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# Current Approaches and Therapeutic Strategies for Hypothalamic Syndrome in Patients with Childhood-onset Craniopharyngioma

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## ABSTRACT

Patients diagnosed with craniopharyngioma often experience rapid and pronounced weight gain that can progress to severe hypothalamic obesity. This phenomenon is predominantly attributed to disruption of critical hypothalamic regulatory circuits, caused either by direct tumor infiltration or by treatment-related injury. Hypothalamic obesity is best conceptualized within the broader framework of hypothalamic syndrome, a complex clinical disorder encompassing multiple neuroendocrine deficits, impairments in circadian homeostasis, dysregulation of hunger, satiety, and thirst mechanisms, disturbances in thermoregulatory control, and a wide range of cognitive, sleep-related, and psychosocial abnormalities. Hypothalamic syndrome may also develop secondary to nonmalignant parasellar pathologies, including germ cell tumors, gliomas, Rathke's cleft cyst, and Langerhans cell histiocytosis, as well as traumatic hypothalamic injury following traumatic brain insult. Long-term prognosis is frequently poor, driven by elevated risks of metabolic syndrome, cardiovascular disease, diminished health-related quality of life, and increased rates of premature mortality. Management remains particularly challenging. Recently, a personalized and risk-stratified therapeutic framework has been proposed to guide clinical decision-making and optimize outcomes. Several pharmacologic interventions, such as centrally acting stimulants, glucagon-like peptide-1 receptor agonists, and the melanocortin-4 receptor agonist setmelanotide, have demonstrated potential in promoting weight reduction. Bariatric surgery may also yield clinical benefit; however, the use of irreversible procedures in pediatric populations presents substantial ethical and legal challenges. There remains an urgent need for therapeutic strategies that emphasize preservation of hypothalamic structure and function, alongside continued research into targeted and emerging interventions for more effective management of hypothalamic syndrome.

**Keywords:** Craniopharyngioma, obesity, metabolic syndrome, quality of life, hypothalamus, sequelae

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## Introduction

Craniopharyngiomas (CPs) (1) are embryonic neoplasms exhibiting low-grade histological malignancy. Their annual incidence is estimated at 0.5-2.0 newly diagnosed cases per million individuals (2,3). In the 2021 World Health Organization classification of central nervous system tumors, adamantinomatous CP (aCP) and papillary CP (pCP) were formally designated as two distinct pathological subtypes (4). aCP predominantly occur in children and adolescents, whereas pCP almost exclusively arise in adults. Long-term prognosis is frequently compromised by tumor- and/or treatment-related injury to hypothalamic structures, which may lead to hypothalamic syndrome. Consequently, CP represents a prototypical disorder underlying hypothalamic dysfunction.

## Molecular Pathology

In aCP, activating mutations in *CTNNB1* induce  $\beta$ -catenin accumulation and pathological activation of the WNT signaling cascade. Conversely, pCP is driven by the *BRAF-V600E* mutation, resulting in constitutive MAPK/ERK pathway activation. Recent evidence supports a senescence-mediated pathogenic mechanism in aCP. Senescent epithelial cells secrete pro-inflammatory and trophic factors [the senescence-associated secretory phenotype (SASP)], generating a tumor-supportive microenvironment through paracrine activity. Translational advances have facilitated the clinical application of BRAF/MEK inhibition in pCP, with early studies demonstrating substantial therapeutic efficacy. In parallel, pharmacological strategies targeting SASP mediators or selectively eliminating senescent cells (senolytic therapies) are under investigation for aCP (5).

## Morbidity and Mortality

Patients with CP experience overall mortality rates that are three- to fivefold higher than those in the general population (6). Reported survival in pediatric cohorts ranges from 83% to 96% at 5 years (7), 65% to 100% at 10 years (8), and averages approximately 62% at 20 years of follow-up. While some studies suggest that younger patients demonstrate superior long-term survival, others indicate more favorable outcomes in older individuals. Findings regarding sex differences remain inconsistent: several reports describe increased mortality in female patients (6), whereas others observed no significant sex-related disparities. Late mortality is frequently linked to tumor- or treatment-related complications, including disease progression or recurrence, persistent hypothalamic dysfunction, endocrine insufficiencies, seizures, cerebrovascular events, and metabolic consequences, such as nonalcoholic fatty liver disease, which may evolve into cirrhosis (8,9). A recent review emphasized substantial long-term morbidity, citing standardized overall mortality ratios between 2.88 and 9.28. Cardiovascular mortality was 3- to 19-fold higher in CP patients than in the general population, with the highest

risk observed in female patients (10). In childhood-onset (CO) CP, better baseline performance status has been associated with improved 10-year survival. The prognostic relevance of hydrocephalus at diagnosis remains debated (11). Importantly, Sterkenburg et al. (12) reported significantly reduced 20-year survival among patients with hypothalamic involvement and hypothalamic obesity. Conversely, the extent of surgical resection did not influence 20-year progression-free survival, reinforcing the view that aggressive gross-total resection does not confer a survival benefit with respect to preventing tumor recurrence in this population.

## Hypothalamus and Hypothalamic Syndrome

The hypothalamus is a small yet phylogenetically conserved neuroendocrine center composed of multiple nuclei that coordinate essential physiological processes. It acts as a central integrator, governing pituitary hormonal output and influencing the autonomic nervous system, as well as modulating behavior through connections with other brain regions, including the frontal cortex. Hypothalamic disruption can produce a broad clinical phenotype encompassing (morbid) obesity (13), cachexia (14), hypopituitarism, adipsia, dysregulation of thermoregulation and circadian rhythms (15,16), reduced energy expenditure (17), and behavioral abnormalities (18).

The term hypothalamic syndrome refers to the constellation of symptoms arising from structural or functional compromise of hypothalamic nuclei. Although CPs constitute a leading cause, other etiologies include germ cell tumors, gliomas, Rathke's cleft cysts, Langerhans cell histiocytosis, and specific neurodevelopmental disorders such as Prader-Willi syndrome (PWS) and septo-optic dysplasia, as well as traumatic brain injury (19). Importantly, hypothalamic syndrome encompasses a broader construct than hypothalamic obesity alone and varies considerably between individuals. According to van Santen et al. (20), five major clinical domains characterize hypothalamic syndrome in CO CP: disordered eating, behavioral abnormalities, sleep disturbances, thermoregulatory dysfunction, and endocrine impairments.

## Management of Hypothalamic Syndrome

An individualized management approach for CO CP patients with hypothalamic syndrome was initially proposed by van Iersel et al. (21). A recent update shifts emphasis from isolated obesity treatment to addressing the full spectrum of hypothalamic dysfunction (22,23) (Figure 1). This more comprehensive framework aims to improve not only body mass index (BMI) but also overall vitality and daily functioning. Findings by van Schaik et al. (26) underscore the benefits of centralized care (24,25): following national centralization of CP treatment in the Netherlands, the incidence of hypothalamic obesity in children with CP fell from 33% to 12%.

## Hypothalamic and Pituitary Function

Hypothalamic nuclei exert regulatory control over the pituitary gland by producing releasing hormones. Damage to hypothalamic structures may therefore lead to multiple pituitary hormone deficiencies, including hypogonadotropic hypogonadism, growth hormone (GH) deficiency, central hypothyroidism, and adrenocorticotrophic hormone (ACTH) deficiency. In addition, the hypothalamus secretes arginine vasopressin (AVP), which is stored and released from the posterior pituitary gland.

### GH Deficiency

Insufficient endocrine replacement therapy can result in severe consequences, such as impaired growth (27). GH replacement in patients with confirmed GH deficiency does not increase the risk of CP recurrence or progression (28). Unlike malignant tumors, no mandatory waiting period is required between completion of oncological therapy and initiation of GH treatment in CP. Early GH replacement may assist with weight regulation and improve quality of life (QoL) (29). A recent consensus statement from the Growth Hormone Research Society concluded that GH therapy is safe in CP (28). Although GH does not correct hypothalamic

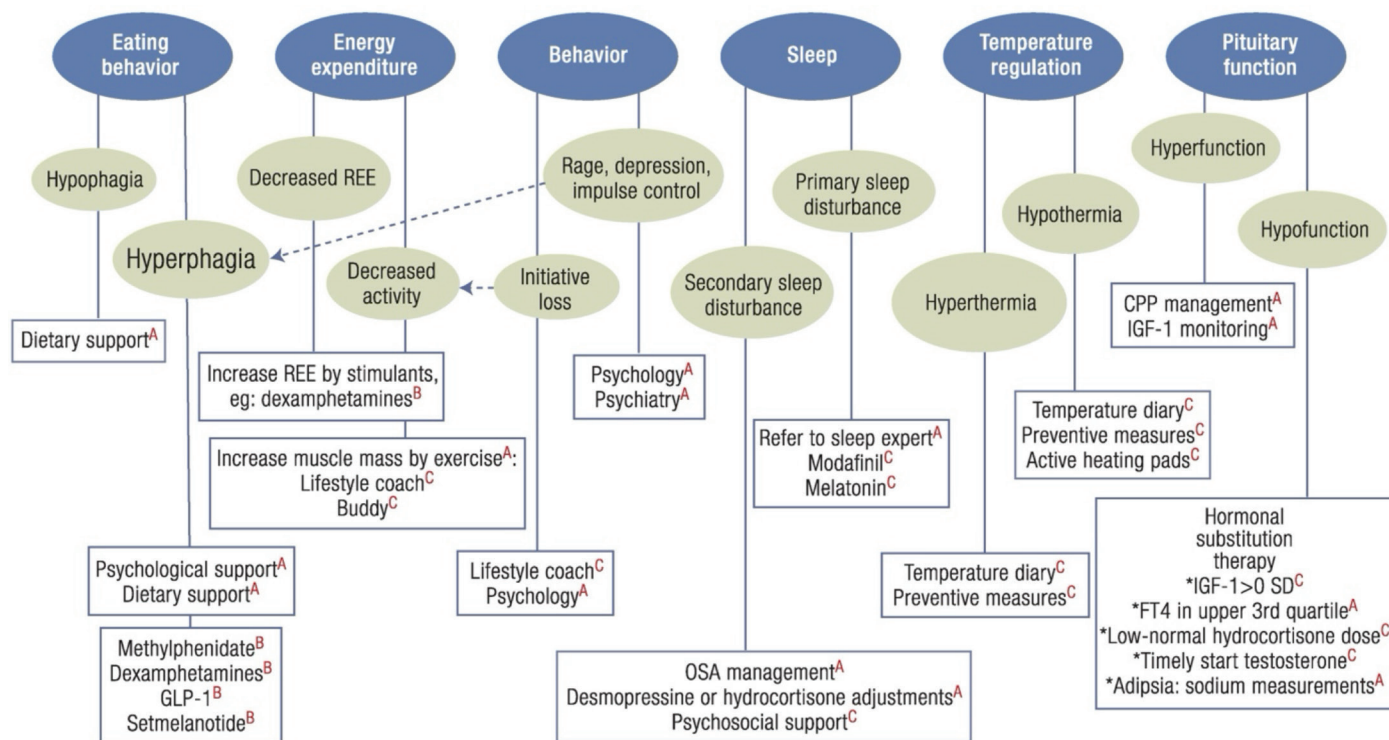
obesity, it supports healthier body composition and reduces metabolic complications (29).

### Adrenocorticotropin Deficiency

ACTH deficiency, typically resulting from tumor-associated damage or therapeutic interventions, necessitates hydrocortisone replacement with stress-adjusted dosing. Cortisol deficiency may clinically present with headaches, nausea, or reduced stress tolerance, and can progress to life-threatening adrenal crisis. Excessive glucocorticoid administration increases obesity risk. While perioperative corticosteroid therapy may cause short-term weight gain, it has not been linked to long-term obesity (30). Physiological dosing of hydrocortisone substitution should not elevate obesity risk.

### Hypothyroidism

Central hypothyroidism may be overlooked if free thyroxine (T4) levels remain in the lower half of the reference interval. A reduction of >20% in free T4 should prompt suspicion and consideration of levothyroxine therapy (31). Replacement should maintain free T4 concentrations in the mid-to-upper reference



**Figure 1.** Algorithm for the management of (acquired) hypothalamic dysfunction. Hypothalamic dysfunction may lead to different signs and symptoms that may all contribute to the development of hypothalamic overweight or obesity and feelings of fatigue. By evaluating all 6 different clinical domains of hypothalamic dysfunction, with a step wise approach, a personalized approach is enabled improving feelings of fatigue and decreasing obesity. Suggested interventions are categorized as existing guidelines **A**, clinical trial or case series data **B**, and expert opinion **C**. (Reproduced from van Santen and Müller, Endocr Rev, 2025 (22), with kind permission of Illustration Presentation ENDOCRINE SOCIETY).

CPP, central precocious puberty; OSA, obstructive sleep apnea; REE, resting energy expenditure

range. Insufficient replacement may contribute to weight gain, emphasizing the need for optimal dosing.

### Gonadotropin Deficiency

Gonadotropin deficiency often requires induction of puberty and, in some cases, assisted reproductive techniques (32). Adults treated for CP in childhood show high rates of psychosexual dysfunction and reduced sexual activity (32). In males, low testosterone is associated with adverse metabolic profiles and increased mortality risk. Adequate testosterone replacement can improve body composition through reduction of fat mass and increase in lean mass.

### Oxytocin

Oxytocin deficiency in CP arises primarily from hypothalamic injury, contributing to hypothalamic syndrome. Compared with healthy individuals, CP patients show reduced basal and stimulated salivary oxytocin levels (33,34,35,36). Lower levels correlate with increased anxiety and impaired social cognition. Individuals with anterior hypothalamic lesions exhibit the lowest oxytocin concentrations and respond most favorably to single-dose intranasal oxytocin compared with patients with posterior lesions or healthy controls (34,35). These data indicate potential for oxytocin-based interventions to treat neuropsychological symptoms of hypothalamic syndrome (37).

### AVP Deficiency (AVP-D)

AVP-D commonly results from posterior hypothalamic injury and predisposes to hypothalamic obesity. It therefore serves both as a marker of hypothalamic damage and an independent risk factor for obesity and reduced QoL (38). When thirst regulation is also impaired, adipsic AVP-D may occur, carrying substantial risk for sodium imbalance and systemic instability.

### Sleep Disorders

Children with CP and hypothalamic syndrome may develop primary hypothalamic sleep disturbances, including hypersomnia (15), narcolepsy (39) and circadian rhythm dysregulation (16). Secondary sleep problems can arise from tumor therapy, severe obesity, or visual impairment. These include psychosocial stressors, obstructive sleep apnea, poorly controlled AVP-D with nocturia, and other comorbidities. Sleep-wake disruption and circadian disturbances are hallmark manifestations of hypothalamic syndrome (40). Hypersomnia is defined by excessive daytime sleepiness (EDS) despite adequate nighttime sleep. Affected individuals often struggle to remain awake during daily activities (40). In a cohort of 115 CO CP patients, Müller et al. (39) reported EDS in 30% of cases, including hypersomnia and secondary narcolepsy. Central stimulants such as modafinil or methylphenidate improved alertness and daily functioning (39).

### Temperature Regulation

Thermoregulation is governed by interconnected hypothalamic circuits, including the arcuate nucleus (thermogenesis), the preoptic area-dorsomedial hypothalamic circuit (temperature sensing), and the ventromedial hypothalamus (cold-induced thermogenesis) (41). Hypothalamic injury can impair these pathways, resulting in hypothermia (<36 °C) or hyperthermia (>37.5 °C) (42,43). Some patients maintain normal core temperatures but experience subjective thermal dysregulation. Management is largely supportive: external warming for hypothermia and light clothing for hyperthermia. Hydrocortisone stress dosing should be considered when temperatures fall below 35.5 °C or exceed 38 °C.

### Behavioral Problems

As the hypothalamus is tightly connected to limbic structures, hypothalamic dysfunction may cause diverse neurobehavioral abnormalities. Anxiety disorders are common, potentially due to perturbations of the Papez circuit (44), and memory impairments may also occur (18,45). Lesions involving the nucleus accumbens have been associated with addictive behaviors, obsessive tendencies, hoarding, and compulsive eating (18). Combined with disrupted satiety signaling, these alterations contribute to severe obesity (20,46). Cognitive dysfunction may also be present (47).

### Neurocognitive Outcome

Studies of childhood CP survivors reveal wide variability in psychosocial and physical outcomes ranging from excellent functioning in most patients to significant impairment in nearly half (8,48,49,50). Social and emotional functioning are frequently affected, with many patients rating psychosocial health lower than physical well-being (8). Challenges include learning difficulties, emotional dysregulation, peer relationship problems, and body-image concerns (51,52). Worse outcomes are associated with preoperative impairment, younger age at CP diagnosis, hypothalamic involvement, larger tumors, and certain treatment strategies. Surgery alone yields poorer results than limited resection followed by radiotherapy; repeated surgeries also worsen long-term outcomes. Endocrine, neurological, and ophthalmological sequelae further diminish QoL (8,48). Hypothalamic dysfunction exerts the greatest negative effect on social functioning, physical capacity, and body image (7,8,48).

Long-term survivors frequently experience cognitive deficits, particularly in episodic memory, executive functions, and attention (8,51,52). Ozyurt et al. (53) demonstrated that hypothalamic injury disrupted medial prefrontal cortex mechanisms during memory retrieval, indicating reduced executive control efficiency. Incomplete tumor resection followed by radiotherapy was associated with psychological and educational difficulties (52). Although most patients retain

normal overall intelligence, visual memory is frequently impaired despite preserved visuospatial skills (51,52). Early deficits in attention often predict poor academic performance.

### Psychosocial Functioning

At a median follow-up age of 29 years, adults with CO CP reported similar psychosomatic and emotional well-being when compared to controls (54). Social interaction scores were comparable, though social integration appeared less adequate in patients. Educational attainment was slightly lower in the CP group, and employment rates were reduced (48% vs 62%), although unemployment benefits were similar. Notably, 14% of CP survivors, but none of the controls, were on long-term sick leave or disability pension. Dekkers et al. (55) reported reduced QoL in a mixed adult- and CO cohort with a mean follow-up of 20 years. Greater QoL impairment in adults may reflect a heightened sense of loss when diagnosis occurs later in life. In children, Müller et al. (49) found reduced QoL at 4.5 years post-diagnosis, particularly in those with hypothalamic involvement (Table 1). Some studies suggest that outcomes improve over time due to psychological adaptation. However, CO CP survivors with hypothalamic damage consistently report reduced satisfaction with social participation and overall health, alongside lower educational and employment attainment, and constitute all cases receiving disability pension or long-term sick leave (54).

Despite extensive documentation of neurocognitive and psychosocial difficulties in CP survivors, targeted interventions remain scarce. Recent case studies have piloted cognitive rehabilitation for executive dysfunction and behavioral instability (56). One program combining goal-management therapy with structured workplace tasks yielded improvements in tasks requiring organization. Additional behavioral difficulties, including aggression, are common (8). In some individuals, behavioral analysis followed by reinforcement strategies and extinction techniques reduced aggressive

Table 1. Health-related quality of life after craniopharyngioma. Selected publications (2019-2025). Modified from Müller HL, 2025, biomedicines (1) with kind permission of mdpi							
Diagnosis	Pat. no.	Age at craniopharyngioma diagnosis (years)	Follow-up interval (years)	Treatment	Quality of life/outcome	Authors/year of publication	
CO CP with presurgical grade 2 HI	109	Median 9.5 (range: 1.3-17.9)	Mean 6.1 (range: 3.0-10.2)	Surgery leading to 23 grade 0 HL, 29 grade 1 HL, 57 grade 2 HL	Worse PEDQOL for grade 3 patients in terms of physical, social and emotional functionality when compared with HL grade 0 and 1.	Bogusz et al. (95), 2019	
CO CP	131	Median 9.7 (range: 1.3-17.6)	3 years	21 (18%) complete resection; 94 (82%) incomplete resection	Grade 2 HI, grade 2 HL and complete surgical resection were associated with low QoL.	Eveslage et al. (94), 2019	
Hypothalamic dysfunction + CO CP	290	n.a.	n. a.	n. a.	Worldwide online survey: Obesity (51%) and fatigue (48%). Needs for improvement in the domains of obesity, fatigue and lifestyle.	Van Roessel et al. (99), 2020	
CO CP	78	Mean: 10.8±3.11 SD	n. a.	56 surgical resections, 16 catheter implantations	Poorer parental-reported QoL, AVP-D directly predicted greater global executive functioning impairment.	Niel et al. (100), 2021	
Caregivers of CO CP patients	106	<18 years	n. a.	48 RT, 134 surgical interventions	Online survey: reduced social functioning.	Craven et al. (101), 2022	
CO CP	48	GTR: Median 6.4 (range: 2.2-16.8) PR+RT: Median 8.5 (range: 3.8-16.4)	10 years	21 GTR, 22 PR+RT	No differences in the trajectory of intellectual functioning or QoL scale scores between the two groups (GTR vs. PR + RT).	Aldave et al. (102), 2023	
Caregivers of CO CP patients	82	Mean 9.3±4.5 SD	Duration of caregiving: mean 7.4 (SD: 6.0), median: 5.5, (range: <1-28) years	52.4 % GTR	Survivor poly-symptomatology predicted caregiver burden. The study separated hyperphagia and obesity and identified hyperphagia and other hypothalamic dysfunction symptoms as understudied issues.	Kavadjian et al. (103), 2023	

Table 1. Continued

Diagnosis	Pat. no.	Age at craniopharyngioma diagnosis (years)	Follow-up interval (years)	Treatment	Quality of life/outcome	Authors/year of publication
CO CP and parents/caregivers	120	Median 10.0 (range: 1.3-16.8)	3 years	25 complete resections 95 incomplete resections 61 RT	Reduced autonomy was found three years after diagnosis in self-assessments and parental assessments of QoL (PedQoL).	Sowthayasakul et al. (104), 2023
CO CP with RT	99	Median 9.5 (range: 1.6-17.9)	Median 6.4 (range: 0.9-14.7)	64 PBT 35 photon-based RT	No significant difference between PBT and photon-based RT in terms of QoL (PedQoL), functional capacity (FMH), and body mass index.	Friedrich et al. (105), 2023
CO CP	87	Mean 7.39±3.67 SD	Median 6.54 (IQR: 3.11-10.69)	25% complete resection 44% incomplete resection 30% cyst drainage 46% RT	BMI at diagnosis and grade of HL were associated with hypothalamic obesity.	Van Schaik et al. (26), 2023
CO CP	709	< 2 years: 3% 2-5 years: 16% 56-11 years: 46% 12-18 years: 35%	Median 8.37 (range, 0.04 to 38.87)	33% RT; 35% PBT; 46% photon-based 27% GTR	BMI>3SD in 45%; risk factor for obesity: HI and HL Patients <2yrs at dxg: low functional capacity (FMH); Patients >12 yrs at dxg: low QoL (PedQoL); Lower EFS in younger age groups	Beckhaus et al. (57), 2023
AO CP: 90% CO CP: 10%	109	Median 40.0 (range: 28.5-56.0)	Median 10.0 (range: 2.5-24.0)	25.6%: surgery 4.6%: RT	SF-36: impaired QoL compared with general population. MCS, GAD7, PHQ9: adverse effect of AVP-D in multivariate linear regression. AVP-D risk factor for developing depressive symptoms.	Lin et al. (38), 2024
CO CP from a lower-middle-income country	29	Mean 13.5±4.2 SD	Mean: 4.4±2.2 SD	15 GTR 11 Debulking 3 Reservoir and biopsy	PedsQL: GTR 56.6±7.12 Debulking: 93.8±3.37 Biopsy: 83.3±5.69	Baqai et al. (106), 2024
CO OP	92	Mean 10.5±4.0 SD	n. a.	PBT after surgical intervention	Fatigue, QoL, and brain tumor symptoms improved over time during proton beam therapy.	Mandrell et al. (107), 2024
CO CP	11	Median 15.2 years (IQR: 9.7-17.9)	Mean 5.3±3.2 (SD)	73% surgery 82% RT	PEDS-QL4.0: Worse QoL in global, physical, emotional, and psychosocial dimensions linked to HI. Irradiated patients had worse global QoL.	Pereira Neto et al. (108) 2024
CO CP	66	Median 5 (IQR: 3-8)	Median 7.4 (IQR: 2.8-9.7).	100% surgery 44% RT 24% intracystic therapy	PedsQL: QoL was impaired by repeated surgeries, RT, and longer follow-up interval.	Perez-Torres et al. (109) 2024
CO CP	119	Median 12 (range: 2-17)	Mean 10 (range: 1-39)	CR in 34 (29%) 6 HL grade 0 23 HL grade 1 55 HL grade 2	QoL (EORTC QLQ-C30) was negatively correlated with daytime sleepiness (ESS), highest ESS in patients with HL grade 2.	Mann-Markutzkyk et al. (15), 2025
CO CP with PBT	47	Median 9.7 (range: 2.4-22.1)	Median 11.2 (range: 1.3-17.3)	55% surgery 100% RT (PBT)	PedsQL: PPR and CSR TCS lower than normal controls at last follow-up, and lower in patients with AVP-D, sex hormone deficiency, and hyperphagia	Rose et al. (110) 2025

AO CP, adult-onset craniopharyngioma; CO CP, childhood-onset craniopharyngioma; QoL, quality of life; GTR, gross total resection; HI, presurgical hypothalamic involvement; HL, surgical hypothalamic lesions; PR, partial resection; RT, radiotherapy; PBT, proton beam therapy; dgn, diagnosis; AVP-D, arginine vasopressin deficiency; n. a., data not available; IQR, interquartile ratio; SD, standard deviation; ESS, Epworth Sleepiness Scale; pat, patients; FMH, functional ability scale Münster Heidelberg; GAD7, Generalized Anxiety Disorder Questionnaire scale; PHQ9, Patient Health Questionnaire Depression; SF-36, Short Form 36; PEDS-QL4.0., Pediatric Quality of Life Inventory; PPR, parent-proxy reports; CSR, Child-self report; TCS, total core scores

episodes by >88% and increased adaptive behaviors (56). These observations indicate that structured rehabilitation may enable survivors of CO CP to develop compensatory strategies for neurocognitive and psychosocial deficits.

### Quality of Life

Beckhaus et al. (57) analyzed the largest cohort reported to date (n=709) of individuals with CO CP, assessing clinical features at presentation and long-term outcomes including QoL. The study specifically examined whether age at diagnosis affected disease characteristics, therapeutic management, and prognosis. At final follow-up, severe obesity [BMI >3 standard deviation score (SDS)] was documented in 45.4% of patients. Posterior hypothalamic involvement and structural hypothalamic damage were identified as independent predictors of both reduced event-free survival and the presence of obesity at follow-up. Although overall survival did not vary by age at diagnosis, younger age (<12 years) was associated with an increased risk of disease progression and recurrence. Notably, children diagnosed before 6 years of age demonstrated lower event-free survival but reported higher QoL compared with those diagnosed at ≥6 years. Lower functional capacity percentiles were associated with higher BMI SDS at final assessment and with diagnosis before 2 years of age. These observations suggest that differences in management strategies such as the timing or modality of radiotherapy or intrinsic tumor biology may account for age-related outcome variability. Despite these disparities, overall survival remained comparable across age groups, implying that re-irradiation and surgical reintervention were effective in controlling tumor recurrence or progression. Functional capacity, reflecting performance in daily activities, differed substantially between age subgroups, with younger age at diagnosis predicting poorer long-term functional outcomes. Paradoxically, QoL scores based on both patient and parent reports were less favorable among those diagnosed at an older age, particularly regarding body image. Developmental factors may help explain this finding. In very young children, neurological and endocrine impairments heavily shape overall development. Conversely, older children and adolescents, whose brain maturation is more advanced, may experience fewer disruptions to developmental trajectories but are more capable of perceiving and evaluating changes in QoL compared with their pre-diagnosis baseline. Consequently, adolescents may be more sensitive to alterations in body image. Body shape and appearance constitute central determinants of QoL in adolescence.

### Energy Balance

Energy homeostasis is maintained through the dynamic interaction between energy intake and energy expenditure, orchestrated by hypothalamic nuclei that integrate central and peripheral signals within complex neural circuits (21,41). Energy

intake is regulated by three principal processes: initiation of eating, cessation of eating, and food selection. The hypothalamus modulates these processes via orexigenic mediators such as orexin A/B, ghrelin, and neuropeptide Y and anorexigenic mediators, including adiponectin, leptin, brain-derived neurotrophic factor, and insulin. While gastrointestinal satiety signals contribute to terminating meals, food preference is influenced by the mesolimbic reward system and by prefrontal-amygdala networks that interact with hypothalamic centers. Energy expenditure consists of resting metabolic rate (60-75%), activity-related thermogenesis (~20%), and diet-induced thermogenesis (10-15%), all of which are modulated by sympathetic nervous system activity under hypothalamic regulation. Damage to the hypothalamus may disrupt parasympathetic control, leading to hyperinsulinemia and promoting adipose tissue deposition, thereby increasing the risk of obesity. The extent and nature of hypothalamic impairment depend on factors such as age at onset, tumor-related characteristics, and comorbidities, and may affect endocrine axes, neuroendocrine pathways, or inter-regional neural connections to varying degrees.

A key pathway in appetite control is the melanocortin system. Following food intake, leptin binds to its receptors on pro-opiomelanocortin neurons, stimulating the release of  $\alpha$ - and  $\beta$ -melanocyte-stimulating hormones ( $\alpha/\beta$ -MSH). These peptides activate melanocortin-4 receptors (MC4R), increasing satiety and energy expenditure. Disruption of this system contributes to hyperphagia and obesity (58). In addition, hypothalamic efferent pathways regulate sympathetic outflow, thereby influencing energy expenditure. Among 67 children with hypothalamic syndrome, 67.2% demonstrated a measured resting energy expenditure (mREE) below 90% of predicted REE (pREE) values, with the lowest mREE/pREE ratios observed in patients with severe or posterior hypothalamic injury, corresponding to higher rates of hypothalamic obesity (59). REE is also closely associated with muscle mass, which is metabolically more active than fat mass. Physical activity increases REE both directly, through muscle hypertrophy, and indirectly, via enhanced thermogenesis. In contrast, children with hypothalamic obesity typically exhibit reduced muscle mass due to low activity levels.

### Physical Activity and Energy Expenditure

Accelerometry studies show that patients with CO CP engage in substantially less physical activity than BMI-matched controls (13). Reduced activity levels persist into adulthood (17). Patients report diminished participation in recreational physical activity year-round, and pedometer data corroborate lower daily step counts compared with healthy individuals. Severe hypothalamic obesity is commonly accompanied by EDS (60). CP survivors also exhibit reduced morning and nighttime salivary melatonin levels, which correlate with daytime somnolence

and hypothalamic obesity. Melatonin supplementation (6 mg/day) can normalize melatonin profiles and transiently improve sleepiness and activity, though long-term benefit remains uncertain (61). Polysomnographic assessments in CP patients with pronounced hypothalamic obesity frequently reveal hypersomnia or secondary narcolepsy, including frequent sleep-onset REM periods. In such cases, central stimulants (e.g., methylphenidate, modafinil) significantly ameliorate daytime sleepiness and enhance activity (39).

Management strategies should emphasize increasing REE, for example through structured physical training, testosterone therapy to augment muscle mass, and active warming when hypothermia is present. Optimization of endocrine replacement (GH, thyroid hormone) is also essential. Pharmacological measures, such as dexamphetamine, may be appropriate in selected patients to further elevate energy expenditure (62,63). Measurement of REE using ventilated-hood calorimetry offers clinically valuable insights into weight trajectories and informs individualized nutritional planning (59).

### Hypothalamic Obesity and Disordered Eating

Under normal physiological conditions, satiety and body-weight regulation arise from a balanced interaction between anorexigenic and orexigenic signaling pathways. In hypothalamic obesity, this tightly coordinated network becomes impaired due to structural or functional disruption of key hypothalamic regions (58), resulting in dysregulated appetite control and inappropriate food intake (21). In patients with CP, increased parasympathetic activity mediated by heightened vagal tone contributes to hyperinsulinemia and persistent hunger, thereby promoting excessive weight gain (21). Concurrently, diminished sympathetic activity reduces total energy expenditure and lipolysis. Many individuals with hypothalamic obesity also exhibit reduced concentrations of  $\alpha$ -MSH, a neuropeptide involved in driving energy expenditure.

A recently proposed consensus definition for acquired hypothalamic obesity (64) included the following diagnostic criteria:

- A traumatic event or oncologic disease resulting in hypothalamic damage detectable on magnetic resonance imaging;
- A rapid (within 12 months of surgery/diagnosis), persistent (for at least 24 months), and clinically significant increase in BMI ( $\geq 5\%$  increase in adults;  $\geq 1.0$  SDS increase in children) beginning within 12 months after the onset of hypothalamic injury, with clinical and anthropometric monitoring at 3-month intervals;
- Development of obesity meeting defined thresholds (BMI SDS  $\geq +2.0$  SD in children; BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup> in adults, with adjustment for racial and ethnic factors).

Long-term follow-up showed that approximately half of CO CP patients with hypothalamic lesions developed hypothalamic obesity (7,65). In a study by Rovani et al. (66), 54% of CP survivors were overweight or obese, with risk factors including female sex, hypothalamic involvement, and baseline BMI  $> +2$  SDS. Beckhaus et al. (67) further demonstrated that familial susceptibility, reflected by elevated maternal and paternal BMI at the patient's time of diagnosis, was strongly associated with the development of severe hypothalamic obesity. In a mixed AO/CO cohort, the prevalence of excessive weight gain or hyperphagia increased from 39% at 10 years to 67% at 20 years post-diagnosis. Once severe obesity is established, weight reduction becomes extremely difficult (21) and many patients reach a high but stable BMI plateau (27). Currently, no uniformly effective therapy exists (58). Therapeutic efforts therefore focus on preventing hypothalamic injury through hypothalamus-sparing surgical techniques, precision radiation modalities (e.g., proton beam therapy), and emerging pharmacologic treatments specifically targeting hypothalamic obesity (5). In pCP harboring the *BRAF* V600E mutation, targeted therapy with BRAF inhibitors has also demonstrated encouraging results (68).

### Hyperphagia

Hyperphagia in children with hypothalamic obesity may be profound, sometimes necessitating strict household controls to prevent food seeking and food theft. However, hyperphagia is not universally present in all affected individuals (43). When designing dietary interventions, it is important to recognize that hypothalamic dysfunction is typically lifelong rather than transient. A systematic review evaluating lifestyle and dietary interventions for hypothalamic obesity included 12 studies involving 118 patients with CP, monogenic obesity, PWS, or rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation syndrome. Four studies concluded that dietary interventions were feasible but reported multiple challenges. Among the seven studies assessing efficacy, both balanced hypocaloric diets (30% fat, 45% carbohydrates, 25% protein) and more stringent regimens (8-10 kcal/cm/day) were associated with stabilization or reduction of body weight (69).

### Hypophagia

Although less common, hypophagia can also occur in individuals with hypothalamic dysfunction. In CO CP, anorexia or reduced intake is unusual but has been documented, especially in younger children. The German KRANIOPHARYNGEOM cohort reported that 11 of 485 patients initially presented with anorexia (14). In infants with PWS, atypical eating behavior has been linked to altered ghrelin acylation patterns. Management is primarily dietary. But given the potential transition from hypophagia to hyperphagia over time, continuous monitoring and timely intervention are crucial.

## Treatment of Hypothalamic Obesity

### Lifestyle Interventions

Lifestyle approaches have typically produced only short-term reductions in BMI, indicating that sustained weight control requires long-term, structured behavioral support (Table 2). A stable and supportive home environment is essential, particularly given the persistent combination of hyperphagia, pituitary hormonal deficits, and behavioral challenges (70). Data from the German KRANIOPHARYNGEOM cohort (n=291) showed that BMI at final follow-up strongly correlated with maternal and paternal BMI at diagnosis (67) underscoring the need for family-centered obesity management. Engaging caregivers and family members is therefore critical to achieving durable therapeutic outcomes.

### Antidiabetic Medications

Multiple antidiabetic agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, diazoxide, fenofibrate, pioglitazone, and various combination regimens (71) have demonstrated potential benefits in limiting weight gain and enhancing insulin sensitivity in individuals with hypothalamic obesity. Among these, metformin appears particularly advantageous when used alongside lifestyle modification, as it offers moderate weight stabilization with a generally favorable safety profile (72). Nevertheless, the long-term efficacy and safety of metformin specifically for hypothalamic obesity have not yet been fully characterized (73).

### GLP-1 receptor agonists

A small study including 26 adults with hypothalamic obesity reported that all but one patient achieved weight reduction during semaglutide therapy, with an average weight loss of 13.4 kg and a corresponding BMI decrease of 4.4 kg/m<sup>2</sup> after one year (74). Consistent with these findings, a systematic review of 10 studies concluded that GLP-1 receptor agonists may represent a safe and effective intervention for weight management in this population (75). Despite encouraging results, the therapeutic effect of GLP-1 receptor agonists in adults with hypothalamic obesity remains under discussion. Several investigations have documented improved glycemic control and reductions in food intake (75,76), yet Shoemaker et al. (76) observed an unexpected decline in total energy expenditure following weekly exenatide administration, out of proportion to weight loss and unrelated to physical activity or leptin levels. Conversely, Perez et al. (77) reported that individuals with more extensive hypothalamic injury experienced greater adiposity reductions under the same exenatide dose. The GLP-1 analogue liraglutide, approved for long-term management of general obesity, has been used in adults with CP-related hypothalamic obesity, leading to weight reductions of 9-22 kg (78). Semaglutide is similarly approved

Table 2. Therapeutic approaches for treating acquired hypothalamic obesity and effects on weight development/obesity. Modified from Müller HL, biomedicines, 2025 (1), with kind permission of mdpi

	Intervention	#	Age (years)	BMI/weight at intervention	BMI/weight change during / after intervention	Authors/year of publication
Pharmacological agent	Dextroamphetamine	19	12.3±4.0	BMI 3.58±0.85 SD	ΔBMI SDS -0.14	van Schaik et al. (63), 2022
	Dextroamphetamine	7	0.5, 11.1, 11.8, 12.5, 14.7, 14.8, 21.0	BMI +3.17±0.9 SD Range: +1.9 to +4.4 SD	Mean BMI SDS decelerated to -0.18±0.12/year during the 1 <sup>st</sup> year of treatment and stabilized at +0.05±0.32/year during the 2 <sup>nd</sup> year of treatment.	Denzer et al. (62), 2019
	Diazoxide/metformin	9	15.4±2.9	BMI +1.8-+2.96 SD	ΔBMI -0.3±2.3 kg/m <sup>2</sup>	Hamilton et al. (111), 2011
	Octreotide (RCT)	10	13.8±1.2	BMI 37.1±1.3 kg/m <sup>2</sup>	ΔBMI -0.2±0.2 kg/m <sup>2</sup> (vs placebo +2.2±0.5 kg/m <sup>2</sup> )	Lustig et al. (89), 2003
	Semaglutide	26	52 (18-65)	BMI 38 (28-58) kg/m <sup>2</sup>	Mean TWL 13.4 kg (95% CI 10.3-16.5 kg)	Svendstrup et al. (74), 2024
	Semaglutide	4	22, 44, 57, 69	BMI 48.0 (35.0-55.5) kg/m <sup>2</sup>	ΔBMI 7.9 BMI (6.7-10.1); weight loss of 17.0% (11.3-22.4%)	Gjersdal et al. (112), 2024
	Exenatide / liraglutide	9	46 (22-49)	BMI 37.6±7.2 kg/m <sup>2</sup>	Exenatide: ΔBMI -6.1 to -2.8 kg/m <sup>2</sup> ; liraglutide: Δweight -22 to -9 kg	Zoicas et al. (78), 2013
	Exenatide	8	27.5±7.8	BMI 47.5±10.8 kg/m <sup>2</sup>	Mean Δweight -1.4 kg	Lomenick et al. (113), 2016
	Tesomet (tesofensine and metoprolol)	18	45.4±13.3	BMI 37.3±5.6 kg/m <sup>2</sup>	Δweight: -6.3% (tesomet -6.6% vs. placebo -0.3%)	Huynh et al. (88), 2022

Table 2. Continued

	Intervention	#	Age (years)	BMI/weight at intervention	BMI/weight change during / after intervention	Authors/year of publication
	Setmelanotide	18	15.0±5.3	BMI 38.0±6.5 kg/m <sup>2</sup>	ΔBMI: -15% (SDS 10%) after 4 mo; Extension 12 mo (12 patients): -26% (12 SDS)	Roth et al. (81), 2024
	Setmelanotide	120	19.9 (4 - 66)	≥18 years: BMI 41.2 (95% CI: 38.4 - 44.0 kg/m <sup>2</sup> ; <18 years: BMI Z score 3.61 SDS (95% CI: 3.21-4.00SD).	RCT: mean BMI reduction of 16.5% after 52 weeks in the treatment group (n=81), compared to a 3.3% increase in the placebo group (n=39). Good tolerability: adverse events leading to treatment discontinuation in 7.4% (setmelanotide) and 7.7% (placebo)	Roth et al. (86), 2025
Lifestyle modification	Regular visits at a comprehensive care clinic	39	13.4 (4.3-18.2)	BMI 1.93 (0-3.2) SD	Median ΔBMI rate +4.5 kg/m <sup>2</sup> /y (-17.8 to+8.4); Median ΔBMI SDS rate 0.0/y (-5.2 to +0.5)	Rakhshani et al. (114), 2010
Bariatric surgery	SG (n=3); RYGB (n=5)	8	33.4±13.6	BMI 43.3 ± 4.1 kg/m <sup>2</sup>	SG (n=3): mean Δweight -10%; RYGB (n=5): mean Δweight -25%	Wijnen et al. (115), 2017
	LAGB (n=4)	4	13, 17, 21, 23	BMI +7.3+12.3 SD	ΔBMI +1.7 to +8.7 kg/m <sup>2</sup>	Müller et al. (116,117) 2007, 2011
	SG (n=2); RYGB (n=2)	4	24, 30, 43, 51	BMI 37.6, 37.7, 43.7, 51.0 kg/m <sup>2</sup>	ΔBMI: SG -10, -3.6; RYGB: -6.2, +11.3 kg/m <sup>2</sup>	Gatta et al. (118), 2013
	LAGB (n=6); SG (n=4); RYGB (n=2)	9	17 (12-30)	BMI 44.7 (40.2-61.6) kg/m <sup>2</sup>	LAGB: no change; SG: no change; RYGB: mean Δweight -30%	Weismann et al. (119), 2013
	LAGB (n=6); SG (n=8); RYGB (n=6); BPD (n=1)	21	24 (12-54)	BMI 49.6 kg/m <sup>2</sup>	TWL (%) LAGB: 10.5%; SG: 20.7%; RYGB: 20.2%; BPD: 24.8%	Bretault et al. (91), 2013
	SG	3	21, 22, 24	BMI 49.2 (41.6-58.1) kg/m <sup>2</sup>	Mean ΔBMI -13.9 kg/m <sup>2</sup> ; Δweight -17.6%, -25.0%, -41.1%	Trotta et al. (120), 2017
	SG (n=2), RYGB (n=3)	5	38 (27-47)	BMI 41.3 (37.9-46.3) kg/m <sup>2</sup>	ΔTWL (%) -14.7% (23.7; 5.8)	Garrez et al. (121), 2020
	RYGB (n=12), SG (n=4)	16	26±12	BMI 46±8 kg/m <sup>2</sup>	Mean Δweight: -22% after 5 years	van Santen et al. (122), 2021
	SG (39%), RYGB (61%)	23	35 (25-43)	BMI 44.2 (40.7-51.0) kg/m <sup>2</sup>	ΔTWL (%) -39.0% (14.0; 53.3)	Faucher et al. (123), 2022
Vagotomy	Truncal vagotomy	1	19	BMI 43.0 kg/m <sup>2</sup>	Δweight -7.0 kg	Smit et al. (124), 1983
DBS	Nucleus accumbens DBS	1	19	BMI 52.9 kg/m <sup>2</sup>	ΔBMI -5.2 kg/m <sup>2</sup>	Harat et al. (125), 2016

#, patient number; TWL, total weight loss; BMI, body mass index; SDS, standard deviation score; LAGB, laparoscopic adjusted gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; DBS, deep brain stimulation; RCT, randomized controlled trial; n. a., data not available.

for obesity treatment in adolescents, achieving a median BMI reduction of approximately 17%. Early evidence suggests that semaglutide and exenatide may hold therapeutic value for weight control in hypothalamic obesity (79).

### Setmelanotide

Setmelanotide, a MC4R agonist, has shown marked effectiveness in children with monogenic obesity syndromes such as Bardet-Biedl syndrome. Originally developed for congenital hypothalamic obesity caused by proopiomelanocortin or leptin receptor deficiency (80), setmelanotide activates remaining MC4R-expressing neurons within the hypothalamus. Impairment of this pathway leads to profound hyperphagia and subsequent hypothalamic obesity. In a phase 2 study including pediatric and adult participants with acquired hypothalamic obesity, setmelanotide resulted in a mean BMI decrease of  $15 \pm 10\%$ , together with notable improvements in hyperphagic symptoms and QoL (81).

Preliminary data from a prospective, placebo-controlled clinical trial (NCT05774756) involving 120 affected individuals revealed that 52-week treatment produced a mean BMI reduction of 16.5% in the setmelanotide group ( $n=81$ ), compared with a 3.3% BMI increase in the placebo cohort ( $n=39$ ). Furthermore, 80% of treated patients achieved at least a 5% BMI reduction at 52 weeks (82). Collectively, these findings indicate that setmelanotide might represent a promising pharmacologic therapy for hypothalamic obesity (83) (Table 2).

### Combination of oral phentermine and topiramate (Ph/T)

Phentermine is a sympathomimetic amine, while topiramate is a GABAergic agent commonly used as an anticonvulsant. Given that patients with hypothalamic obesity frequently exhibit diminished sympathetic nervous system activity (84), they may theoretically benefit from the appetite-suppressing effects of central stimulants (85,86). The combination of oral phentermine and topiramate (Ph/T) is approved by the U.S. Food and Drug Administration for use in individuals aged 12 years and older with obesity (87). Nevertheless, the efficacy and safety of Ph/T have not yet been systematically investigated in patients with confirmed hypothalamic obesity.

### Tesofensine

Tesofensine is a centrally acting triple monoamine reuptake inhibitor that may counter the reduced sympathetic tone commonly observed in hypothalamic obesity. By blocking presynaptic reuptake of dopamine, serotonin, and noradrenaline and inhibiting the dopamine active transporter, tesofensine reduces caloric intake and promotes weight loss. To attenuate potential adrenergic adverse effects, it is administered in combination with the beta-blocker metoprolol. A randomized, double-blind, placebo-controlled phase 2 trial involving 21

individuals assessed Tesomet (tesofensine plus metoprolol) for hypothalamic obesity (88). Patients in the treatment arm exhibited reductions in body weight, waist circumference, and blood glucose relative to placebo.

### Somatostatin and the autonomic nervous system

Lustig et al. (89) proposed that patients with CO CP may experience a loss of hypothalamic inhibitory control, resulting in increased vagal output and overstimulation of pancreatic  $\beta$ -cells. This leads to hyperinsulinemia and contributes to severe obesity. Based on this model, they tested the somatostatin analogue octreotide, which suppresses  $\beta$ -cell activity (89). However, its clinical utility has been limited by modest efficacy and frequent adverse effects, including gastrointestinal symptoms and gallstone formation. Other studies have implicated reduced sympathetic activity in decreased physical activity and pronounced obesity. Supporting this, Roth et al. (84) reported lower urinary catecholamine metabolite levels, correlating with both severity of obesity and reduced activity.

### Central stimulating agents

A range of central nervous system stimulants, including methylphenidate, phentermine, dextroamphetamine, mazindol, caffeine, and ephedrine, has been used off-label in hypothalamic obesity (62,63,85). Two small pediatric case series documented that dexamphetamine therapy resulted in reductions in BMI, increased REE, and improved energy levels among affected children (62).

### Oxytocin treatment

Oxytocin, a neuropeptide playing a central role for social behavior and reproduction, also influences appetite regulation and satiety. It has been shown to reduce food intake and suppress hunger. In CP patients, altered salivary oxytocin responses to food and exercise have been associated with differences in BMI and disordered eating behaviors (90). These findings suggest potential therapeutic utility for oxytocin in hypothalamic obesity. However, the mechanisms underlying its metabolic effects in the setting of hypothalamic injury remain poorly defined, and optimal dosing, delivery approaches, and long-term safety require further investigation.

### Bariatric Interventions

Bariatric surgery has demonstrated meaningful weight-loss efficacy and safety in individuals with CP (Table 1). In an individual-level meta-analysis of 21 cases, Bretault et al. (91) reported total weight loss of -0.9% at 6 months and -15.1% at 12 months post-operatively, with the greatest reductions observed after Roux-en-Y gastric bypass (RYGB). In children and adolescents, irreversible bariatric procedures such as RYGB remain ethically and legally challenging, and their use is

generally restricted to clinical trial settings (92). The Endocrine Society's Clinical Practice Guideline (93) recommends considering bariatric surgery only for adolescents with morbid obesity, who have reached advanced pubertal maturation and near final or final adult height, and who have demonstrated adherence to lifestyle interventions.

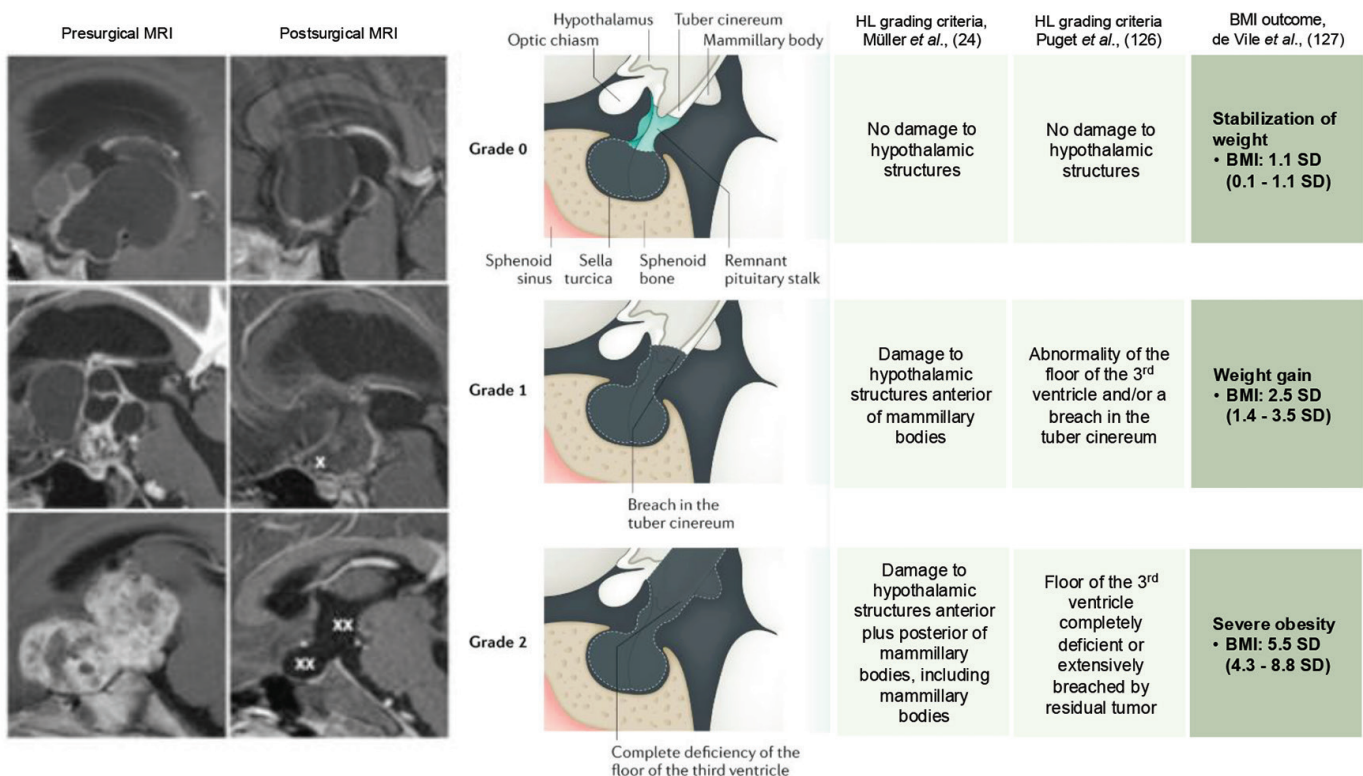
### Prevention of Hypothalamic Dysfunction through Hypothalamus-Sparing Approaches

Evelsage et al. (94) demonstrated that preoperative hypothalamic involvement and intraoperative damage to anterior and posterior hypothalamic nuclei are associated with reduced QoL and increased BMI in CP survivors. Complete surgical resection was linked to worse BMI and QoL outcomes compared with subtotal surgery (94) (Figure 2). Lesions confined to the anterior hypothalamus tended to produce fewer adverse effects, whereas injury to posterior regions markedly increased the risk of hypothalamic syndrome and impaired QoL (95). Consequently, surgical strategies should emphasize preservation of posterior hypothalamic structures. These hypothalamus-sparing techniques may increase the likelihood of tumor recurrence or progression. Radiotherapy therefore plays a pivotal role in

managing residual disease and preventing relapse, forming a central component of hypothalamus-preserving treatment paradigms for CP (2,96).

### Conclusion

Hypothalamic syndrome substantially affects morbidity and QoL in patients with CP, and current therapeutic outcomes remain unsatisfactory. The heterogeneity of hypothalamic syndrome indicates that a standardized treatment approach is unlikely to be effective. Accordingly, personalized management algorithms have been proposed to improve care (20,21). Treatment decisions that prioritize the preservation of hypothalamic, neuroendocrine, and visual function should be made within experienced multidisciplinary teams. Establishing multicenter reference networks is essential to ensure standardized, high-quality care and access to specialized expertise (97). Future strategies to improve outcomes should include deeper investigation into the molecular pathogenesis of CP, facilitating the development of targeted therapies that address tumor progression and hypothalamic involvement. Advances in surgery and radiotherapy should focus on hypothalamus-sparing approaches to limit long-term neuroendocrine and metabolic



**Figure 2.** Hypothalamic lesions (HL) in craniopharyngioma: pre- and postoperative grading on MRI and outcome/body mass index (BMI). Definition of different grades of hypothalamic lesions based on postsurgical magnetic resonance imaging (MRI) as published by Puget et al. (126), de Vile et al. (127), and Müller et al. (24). Outcome (BMI) SDS according to de Vile et al. (127) in terms of weight gain and the development of hypothalamic obesity with regard to grade of hypothalamic lesion. Median BMI and interquartile ranges are shown for BMI SDS. X indicates anterior hypothalamic area, XX indicate anterior and posterior hypothalamic area.

consequences (98). In addition, policy-level initiatives are needed to define and implement quality standards for comprehensive multidisciplinary management of CP.

#### Footnotes

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