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Endocrine and metabolic consequences of childhood-onset craniopharyngioma during the transition age: A literature review by the TALENT study group

Dario De Alcubierre[1,2] · Tiziana Feola[1,2] · Giulia Puliani[3] · Rosario Ferrigno[4] · Maria Elisa Amodeo[5] · Francesco d'Aniello[5] · Rosa Pirchio[6] · Valentina Sada[1] · Carla Pandozzi[1] · Franz Sesti[1] · Daniele Gianfrilli[1] · Andrea M. Isidori[1,7] · Ashley B. Grossman[8,9] · Emilia Sbardella[1]

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Abstract

Craniopharyngiomas are frequently diagnosed during childhood and adolescence, crucial periods for physical and psychosocial development. Despite improvements in survival rates, patients with childhood-onset craniopharyngioma face a wide array of lifelong complications, which emerge or worsen during adolescence, complicating the transition to adult care. Nevertheless, the transition age (15–25 years) remains an understudied phase in clinical practice. This narrative review synthesises current literature on the endocrine, neurocognitive, and metabolic consequences of transition-age childhood-onset craniopharyngiomas, providing a practical clinical approach to their diagnosis and management, along with an overview of emerging treatment strategies. Childhood-onset craniopharyngiomas are frequently associated with pituitary hormone deficiencies, which typically worsen post-treatment. While replacement protocols largely mirror those for adult patients, particular emphasis should be placed on patient education and optimal timing of treatment, especially regarding puberty induction and growth hormone replacement. Emerging therapies, such as long-acting growth hormone and modified-release hydrocortisone, should be considered to improve compliance. Hypothalamic dysfunction, both pre- and post-treatment, can lead to obesity, sleep disorders, and cognitive impairment. GLP-1 receptor agonists and melanocortin receptor agonists have recently shown promise in managing hypothalamic obesity. Sleep disturbances and cognitive impairment, often overlooked in clinical practice, should be systematically assessed in patients with hypothalamic involvement. Cardiovascular and bone health complications should be proactively addressed to improve long-term outcomes. Childhood-onset craniopharyngioma survivors require multidisciplinary care, particularly during the transition to adulthood. Timely endocrine management, individualised treatment strategies, and emerging targeted therapies are crucial for optimising quality of life and metabolic and neurocognitive outcomes.

Keywords Craniopharyngiomas · Transition age · Adolescence · Childhood · Complications

✉ Dario De Alcubierre
dario.dealcubierre@uniroma1.it

✉ Emilia Sbardella
emi.sbardella@uniroma1.it

[1] Department of Experimental Medicine, Sapienza University, Viale del Policlinico 155, 00161 Rome, Italy

[2] Neuroendocrinology, Neuromed IRCCS, Pozzilli, Italy

[3] Oncological Endocrinology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[4] UOSD Di Auxologia Ed Endocrinologia, AORN Santobono-Pausilipon, Naples, Italy

[5] Endocrinology and Diabetology Unit, IRCCS 'Bambino Gesù' Children's Hospital, Rome, Italy

[6] Dipartimento Di Medicina Clinica E Chirurgia, Sezione Di Endocrinologia, Diabetologia, Andrologia e Nutrizione, Università Federico II Di Napoli, Naples, Italy

[7] Centre for Rare Diseases (Endo-ERN Accredited), Policlinico Umberto I, Rome, Italy

[8] Green Templeton College, University of Oxford, Oxford, UK

[9] Centre for Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, UK

Abbreviations

CP	Craniopharyngioma
CO	Childhood-onset
ACTH	Adrenocorticotropic hormone
GH	Growth hormone
GHD	Growth hormone deficiency
IGF-1	Insulin-like Growth Factor 1
ITT	Insulin tolerance test
GHRH	Growth-hormone-releasing hormone
GHRT	Growth hormone replacement therapy
TSH	Thyroid-stimulating hormone
GnRHa	Gonadotrophin-releasing hormone agonist
CAI	Central adrenal insufficiency
HPA	Hypothalamo-pituitary-adrenal
MR-HC	Modified-release hydrocortisone
ADH	Anti-diuretic hormone
ADH-D	Anti-diuretic hormone deficiency
DI	Diabetes insipidus
HS	Hypothalamic syndrome
POMC	Pro-opiomelanocortin
BMI	Body mass index
MRI	Magnetic resonance imaging
HO	Hypothalamic obesity
QoL	Quality of life
α-MSH	Alpha melanocyte-stimulating hormone
SD	Sleep disorder
EDS	Excessive daytime sleepiness
SBD	Sleep-related breathing disorders
OSAS	Obstructive sleep apnoea syndrome
CRSWD	Circadian rhythm sleepwake disorders
ICSD-3	International Classification of Sleep Disorders 3
PSQI	Pittsburgh Sleep Questionnaire Index
MSLT	Multiple sleep latency test
PAP	Positive air pressure
IQ	Intelligence quotient
DTI	Diffusion tissue imaging
CV	Cardiovascular
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
BMD	Bone mineral density
vBMD	Volumetric bone mineral density
PEDQOL	Pediatric Quality of Life
ZBI	Zarit Burden Interview
HRQoL	Health-related quality of life

1 Introduction

Craniopharyngiomas (CPs) are rare primary brain tumours, accounting for 1.2–4.6% of all intracranial tumours, with an incidence of 0.5–2.5 new cases per 1 million population per year globally [1–3]. The prognosis and clinical outcomes of CP patients are often compromised due to the hypothalamo-pituitary localisation of these neoplasms and the consequent damage to these anatomical areas, which can be related to both the tumour itself and its treatment; therapies comprise neurosurgery with or without radiotherapy, with a rising impact of medical therapies in recent years [4]. Consequently, CPs are frequently associated with a wide array of comorbidities, including endocrine deficiencies, visual disturbances, obesity, metabolic and cardiovascular derangements, sleep disorders and cognitive sequelae, all of which can negatively impact patients' functional capacity and quality of life [5], leading to an increase in overall mortality (3- to fivefold higher than that observed in the general population [6]); this increase has been linked to multiple factors, including higher cardiovascular morbidity, and with tumour- and/or treatment-related risk factors, such as disease progression with multiple recurrences, cerebrovascular disease (stroke), neurological disorders like epilepsy, and chronic neuroendocrine deficiencies [7–9]. This statement gains further relevance when considering that 30–50% of CPs are diagnosed during childhood and adolescence [2], both critical developmental periods, positioning them as the most common non-neuroepithelial intracerebral neoplasm in individuals aged less than 18 years and accounting for 5–11% of all intracranial tumours in this age group [10–12]. While advances in surgical and radiotherapy techniques have significantly improved the overall survival rates in these patients, not all the CP-related complications are reversible after successful treatment which, on the contrary, can often even exacerbate them due to the damage to critical neural structures. As a result, patients with childhood-onset (CO) CP often face a lifetime of comorbidities that begin in adolescence (summarised in Fig. 1), further complicating the transition to adulthood.

The persistent nature of these comorbidities underscores the necessity for comprehensive long-term management strategies that address both the physical and psychosocial aspects of care for this unique population. Therefore, this review aims to address the main complications stemming from CO CP, providing a practical clinical approach to their diagnosis and management, with a specific focus on the transition age (15–25 years).

2 Endocrine complications

Pituitary hormone deficiencies are among the major long-term consequences of CO CP [13]. At diagnosis, from 40 to 87% of patients present with at least one pituitary deficiency, this prevalence further increasing after treatment [14]. Different treatment modalities for CO CP do not seem to affect the development of endocrine deficiencies. Aside from a single German report observing lower rates

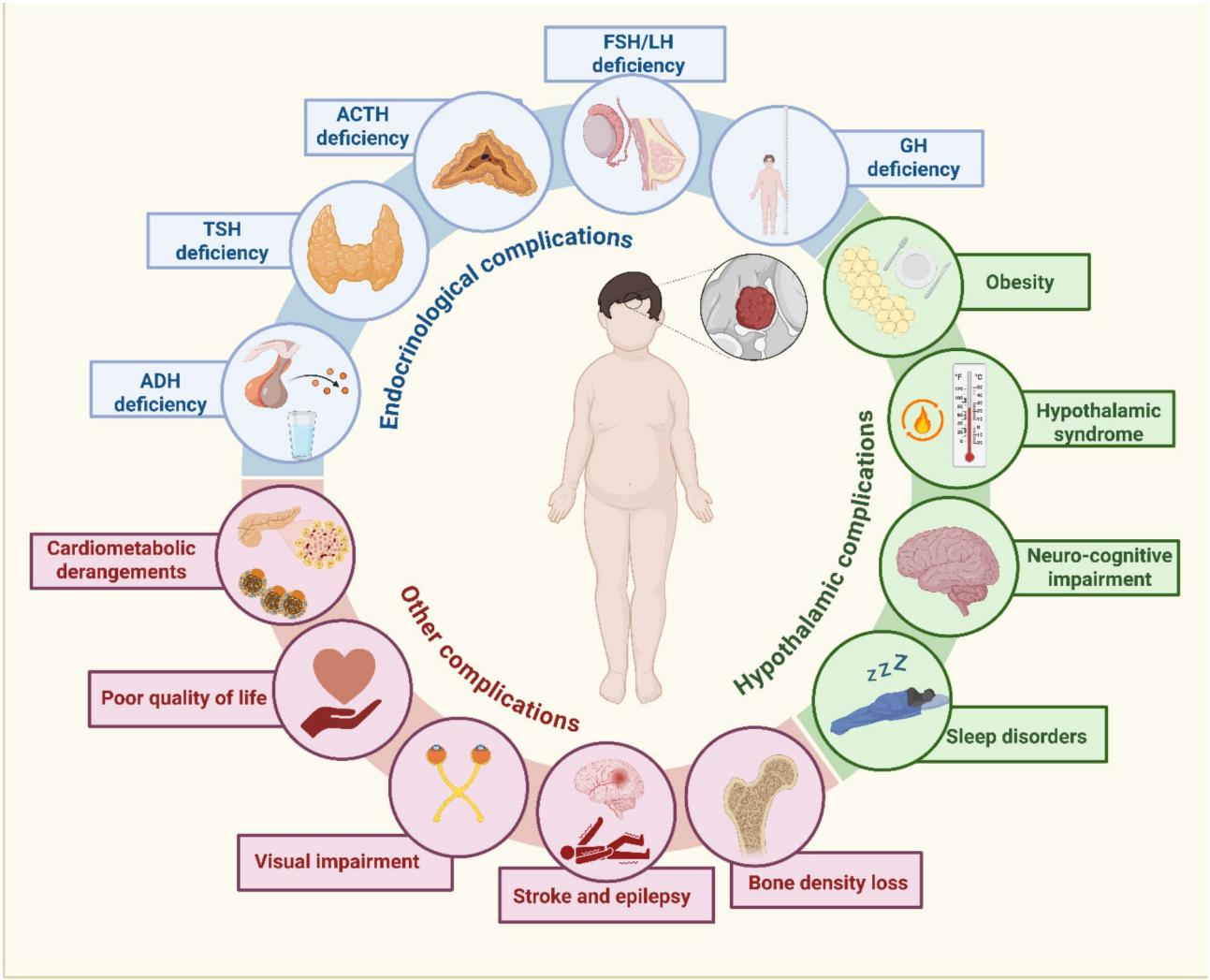

Fig. 1 Endocrine, hypothalamic, and general complications in transition-aged patients with childhood-onset craniopharyngiomas. Abbreviations: *ACTH* adrenocorticotropic hormone, *ADH* anti-diuretic hormone, *FSH* follicle-stimulating hormone, *GH* growth hormone, *LH* luteinizing hormone, *TSH* thyroid-stimulating hormone

of post-operative ACTH deficiency in patients treated with hypothalamus-sparing compared to extensive-resection neurosurgery [15], most studies have shown no significant differences in the prevalence of pituitary dysfunction based on the surgical approach, such as transsphenoidal surgery vs. craniotomy, subtotal vs. gross total resection [16], extensive-resection vs hypothalamus-sparing neurosurgery [15]) or different radiotherapy techniques (*i.e.*, proton beam therapy vs conformal photon radiation [17]). Similarly, hypopituitarism rates are comparable among patients treated with neurosurgery alone, radiotherapy alone, or a combination of both [18, 19]. Conversely, recent evidence has shown that proton beam therapy might reduce long-term neurocognitive and endocrine sequelae and improve functional outcomes and quality of life in patients with CO CP [20, 21] by offering superior dose conformity that spares surrounding healthy brain tissue, particularly the hypothalamus and pituitary gland, while also achieving tumour control rates comparable to photon therapy while potentially improving functional outcomes and quality of life [22]. Interestingly, pre-operative tumour location does not seem to significantly affect the risk of developing endocrine deficiencies [16, 19], despite a single study showing higher rates of ACTH deficiency in patients with intrasellar CPs than those with third ventricle floor CPs [19]. Of note, an English study found a lower prevalence of endocrine deficiencies in patients treated more recently compared to earlier decades [23], suggesting that improvements in the standard-of-care practices may have positively impacted treatment-related endocrine complications.

2.1 GH deficiency

Growth hormone deficiency (GHD) is the most frequent endocrine complication of CO CP, affecting 26–75% of patients at diagnosis [15, 18, 19, 24–41] and increasing to 40–100% post-treatment [15, 19, 26, 34, 35, 37, 39]. However, this prevalence may be overestimated due to inadequate distinction between pre-existing and treatment-related GHD [18, 24, 25, 27–29, 31–33, 36, 38, 40–42], along with the inclusion of larger registry studies with GHD as an inclusion criterion, leading to a reported 100% prevalence [27, 31, 40]. Additionally, most studies did not perform basal and dynamic testing, instead defining GHD based on low IGF-1 levels and clinical parameters, such as growth rate decrease, failure to thrive, and persistent short stature [15, 19, 26, 34, 35, 37, 39]. Of note, some patients achieve normal growth despite GHD, a phenomenon known as "growth without growth hormone," [43], probably due to compensatory mechanisms involving insulin and/or leptin [14]. Indeed, patients with hypothalamic involvement, who are at higher risk of obesity and therefore often exposed to higher insulin and leptin levels, were more likely to achieve normal adult height than those without hypothalamic involvement [33]. The insulin tolerance test (ITT) remains the gold standard for the diagnosis of GHD in CO CP treated patients, with diagnostic cut-offs similar to those for GHD of other causes [44]. However, many CO CP patients may present clinical contraindications to ITT, including history of seizures, and therefore second-line GH provocative tests, including glucagon, clonidine, and arginine, are usually adopted in clinical practice [44]. Macimorelin, an orally-administered ghrelin receptor agonist and GH secretagogue, has also been recently approved for diagnosing GHD in adults [45] and is currently pending approval in patients with childhood-onset GHD following the recent completion of a Phase 3, multicentre, open-label trial ('DETECT' trial, NCT047868733). The use of GHRH stimulation, alone or combined with arginine, remains controversial, with some studies reporting frequent false positives [44] and others reporting similar GH responses to that obtained with the ITT [46].

In patients with CO GHD, particularly those with idiopathic GHD, retesting during the transition age—after attainment of final height or completion of pubertal development—is generally recommended to assess whether GHD persists and to determine the need for ongoing GH replacement therapy (GHRT) [47]. This is important because a significant proportion of idiopathic childhood GHD cases may resolve by late adolescence, and unnecessary continuation of therapy can be avoided with appropriate retesting. While this notion is also applicable for transition-age CO CP patients, increasing evidence has demonstrated that retesting for GHD in these patients is generally unnecessary, as most exhibit clinical features consistent with permanent GHD, such as a history of hypothalamic involvement, previous hypothalamo-pituitary surgery, or previous high-dose radiotherapy (> 30 Gy) [44]. This notion was supported by a study in young adults with childhood-onset GH deficiency, which confirmed that all CP-related cases had a maximal GH response of < 3 µg/L regardless of testing method [48]. However, retesting may still be considered in selected cases where the initial diagnosis was uncertain, there is clinical suspicion of recovery, or when the patient had received only low-dose cranial irradiation [49]. For accurate assessment of GH status, GHRT should be discontinued for a washout period of at least 1–2 months prior to dynamic testing, as shorter intervals may yield false-negative results. If persistent GHD is confirmed, GH replacement should be promptly resumed, typically at lower, individualized doses appropriate for adults, with gradual titration based on clinical response and IGF-1 levels. Early re-initiation of GHRT after confirmation of persistent deficiency is essential to support optimal metabolic health, bone density, and quality of life during the transition to adulthood [47]. Growth hormone replacement therapy (GHRT) in CO CP has historically been approached with caution, with some reports recommending a waiting period of up to five years of disease stability before initiation, due to theoretical concerns about stimulating tumor recurrence [44, 49, 50].

Nevertheless, increasing evidence from retrospective and prospective studies demonstrates that GHRT.

in CP-treated patients has been proven effective and safe [51, 52], and it does not significantly affect event-free survival [53] or recurrence risk [54–56]. While treatment protocols mirror those for other GHD causes in the transition age, the timing of GHRT initiation should be carefully evaluated to minimise both the GHD burden and potential risks of neoplastic progression during treatment [44, 50]. Importantly, delaying GHRT for extended periods may compromise the achievement of optimal anthropometric targets, particularly final height, as adolescence is a critical window for linear growth and bone accrual. A recent French retrospective study further supports the safety of GHRT initiation as early as six months post-treatment, showing no increased risk of tumour progression or recurrence compared to a more delayed start after primary treatment [50]. However, in cases of severe GHD-related symptoms, early initiation may be considered after three months of stability [44]. The monitoring of GHRT should be performed according to general recommendations, although some adverse events, including increased intracranial pressure, slipped capital femoral epiphysis, and worsening of scoliosis may be more frequent in CO CP patients, especially those starting treatment at younger ages [44].

The recent availability of long-acting GH formulations may improve treatment adherence and outcomes by reducing injection frequency and treatment burden, which is

especially relevant during a vulnerable period of development such as the transition age. However, data on CO CP patients are currently lacking [57].

2.2 TSH deficiency

TSH deficiency is present in 2–25% of paediatric patients with CP [58] and usually manifests as weight gain, fatigue, dry skin, cold intolerance, constipation, and failure to thrive. Notably, its prevalence has been reported to rise significantly following surgical or radiation treatment, rising to 29–85% of cases, as observed in the multinational prospective trial, KRANIOPHARYNGEOM 2000 [34]. No specific recommendations for diagnosis and treatment of hypothyroidism in these patients have been provided. The optimal approach to thyroid hormone replacement is daily oral administration of synthetic levothyroxine, aiming to produce a circulating thyroxine level at the upper end of the normal range. Before initiating treatment, it is crucial to assess adrenal function, as thyroid hormone therapy can accelerate glucocorticoid metabolism, potentially triggering an adrenal crisis in patients with undiagnosed or untreated adrenal insufficiency.

2.3 FSH/LH deficiency

Delayed puberty, traditionally defined as the absence of breast development by age 13 years in girls and the absence of testicular growth by the age of 14 in boys [59], is a common feature at CP diagnosis, occurring in more than 20% of cases [41], with its prevalence increasing to 80% following treatment [60, 61]. A recent multicentre Italian study retrospectively evaluated endocrine, auxologic, and clinical outcomes in 145 CO CP patients, revealing that, of patients diagnosed at a 'pubertal age', puberty induction was performed in 63.5% of cases [41]. A recent study assessing hypothalamo-pituitary–gonadal axis function in CO CP patients found that the probability of hypogonadotrophic hypogonadism proportionately increases with age at diagnosis (68.7% before age 5, 73.7% between ages 5–10, 80.9% after age 10). Of note, the same study identified GHD as the main prediction factor for hypogonadotrophic hypogonadism, with a positive predictive value of 73.6% compared with 0% in the absence of GHD [62].

Appropriate puberty induction and replacement therapy are extremely relevant in transition-age CO CP patients, as insufficient oestrogen and androgen supplementation during adolescence could result in bone impairment during adulthood, particularly in women [63], as detailed below. Moreover, delayed or disrupted puberty can have profound psychological effects on young patients, including issues related to body image, social interactions, and emotional well-being [64]. Therefore, puberty induction should generally be considered from the age of 11 years in girls and 12 years in boys [65], but should ultimately be individualised depending on the patient's chronological age, bone age and growth pattern, as earlier treatment with sex steroids could lead to premature cessation of growth. In this regard, GnRH analogues (GnRHa) can suppress puberty by reducing the secretion of sex hormones, which in turn delays bone maturation and prolongs the period of linear growth [66]. Therefore, GH-treated children who start puberty spontaneously with an expected adult height ≤ 2.5 standard deviations may benefit from additional treatment with a GnRH analogue (GnRHa) for 2 years from onset of puberty to maximise growth potential [67]. Gonadotropin replacement therapy can also be used for pubertal induction in patients with hypogonadotropic hypogonadism, providing a more physiological approach to sexual development in selected cases [68]. Furthermore, while not an immediate concern, the possibility of future fertility should be considered and discussed with adolescent patients. In girls, puberty induction should generally start with very low doses of oestrogen, gradually increasing over time, eventually with periodic progesterone treatment to prevent uterine hyperplasia. In boys, specific induction protocols should be tailored based on age at diagnosis and, in older patients, potential desire of fertility, between testosterone (either intramuscular or transdermal, to be started between 12 and 15 years with gradually increasing doses) or gonadotrophin replacement, especially in young adult males seeking fertility, to allow maturation of testes.

2.4 ACTH deficiency

ACTH deficiency, or central adrenal insufficiency (CAI), is a frequent endocrine complication of CO CP treatment, affecting 29–96.8% of patients [15, 18, 19, 24–32, 34–42, 69]. However, as with GHD, most studies have focused on the overall prevalence during follow-up of CO CP, not properly distinguishing between pre-existing and treatment-related CAI [18, 25, 27–29, 31, 32, 34, 36, 38, 40–42]. Moreover, the frequent use of dexamethasone, a highly potent synthetic glucocorticoid, in post-neurosurgical care may contribute to a potential overestimation of CAI prevalence due to the interference with the biochemical assessment of hypothalamo-pituitary-adrenal (HPA) axis integrity. Of note, post-treatment CAI prevalence seems to be slightly lower, accounting for 12.9–85.7% of patients [15, 19, 24, 26, 30, 37, 39, 69], though underestimation of pre-treatment CAI remains possible due to the frequent lack of baseline dynamic testing and the reliance on baseline ACTH and cortisol levels or clinical records[15, 19, 24, 30, 37, 39, 69]. Diagnosis of CAI in CO CP patients follows standard protocols, with first-line assessment based on morning serum cortisol and ACTH levels, followed by eventual dynamic testing, including low-dose and standard-dose ACTH stimulation test and ITT. The need for dynamic testing will depend

on the basal cortisol, with varying opinions regarding the threshold/cut-off; one suggestion has been that such testing is unnecessary with morning serum cortisol levels ≤ 3 mcg/dl [70]. As for other types of pituitary surgery, HPA axis recovery has been documented in CO CP patients[19], warranting periodic re-evaluation during follow-up [71].

The treatment of CAI does not differ between patients surviving CPs and those with other causes [70]. Given the high prevalence of multiple pituitary deficiencies, CAI replacement should be started first, as other replacement treatments may further reduce endogenous glucocorticoid bioavailability, increasing the risk of adrenal crises [70]. During the transition age, patients require dose adjustments to accommodate body surface growth, necessitating careful monitoring to ensure adequate glucocorticoid replacement but not over-replacement; moreover, they should be properly educated to reinforce treatment adherence and stress-dose adjustments, especially in case of persistent or recurrent disease requiring further surgical or radiotherapy treatments [70]. In this regard, patients with CO CP and CAI might gain more benefit may benefit from hydrocortisone formulations that mimic physiological cortisol rhythms, such as continuous subcutaneous infusion or modified-release hydrocortisone (MR-HC) [72, 73]. Compared to conventional, short-acting therapy, MR-HC has been shown to reduce body weight, normalise immune function, decrease infections, and improve quality of life [74]. Additionally, its once-daily administration could enhance treatment adherence, particularly in transition-age patients, but data on CO CP patients are still lacking. A cheaper alternative may be a single morning dose of prednisone.

2.5 ADH deficiency

Vasopressin deficiency (ADH-D), or central diabetes insipidus (DI), is a common comorbidity in CO CP, presenting as the first clinical symptom in 8–15% of patients at diagnosis and the most frequent post-operative disorder, affecting 60%−90% of children and 50%−70% of adults [6, 15, 17, 30, 39]. ADH-D generally results from tumour invasiveness or surgical manipulation of the neurohypophysis, pituitary stalk, or hypothalamus, particularly in patients undergoing gross or near-total resection [8, 15, 36]. Of note, employing pituitary stalk-sparing approaches does not ensure a normal pituitary function [69]. While damage to the infundibulum could be deemed acceptable to improve local tumour control [36], hypothalamic damage should be avoided to reduce the risk of developing adipsia, which can lead to severe and potentially fatal dehydration [36]. Interestingly, a study by Yuen et al. [75] identified ADH-D as a predictor of worse postoperative anterior pituitary function and subsequent weight gain, reinforcing its role as a marker for hypothalamic impairment [31].

Considering the high prevalence of postoperative ADH-D, careful fluid balance monitoring should be performed following CP surgery to differentiate hypotonic polyuria from physiological responses to fluid overload or osmotic diuresis. Of note, diagnostic criteria of ADH-D have been widely variable across available studies, including: i) increased urinary output with low urine versus high plasma osmolality; ii) hypernatraemia during a fluid deprivation test; iii) urinary osmolality > 450–600 mOsm/kg in response to nasal desmopressin [26, 76]. Due to this variability, Fountas et al. [77] proposed standardised criteria for immediate postoperative ADH-D: (1) polyuria (> 250–300 mL/h for 3 consecutive hours); (2) hypotonic urine (urine osmolality < 300 mOsm/kg or specific gravity < 1.005); (3) serum sodium > 145 mmol/L. The presence of excessive thirst should be considered as a relative criterion, particularly in CO CP patients who may be affected by thirst disturbances.

Postoperative ADH-D can also manifest as triphasic DI, characterised by immediate postoperative ADH-D, followed by hyponatraemia and subsequent permanent ADH-D. Finken et al. [78] reported triphasic DI in 29% and isolated ADH-D in 48% of cases, with longer surgery duration predicting the occurrence of triphasic DI. Postoperative ADH-D generally develops within the first postoperative year, and most frequently within 48 h or between 5 and 60 days from surgery [79]. Of note, delayed ADH-D onset has been associated with tumour progression [30].

The treatment of ADH-D in CO CP patients does not vary according to the surgical approach [15, 37] and follows standard desmopressin replacement protocols used in ADH-D due to other causes. Special consideration should be given to alcohol consumption in transition-age patients with ADH-D, as ethanol acutely inhibits the secretion of ADH, resulting in increased diuresis and a heightened risk of dehydration [80–82]. In patients with ADH-D, who already lack endogenous ADH and rely on desmopressin for water balance, alcohol's diuretic effect can exacerbate polyuria and fluid loss, increasing the likelihood of hypernatremia and associated complications. Therefore, patient education regarding these risks is essential during adolescence and young adulthood when social alcohol consumption typically begins [83]. Therefore, it is recommended that patients with ADH-D should be counseled on the importance of maintaining their desmopressin therapy and adequate hydration, increasing fluid intake when consuming alcohol, and recognizing symptoms of dehydration or hypernatremia (e.g., thirst, dry mouth, dizziness) to minimize the risk of dehydration and electrolyte imbalance.

3 Hypothalamic comorbidities

3.1 Hypothalamic syndrome

The hypothalamus, despite its small size, plays a central role in maintaining internal homeostasis by regulating critical functions such as body temperature, hunger

and thirst, blood pressure, heart rate, and the sleep–wake cycle, partly mediated by the autonomic nervous system. Due to the frequent proximity to the hypothalamic structures, CPs and their treatment— either surgery or radiotherapy —can significantly impair these functions [84]. This condition, termed Hypothalamic Syndrome (HS), encompasses a spectrum of symptoms, including hypothalamic obesity (characterized by rapid, uncontrollable weight gain despite caloric restrictions), disordered eating behaviours (uncontrollable hyperphagia, insatiable hunger, food-seeking behaviour), neurocognitive and behavioral changes (memory deficits, emotional lability, depression), sleep disturbances (hypersomnia, narcolepsy, circadian rhythm disruption), fatigue, and autonomic dysfunction (imbalances in body temperature, thirst, heart rate, and blood pressure regulation) [85, 86]. These manifestations result from hypothalamic damage due to the tumor itself or its treatment, affecting critical centers regulating energy homeostasis, circadian rhythms, and autonomic function, significantly impacting quality of life and contributing to long-term morbidity in CP survivors [85]. The pathogenetic mechanisms underlying this syndrome include disruption of hunger/satiety centers (damage to arcuate, ventromedial, and paraventricular hypothalamic nuclei), leptin resistance despite elevated circulating leptin levels, autonomic dysregulation with reduced energy expenditure, hypothalamic-pituitary axis dysfunction, and local inflammatory processes [87, 88]. The prevalence of HS is approximately 35% at diagnosis but increases to 65–80% after surgical treatment [89, 90], particularly after gross total resection [91]. The risk of HS correlates with the degree of hypothalamic involvement and the invasiveness of surgery. Notably, a MRI-based classification has been validated to objectively assess the extent of hypothalamic involvement in patients with CP, categorizing hypothalamic damage into three grades: Grade 0 (no hypothalamic involvement), Grade 1 (compression without involvement), and Grade 2 (hypothalamic involvement/damage) [92]. This system has demonstrated significant correlation with clinical outcomes, particularly regarding obesity development and metabolic complications. Studies show that higher grades (especially Grade 2) are associated with increased risk of hypothalamic obesity, metabolic syndrome, and poorer quality of life [93], serving as a valuable tool for risk stratification and personalized follow-up planning, with hypothalamus-sparing strategies recommended for patients with higher grades. Therefore, to minimise damage, treatment strategies often favour a less radical surgical approach combined with radiotherapy for patients with significant hypothalamic involvement [41, 84, 90].

Of hypothalamic comorbidities, weight gain is generally the most common, as demonstrated by the significantly higher prevalence of obesity in CO CP survivors with hypothalamic involvement compared to those without (90% vs. 31%) [33]. Although obesity itself is the most prevalent issue associated with HS, these patients often exhibit reduced physical activity, increased daytime sleepiness, and disrupted sleep–wake cycles, which are further exacerbated by visual and neurological deficits from CP treatment [91]. Reduced energy expenditure is a key contributor to weight gain [90], potentially linked to low melatonin levels, with studies showing that melatonin supplementation improves daytime alertness and physical activity [94]. Other possible mechanisms include impaired sympathetic nervous system regulation, as evidenced by reduced urinary catecholamine metabolites [91]. Such dysregulation could, in turn, contribute to the constitutive hyperinsulinism, mediated by persistent β-cell stimulation, which is often observed in these patients [85]. Lastly, a small subset of patients (approximately 4%) present with initial weight loss and cachexia due to the diencephalic syndrome, though significant weight regain is generally observed following surgery [95]. To date, management of HS remains challenging, primarily targeting obesity through pharmacological interventions (e.g., central stimulants, glucagon-like peptide-1 receptor agonists, and setmelanotide in POMC deficiency), bariatric surgery, and neuropsychological and rehabilitative therapies.

3.2 Hypothalamic obesity

In paediatric populations, obesity is defined by a body mass index (BMI) at or above the 95 th percentile for age and sex or exceeding 2 standard deviations (depending on the utilised growth charts), or above 30 kg/m^2 at the end of stature growth [96]. It is a major cause of morbidity and mortality excess in CP patients [8, 40], affecting 50–56% of CO CP survivors [9, 97], with a marked increase following surgical treatment [69]. As a hallmark of HS, the risk of developing obesity is directly related to the presence of hypothalamic involvement [36, 42, 98] (as exemplified in Fig. 2).

A 14-year-old boy presented with frontal headache, fatigue, persistent low-grade fever, growth failure, and weight gain before being diagnosed with a large suprasellar mass invading the third ventricle, causing obstructive hydrocephalus with dilatation of the lateral ventricles. Biochemical testing confirmed ACTH and GH deficiency. The patient subsequently underwent transcranial surgery, with the pathology report confirming the diagnosis of adamantinomatous craniopharyngioma. Postoperative assessments up to 5 years revealed a complete removal of the lesion with no recurrences, along with persistent panhypopituitarism and the worsening of obesity. The latter was initially treated with daily liraglutide treatment, which was not effective in controlling weight gain, and was therefore switched to weekly semaglutide, with good safety and effectiveness.

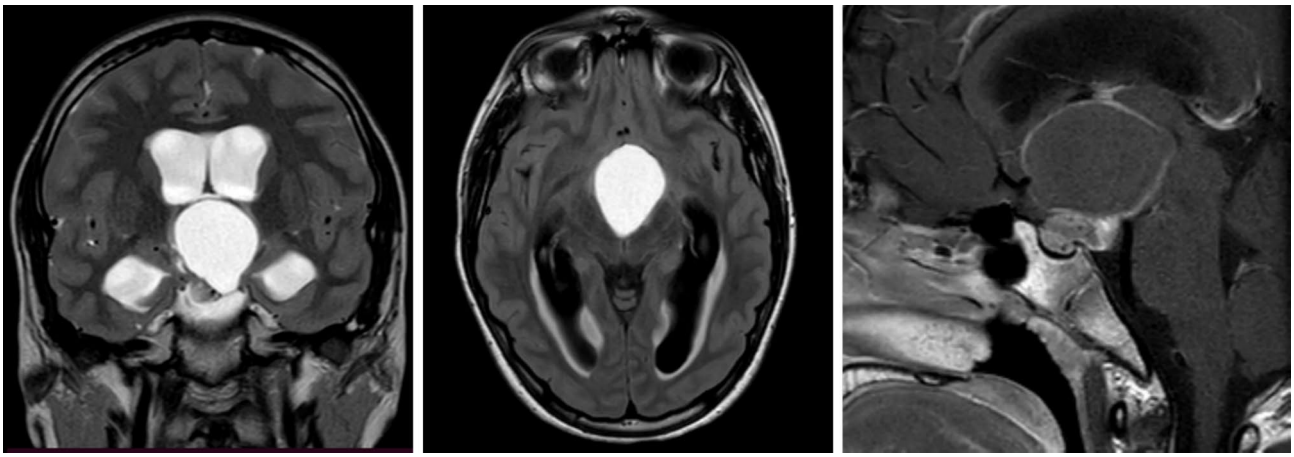

Fig. 2 Baseline MRI of a 14-year-old patient diagnosed with a cystic, adamantinomatous craniopharyngioma with hypothalamic involvement

Left panel = coronal T2-weighted scan; middle panel = axial fluid-attenuated inversion recovery (FLAIR) T2-weighted scan; right panel = sagittal, contrast-enhanced T1-weighted scan.

As a result, surgical damage to the hypothalamus is a key contributor to the risk of postoperative weight gain[99], which, perhaps surprisingly, does not seem to be exacerbated by radiation-based adjuvant treatment [31]. Of note, post-surgical obesity rates have significantly decreased in recent years, probably reflecting the improvement in treatment strategies (i.e., hypothalamic-sparing techniques, transsphenoidal approaches) [5, 9, 15, 24, 34, 41]. Importantly, obesity can also manifest pre-operatively due to hypothalamic tumour involvement. Pre-operative obesity is one of the main predictors of post-operative weight gain [33, 100], while also being associated with several baseline radiological features, including tumour size [36, 99, 100], the presence of hydrocephalus [101], and alterations in the third ventricle floor or the tuber cinereum [99]. Tumour location is also relevant, with suprasellar and third ventricle tumours leading to a higher risk of obesity development in most [16, 41], but not all [19], available reports, a discrepancy likely attributable to differences in the populations and in the MRI classifications used in the various studies.

Beyond tumour characteristics, hormone deficiencies such as central hypothyroidism and GHD can play a role in the development of obesity, often compounded by impaired sensitivity to leptin, insulin, and ghrelin [102]. Similarly, ADH-D has been identified as a predictor of sex-independent weight gain, being correlated with BMI and waist circumference in surgically treated patients with CP [75]. Hypothalamic impairment can also contribute to the development of eating disorders via a decrease in oxytocin secretion [103], further disrupting metabolic regulation. Lastly, the reduced physical activity and basal metabolic rates observed in CP patients have also been identified as key contributors to obesity development [95, 104], further underscoring the complex aetiology of obesity in this context.

Hypothalamic obesity (HO) in CO CP patients is a risk factor for metabolic syndrome [43], cardiac remodeling [105], and cardiovascular disease [106], as discussed in the dedicated paragraph below, while also negatively affecting sleep quality, as highlighted by worse scores on the Epworth Sleepiness Scale and lower levels of melatonin levels [94], and overall quality of life (QoL) for both patients [32] and their parents [107]. Finally, the presence of HS, including obesity, is a predictor of poor general prognosis even after radical surgery [108].

While the diagnosis of obesity itself is not challenging, identifying predictive markers might enable early detection of patients at high risk for the development of obesity. Elevated α-MSH levels have been observed in CP patients with obesity, suggesting it as a potential marker of hypothalamic injury, whereas brain-derived neurotrophic factor and leptin levels were positively associated with BMI in both CP patients and controls [76]. Considering MRI parameters, nuchal skinfold thickness on MRI has been proposed as an indicator of body composition, correlating with waist-to-height ratio and BMI standard-deviation score [98]. Likewise, smaller hypothalamic volumes during volumetric MRI analyses are negatively associated with fat mass and leptin levels in patients with CP [109].

Unfortunately, no clear guidelines are available for the management of obesity in CO CP patients. Given the high prevalence of eating disorders and the unique challenges of CP survivors, effective management requires a multidisciplinary approach involving endocrinologists, dietitians, and psychologists. Usually, HO is poorly responsive to lifestyle modifications [110]. Managing hormonal deficiencies, such as hypothyroidism, ADH, and GH deficiency, is essential; while the impact of GH replacement therapy on weight remains unpredictable in CO CP patients[111], it is known

to help prevent obesity [112] and reduce visceral adiposity in most settings [113].

Pharmacological interventions have shown more promise. Stimulant therapy, including methylphenidate or dextroamphetamine, has demonstrated efficacy in increasing metabolic rate and reducing appetite with a good safety profile even in childhood and transition age, with a recent study showing a 69.9% mean reduction in BMI slope within 6 months of treatment [114]. In addition, most of the patients with HO treated with glucagon-like peptide-1 receptor agonists have also exhibited significant weight loss, the main side effects including nausea, vomiting, and gastrointestinal discomfort [115, 116]. Conversely, the use of intranasal oxytocin has not proven effective in reducing BMI in patients (aged 10–35 years) with HO in a randomised, double-blind, placebo-controlled, crossover pilot study [117]. Recently, Setmelanotide, a melanocortin-4 receptor agonist, has been approved for the treatment of children with monogenic obesity related to mutations in the leptin-melanocortin pathway [118]. Preliminary data have shown that this drug could be effective also in acquired HO [119] and a prospective, randomised, blinded trial over a 12-month treatment period is ongoing to better define its promising role in this clinical setting (NCT05774756).

Data on the efficacy of bariatric surgery for obesity in CP patients are scarce. In a 29-year-old patient, surgically treated for CP at the age of 8, distal gastric bypass was effective in reducing BMI (from 52 to 31.8 kg/m^2) within 18 months of treatment [120]. Another small case series demonstrated that laparoscopic adjustable gastric banding had promising short-term results in patients with CO CP and morbid obesity [121]. However, in another small case series, laparoscopic gastric banding and laparoscopic sleeve gastrectomy were not effective in treating HO in patients with CP compared to control patients with obesity [122]. Further research is warranted to establish the role of bariatric surgery in this context, as it may offer benefits in carefully selected cases [123].

3.3 Sleep disorders

In light of the central role of the hypothalamus in sleep–wake regulation [124], a wide spectrum of sleep disorders (SDs) have been reported in patients with CP; including 1) excessive daytime sleepiness (EDS), 2) sleep-related breathing disorders (SBDs), such as obstructive sleep apnoea syndrome (OSAS), 3) central hypersomnia and secondary narcolepsy, and 4) circadian rhythm sleepwake disorders (CRSWDs) [125], classified according to the third edition of the *International Classification of Sleep Disorders (ICSD-3)* of the *American Academy of Sleep Medicine* [126].

So far, SDs have been predominantly described in paediatric cohorts, including long-term survivors of CO CP [127, 128], with a variable prevalence depending on the heterogeneous diagnostic tools used, ranging from self-assessment questionnaires of early works [127] to specific sleep-medicine tools in more recent reports [128, 129]. EDS is the most frequent SD (70–80% of cases), followed by secondary narcolepsy (14–35%) and SBDs (4–46%) [125, 130]. No clear prevalence data are available regarding CRSWDs [131, 132]. Notably, these disturbances may persist even after treatment in about 60–80% of cases, as observed in long-term survivors of CO CP [133, 134].

The pathophysiology of SDs is complex. Firstly, direct damage to the hypothalamic suprachiasmatic nuclei—either from the tumour itself and/or by surgical treatment—may lead to an abnormal circadian rhythm, affecting sleep and wakefulness. Similarly, lesions of the ventrolateral preoptic area and median preoptic nuclei can affect sleep regulation, impairing the secretion of local neurotransmitters such as hypocretin or orexin, which are deficient in narcolepsy [135]. Furthermore, diurnal somnolence promotes lower energy expenditure and higher appetite, leading to weight increase [136]; on the other hand, obesity itself is an important risk factor for OSAS [137]. Despite this tight connection, the lack of significant associations between BMI and OSAS in some studies suggests that the screening of OSA in CP patients should not be limited to subjects living with obesity [138]. Other potentially causative mechanisms include: an alteration in melatonin secretion, as demonstrated in CO CP patients, in which low nocturnal levels are associated with daytime somnolence [139] and disrupted circadian rhythm [131]; a dysfunction of the upper airway dilator muscles, often associated with suboptimal replacement of GH and thyroxine deficiency [138]; fatigue and psychosocial disorders, typically occurring in these patients, that may influence daytime somnolence and quality of sleep.

SDs significantly contribute to insulin resistance, obesity, diabetes mellitus, and cardiovascular disease [140]; notably, OSAS with intermittent hypoxaemia is an independent risk factor for cardiovascular disease [141] and respiratory mortality, and has been associated with neurocognitive decline [142] and an increased risk and neoplastic progression [143]. Despite their high prevalence and clinical impact, SDs are often underdiagnosed and undertreated. The diagnostic approach to SDs should be based on a stepwise protocol [125], starting with open questions regarding sleep habits, non-restorative sleep, history of observed snoring, apnoeas, obesity, diurnal somnolence, and fatigue. A second step should include specific questionnaires (i.e., STOP BANG for sleep apnea, Pittsburgh Sleep Questionnaire Index (PSQI) for SDs, Epworth Sleepiness Scale for EDS, Morningness-Eveningness Questionnaire to identify chronotype), followed by specific sleep-medicine tools based on clinical suspicion, such as home sleep apnoea testing for SBDs/OSAS, polysomnography for hypersomnia and multiple sleep latency

test (MSLT) for narcolepsy and other central hypersomnias [126]. Notably, current criteria for diagnosing SDs are tailored specifically for paediatric or adult patients, with no established cut-offs for individuals in the transition age, even though many patients fall into the latter category.

The management of SDs in patients with CP requires a multidisciplinary approach, starting with neurosurgical strategies to minimise hypothalamic damage, followed by endocrine-metabolic follow-up to optimise lifestyle interventions, hormone replacement therapy, and treatment of metabolic disorders, including central stimulating drugs [125]. Specific sleep-medicine strategies should include sleep hygiene rules [144], non-invasive ventilation, and stimulant agents. So far, only few case reports or case series have reported specific treatment of SDs in patients with CP. Crowley et al. [138] reported symptom improvement following PAP (positive airway pressure) treatment in 6 out 13 (46%) CP patients with OSA. Moreover, a small case series reported a positive effect of modafinil, a dopaminergic stimulant, on EDS in CP patients with secondary narcolepsy or OSA in which PAP treatment was ineffective or poorly tolerated [145]. More recently, Cordani et al. described a 19-year-old CP patient with secondary narcolepsy who showed a positive response to pitolisant, a histamine H3 receptor antagonist/inverse agonist [130]. Data on melatonin use are conflicting; while one small cohort showed improvements in EDS and physical activity [94], other studies failed to demonstrate efficacy [132, 134], possibly due to preserved endogenous melatonin secretion [132]. Given the limited existing evidence, further studies are needed to establish the most effective pharmacological approaches for managing SDs in this unique patient population.

3.4 Cognitive and neuropsychiatric disorders

Already in 1986, Stelling et al. speculated that the assessment of neuropsychological status was an important aspect of the evaluation in children with CP [146]. Early studies mainly focused on global cognitive functioning using standardised intelligence testing [35, 147, 148] with initially conflicting results, especially regarding memory, executive functions, and attention [149–151]. General cognitive functioning was usually investigated using intelligence quotient (IQ) score, which has been reported to be in the normal range in most CO CP patients, suggesting a limited negative effect on overall intellectual function [151–153]. However, in recent years, several studies have focused on the potential impact of CP on specific cognitive domains. Regarding memory performance, patients with previous CP have shown deficits in immediate and/or delayed memory retrieval. Conversely, short-term, working, and semantic memory do not seem to be affected [151, 153, 154]. Moreover, patients with CP did not show significant alterations in word retrieval, passage comprehension [151], visuo-spatial and visuo-perceptual abilities [154], while exhibiting impaired performance in processing speed, attention, and executive functioning. Of note, high-grade hypothalamic damage was associated with a worse performance in memory retrieval, executive functioning and reduced functional capabilities for daily life actions [98, 151, 153, 154], confirming the dominant role of hypothalamic involvement in affecting cognitive prognosis in CO CP patients [38]. Surgical approach significantly impacts cognitive outcomes, with a higher degree of post-operative hypothalamic involvement successfully predicting worse cognitive performance [153]. While age at first surgery does not appear to affect long-term cognition—likely due to the younger brain's compensatory capacity—radical surgery in intraventricular CPs has been linked to poorer cognitive function and quality of life, largely due to the development of HS [155]. Additionally, patients undergoing multiple operations for tumour recurrence [156] or those requiring hydrocephalus shunting [149] are at higher risk of cognitive decline.

Interestingly, MRI studies have linked cognitive impairment in CP survivors to structural brain changes, including reduced gray and white matter volumes in limbic areas connected to the hypothalamus, as well as an association between impaired long-term memory and reduced gray matter volumes in the posterior cingulate cortex in adolescents with CO CP [157]. Diffusion tensor imaging (DTI) also revealed microstructural white matter alterations (integrity loss, demyelination, and edema) in the hippocampus, hypothalamus, dorsal cingulum, ventral cingulum, and uncinate fasciculus, which were associated with a decline in several cognitive domains in CP survivors [158]; conversely, a functional assessment of the cingulo-fronto-parietal attention network did not highlight significant differences between adults with CO CP and controls [38].

Radiotherapy has also emerged as a potential risk factor for cognitive impairment, particularly in CO CP patients with hypothalamic involvement. Longitudinal studies suggest a negative correlation between time since treatment and cognitive performance, most probably reflecting late radiation effects [158]. Furthermore, younger age at radiotherapy is a predictor of worse cognitive outcomes, supporting efforts to delay radiation in very young patients whenever possible [159]. Other clinical variables, such as female sex and pre-irradiation chemotherapy (i.e., interferon), have also been associated with faster cognitive decline [148].

Collectively, given the significant cognitive risks in these patients, individualised treatment strategies, including detailed neuroimaging mapping, are crucial.to preserve as much brain function as possible [154].

4 Other complications

4.1 Cardiometabolic impairment

Cardiovascular (CV) mortality in individuals with CP is reported to be 3 to 19 times higher than in the general population [160]. Metabolic dysfunction and elevated CV risk are also more prevalent in surgically-treated CP compared to those treated for other causes, such as non-secreting pituitary tumours [161, 162]. Accordingly, 40–50% of postoperative CP patients have been shown to develop the metabolic syndrome, a risk significantly higher in young adulthood compared to healthy controls [39, 163]. Notably, female sex, age, tumour location, hypothalamic damage, and specific treatments (i.e., 90Yttrium brachytherapy and glucocorticoid replacement therapy) were identified as independent predictors of metabolic syndrome development.

While HO exerts the most significant negative impact on 20-year overall survival and CV health in CO CP children treated during the transition period [98], the heightened CV risk observed in these patients is multifactorial, also resulting from neuropsychological impairment, eating disorders, hormonal deficiencies (e.g., hypothyroidism and GHD), and associated lipid and glucose disorders [43, 164]. Postoperative CP patients—especially those aged 10–21 years—often exhibit impaired glucose tolerance and insulin resistance, contributing to the increase in their overall CV risk. Moreover, transition-age patients treated for CP with HO displayed abnormal insulin secretion and sensitivity, leading to impaired glucose tolerance during oral glucose tolerance tests, compared to obese age-matched controls without hypothalamic injury [165].

Similarly, dyslipidaemia is an independent risk factor for CV disease observed in transition-age postoperative CP patients, affecting adolescents both with and without obesity. A recent study of 79 postoperative CP patients aged ≤ 20 years at first presentation found that even patients without HO exhibited higher levels of total LDL cholesterol and triglycerides, along with lower HDL cholesterol levels, compared to age-matched healthy controls with similar BMI [166].

Lastly, increasing evidence suggests that the early cessation of GH replacement therapy during the transition period could represent an additional risk factor for cardiovascular disease in CO CP patients. Several studies in adults with non-idiopathic childhood-onset GHD have indicated that discontinuing GH therapy during the transition period is a major risk factor for dyslipidaemia [167–169], as suggested by a recent study showing a significant reduction in HDL-C levels in 33 patients who discontinued therapy at an average age of 15.3 ± 3.1 years [106]. Other mechanisms leading to increased atherosclerotic and cardiovascular risk in adolescents discontinuing GH therapy include elevated total and LDL cholesterol, increased small dense LDL particles, and heightened truncal adiposity with subsequent non-alcoholic fatty liver disease [170, 171].

4.2 Bone density loss

Adolescence represents a critical window for the acquisition of peak bone mass (PBM), with up to 40–60% of adult bone mineral density (BMD) accrued during this period [172, 173]. Patients with CP exhibit an increased prevalence of skeletal fragility, with 46% and 24% of patients showing osteopenic and osteoporotic BMD T- or Z-scores [174], and 15% to 25% presenting with at least one fracture over their lifetime [174–176]. The pathogenesis of bone density loss in patients with CP is multifactorial, primarily involving hormonal deficiencies, mechanical factors, and treatment-related effects. Nevertheless, data on BMD in transition-age CO CP patients are still scarce. In 2003, Müller et al. evaluated volumetric BMD (vBMD) in 61 CO CP young adults, reporting lower total radial and trabecular BMD compared to controls. Interestingly, young males, showed lower radial and trabecular vBMD, along with a positive association between vBMD and BMI[175]. Overall, these results are not surprising, as increased body weight results in greater mechanical loading on bones, enhancing osteoblast activity while inhibiting osteoclasts, leading to increased BMD [177]; accordingly, a recent longitudinal retrospective study conducted on 86 CP patients with a mean follow-up of 10 years showed a progressive increase in BMD over time, which was associated by the authors with the high obesity rate (75%) [174]. Of note, increased leptin levels have been observed in CO CP patients, which have been negatively associated with BMD; while this might seem counterintuitive, given that leptin is known to promote osteoblastic differentiation and enhance bone formation [178, 179], it should be noted that patients with obesity generally exhibit a condition of leptin resistance, characterised by a decreased peripheral activity of leptin despite increased serum levels, making it difficult to ascertain its actual impact on bone health in these patients.

Moreover, pituitary hormone deficiencies, which are commonly observed in CO CP patients, are notoriously key contributors to the early onset of BMD loss. Interestingly, a comparison between adults with CO CP on complete hormone replacement, including GHRT, and matched controls revealed that male patients had BMD, bone mineral content (BMC), and Z-scores comparable to controls, along with elevated bone markers, underscoring the importance of promptly initiating hormone replacement therapies in these patients. Of note, women showed significantly lower BMD scores at all sites [63], in line with previous studies showing increased fracture incidence in women, but not men,

with childhood-onset GHD on long-term GHRT [180]. Regarding the impact of sex, the few available studies on CO CP patients have yielded controversial results, with some authors reporting lower BMD in women [63]. Overall, these discrepancies might be attributed to several factors, including the relatively low sample size of the available studies, possible insufficient sex steroid replacement in females, and late puberty induction, which is associated with low peak bone mass in both sexes but is more harmful to females [181, 182]. Indeed, sex steroids play a fundamental role in stimulating osteoblastic activity, promoting longitudinal growth, and facilitating epiphyseal closure [173]. In patients with hypogonadism, such as those with CO CP, insufficient or delayed sex steroid replacement therapy during the pubertal window can lead to suboptimal PBM, decreased bone accrual and altered bone geometry, predisposing to osteoporosis and increased fracture risk in adulthood [183, 184]. Vitamin D status is equally critical in this context, due to its ability to facilitate intestinal calcium absorption and maintain serum calcium and phosphate levels necessary for mineralization of the bone matrix. As a result, its deficiency is known to exacerbate bone mineral deficits by limiting calcium availability and impairing bone mineralization [185]. In CO CP survivors, who often present with multiple pituitary hormone deficiencies and hypothalamic dysfunction, optimizing sex steroid and vitamin D replacement during the transition age is paramount to improve skeletal health outcomes and quality of life. Sex steroid replacement therapy should be initiated early with gradual dose escalation to mimic physiological puberty, alongside regular monitoring and correction of vitamin D deficiency to maintain serum 25-hydroxyvitamin D levels above 30 ng/mL. This combined approach maximizes bone mineral accrual during adolescence, thereby reducing the risk of osteoporosis and fractures in adult life [186]. Lastly, treatment-related features have been linked to worse bone health outcomes, as highlighted by negative correlations between Z-scores and glucocorticoid dose, previous radiation treatment and hypothalamic tumour involvement [63, 174].

No specific recommendations for treatment of bone loss have been provided for CO CP patients, other than specific antiresorptive treatment and optimised and prompt hormone and vitamin D replacement therapy.

4.3 Quality of life impairment

The high morbidity associated with CP often results in a variety of physical, cognitive, and psychological deficits. In one study, Müller et al. [32] proved that as many as 44% of paediatric CP survivors eventually develop severe obesity, which was especially linked with hypothalamic involvement and high maternal BMI. On the other hand, obesity has been negatively associated with quality of life (QoL), as measured using the *Fertigkeitenskala Münster/Heidelberg and Pediatric Quality of Life* (PEDQOL) questionnaires. Indeed, CO CP patients reported a more negative perception of their QoL regarding physical abilities, cognitive functioning, and social functioning when compared to healthy children. Furthermore, patients with severe obesity rated their QoL lower for all domains except for autonomy, cognition, and familial integration compared to those with normal weight.

The divergence between subjective and objective assessments of QoL is not uncommon. Pedreira et al. [35] demonstrated significant deficits in adults'physical and psychological domains, especially energy and mobility. Although patients often perceive their QoL to be higher than external measures might indicate, the findings point to significant functional difficulties associated with hypothalamic damage, pituitary hormone deficiencies, and visual disturbances.

Interestingly, a recent study investigating CO CP caregiver burden found that caregivers report an average management of 13 health conditions in survivors [187], with symptoms such as hyperphagia, rather than obesity per se being some of the most burdensome to deal with. Of note, a comprehensive QoL assessment, including both *Zarit Burden Interview* (ZBI) and PEDQOL questionnaires, demonstrated significant correlations between caregiver stress and symptoms in survivors, independent of sociodemographic factors.

Interventional strategies have had variable effects on QoL. The seminal KRANIOPHARYNGEOM 2007 trial reported, over a three-year follow-up, that GH substitution stabilised QoL outcomes, especially regarding autonomy and cognitive function, which was more pronounced in paediatric patients than in adults [111]. Conversely, untreated survivors showed a significant decline in these domains. From a broader perspective, Kendall-Taylor et al. [31] noted that adults with CP, both childhood and adult-onset, suffer from unrelenting metabolic and psychosocial complications such as ADH-D and abnormal lipid metabolism. These problems require personalised management strategies that must address not only endocrine rehabilitation but also psychosocial rehabilitation. Barakat et al. [188] broadened the focus by examining the family functioning mediation. While family support was strongly associated with caregiver-proxy health-related quality of life (HRQoL) ratings, it was less strongly related to self-reported HRQoL by survivors. These results highlight the importance of addressing risk factors such as hypothalamic dysfunction and a familial predisposition to obesity at an early stage. Regular psychosocial evaluations, combined with tailored interventions such as GHRT and support for family dynamics, are fundamental to delivering comprehensive care for survivors of childhood cancer. Laffond et al. [107] emphasised the importance of incorporating routine neuropsychological and psychosocial assessments into post-treatment follow-up to ensure long-term well-being.

5 Conclusions

Patients with CO CP face several lifelong comorbidities requiring long-term, multidisciplinary care, especially during the critical transition to adulthood. Hormone deficiencies should be correctly diagnosed as early as possible, followed by optimised replacement therapy. More specifically, GHRT is particularly effective and safe in COCP survivors, improving metabolic outcomes and quality of life, without significantly increasing the risk of tumour recurrence. However, its initiation should be carefully timed to mitigate potential risks of progression. Moreover, transition-aged individuals with CP face an elevated cardiovascular risk; therefore, obesity should be promptly addressed, as it is one of the most prevalent complications in CO CP survivors, particularly those with hypothalamic involvement. Recent therapies, such as GLP-1 receptor agonists and setmelanotide, have shown promising results, although their long-term efficacy and safety remain under investigation. Bariatric surgery, though effective in select cases, requires further research to define its role. Furthermore, in the subset of transition-aged individuals surgically treated for CP, there is an additional heightened risk of dyslipidaemia independent of BMI, as well as an increased risk of poor glycaemic control and impaired insulin secretion. Close monitoring of glycaemic and lipid profiles is therefore crucial, with abnormalities requiring prompt and appropriate therapeutic interventions. Lastly, albeit often unaddressed or underexplored, cognitive impairments and sleep disorders remain prevalent in 60–80% of survivors, even after treatment, and can significantly impact the quality of life in these patients. Therefore, establishing regular neuropsychiatric follow-up through standardised testing is critical, as the implementation of cognitive rehabilitative measures and targeted sleep therapies have shown improvements in neuropsychological and functional outcomes. In conclusion, the complex interplay of endocrine, metabolic, and neuropsychiatric complications in CO CP survivors highlights the need for personalized, multidisciplinary care, especially during the transition age. Further research is essential to refine treatment strategies, investigate innovative therapies, and ultimately improve the prognosis and quality of life for these patients.

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Declarations

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