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Obesity in patients with craniopharyngioma in the South Asian region – A distinct phenotype

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ABSTRACT

Background: Craniopharyngiomas are rare benign tumors located in the sellar and suprasellar region, with an incidence of 0.5–2 cases per million as reported in Western studies. Post-treatment, including surgery and/or radiotherapy, many patients develop significant obesity, primarily due to hypothalamic damage and associated complications such as hypopituitarism. In the South Asian population, genetic predisposition to obesity at lower BMIs, coupled with a carbohydrate-rich diet, may exacerbate obesity in craniopharyngioma patients, presenting a unique challenge.

Methods: This submission is a commentary based on a comprehensive literature review. The authors conducted the review using PubMed to focus on English-language articles covering hypothalamic obesity, craniopharyngioma and obesity in the South Asian population from 1939 to the present.

Results: The literature review revealed that 50–60 % of patients treated for craniopharyngioma develop obesity, predominantly linked to hypothalamic damage, although these data are mainly derived from Western studies. Hypopituitarism was frequently observed, further contributing to the obesity. Despite a caloric intake appropriate for the age and gender, these patients exhibited reduced physical activity as measured by wrist accelerometers. Patients with hypothalamic obesity due to craniopharyngioma are at risk for metabolic syndrome and cardiovascular morbidity. Additionally, visual impairment was common, leading to a decreased quality of life. The South Asian population, genetically predisposed to visceral obesity and a carbohydrate-rich diet, may display a distinct phenotype. Although multiple treatment modalities have been tried, there is no definite treatment modality available to counteract this condition at present.

Conclusion: South Asian phenotype of craniopharyngioma-related obesity is characterized by significant metabolic and hormonal dysregulation, influenced by both dietary and genetic factors. Nevertheless, there may be a lot to be still understood about this devastating, rapid, relentless hypothalamic obesity syndrome. Also, a higher morbidity rate within this population, underscores the need for further research to develop targeted interventions.

1. Introduction

1.1. Background and objectives

A link between hypothalamic injury and obesity was first described over a century ago in 1939, when Dr. Fröhlich reported a case of a 14-year-old boy with rapid weight gain, hypogonadism, and vision loss in the setting of a hypophyseal tumor destroying the body of the sphenoid and dorsum of the Sella giving rise to the eponymous condition known as Frohlich syndrome or adiposo genital dystrophy [1]. Hypothalamic obesity (HO) may be associated with any disorder that affect the hypothalamus like trauma, aneurysm, infiltrative disorders, hypothalamic tumors, Prader Willi syndrome, leptin and or leptin receptor deficiency, POMC mutation and melanocortin 4 receptor (MC4R) mutations.

Craniopharyngioma (CP) constitute about 1.5–11.6 % of all paediatric brain tumors and is the most common neoplasm of the hypothalamic-pituitary area in children, accounting for approximately 50–80 % of tumors in this location [2]. It is often locally invasive and invades the hypothalamus, cavernous sinus and the optic chiasm, hence, not often amenable to complete resection resulting in vision defects and

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multiple endocrine deficiencies. Obesity due to CP may occur due to the tumor per se, the surgery to extirpate it, or due to radiotherapy (RT).

The South Asian phenotype of obesity is different as compared to the West in that South Asians have obesity at lower body mass indices (BMI) s and tend to develop normal BMI abdominal adiposity, underpinning a tendency to gain visceral fat at a rapid rate. How this phenotype behaves in conditions with hypothalamic damage as in CP is an interesting area of research.

2. Methods

2.1. Search strategy

The authors conducted a PubMed search of all publications in English language from 1939 till date mentioning the MeSH "craniopharyngioma", "obesity", "hypothalamic obesity" for this commentary.

3. Results

3.1. Disease burden/incidence

The prevalence of obesity in Craniopharyngioma survivors is around 50–60% according to various studies [2–10]. In a study by Srinivasan et al. [2], they followed 15 patients with CP post-surgery, and prospectively evaluated the anthropometric and body composition using DXA (dual energy x-ray absorptiometry) over 13 years. They found that 73 % of the subjects were living with obesity and all of them had increased abdominal adiposity (p 0.008), though there was no significant difference in the total body fat percentage or fat free mass compared to controls suggesting a dystrophy or redistribution of fat. This was the first report of HO in patients with CP.

In a study done by Gunna Sriharsha et al. [11] at a tertiary hospital in north India, 62 patients of Craniopharyngioma diagnosed under 18 years between 2003 and 2018 were followed 3 monthly for a period of 1 year. The prevalence of obesity increased from 3 (4.8 %) at presentation to 9 (14.5 %) at 1-year post-surgery and to 14 (22.6 %) at last follow-up. The prevalence of obesity increased by nearly fivefold at last follow-up ($p < 0.01$) and 28 (45 %) children had abnormal BMI (overweight and obese) at last follow-up.

Studies have shown that among those with childhood CP, 76 % of individuals with obesity and 96 % of those with severe obesity have a hypothalamic tumoral invasion [12–15]. Muller et al. [12] described that up to 52 % of paediatric CP patients develop obesity following tumor resection and a large number of them suffer from recalcitrant hyperphagia and weight related reduction in the quality of life (QOL). Following surgery, mean BMI standard deviation score (SDS) increased from 0.0 to 2.7 at 6 months and to 2.4 at 1 year [15].

3.2. Predictors of obesity in patients with craniopharyngioma

Studies have found various factors predicting the risk of HO in patients with CP. The risk factors include tumor localisation to the hypothalamus/thalamus, posterior hypothalamic involvement, direct radiation exposure to the hypothalamus of more than 51 Gy, associated hypothalamic endocrinopathy (i.e., growth hormone (GH) deficiency, hypothyroidism, precocious or delayed puberty, adrenocorticotrophic hormone (ACTH) deficiency, diabetes insipidus), higher BMI at presentation and pre-operative hydrocephalous.

3.3. Negative feedback energy balance pathway

Understanding the negative feedback energy pathway is the key to understand the pathophysiology behind HO. The hypothalamus is integrated in bidirectional energy balance signaling that includes hormonal and neurologic input and output. The arcuate nucleus (ARC) plays an important role in the regulation of feeding and metabolism. The ARC has anorexic POMC neurons and orexigenic neuropeptide Y (NPY)/ agouti related peptide (AgRP) neurons that have opposite effects on the regulation of energy homeostasis. The ARC project to the paraventricular nucleus (PVN) of the hypothalamus, where they synapse with neurons expressing the MC4R to regulate food intake. Peptide ligands called melanocortin derived from the larger POMC precursor act as anorectic agonist ligands at MC4R, while AgRP is antagonist and has an orexigenic effect. Peripheral nutrient-derived signals such as leptin stimulate the expression of POMC derived melanocortin peptides, which reduce food intake and body weight by acting as endogenous ligands for the brain-expressed MC4R (Fig. 1). In addition to the hunger hormones mentioned above, afferent and efferent neurologic pathways may also affect hunger. Afferent vagus nerve fibres from the stomach stretch receptors transmit parasympathetic signals to the brain and hypothalamus after a meal; efferent hypothalamic nerves signal hunger centers of other parts of the brain, as well send signals to peripheral tissues applicable to energy balance and fat deposition [16].

In the energy replete state, elevated leptin and insulin levels cause the anorexigenic arm to activate the sympathetic nervous system (SNS) and increase the expression of numerous genes in skeletal muscle, promoting mitochondrial biogenesis, glycogenolysis and thermogenesis leading to increased energy expenditure. On the other hand, in the fasting state, leptin and insulin are low, leading to reduced SNS tone, and reduced skeletal muscle thermogenesis, and reduced adipose tissue lipolysis [17].

3.4. Pathogenesis of obesity in craniopharyngioma

Dysfunction of the hypothalamus may impair post-meal negative feedback on hunger, resulting in "central nervous system starvation," which in turn, may blunt or mitigate otherwise anorexigenic signaling leading to hyperphagia (seen in 25 % of CP operated patients). Additionally, disruption of this bidirectional pathway may not only affect hunger and appetite, but may also affect thermogenesis, energy expenditure, blood pressure, and lipolysis in adipose tissue. The VMN controls the parasympathetic tone and any lesion of this nucleus causes parasympathetic disinhibition causing increased vagal tone, increased hunger and increased gastric motility, increased pancreatic beta cell insulin production, anabolism and weight gain. There are other mechanisms also responsible like hormonal deficiencies – for example, hypothyroidism, growth hormone deficiency and hypogonadism which contribute to weight gain.

Decrease in resting energy expenditure and voluntary energy expenditure in patients with CP, contribute to HO [18]. Reductions in basal metabolic rate and physical activity contribute to hypothalamic obesity [19]. Hence, in these patients, calorie restriction does not have much effect on weight gain. The decrease in energy expenditure is mediated through suppression of SNS activity by the hypothalamic damage. The decrease in sympathetic tone probably may account for decreased rates of lipolysis through the adipocyte β_3-adrenergic receptor leading to decrease in resting and voluntary energy expenditure [17]. Hypopituitarism also contributes to decrease in energy expenditure in these patients. In a study by Lorenzo et al. [3], at diagnosis 71 % of patients with CP had symptoms suggesting the presence of an endocrinopathy. Among them, 15 % presented with rapid and excessive weight gain. After a mean of 7 years from the initial surgery, multiple endocrinopathies are almost universal and 75 % of children have panhypopituitarism. These hormone deficiencies like hypothyroidism, hypogonadism and growth hormone deficiency could also contribute to excess weight gain.

In addition, disruption of responses to leptin and insulin from hypothalamic damage and insensitivity to high leptin levels has been proposed as a possible mechanism contributing to HO(14) as well as a loss of leptin feedback inhibition on neuropeptide Y and appetite [20]. The various factors proposed to be contributing to HO has been illustrated in Fig. 2. The hyperghrelinemia observed in Prader Willi

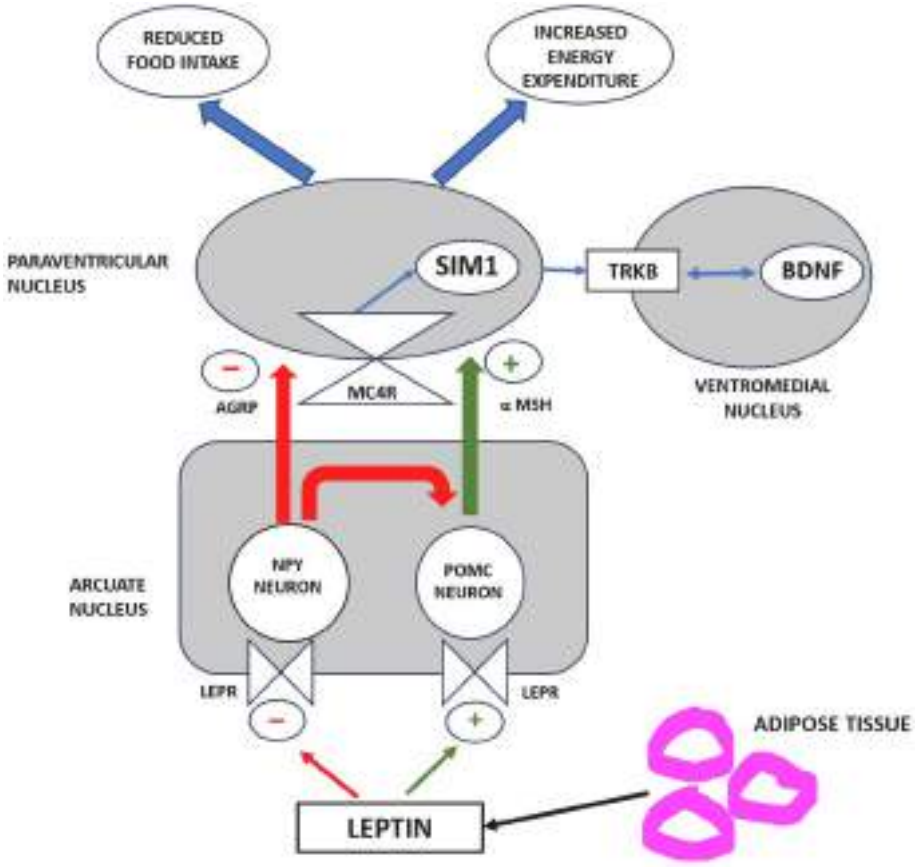

Fig. 1. Mechanism of appetite regulation by hypothalamus
NPY – neuropeptide Y; LEPR-leptin receptor; α MSH - alpha – melanocyte stimulating hormone; MC4R-melanocortin 4 receptor; AGRP – agouti related peptide; POMC – Pro-opiomelanocortin; SIM 1- single minded 1; BDNF – brain derived neurotrophic factor; TRKB - tropomyosin-related kinase receptor type B.

Fig. 2. Factors contributing to obesity in craniopharyngioma.

syndrome is not to be found in CP patients post-surgery [21].

To summarise, in CP, there is direct damage to the hypothalamus leading to impairment of brain's ability to regulate hunger and satiety. However, in addition to these, the decrease in energy expenditure has a greater role in development of HO [18] in contrary to genetic conditions causing HO (see Table 1). In PWS there is elevated ghrelin level leading to hyperphagia, in BBS hyperphagia is secondary to impaired leptin signalling and in leptin deficiency the deficiency of leptin leads to loss of inhibition on the orexigenic pathways thus leading to hyperphagia.

3.5. South Asian obesity phenotype may amplify metabolic risks in HO due to CP

South Asians are at higher risk for development of obesity and metabolic complications than White Caucasians. The factors associated with increased risk of obesity in South Asians include specific body phenotype with high body fat, high truncal, subcutaneous and intra-abdominal fat, and low muscle mass, biochemical parameters like hyperinsulinemia, hyperglycemia, dyslipidemia, hyperleptinemia, low levels of adiponectin and high levels of C-reactive protein and endothelial dysfunction. Also, the metabolic complications of obesity occur early among South Asians and even at low BMI. Hence, lower cut-offs for obesity and abdominal obesity have been advocated for Asian Indians (BMI cut-off; overweight 23–24.9 kg m^2 and obesity >25 kg m^2; and WC; men >90 cm and women >80 cm, respectively) [22]. Various factors like imbalanced nutrition, physical inactivity, perinatal adverse events, lower disease awareness and health-seeking behaviour and genetic factors has been considered to be contributing to this unique phenotype in South Asians. Data from genome wide association studies (GWAS) in South Asians have showed the association of multiple genetic variants with obesity. Few notable gene variants among them include *FTO*, *CLIP1* rs11583200, *CADM2* rs13078960, *GALNT10* rs7715256, *PTBP2* rs11165643, *HIP1* rs1167827, *C6orf106* rs205262 and *GRID1* rs7899106(24).

As discussed above, the Asian Indian phenotype of obesity is different as compared to the Caucasians in that Indians have high body fat at lower BMIs and tend to develop normal BMI abdominal adiposity with accompanying metabolic complications. Hence, how weight gain and complications in Asians with CP would be different compared to Caucasians may need to be studied.

3.6. The peculiar phenotype in hypothalamic obesity

Hypothalamic Obesity was classically described by Frohlich in his landmark case report as, "the largest accumulation of fat was in the subcutaneous tissue of the trunk, particularly on the abdomen and in the neighbourhood of the genitals. There the accumulation of fat was so enormous that it protruded markedly around the genitals. The penis, which was normally developed, appeared so deeply embedded in the fat tissue that the genitals approached the feminine type (sic)"(1).

Table 1
Predictors of obesity in craniopharyngioma - evidence.

Author/year	Population (n)/years of follow-up	Factors predicting obesity
Lustig et al., 2003 [17]	N = 148 (children with brain tumors) >5 years disease free survival (10 CP)	Tumor localisation to the hypothalamus/thalamus (p 0.001) Direct radiation exposure to the hypothalamus of more than 51 Gy (p 0.002) Associated hypothalamic endocrinopathy (p 0.03) Age at diagnosis <6 years (0.04)
Ahmet et al., 2006 [14]	N = 43 children with CP	Higher BMI SDS at presentation (OR 4.89 95 % CI 1.84–12.99, p = 0.0015) Pre-operative hydrocephalus (OR 15.28 95 % CI 1.28–181.75, p < 0.05)
Muller et al., 2004 [13]	N = 183 children with CP	Larger sellar/parasellar mass (p < 0.05) Hypothalamic extension (p < 0.001)
Muller 2004 [12]	N = 90 children with CP	Hypothalamic involvement (95 % CI 2.10- 4.93 p < 0.001)
Beckhaus et al., 2023 [31]	N = 709 children with CP	Posterior hypothalamic involvement (OR = 2.94, 95 % CI 1.73-5.08 p < 0.001)

3.7. Obesity in Craniopharyngioma operated patients – rapid, relentless and Resistant

Muller et al. described that the pattern of obesity in such patients is distinct in that these children with hypothalamic obesity have a significant and rapid BMI increase over the first 6 months after treatment, followed by stabilization at a high plateau, with no subsequent loss of weight (Fig. 3) [9].

Patients who have obesity at follow up were generally the ones who had higher BMI at the time of diagnosis probably due to hypothalamic obesity existing pre-operatively. The caloric intake of patients with hypothalamic obesity from craniopharyngioma, when determined by a validated food diary, did not exceed that of control patients with common obesity, but their movement activity, assessed by accelerometer, was reduced both in the ambulatory setting and in a clinically monitored weight loss environment [21]. Moreover, Müller in 2003, reported an increased daytime sleepiness and reduced nocturnal melatonin levels in patients with childhood craniopharyngioma supporting the hypothesis that in these patients physical activity might be decreased due to as yet unknown neuroendocrine disorders [23].

3.8. Cardiometabolic impact of obesity in patients with Craniopharyngioma

An increased risk of cardio- and cerebrovascular mortality was observed in a study of 60 patients treated for craniopharyngioma compared to the general population during a median follow-up time of 12 years [17]. It has already been demonstrated convincingly that adult patients with growth hormone deficiency (GHD) are at an increased risk for CVD [24].

In a study by Scarano et al., 20 patients with CP and 20 age and BMI matched controls were followed up for a period of 5 years. At baseline and at 5 years follow-up, patients with CP had significantly higher systolic blood pressure (SBP), total cholesterol, LDL cholesterol and lower HDL cholesterol in comparison to the controls [25]. The data on extend of hypothalamic damage in patients with CP was not available in this cohort. Similarly, a study by Somma et al., which involved 28 patients

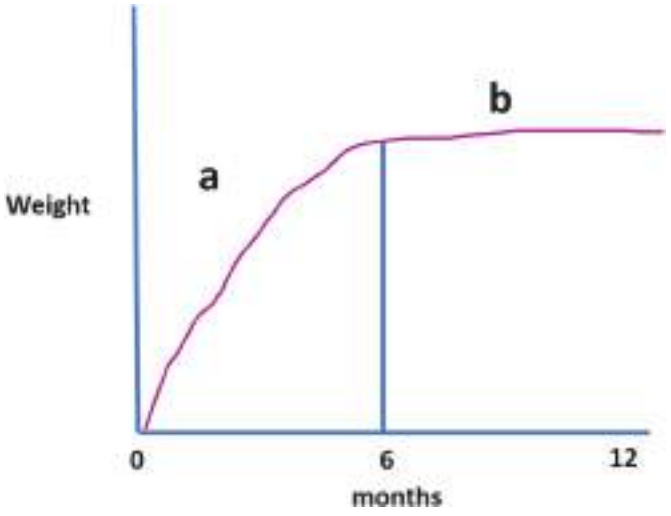

Fig. 3. Pattern of weight gain in patients with craniopharyngioma.

with CP and BMI matched controls, patients with CP had higher waist circumference, SBP, total cholesterol, LDL cholesterol compared to the controls [26].

3.9. Impact of obesity on the quality of life in patients with craniopharyngioma

Craniopharyngiomas, despite high survival rates (87–95 %) 20 year overall survival in childhood-onset CP), the QoL is frequently impaired in long-term survivors due to sequelae caused by the anatomical proximity of the tumor to the optic nerve/chiasma and hypothalamic–pituitary axes [9].

The cause for impaired QoL in patients with CP is multifactorial. Studies have found that visual field defect, repeat surgery, radiotherapy, obesity, hypothalamic involvement and pituitary hormone deficits have been associated with low QoL in them [27–30]. In a systematic review by Castle Kirazbaum et al. [27], it was found that the strongest predictor of QoL was hypothalamic involvement. Also, endocrinopathy was found to be contributing to morbidity. Hypothalamic damage/involvement being a strong predictor of HO, obesity may be a significant contributor to impaired QoL in these patients. This is further exacerbated by the disturbed sleep wake cycle contributed by hypothalamic damage.

GH replacement therapy improves the physical and psychosocial impairment in adults but does not appear to improve the QoL of children probably due to concomitant deficiencies in the younger age group.

3.10. Treatment of hypothalamic obesity

Currently, the therapy for HO has been limited to strategies to manage obesity and the benefit so far has been variable. The commonly practiced treatment modalities include pituitary hormone replacement, calorie restriction, increased energy expenditure through physical activity, pharmacotherapy and bariatric surgery. Current pharmacotherapeutic approaches include stimulants that increase energy consumption, anti-diabetic agents, octreotide, and methionine aminopeptidase 2 (MetAP2) inhibitors. Most of the pharmacological studies of HO that have reported weight loss or stabilization have been of short duration [32–35]. Due to the inconsistency in the reported benefits, combined approaches to manage HO are thus required to achieve credible and sustained weight loss. Thus, identifying the various etiological factors contributing HO may lead to multi-faceted interventions targeting hyperphagia, insulin resistance, decreased energy expenditure, sleep disturbance, hypopituitarism and psychosocial morbidity. Novel agents including those targeting pro-opiomelanocortin-C and AgRP/NPY expressing neurons and the MC4 receptor may result in better outcomes [36]. The various targeted pharmacotherapies tried in HO has been enumerated in Table 2.

Table 2
Targeted pharmacological therapies tried in hypothalamic obesity.

Drug	Mechanism of action	Benefit – evidence
Targeting insulin hypersecretion		
Metformin	It improves insulin sensitivity and decreasing hepatic gluconeogenesis and intestinal glucose absorption	In a prospective open-label 6-month pilot treatment trial in 9 obese subjects with CP the administration of diazoxide (2 mg/kg/day) and metformin, (1000 mg twice daily) resulted in an overall reduction in weight gain over a 6-month period compared with the weight gain observed over the 6-month period prior to the intervention [37]
Diazoxide	It reduces insulin secretion from the pancreas	
Octreotide	It is a somatostatin analogue that improves insulin sensitivity	In study of octreotide depot compared with saline control in paediatric HO patients, there was no significant change in BMI between the groups after 6 months of trial [38]
Intervention on energy expenditure		
Tri-iodothyronine	Increase metabolic rate and energy expenditure to overcome the negative impact on energy expenditure in HO	In a small number (n = 3), tri-iodothyroine monotherapy (T3) has also been tried in patients with HO, with a sustained reduction in weight observed over a 2-year period and with improvement in daytime somnolence [39]
Intervention on appetite suppression		
Dextroamphetamine	Mediates central anorexigenic control through stimulation of cocaine-amphetamine regulated transcript (CART) production in the ventromedial hypothalamus, to induce appetite suppression	In a study of 12 patients with HO treated with low dose dextroamphetamine (5mg twice daily), 10 of the patients either lost weight or demonstrated weight stabilization and improvement in day time somnolescence [40]
Intranasal oxytocin	Induces appetite suppression and feeding reward behavior in the hypothalamus	In patients with Prader Willi syndrome aged 3–11 years, 3 months of intranasal oxytocin as positive effects on social and eating behaviour without safety concerns [41]
GLP 1 analogues	Potentiate nucleus tractus solitarus in the brain stem sensitivity to GLP1 reducing the frequency and quantity of food consumed, leading to weight loss in HO	In a RCT which included 10 to 25-year-old with hypothalamic injury following intracranial tumour and HO, once weekly subcutaneous injections of exenatide 2 mg for 36 weeks did not show significant reduction in BMI in the treatment group compared to controls. There was a reduction in total body fat mass as measured by DXA in and stabilization of waist circumference in 50 % of the treatment group, compared to controls [42].
Tesomet (tesofensine and metoprolol)	Acts on the brain to block reabsorption of three monoamine neurotransmitters (serotonin, noradrenaline and	Tesofensine originally developed to treat Alzheimers and Parkinson's disease, was found to be ineffective and the unintended side effect

(continued on next page)

4. Need for future research

After CP removal, children and adolescents are at risk of excess weight gain, and together with GHD, this increases the likelihood of abdominal adiposity and dyslipidemia. As a result, they could be at higher risk of atherogenic complications from the metabolic syndrome compared with BMI-matched healthy controls. As these patients progress into adulthood, they should be monitored for features of the metabolic syndrome, including insulin resistance, type 2 diabetes mellitus, dyslipidemia, and hypertension. There is no long term follow up data on how the QOL, hyperphagia and weight trajectory behave in such patients.

5. Conclusion

1. **Significant Knowledge Gaps**: There is still much to learn about hypothalamic obesity syndrome, especially in patients treated for craniopharyngioma, where obesity can lead to lifelong stigma and

Table 2 (*continued*)

Drug	Mechanism of action	Benefit – evidence
	dopamine) leading to a reduction in food cravings	of weight loss. Tesofensine has been combined with metoprolol to counteract previously observed side effects of tachycardia and hypertension at higher doses [43]. There is an ongoing phase 2 trial to evaluate the safety and efficacy of Tesomet in subjects ≥16 years of age with HO (ClinicalTrials.gov Identifier: NCT05147415)
Selective MC4R agonists (Setmelanotide)	Directly induce appetite suppression at the level of the hypothalamus to mimic the action of POMC	Setmelanotide has shown promising results with respect to weight loss in patients with Bardet-Biel syndrome with no major adverse events [44]. Phase 2, open label study to evaluate the safety and efficacy of Setmelanotide in subjects with HO is ongoing (ClinicalTrials.gov Identifier: NCT04725240)
Methionine Aminopeptidase Inhibitors (MetAP2) (Beloranib)	Acts on unknown target and leads to increased adiponectin and decreased leptin, leading to decreased lipogenesis, increased fat oxidation, and increased lipolysis	In a Phase 2a, double-blind, placebo-controlled study of 14 adults with HO, randomized to receive beloranib 1.8 mg or placebo subcutaneously twice weekly for 4 weeks resulted in weight loss without any major adverse events [45]. However the same drug in a 26 week trial among children Prader Willi Syndrome was associated serious thromboembolic events leading to termination of the trial [46].

serious health complications, including diabetes and cardiovascular disease. Also, there is a lack of robust evidence on this subject in the South Asian population.

2. **Increased Risk in South Asians**: Due to higher susceptibility to obesity & sarcopenia in South Asians, driven by both environmental and genetic factors, there is a heightened expectation of encountering obesity & impaired QoL in craniopharyngioma patients from this population.
3. **Need for Further Studies:** Recognizing the unique challenges faced by South Asian craniopharyngioma patients, initiative-taking strategies are essential to manage and mitigate the impact of obesity in this vulnerable group.

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Methodology: [NK AHS]
Formal Analysis: [NK, RR]
Investigation: [ST]
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Writing - Review & Editing: [RR, AHS, NK]
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Declaration of Artificial Intelligence (AI) and AI-assisted technologies utilized

AI and AI-assisted Technologies Declaration: AI-assisted technologies were used in the spell check and grammar proofing of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

As permitted for guest editor, this would be the only publication submitted to this special issue from the guest editor's desk. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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