doi:10.1016/j.ghir.2006.03.002
54. Manley, P. E., McKendrick, K., McGillicuddy, M., Chi, S. N., Kieran, M. W., Cohen, L. E., ... Ullrich, N. J. (2012). Sleep dysfunction in long term survivors of craniopharyngioma. *Journal of Neuro-Oncology*, 108(3), 543–549. doi:10.1007/s11060-012-0859-7
55. Müller, H. L., Handwerker, G., Gebhardt, U., Faldum, A., Emser, A., Kolb, R., & Sörensen, N. (2006). Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. *Cancer Causes & Control*, 17(4), 583–589. doi:10.1007/s10552-005-9012-7
56. Snow, A., Gozal, E., Malhotra, A., Tiosano, D., Perlman, R., Vega, C., ... Pillar, G. (2002). Severe hypersomnolence after pituitary/hypothalamic surgery in adolescents: clinical characteristics and potential mechanisms. *Pediatrics*, 110(6), e74.
57. Benoit, S. C., Air, E. L., Coolen, L. M., Strauss, R., Jackman, A., Clegg, D. J., ... Woods, S. C. (2002). The catabolic action of insulin in the brain is mediated by melanocortins. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 22(20), 9048–9052.
58. García-García, F., Juárez-Aguilar, E., Santiago-García, J., & Cardinali, D. P. (2014). Ghrelin and its interactions with growth hormone, leptin and orexins: Implications for the sleep–wake cycle and metabolism. *Sleep Medicine Reviews*, 18(1), 89–97. doi:10.1016/j.smrv.2013.04.003

59. Cowley, M. A., Smith, R. G., Diano, S., Tschöp, M., Pronchuk, N., Grove, K. L., ... Horvath, T. L. (2003). The Distribution and Mechanism of Action of Ghrelin in the CNS Demonstrates a Novel Hypothalamic Circuit Regulating Energy Homeostasis. *Neuron*, 37(4), 649–661. doi:10.1016/S0896-6273(03)00063-1
60. Depoortere, I. (2009). Targeting the ghrelin receptor to regulate food intake. *Regulatory Peptides*, 156(1–3), 13–23. doi:10.1016/j.regpep.2009.04.002
61. Hochberg, I., & Hochberg, Z. (2010). Expanding the definition of hypothalamic obesity. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, 11(10), 709–721. doi:10.1111/j.1467-789X.2010.00727.x
62. Hochberg, I., & Hochberg, Z. (2010). Hypothalamic obesity. *Endocrine Development*, 17, 185–196. doi:10.1159/000262539
63. Choi, S., & Dallman, M. F. (1999). Hypothalamic obesity: multiple routes mediated by loss of function in medial cell groups. *Endocrinology*, 140(9), 4081–4088. doi:10.1210/endo.140.9.6964
64. Choi, S., Sparks, R., Clay, M., & Dallman, M. F. (1999). Rats with hypothalamic obesity are insensitive to central leptin injections. *Endocrinology*, 140(10), 4426–4433. doi:10.1210/endo.140.10.7064
65. Maffei, M., Fei, H., Lee, G. H., Dani, C., Leroy, P., Zhang, Y., ... Friedman, J. M. (1995). Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. *Proceedings of the National Academy of Sciences of the United States of America*, 92(15), 6957–6960.
66. Roth, C., Wilken, B., Hanefeld, F., Schröter, W., & Leonhardt, U. (1998). Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 138(1), 89–91.

67. O'gorman, C. S., Simoneau-Roy, J., Pencharz, P., Adeli, K., & Hamilton, J. (2011). Delayed ghrelin suppression following oral glucose tolerance test in children and adolescents with hypothalamic injury secondary to craniopharyngioma compared with obese controls. *International Journal of Pediatric Obesity*, 6(3-4), 285–288. doi:10.3109/17477166.2010.519388
68. Bartness, T. J., & Song, C. K. (2007). Brain-adipose tissue neural crosstalk. *Physiology & Behavior*, 91(4), 343–351. doi:10.1016/j.physbeh.2007.04.002
69. Coutant, R., Maurey, H., Rouleau, S., Mathieu, E., Mercier, P., Limal, J. M., & Le Bouil, A. (2003). Defect in epinephrine production in children with craniopharyngioma: functional or organic origin? *The Journal of Clinical Endocrinology and Metabolism*, 88(12), 5969–5975. doi:10.1210/jc.2003-030552
70. Bray, G. A., & Gallagher, T. F., Jr. (1975). Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. *Medicine*, 54(4), 301–330.
71. Roth, C. L., Hunneman, D. H., Gebhardt, U., Stoffel-Wagner, B., Reinehr, T., & Müller, H. L. (2007). Reduced Sympathetic Metabolites in Urine of Obese Patients With Craniopharyngioma. *Pediatric Research*, 61(4), 496–501. doi:10.1203/pdr.0b013e3180332cd6
72. Lustig, R. H., Rose, S. R., Burghen, G. A., Velasquez-Mieyer, P., Broome, D. C., Smith, K., ... Kun, L. E. (1999). Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *The Journal of Pediatrics*, 135(2 Pt 1), 162–168.
73. Pinto, G., Bussières, L., Recasens, C., Souberbielle, J. C., Zerah, M., & Brauner, R. (2000). Hormonal factors influencing weight and growth pattern in craniopharyngioma. *Hormone Research*, 53(4), 163–169. doi:23562
74. Nishi, S., Seino, Y., Ishida, H., Seno, M., Taminato, T., Sakurai, H., & Imura, H. (1987). Vagal regulation of insulin, glucagon, and somatostatin secretion in vitro in the rat. *Journal of Clinical Investigation*, 79(4), 1191–1196.

75. Fan, W., Dinulescu, D. M., Butler, A. A., Zhou, J., Marks, D. L., & Cone, R. D. (2000). The central melanocortin system can directly regulate serum insulin levels. *Endocrinology*, 141(9), 3072–3079. doi:10.1210/endo.141.9.7665
76. Brüning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., ... Kahn, C. R. (2000). Role of brain insulin receptor in control of body weight and reproduction. *Science (New York, N.Y.)*, 289(5487), 2122–2125.
77. Scalfani, A. (1981). The role of hyperinsulinemia and the vagus nerve in hypothalamic hyperphagia reexamined. *Diabetologia*, 20 Suppl, 402–410.
78. Scalfani, A., Aravich, P. F., & Landman, M. (1981). Vagotomy blocks hypothalamic hyperphagia in rats on a chow diet and sucrose solution, but not on a palatable mixed diet. *Journal of Comparative and Physiological Psychology*, 95(5), 720–734.
79. Kiba, T., Tanaka, K., Numata, K., Hoshino, M., Misugi, K., & Inoue, S. (1996). Ventromedial hypothalamic lesion-induced vagal hyperactivity stimulates rat pancreatic cell proliferation. *Gastroenterology*, 110(3), 885–893.
80. Grundy, S. M. (2004). Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*, 109(3), 433–438. doi:10.1161/01.CIR.0000111245.75752.C6
81. Lee, C., Tsenkova, V., & Carr, D. (2014). Childhood trauma and metabolic syndrome in men and women. *Social Science & Medicine*, 105, 122–130. doi:10.1016/j.socscimed.2014.01.017
82. Musunuru, K. (2010). Atherogenic Dyslipidemia: Cardiovascular Risk and Dietary Intervention. *Lipids*, 45(10), 907–914. doi:10.1007/s11745-010-3408-1
83. Körner, A., Kratzsch, J., Gausche, R., Schaab, M., Erbs, S., & Kiess, W. (2007). New predictors of the metabolic syndrome in children--role of adipocytokines. *Pediatric Research*, 61(6), 640–645. doi:10.1203/01.pdr.0000262638.48304.ef

84. Tiosano, D., Eisentein, I., Militianu, D., Chrousos, G. P., & Hochberg, Z. (2003). 11 beta-Hydroxysteroid dehydrogenase activity in hypothalamic obesity. *The Journal of Clinical Endocrinology and Metabolism*, 88(1), 379–384. doi:10.1210/jc.2002-020511
85. Harno, E., Cottrell, E. C., Keevil, B. G., DeSchoolmeester, J., Bohlooly-Y, M., Andersén, H., ... White, A. (2013). 11-Dehydrocorticosterone causes metabolic syndrome, which is prevented when 11 β -HSD1 is knocked out in livers of male mice. *Endocrinology*, 154(10), 3599–3609. doi:10.1210/en.2013-1362
86. Draper, N., Echwald, S. M., Lavery, G. G., Walker, E. A., Fraser, R., Davies, E., ... Stewart, P. M. (2002). Association studies between microsatellite markers within the gene encoding human 11beta-hydroxysteroid dehydrogenase type 1 and body mass index, waist to hip ratio, and glucocorticoid metabolism. *The Journal of Clinical Endocrinology and Metabolism*, 87(11), 4984–4990. doi:10.1210/jc.2001-011375
87. Rosenbaum, M., Goldsmith, R., Bloomfield, D., Magnano, A., Weimer, L., Heymsfield, S., ... Leibel, R. L. (2005). Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *The Journal of Clinical Investigation*, 115(12), 3579–3586. doi:10.1172/JCI25977
88. Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *The Journal of Clinical Investigation*, 118(7), 2583–2591. doi:10.1172/JCI35055
89. Greenway, F. L., & Bray, G. A. (2008). Treatment of hypothalamic obesity with caffeine and ephedrine. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, 14(6), 697–703. doi:10.4158/EP.14.6.697
90. Astrup, A., Buemann, B., Christensen, N. J., Toubro, S., Thorbek, G., Victor, O. J., & Quaade, F. (1992). The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. *Metabolism: Clinical and Experimental*, 41(7), 686–688.

91. Lustig, R. H., Hinds, P. S., Ringwald-Smith, K., Christensen, R. K., Kaste, S. C., Schreiber, R. E., ... Xiong, X. (2003). Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *The Journal of Clinical Endocrinology and Metabolism*, 88(6), 2586–2592. doi:10.1210/jc.2002-030003
92. Louis, D. N., Ohgaki, H., Wiestler, O. D., Cavenee, W. K., Burger, P. C., Jouvett, A., ... Kleihues, P. (2007). The 2007 World Health Organization Classification of Tumours of the Central Nervous System. *Acta Neuropathologica*, 114(2), 97–109. doi:10.1007/s00401-007-0243-4
93. Eldevik, O. P., Blaiwas, M., Gabrielsen, T. O., Hald, J. K., & Chandler, W. F. (1996). Craniopharyngioma: radiologic and histologic findings and recurrence. *American Journal of Neuroradiology*, 17(8), 1427–1439.
94. Karavitaki, N., Cudlip, S., Adams, C. B. T., & Wass, J. A. H. (2006). Craniopharyngiomas. *Endocrine Reviews*, 27(4), 371–397. doi:10.1210/er.2006-0002
95. Müller, H. L., Emser, A., Faldum, A., Bruhnken, G., Etavard-Gorris, N., Gebhardt, U., ... Sörensen, N. (2004). Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *The Journal of Clinical Endocrinology and Metabolism*, 89(7), 3298–3305. doi:10.1210/jc.2003-031751
96. Weiner, H. L., Wisoff, J. H., Rosenberg, M. E., Kupersmith, M. J., Cohen, H., Zagzag, D., ... Miller, D. C. (1994). Craniopharyngiomas: a clinicopathological analysis of factors predictive of recurrence and functional outcome. *Neurosurgery*, 35(6), 1001–1010; discussion 1010–1011.
97. Parisi, J. E., & Mena, H. (1993). *Nonglial tumors. Principles and practice of neuropathology*. St Louis: Mosby, 203-266.
98. Van Effenterre, R., & Boch, A.-L. (2002). Craniopharyngioma in adults and children: a study of 122 surgical cases. *Journal of Neurosurgery*, 97(1), 3–11. doi:10.3171/jns.2002.97.1.0003
99. Banna, M., Hoare, R. D., Stanley, P., & Till, K. (1973). Craniopharyngioma in children. *The Journal of Pediatrics*, 83(5), 781–785. doi:10.1016/S0022-3476(73)80369-5

100. Müller, H. L., Gebhardt, U., Teske, C., Faldum, A., Zwiener, I., Warmuth-Metz, M., ... Study Committee of KRANIOPHARYNGEOM 2000. (2011). Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 165(1), 17–24. doi:10.1530/EJE-11-0158
101. Maira, G., Anile, C., Rossi, G. F., & Colosimo, C. (1995). Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. *Neurosurgery*, 36(4), 715–724.
102. Choux, M., Lena, G., & Genitori, L. (1991). Craniopharyngioma in children. *Neurochirurgie*, 37(suppl 1), 1-174.
103. Holmer, H., Ekman, B., Bjork, J., Nordstom, C.-H., Popovic, V., Siverson, A., & Erfurth, E.-M. (2009). Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy. *European Journal of Endocrinology*, 161(5), 671–679. doi:10.1530/EJE-09-0449
104. De Ferranti, S. D., & Rifai, N. (2007). C-reactive protein: a nontraditional serum marker of cardiovascular risk. *Cardiovascular Pathology*, 16(1), 14–21. doi:10.1016/j.carpath.2006.04.006
105. Pereira, A. M., Schmid, E. M., Schutte, P. J., Voormolen, J. H. C., Biermasz, N. R., Van Thiel, S. W., ... Romijn, J. A. (2005). High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clinical Endocrinology*, 62(2), 197–204. doi:10.1111/j.1365-2265.2004.02196.x
106. De Vile, C. J., Grant, D. B., Hayward, R. D., Kendall, B. E., Neville, B. G., & Stanhope, R. (1996). Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. *The Journal of Clinical Endocrinology & Metabolism*, 81(7), 2734–2737. doi:10.1210/jcem.81.7.8675604

107. Armstrong, G. T., Conklin, H. M., Huang, S., Srivastava, D., Sanford, R., Ellison, D. W., ... Morris, E. B. (2011). Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro-Oncology*, 13(2), 223–234. doi:10.1093/neuonc/noq178
108. Sievert, A. J., & Fisher, M. J. (2009). Pediatric Low-Grade Gliomas. *Journal of Child Neurology*, 24(11), 1397–1408. doi:10.1177/0883073809342005
109. Stokland, T., Liu, J.-F., Ironside, J. W., Ellison, D. W., Taylor, R., Robinson, K. J., ... Walker, D. A. (2010). A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). *Neuro-Oncology*, 12(12), 1257–1268. doi:10.1093/neuonc/noq092
110. Ruiz, J., & Lesser, G. J. (2009). Low-Grade Gliomas. *Current Treatment Options in Oncology*, 10(3-4), 231–242. doi:10.1007/s11864-009-0096-2
111. Levin, V. (2002). *Cancer in the Nervous System*, 2nd edition. Oxford University Press, 158-170.
112. Smith, J. S., Chang, E. F., Lamborn, K. R., Chang, S. M., Prados, M. D., Cha, S., ... Berger, M. S. (2008). Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas. *Journal of Clinical Oncology*, 26(8), 1338–1345. doi:10.1200/JCO.2007.13.9337
113. Benesch, M., Lackner, H., Sovinz, P., Suppan, E., Schwinger, W., Eder, H.-G., ... Urban, C. (2006). Late sequela after treatment of childhood low-grade gliomas: a retrospective analysis of 69 long-term survivors treated between 1983 and 2003. *Journal of Neuro-Oncology*, 78(2), 199–205. doi:10.1007/s11060-005-9091-z
114. Sutton, L. N., Molloy, P. T., Sernyak, H., Goldwein, J., Phillips, P. L., Rorke, L. B., ... Packer, R. J. (1995). Long-term outcome of hypothalamic/chiasmatic astrocytomas in children treated with conservative surgery. *Journal of Neurosurgery*, 83(4), 583–589. doi:10.3171/jns.1995.83.4.0583
115. Russell, A. (1951). A diencephalic syndrome of emaciation in infancy and childhood. *Archives of Disease in Childhood*, 26(274), 8.

116. Perilongo, G., Carollo, C., Salviati, L., Murgia, A., Pillon, M., Basso, G., ... Laverda, A. (1997). Diencephalic syndrome and disseminated juvenile pilocytic astrocytomas of the hypothalamic-optic chiasm region. *Cancer*, 80(1), 142–146. doi:10.1002/(SICI)1097-0142(19970701)80:1<142::AID-CNCR19>3.0.CO;2-Y
117. Fleischman, A., Brue, C., Poussaint, T. Y., Kieran, M., Pomeroy, S. L., Goumnerova, L., ... Cohen, L. E. (2005). Diencephalic Syndrome: A Cause of Failure to Thrive and a Model of Partial Growth Hormone Resistance. *Pediatrics*, 115(6), e742–e748. doi:10.1542/peds.2004-2237
118. Brauner, R., Trivin, C., Zerah, M., Souberbielle, J.-C., Doz, F., Kalifa, C., & Sainte-Rose, C. (2006). Diencephalic Syndrome due to Hypothalamic Tumor: A Model of the Relationship between Weight and Puberty Onset. *The Journal of Clinical Endocrinology & Metabolism*, 91(7), 2467–2473. doi:10.1210/jc.2006-0322
119. Rodriguez, L. A., Edwards, M. S., & Levin, V. A. (1990). Management of hypothalamic gliomas in children: an analysis of 33 cases. *Neurosurgery*, 26(2), 242-247.
120. Jooma, R., Hayward, R. D., & Grant, N. D. (1984). Intracranial neoplasms during the first year of life: analysis of one hundred consecutive cases. *Neurosurgery*, 14(1), 31-41.
121. Laithier, V., Grill, J., Le Deley, M. C., Ruchoux, M. M., Couanet, D., Doz, F., ... & Kalifa, C. (2003). Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy—results of the first French prospective study for the French Society of Pediatric Oncology. *Journal of Clinical Oncology*, 21(24), 4572-4578.
122. Vlachopapadopoulou, E., Tracey, K. S., Capella, M., Gilker, C., & Matthews, D. E. (1993). Increased energy expenditure in a patient with diencephalic syndrome. *The Journal of Pediatrics*, 122(6), 922–924. doi:10.1016/S0022-3476(09)90021-X
123. Fishman, M. A., & Peake, G. T. (1970). Paradoxical growth in a patient with the diencephalic syndrome. *Pediatrics*, 45(6), 973-982.

124. Drop, S. L. S., Guyda, H. J., & Colle, E. (1980). Inappropriate Growth Hormone Release in the Diencephalic Syndrome of Childhood: Case Report and 4 Year Endocrinological Follow-Up. *Clinical Endocrinology*, 13(2), 181–187. doi:10.1111/j.1365-2265.1980.tb01040.x

125. Kilday, J.-P., Bartels, U., Huang, A., Barron, M., Shago, M., Mistry, M., ... Tabori, U. (2014). Favorable survival and metabolic outcome for children with diencephalic syndrome using a radiation-sparing approach. *Journal of Neuro-Oncology*, 116(1), 195–204. doi:10.1007/s11060-013-1284-2

126. Velasco, P., Clemente, M., Lorite, R., Ventura, M. C., Gros, L., Sanchez de Toledo, J., & Gallego, S. (2013). The Role of Leptin in Diencephalic Syndrome. *Pediatrics*, 133(1), e263–e266. doi:10.1542/peds.2012-3196

CURRICULUM VITAE

