REVIEW

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Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity

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Purpose of review
Hypothalamic alterations, pathological or treatment induced, have major impact on prognosis in craniopharyngioma patients mainly because of consequent hypothalamic obesity. Recent insight in molecular genetics, treatment strategies, risk factors and outcomes associated with hypothalamic obesity provide novel therapeutic perspectives. This review includes relevant publications since 2013.

Recent findings
Recent findings confirm that alterations in posterior hypothalamic areas because of tumour location and/or treatment-related injuries are associated with severe hypothalamic obesity, reduced overall survival and impaired quality of life in long-term survivors of childhood-onset craniopharyngioma. However, eating disorders are observed because of hypothalamic obesity without clear disease-specific patterns. Treatment options for hypothalamic obesity are very limited. Treatment with invasive, nonreversible bariatric methods such as Roux-en-Y gastric bypass is most efficient in weight reduction, but controversial in the paediatric population because of medical, ethical, and legal considerations. Accordingly, treatment in craniopharyngioma should focus on prevention of (further) hypothalamic injury. Presurgical imaging for grading of hypothalamic involvement should be the basis for hypothalamus-sparing strategies conducted by experienced multidisciplinary teams.

Summary
Until a nonsurgical therapeutic option for hypothalamic obesity for paediatric patients is found, prevention of hypothalamic injury should be the preferred treatment strategy, conducted exclusively by experienced multidisciplinary teams.

Keywords
craniopharyngioma, eating disorders, hypothalamus, obesity, quality of life, survival

INTRODUCTION

Energy homeostasis is regulated by a complex neuroendocrine system, of which the hypothalamus is the centre for said regulation. The functional disruption of the hypothalamic network causes hypothalamic obesity [1▪,2,3,4▪]. Recent studies have illuminated how the hypothalamus regulates appetite and satiety [1▪,5]. The disruptions causing hypothalamic obesity include brain tumours, neurosurgery, and/or cranial irradiation.

In this context, craniopharyngioma is a paradigmatic disease comprising different risk factors for hypothalamic obesity. Childhood-onset craniopharyngiomas are rare intracranial embryonal malformations of the sellar region [6▪,7▪]. These tumours show low-grade histological malignancy (WHO °I), frequently affect hypothalamic/pituitary regions and the optic chiasm. Hypothalamic involvement and/or treatment-related lesions to hypothalamic structures result in impaired physical and social functionality [8▪▪,9▪▪,10,11▪] that includes severe neuroendocrine sequelae, mainly hypothalamic obesity, with major negative impact on quality of life in surviving patients [1▪,6▪,8▪▪,9▪▪,10,12,13▪▪,14]. Unfortunately, attempts to control hypothalamic obesity with diet,

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KEY POINTS

- Initial involvement and treatment-related hypothalamic lesions are major risk factors for impaired survival and reduced quality of life because of hypothalamic obesity in craniopharyngioma.
- Initial assessment of risk factors and execution of hypothalamus-sparing strategies by an experienced multidisciplinary team are recommended for prevention of further hypothalamic damage and consequent hypothalamic obesity.
- In the case of hypothalamic involvement, gross-total resection of craniopharyngioma should not be attempted.
- Treatment options for hypothalamic obesity are very limited. In paediatric craniopharyngioma patients nonreversible bariatric procedures are controversial because of legal and ethical considerations.
- Eating behaviour in craniopharyngioma patients with hypothalamic obesity is altered, but the specificity of these findings is controversial.
- Further research on molecular genetics in craniopharyngioma and neuroendocrine hypothalamic regulation of body composition is imperative to foster novel treatment options for hypothalamic obesity.

exercise, and/or pharmacological treatments have not been satisfactory.

The review summarizes novel insights in hypothalamic appetite regulation, pathophysiology, aetiology, clinical characteristics, and treatment modalities for hypothalamic obesity in patients with childhood-onset craniopharyngioma.

EPIDEMIOLOGY, PATHOLOGY, AND CLINICAL PRESENTATION

Craniopharyngiomas are rare, with an incidence of 0.5 to two cases per million persons per year. A bimodal age distribution has been shown, with peak incidence rates in children of ages 5–14 years and adults of ages 50–74 years [15▪,16]. In childhood and adolescence, its histological type is usually adamantinomatous with cyst formation. More than 70% of the adamantinomatous type of craniopharyngioma bear a mutation of the β-catenin gene, which is not detectable in the adult papillary type of craniopharyngioma [17,18▪▪,19,20]. Recent reports [21,22] on molecular findings in adamantinomatous craniopharyngioma and a novel mouse model [23] indicate tentative perspectives on future treatment and prevention of hypothalamic infiltration in adamantinomatous craniopharyngioma [24]. Brastianos *et al.* [25▪▪] reported on a BRAF mutation in 95% of papillary-type histology, which is not detectable in adamantinomatous craniopharyngioma. This specific finding has important relevance in differential diagnosis of sellar masses [26–28] and is a potential target for pharmaceutical therapy [29].

The main hypothalamic areas involved in energy regulation are the medial hypothalamus, which consists of the ventromedial nucleus, arcuate nucleus, and paraventricular nucleus. Arcuate nucleus neurons generate orexigenic peptides, such as agouti-related protein and neuropeptide Y and secrete anorexigenic peptides-like proopiomelanocortin, a precursor of α-melanocyte-stimulating hormone (α-MSH). α-MSH acts at the melanocortin-4 receptor and reduces appetite and food intake. Afferent signals, including leptin, insulin, ghrelin, and peptide YY, affect the anorexigenic centre of the hypothalamus. Efferent signals from the paraventricular nucleus in turn stimulate the sympathetic nervous system [5,30]).

The diagnosis of childhood craniopharyngioma is often made late – sometimes years after the initial appearance of symptoms – with a clinical picture at the time of diagnosis often dominated by nonspecific manifestations of intracranial pressure [31,32]. Further, primary manifestations are visual impairment (62–84%) and endocrine deficits (52–87%) [9▪▪,33].

Recent reports confirm that initial imaging [12,34▪▪,35,36,37▪,38] and assessment of hypothalamic involvement of craniopharyngioma is essential in estimating prognosis and long-term quality of life [39–41,42▪]. Muller *et al.* [40,41] observed that initial tumour involvement of mammillary bodies confirmed by imaging served as an independent risk factor for impaired long-term prognosis regardless of chosen treatment strategies. These findings are confirmed by further studies on the pathogenic relevance of hypothalamic structures located at mammillary bodies for the development of hypothalamic obesity [43,44].

TREATMENT STRATEGIES AND HYPOTHALAMIC INJURY

For favourably localized tumours, the preferred treatment of choice, especially at primary craniopharyngioma diagnosis, is an attempt at complete resection with preservation of visual and hypothalamic function [6▪,12,39,45–50]. For unfavourably localized tumours – those too close to or too entangled with the optic chiasm and/or the hypothalamus – a planned limited resection should be performed to preserve integrity of and/or to avoid

further damage to the hypothalamic and optic structures [4▪,51▪,52,53,54▪▪,55▪–57▪]. Endoscopic routes provide novel and less traumatic approaches for surgical resection [58▪,59].

The implantation of an intracystic catheter with a subcutaneous reservoir enables the possibility of repeated decompression of the cyst and instillation of sclerosing agents [60▪,61]. Bartels *et al.* [62] report good tolerability and high efficiency of interferon alpha as the intracystic sclerosing agent.

Irradiation is effective in preventing relapses and progression of residual tumour and is therefore a recommended treatment option in cases of limited surgical perspectives [63▪,64]. Preliminary experiences with proton beam therapy applied to craniopharyngioma are promising, offering a more protective radio-oncological option than conventional external irradiation, especially for tumours localized in the vicinity of the optic chiasm, pituitary gland, or hypothalamus [65▪,66]. Stereotactic irradiation and gamma knife treatment are options in rare cases [67,68▪].

HYPOTHALAMIC OBESITY

Symptoms related to hypothalamic dysfunction, such as obesity, daytime sleepiness, disturbed circadian rhythm, behavioural changes, and imbalances in regulation of thirst, body temperature, heart rate, and/or blood pressure, have been found at diagnosis in 35% of childhood craniopharyngioma patients [6▪,12,69,70,71▪,72▪]. The rate of hypothalamic dysfunction dramatically increases following treatment; in some series up to 65–80% [4▪].

Associated with high morbidity, suprachiasmatic lesions are difficult to treat. Surgical removal of tumour tissue beyond the mammillary bodies risks hypothalamic structures and consequent hypothalamic obesity [39,40,51▪,73▪]. With the aid of imaging studies, recent reports have indicated that the degree of obesity of affected patients is positively correlated with the degree of hypothalamic damage [39,40–42▪]. Taking these considerations into account, novel classifications of presurgical involvement and postsurgical lesions of hypothalamic structures based on MRI have been recently published [40,41,51▪] that might help to establish risk-adapted, that is, hypothalamus-sparing surgical strategies.

Weight gain in childhood craniopharyngioma often occurs years before diagnosis [33], with 12–19% of patients reported to be obese at diagnosis [6▪]. Weight gain occurs despite adequate endocrine replacement of pituitary hormone deficiencies. The hypothalamic disturbance in energy management contributes to obesity and is exacerbated by factors limiting physical activity such as marked daytime sleepiness [74]. The degree of obesity frequently increases early after treatment and rapid weight gain occurs the first 6–12 months after treatment [33]. Following treatment, the prevalence of obesity is higher, reaching up to 55% [75]. Obesity results in increased risks of metabolic syndrome and cardiovascular disease [73▪].

The relation of obesity with hypothalamic damage is obvious in craniopharyngioma [5,30]. It is likely that in cases of suprasellar extension, hypothalamic function will be compromised and will remain compromised to a certain extent when treated surgically or with irradiation. The hypothalamus contains many groups of nerve cell bodies forming distinct nuclei, which have highly diverse molecular, structural, and functional organizations [1▪,5]. The hypothalamus plays a major role in keeping the internal environment stable by synchronizing circadian rhythms. Recent data indicate that a proper balance of the autonomic nervous system is crucial for metabolism [76]. It is well known that adipose tissue is richly innervated by sympathetic nerve fibres that control lipolysis. It now appears that lipogenesis is also controlled by parasympathetic innervation of adipose tissue originating from separate sympathetic and parasympathetic neurons in the periventricular nucleus and suprachiasmatic nucleus (SCN) [1▪,30,76]. Such a high level of differentiation puts the SCN in a key position to balance circadian activity of both branches of the autonomous nervous system [30]. Considering the large proportion of patients with damage to suprasellar structures, it is likely that craniopharyngiomas and/or the effects of treatment damage the SCN. This in turn, affects regulation of central clock mechanisms, which predisposes to alterations in metabolism [74]. Clearly, surgical strategies to preserve hypothalamic integrity are mandatory for the prevention of sequelae such as severe obesity owing to hypothalamic lesions [12].

A study involving self-assessment by nutritional diaries revealed that hypothalamic obesity can occur in patients with childhood craniopharyngioma even when their caloric intake is similar to controls matched for BMI [77]. An analysis of physical activity showed that patients with childhood craniopharyngioma had a markedly lower level of physical activity than BMI-matched healthy controls [77]. Aforementioned marked daytime sleepiness and disturbances of circadian rhythms have been demonstrated in patients with childhood craniopharyngioma and obesity [74], which in turn were correlated with low nocturnal and early morning melatonin levels in saliva [78]. The proposed pathogenic mechanism involves impaired

hypothalamic regulation of circadian melatonin rhythms in patients with craniopharyngioma extending to the suprasellar area. Initial experiences with melatonin substitution in patients with childhood craniopharyngioma were promising: melatonin levels normalized and daytime sleepiness and physical activity improved [78].

Polysomnographic studies in patients with childhood craniopharyngioma and severe daytime sleepiness have revealed sleeping patterns typical for hypersomnia and secondary narcolepsy [74], leading to the conclusion that secondary narcolepsy should be taken into consideration as a pathogenic factor in severely obese children and adolescents with craniopharyngioma. Treatment with central-stimulating agents (methylphenidate, modafinil) has had a significantly beneficial effect on daytime sleepiness in these patients [79].

A decreased metabolic rate, in terms of both resting and total energy expenditure, is likely to contribute to weight gain in this population. Adults and paediatric patients with childhood-onset craniopharyngioma were found to have a lower resting energy expenditure (REE) compared with controls that were not explained by differences in body composition [80▪]. This energy intake/REE ratio was significantly lower in those with tumours involving the third ventricle [81]. Further, factors that could potentially contribute to decreased physical activity are neurological and visual deficits [82,83], increased daytime sleepiness [74,78], and psychosocial difficulties [75].

Roemmler-Zehrer and colleagues [84▪] recently analysed the gastrointestinal hormones ghrelin and peptide YY and their effect on satiety in obese craniopharyngioma patients. Their findings support the hypothesis that reduced ghrelin secretion and reduced postprandial suppression of ghrelin and severe obesity leads to disturbed regulation of appetite in craniopharyngioma patients. However, peptide YY levels did not differ between normal weight, obese, and very obese patients. Further potential pathogenic roles of peripheral α-MSH and brain-derived neurotrophic factor in childhood craniopharyngioma obesity have been postulated [85,86].

CHALLENGES IN TREATING HYPOTHALAMIC OBESITY

Owing to the above-reported disturbances in energy expenditure, central sympathetic output, and appetite-regulation, it is clear why craniopharyngioma patients with hypothalamic obesity typically develop morbid obesity that is mainly unresponsive to conventional lifestyle modifications [1▪,6▪,10,12,49,87].

Recent studies on novel pharmaceutical treatment options in craniopharyngioma patients with hypothalamic obesity report mixed results. Based on impairment of sympatho-adrenal activation and epinephrine production manifesting as a reduced hormonal response to hypoglycaemia, treating this disorder with amphetamine derivatives has been suggested [79]. Zoicas *et al.* [88] treated eight adult patients (six craniopharyngioma) with hypothalamic obesity with glucagon-like peptide 1 (GLP-1) analogues and observed a substantial and sustained weight loss associated with improvements in metabolic and cardiovascular risk profiles. Kalina *et al.* [89▪] analysed the effect of metformin and fenofibrate treatment on metabolic status in 22 patients with childhood-onset craniopharyngioma. The authors reported a positive effect on dyslipidemia and homeostatic model assessment during short-term follow-up of 6 months. van Santen *et al.* [90▪] reported a hypothalamic obesity case resulting from treatment of craniopharyngioma in which T3 monotherapy was not effective in increasing REE or brown adipose tissue activity. This may be explained by damage to the ventromedial hypothalamic region, which is a key area in the hypothalamus for T3-mediated brown adipose tissue activation. Whereas substitution therapy with recombinant growth hormone is safe and efficient in promoting normal growth, relevant weight reducing effects are not observed in patients with hypothalamic obesity [91,92].

Childhood craniopharyngioma patients with hypothalamic obesity have a parasympathetic predominance of the autonomic nervous system induced by vagal activation, manifesting as daytime sleepiness and reduced heart rate variability [76]. Parasympathetic stimulation causes insulin secretion by way of direct activation of β cells as well as adipogenesis. As insulin is an anabolic hormone, it is likely to be an important driver of weight gain in hypothalamic obesity. As octreotide is a somatostatin analogue and thus causes reduction in insulin secretion, Lustig *et al.* [93] used octreotide in a double-blind randomized controlled study in children with hypothalamic obesity, demonstrating moderate reductions in weight gain in which insulin levels during a proof-of-concept oral glucose tolerance test decreased without leading to major changes in glucose tolerance.

Initial experiences with bariatric surgery in severely obese childhood craniopharyngioma patients achieved sufficient tolerability and short-term weight reduction [94,95]. An instant improvement of binge-eating behaviour in patients immediately after laparoscopic adjustable gastric banding was observed, but failed in long-term weight

reduction. Nevertheless, weight stabilization could be achieved with regular follow-up monitoring [96]. Treatment with invasive, nonreversible bariatric methods such as Roux-en-Y gastric bypass is most efficient in weight reducing [94] but controversial in the paediatric population because of medical, ethical, and legal considerations [96]. Reports on tolerability and efficacy of deep brain stimulation [97] and gastric pacemaking devices [98] in treatment of craniopharyngioma patients with hypothalamic obesity have not been published.

Despite the availability of these promising therapeutic approaches [99▪], it must be emphasized that currently no generally accepted (pharmacological or bariatric) therapy for hypothalamic obesity in craniopharyngioma has been shown to be effective in randomized studies. Furthermore, structured rehabilitation programs for weight reduction in survivors of craniopharyngioma have no proven long-term effect on long-term weight stabilization [100▪].

However, a purposeful care home environment [101▪] and adequate communication of interdisciplinary decisions with patients' families [102▪] have been reported to exert beneficial effects on follow-up treatment of craniopharyngioma patients.

EATING BEHAVIOUR

Strong associations between obesity and an obesogenic environment [103] and consequent eating behaviour have been confirmed in children and adolescents [104▪]. Owing to the dearth of studies on eating behaviour in craniopharyngioma patients, Hoffmann *et al.* [13▪▪] analysed eating behaviour and eating disorders in 101 survivors of childhood craniopharyngioma and 85 BMI-matched healthy controls. Severely obese patients (BMI > 8 SD; $N = 9$) presented with pathological eating behaviours and more weight problems and eating disorders, as compared with obese (BMI 3–8 SD; $N = 44$) and normal or overweight patients (BMI < 3 SD; $N = 48$). However, craniopharyngioma patients with different degrees of obesity showed similar or even less pathological findings as compared with BMI-matched normal controls. The authors conclude that the observed eating disorders are not disease-specific in craniopharyngioma patients.

Using functional MRI, Roth *et al.* [105▪,106] assessed pre and post-meal responses to visual food cues in craniopharyngioma patients' brain regions of interest. Following the test meal, BMI-matched controls showed suppression of activation by high-calorie food cues whereas craniopharyngioma patients showed trends toward higher activation. These data support the hypothesis that perception of food cues may be altered in craniopharyngioma patients with hypothalamic obesity, especially after food intake.

Roemmler-Zehrer *et al.* [107▪] compared eating behaviour in 26 craniopharyngioma patients (four childhood-onset cases) with 26 patients with non-functioning pituitary adenoma. Whereas craniopharyngioma patients scored higher in conscious hunger perception, the rate of eating disorders was similar in both groups, supporting the speculation that eating disorders in patients with hypothalamic obesity are not disease specific.

Even though hypothalamic obesity is a frequent sequela in craniopharyngioma, diencephalic syndrome leading to weight loss and cachexia can occur as a rare hypothalamic disturbance of body composition in craniopharyngioma [108,109▪▪]. Hoffmann *et al.* [109▪▪] analysed the incidence of diencephalic syndrome, its clinical manifestations before and after diagnosis of craniopharyngioma, and outcome in 485 patients recruited in the German Childhood Craniopharyngioma Registry. Only 4.3% of all craniopharyngioma patients presented with a low weight (BMI ≤ 2-SD) at time of diagnosis. Initial significant differences between patients with low weight at diagnosis and normal weight patients at diagnosis are usually observed at 5 years of age. Within the first 2 years after diagnosis, the BMI of diencephalic syndrome patients and normal weight patients converge to a similar level. The authors concluded from their analysis of patients' histories that diencephalic syndrome at the time of diagnosis does not preclude subsequent weight gain caused by a craniopharyngioma with hypothalamic involvement.

SEQUELAE, PROGNOSIS, AND QUALITY OF LIFE

The standardized overall mortality rate varies between 2.88 and 9.28 in cohort craniopharyngioma studies. Patients with craniopharyngioma have a 3 to 19-fold higher cardiovascular mortality in comparison to the general population; women with craniopharyngioma have an even higher risk [16]. The 20-year overall survival is impaired in patients with hypothalamic involvement of craniopharyngioma [8▪▪,9▪▪]. Hypothalamic obesity has significant negative impact on long-term quality of survival [9▪▪]. Increased daytime sleepiness, fatigue, disturbances of circadian rhythms [74,78,110▪], gastrointestinal and pulmonary complaints (diarrhea, dypnea) [9▪▪], memory deficits [111▪▪,112▪], and neuropsychological imbalances [69,107▪,113–115] are major long-term side-effects in patients with hypothalamic obesity.

Hoffmann *et al.* [116▪▪] recently reported on nonalcoholic fatty liver disease (NAFLD), a severe, previously underestimated sequela in craniopharyngioma patients with hypothalamic obesity. NAFLD occurred in about 50% of craniopharyngioma patients with hypothalamic obesity and was associated with elevated liver enzymes and homeostatic model assessment index. Over half of all patients (60%) with NAFLD were treated by stimulating agents, exerting considerable liver toxicity. The authors recommended that stimulating agents for treatment of daytime sleepiness in craniopharyngioma should be prescribed judiciously.

CONCLUSION

Hypothalamic involvement of craniopharyngioma and treatment-related lesions of hypothalamic areas are major risk factors for impaired survival, neuropsychological deficits [117▪▪], and reduced quality of life mainly because of hypothalamic obesity and the alterations in eating behaviour associated with hypothalamic obesity. As posttreatment options are very limited for hypothalamic obesity, we recommend hypothalamus-sparing treatment strategies conducted exclusively by experienced multidisciplinary teams and in the context of national or international trials/registries [118▪].

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