



LUND UNIVERSITY

Endocrine aspects and sequel in patients with craniopharyngioma

Erfurth, Eva Marie

Published in:
Journal of Pediatric Endocrinology & Metabolism

DOI:
[10.1515/jpem-2014-0419](https://doi.org/10.1515/jpem-2014-0419)

2015

[Link to publication](#)

Citation for published version (APA):
Erfurth, E. M. (2015). Endocrine aspects and sequel in patients with craniopharyngioma. *Journal of Pediatric Endocrinology & Metabolism*, 28(1-2), 19-26. <https://doi.org/10.1515/jpem-2014-0419>

Total number of authors:
1

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Review article

Eva Marie Erfurth*

Endocrine aspects and sequel in patients with craniopharyngioma

Abstract: A craniopharyngioma (CP) is an embryonic malformation of the sellar and parasellar region. The annual incidence is 0.5–2.0 cases/million per year and approximately 60% of CP is seen in adulthood. The therapy of choice is surgery, followed by cranial radiotherapy in about half of the patients. Typical initial manifestations at diagnosis in children are symptoms of elevated intracranial pressure, visual disturbances and hypopituitarism. CPs have the highest mortality of all pituitary tumours. The standardised overall mortality rate varies from 2.88 to 9.28 in cohort studies. Adults with CP have a 3–19-fold higher cardiovascular mortality in comparison to the general population. Women with CP have an even higher risk. The long-term morbidity is substantial with hypopituitarism, increased cardiovascular risk, hypothalamic damage, visual and neurological deficits, reduced bone health and reduction in quality of life and cognitive function.

Keywords: cardiovascular risk; cognitive function; hypopituitarism; hypothalamic damage; morbidity; mortality; quality of life.

DOI 10.1515/jpem-2014-0419

Received October 7, 2014; accepted November 20, 2014; previously published online December 16, 2014

Introduction

A craniopharyngioma (CP) is a benign pituitary tumour, often growing invasively, and thereby affecting the hypothalamus. The tumour is a partly cystic embryonic malformation of the sellar and para-sellar region. Typical manifestations at diagnosis in adults are visual

and endocrine symptoms followed by symptoms of elevated intracranial pressure (headache, nausea) (1). The incidence is 0.5–2.0 cases/million per year (2). The recurrence rate is high. The therapy of choice is surgery, followed by cranial radiotherapy (CRT) in about half of the patients. The primary goal is not to avoid hypopituitarism, but to avoid further hypothalamic damage (3). Due to its growth and/or treatment, hypopituitarism is seen in the vast majority of cases, and obesity due to hypothalamic involvement in up to half of the patients (4, 5). Women and men are equally affected and about 40% of cases are seen in patients <16 years of age (2). CPs have the highest mortality of all pituitary tumours and women are more affected than men (1, 6). The long-term morbidity in patients with CP is substantial and is mainly based on the tumour location and size, recurrence rate and its treatment. Morbidity affects the life of these patients with hypopituitarism, increased cardiovascular risk, hypothalamic damage, visual and neurological deficits, reduced bone health and reduction in quality of life (QoL) and cognitive function (7).

The aim of this review is to highlight the endocrine consequences and morbidity in CP patients and to discuss the causes.

Mortality in craniopharyngioma

CP in adults is associated with significant mortality. The overall survival rates in recent years ranges from 89% to 94% at 5 years, from 85% to 90% at the 10-year follow-up (8, 9) and an average of 62%–76% at 20 years (10, 11). The cause specific late mortality, after 20 years, was multi-factorial, but rarely due to disease progression (10). However, survival is related to choice of therapy that depends on tumour size, extension of the tumour and of recurrence of the tumour. Karavitaki et al. (9) recorded no significant difference in the 10-year survival rates between patients treated with gross total removal (GTR) (100%) and partial removal (PR) (86%). Stripp et al. (12) also found comparable 10-year survival rates in patients treated by surgery

*Corresponding author: Eva Marie Erfurth, Department of Endocrinology and Diabetes, Lund University Hospital, SE-221 85 Lund, Sweden, Phone: +46 46 172 363, Fax: +46 46 176024, E-mail: Eva_Marie.Erfurth@med.lu.se; Department of Endocrinology, Skånes University Hospital, Lund, Sweden; and Department of Clinical Sciences, Medical Faculty of Lund University, Lund, Sweden

alone (GTR or PR) or by surgery followed with CRT (83%). Finally, Rajan et al. (13) found no difference if patients were treated with CRT alone or with surgery and no influence was seen of the degree of surgery. Bülow et al. (1) showed in a multivariate model, including radicality at surgery, radiotherapy (yes vs. no) and recurrence as a time dependent factor with a broad age stratification (<29 years and ≥29 years), a protective effect of radiotherapy [hazard ratio (HR) 0.3; 95% confidence interval (CI) 0.1–0.8]. Furthermore, increased risk of death after recurrence (HR 4.4; 95% CI 1.4–14) was shown, but no obvious positive effect of radicality at surgery (Table 1).

Long-term follow-up of CPs include mixed populations of children and adults and the mortality risk varied in different countries. The standardised overall mortality rate (SMR) from Sweden was 5.5 times (SMR 5.55; 95% CI 3.68–8.22) (1), in the Netherlands, SMR was 2.88 (95% CI 1.35–4.99) (14) and from the UK, 9.28 (95% CI 5.84–14.75) (6). These three cohorts included CP patients on conventional hormone therapy but without growth hormone (GH) therapy. Conventional hormone therapy in these historical cohorts included somewhat higher hydrocortisone doses (15–30 mg/day) (6) and cortisone acetate 37.5 mg/day (1, 6). Untreated gonadal insufficiency and/or un-physiological gonadal substitution among women were prevalent (1, 6). The percentage of childhood onset (CO) CP was mentioned in two of the cohorts and was 40%–43% (1, 14).

Patients with CP have a 3–19-fold higher cardiovascular mortality in comparison to the general population (1, 6, 14). The UK cohort had the highest SMR of 19.4 (95% CI 8.08–46.7) for cerebrovascular deaths (6). In the Swedish cohort of 60 patients, the cardiovascular (including cerebrovascular) mortality was enhanced (SMR 3.21, 95% CI 1.29–6.61), but no specific analysis was made for cerebrovascular deaths, due to the small cohort size (1). Female

gender seemed to be at particular risk for cardiovascular mortality (SMR 11.4) compared to male gender (SMR 4.79). This gender difference was also seen in the Dutch cohort with a higher SMR among females (SMR 3.84; 95% CI 1.47–7.22) compared to males (1.84; 95% CI 0.33–4.58) (14). In a recent study including 70 CP patients from Ireland, the increased overall mortality was confirmed (SMR 8.75; 95% CI 5.4–13.3), and again with a somewhat higher mortality in women (SMR 10.51, 95% CI 5.04–19.3) than among men (SMR 7.55 95% CI 3.77–13.52) (10). In the Irish cohort, a subgroup of the GH deficient CP patients were offered GH therapy, but data did not show any survival benefit from GH treatment (10). However, the sample size was too small to draw any firm conclusions. It has to be pointed out that all CP cohorts were small, thus, the number of deaths was very low (27, 10 and 21 patients) (1, 14, 10), which gives a low statistical power and shows how difficult it is to perform mortality studies in this rare condition.

It is very interesting that all the studies show a higher mortality for women compared to men. This gender difference has also been shown among patients with hypopituitarism of any cause (6, 15, 16), where mortality from cerebrovascular disorders was particularly enhanced. The reason for the increased mortality among women is unknown, but it has been shown that those women who suffered from cerebrovascular deaths, also suffered from a longer duration of hypopituitary symptoms before surgery (17). This provides evidence in favour of hormonal dysfunction as an important step in the causal chain of events leading to cardiovascular or cerebrovascular mortality. The sex difference for cardiovascular and cerebrovascular events possibly results from the fact that women with hypopituitarism not only have un-substituted hypogonadism but also may have an unfortunate exposure to sex hormones. This suggestion is based on the results from the Women's Health Initiative clinical trial, which showed

Table 1 Hazard ratios (HR) and 95% confidence intervals (CI) for death after surgery for craniopharyngioma with respect to tumour recurrence, radicality at surgery and radiotherapy, with and without age stratification (<29 and ≥29 years at operation).

Cox regression models	No age stratification		With age stratification	
	HR 95% CI	p-Value	HR 95% CI	p-Value
All patients (n=60)				
Recurrence (time dependent: yes vs. no)	2.7 (1.0–7.3)	0.05	4.4 (1.4–14)	0.01
Radicality at surgery (subtotal vs. total)	2.0 (0.9–4.5)	0.09	1.1 (0.5–2.5)	0.9
Radiotherapy (yes vs. no)	0.5 (0.2–1.2)	0.1	0.3 (0.1–0.8)	0.01
Patients surviving the first 6 months after surgery (n=50)				
Recurrence (time dependent: yes vs. no)	1.6 (0.5–4.7)	0.4	2.2 (0.6–7.6)	0.2
Radicality at surgery (subtotal vs. total)	1.6 (0.6–4.5)	0.4	0.9 (0.3–2.5)	0.8
Radiotherapy (yes vs. no)	1.4 (0.4–4.1)	0.6	0.7 (0.2–2.4)	0.6

significantly increased risk for both cerebrovascular and coronary heart disease by unfortunate combinations of oestrogens and gestagens (18, 19). Until today, there were no studies looking at the long-term effect of GH replacement on mortality in CP patients and the information of GH therapy in CP children is scarce.

Morbidity

The long-term morbidity in patients with CP is substantial and is mainly based on the tumour location and size, recurrence rate and its treatment. The morbidity includes hypopituitarism, hypothalamic involvement (obesity, thirst disorders, thermoregulatory disorders, somnolence and sleep apnoea and cardiac arrhythmia), cardiovascular risk factors, visual and neurological problems, as well as reduced QoL and cognitive function (7).

The treatment of a CP may be achieved using either primary gross total resection (GTR), which may increase the risk of hypothalamic, neurological, endocrine and visual damage (4), or partial resection (PR) of the tumour followed by CRT, as an effective means of preventing recurrences (20).

Hypopituitarism

Complete hypopituitarism is encountered in a majority of CP patients. At least three pituitary hormone deficiencies have been reported in 54%–100% of patients with CP (7). In a recent study, the long-term prevalence rate of total anterior pituitary insufficiency was 89% (14), and for GH-, gonadotropin-, adrenocorticotropin- and TSH-deficiency it was 91%, 93.5%, 92% and 86%, respectively (10). The prevalence of diabetes insipidus (DI) was 81% (10).

Pituitary deficiency per se and its treatment through various metabolic effects might contribute to the enhanced cardiovascular morbidity and mortality seen in epidemiological studies. However, panhypopituitarism is interrelated to recurrences of the CP, CRT and with hypothalamic involvement by the tumour, thus, it is almost impossible to identify hypopituitarism as an independent risk factor. GH deficiency is probably the most frequent pituitary hormone deficiency and it is associated with increased levels of cardiovascular risk factors (21). GH therapy was shown to have beneficial effects on lean and body fat mass, total and low density lipoprotein cholesterol and diastolic blood pressure, but with reduced insulin sensitivity (22).

In addition, adrenocorticotrophic hormone (ACTH) deficiency and glucocorticoid supplementation is of

importance. This was highlighted by patients with Addison's disease, who suffer from increased premature mortality in comparison to the general population (23). Furthermore, it has been shown that too high substitution doses of cortisone is associated with increased cardiovascular mortality in patients with acromegaly (24).

Subclinical hypothyroidism causes increased cardiovascular risk (25). A recent study from Klose et al. (26) showed that high levels of serum free T4 in the upper normal range was correlated to a lower body mass index (BMI) and lower levels of high density lipoprotein cholesterol.

Cardiovascular risk

The primary pathogenesis of hypothalamic damage seems to start with hyperinsulinaemia, due to the destruction of the ventro medial hypothalamic (VMH) nuclei causing an imbalance of the autonomic nervous system, resulting in suppression of the sympathetic nervous system and stimulation of the vagus (27). Indeed, CP patients have hyperinsulinaemia, with increased levels in the relation to tumour growth (Figure 1) (28). Hyperinsulinaemia increases lipogenesis in liver and adipose tissue and also lipoprotein lipase activity accelerating endogenous (very low density lipoproteins and triglycerides) lipid production (29). Fat mass is accumulated with an increase in weight and BMI (29).

Studies evaluating the effect of GH therapy in CP patients are few and in comparison to patients with

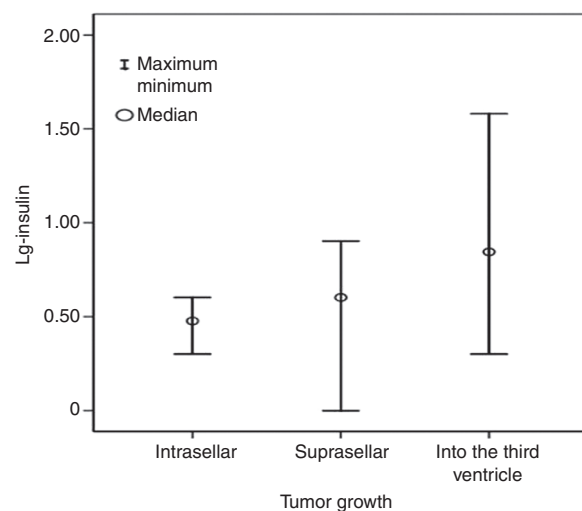


Figure 1 Correlation between tumour growth and the logarithm for serum insulin for all patients.

All patients, $r=0.57$, $p<0.001$; for men, $r=0.53$, $p=0.011$; for women, $r=0.66$, $p=0.002$.

non-functioning pituitary adenoma, CP patients had a higher prevalence of pituitary deficiencies, were more obese and had more dyslipidaemia (30). Two years of GH replacement showed the same effect on fat-free mass and lipids, but CPs was less likely to lose body fat, which is possibly a hypothalamic effect.

Holmer et al. (28) evaluated the prevalence of cardiovascular risk factors after long-term GH therapy in childhood onset CP patients and showed increased cardiovascular risk factors, in particular, CP women and in patients with hypothalamic involvement by the tumour (28). Increased levels of hormone sensitive C-reactive protein and low density lipoproteins levels were shown (28). In addition, significantly more treatment for cardiovascular diseases (anti-hypertensive and anti-diabetes treatments and lipid lowering drugs) and/or manifestations of the metabolic syndrome were present.

This is in accordance with another study showing an increased prevalence of hypertension in CP patients and of other cardiovascular morbidities (14).

Hypothalamic damage

Obesity

Hypothalamic obesity will be discussed in another part of this extensive review.

Thirst disorder, thermoregulatory disorders, somnolence and sleep apnoea and cardiac arrhythmias

Diabetes insipidus (DI) with absent or impaired sense of thirst is one of the most difficult complications to manage in CP (4, 31). Smith et al. (31) reported absence of thirst in 19% of adults with DI treated with surgery combined or not with CRT. A loss of temperature control (very low temperature) was recorded in adult CP patients after surgery for a CP (32). Somnolence is common in adult CP patients and in the majority due to sleep apnoea (33), and disorders of sleep pattern and excessive daytime sleepiness have been recorded in up to one-third of adult CP patients (34). Fatal outcome was recorded in an adult CP patient (35) after GTR together with CRT of a large hypothalamic CP. The patient had sleep disturbance together with hypothermia and cardiac arrhythmia and needed a pacemaker. Sudden cardiac deaths have been reported in CP children (36). In a prospective cardiac screening of 12 survivors, nearly a third were identified with significant QTc prolongation (36). This emphasises that we need electrocardiogram screening to identify those CP patients at risk.

Visual and neurological disturbances and epilepsy

Visual symptoms were the predominant symptom among CP patients >20 years of age (1), and occurred in 47% of the patients at diagnosis. Pereira et al. (14) recorded visual morbidity in 40% and Karavitaki et al. (9) recorded 48% of the CP patients treated by surgery alone or with CRT after 10 years of follow-up. Duff et al. (37) recorded at least quadrant anopia among 63% during an observation period of 10 years in patients treated with surgery alone or combined with CRT. The visual outcome is adversely affected by the presence and duration of visual symptoms at diagnosis (38) and after radiation doses of >2 Gy/day (39).

The prevalence of cranial nerve deficits after long-term follow-up was 26% in the Dutch cohort (14) and the prevalence of hemi/monoparesis 11% in the UK cohort (9). The risk of epilepsy after 10 years in the UK cohort was 12% (9) and in the Dutch cohort, it was 17% (14).

Bone health

In adults with CO GH deficiency (GHD), bone mineral density (BMD) is reduced compared to healthy control subjects (40, 41) and discontinuation of GH therapy before achievement of peak bone mass may be the cause (42).

Smoking, insufficient physical activity and calcium intake, sex steroid deficiency and female gender also tend to decrease BMD (43). However, smoking is less prevalent among patients with CPs (44). Other hormones of importance for bone growth are insulin, thyroid hormones, glucocorticoids and sex steroids, all probably acting through IGF-I (42).

Overweight seems to be protective against low BMD in healthy subjects (45), possibly by the action of increased leptin levels (46). However, in obese CP patients with hypothalamic damage, leptin levels were shown to be higher in relation to BMI, indicating leptin resistance (47), and among adolescents, leptin resistance was shown to be negatively correlated to BMD (48). In children, BMD has been investigated with the use of volumetric BMD (vBMD), showing a lower radial Z-score, which was most obvious in lean male CP patients (49). In contrast, female gender and severe obesity seemed to be protective against low vBMD in childhood (49). A recent study in adults with a childhood onset CP, females, but not CP males, showed significantly lower BMD than matched population controls, despite similarities between gender in pituitary hormone deficiencies and substitution therapies (50).

BMD at the femoral neck was significantly negatively correlated to time from the first operation (Figure 2). About 45% of CP women had Z-scores ≤ -2.0 standard deviation score, despite numerous factors known to be positive for bone formation, for example, increased BMI, fat mass and insulin levels. Suggested contributing factors were late-onset puberty resulting in later than optimal introduction of sex steroids as late-onset puberty is associated with low peak bone mass in both genders (50, 51, 52), but it is more deleterious to the female skeleton (53). Reduced BMD has been shown in healthy adolescents after use of oral contraceptives with an average ethinyl estradiol dose of 20–35 μg (53), which could indicate insufficient sex steroid replacement. Glucocorticoid-induced osteoporosis is well known (54), but long-term glucocorticoid replacement is not reported to affect BMD (55).

Furthermore, Holmer et al. (50) showed that serum leptin levels were significantly increased in both CP women and men and correlated significantly negatively with BMD. Sixty-seven per cent of all CP women and 75% of the whole patient cohort with Z-scores of ≤ -2.0 standard deviation score at L2–L4 were affected by hypothalamic damage from the tumour and the vast majority of these latter patients also had high BMI ($>30 \text{ kg/m}^2$). Thus, high BMI was not protective against low BMD.

The hypothalamus regulates bone and adipose tissue via a complex and fine-tuned interplay of endocrine mechanisms (of which neuropeptide Y is a key

regulator) together with the sympathetic nervous system (56). Whereas many of the effects occur via direct actions on osteoblasts or adipocytes, sex hormones can also mediate effects on bone and adipose tissue via interaction with neuronal pathways. Thus, both early and persistent hypothalamic dysfunction and insufficient sex hormone replacement at disease onset are likely to have attributed to the observed long-term effects on bone in CP patients. Thus, the interaction between the fat-related endocrine system and bone seems to be complex and it may be modulated by central and peripheral mechanisms, as well as local resistance to the putative protective effects of insulin and leptin on bone.

Neurocognitive function

Hypothalamic lesions have been associated with poor functional outcome and disturbances in neurocognitive performance (57, 58). Neurocognitive dysfunction, including memory deficits (14, 59–63), has been described as an important contributor to the increased morbidity among CP patients. Problems with concentration, memory and executive function potentially affecting professional occupation and school performance have received more attention in recent years (8, 9, 14, 62). Studies have shown that up to 50% of CP patients have psychosocial impairment on long-term follow-up (14), and up to one-quarter of patients are unable to work in their previous occupation or they are behind in school (9).

Whether the neurocognitive deficit is due to tumour growth itself or the treatment is still debatable. Numerous newer studies have presented data with no impairment of neuropsychological functioning after surgical removal of CP by microsurgical technique (7, 61, 64). Other authors promote a more conservative approach to surgical treatment in the light of cognitive deficits, especially in patients with tumour growth in the hypothalamic area (65, 66). In a very recent study, Hofmann et al. (67) promotes careful selection of patients for primary open surgery, with patients with hypothalamic deficiencies being candidates for pre-treatment, for example, cyst aspiration prior to surgery in the attempt to preserve neuropsychological function (67).

Symptoms associated with GHD due to suboptimal GH supplementation may affect the neurocognitive results and hamper proper comparison between studies. Pedreira et al. (68) found high levels of psychological disability among young CP patients, stressing the importance of the role of GH treatment in this assessment. It is estimated that at least 75% of patients with CP have GH insufficiency

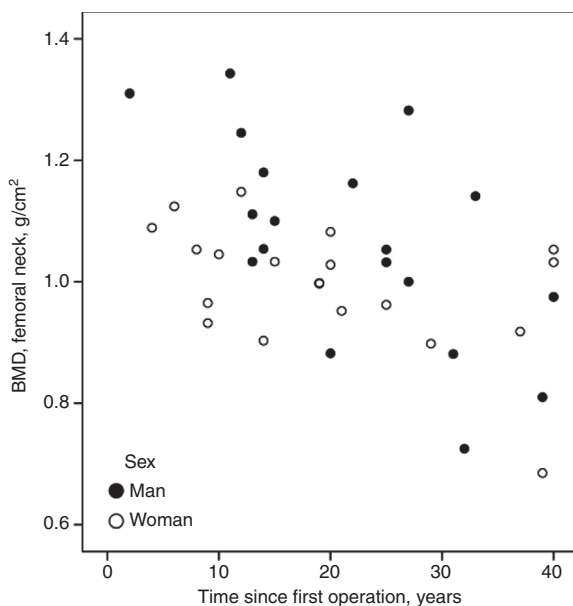


Figure 2 Correlation between bone mineral density at the femoral neck and time since first operation (years). $r = -0.45$, $p = 0.004$ in 39 patients with a childhood onset craniopharyngioma.

preoperatively. However, studies pertaining specifically to the effect of GH therapy on neurocognitive function in GH deficient CP patients are currently lacking.

While many of the previous study results point towards increased neurocognitive morbidity, the studies tend to be heterogeneous with respect to hypothalamic involvement of the tumour and the type of neuropsychological tests applied. In addition, surgical approaches with either GTR or PR, and the effect of CRT need to be evaluated, which is an extremely difficult issue. The study groups tend to involve both children and adults and generally include few patients questioning its representativeness. Given the heterogeneity in cognitive research in CP patients there is a need for a standardized and validated assessment tool that adequately includes the different aspects of CP (69).

Quality of life

According to Dekkers et al. (70) and Sand et al. (71), CP patients show significantly impaired QoL, this being especially prominent in physical subscales. A recent study by Mortini et al. (69) reported a significant decrease in QoL after surgery in CP, with a slight increase in loss of independence in activities of daily living on long-term follow-up.

Growth hormone supplementation has shown to be beneficial in QoL in adults with hypopituitarism and with GH deficiency, in some (72–76), but not all studies (77). Similar studies pertaining specifically to GH deficient patients with CP are currently lacking. Pedreira et al. (68) found high levels of psychological disability among young CP patients and a significant difference between patients and controls on the Adult GH-Deficient Assessment questionnaire stressing the importance of the role of GH treatment in the assessment of QoL. Symptoms associated with GHD due to suboptimal GH supplementation may affect the results of QoL assessment and hamper proper comparison between studies. However, studies pertaining specifically to the effect of GH therapy in GH deficient CP patients are currently lacking.

Conclusion

Among pituitary tumours, a CP has a special status as an aggressive tumour causing high morbidity and increased mortality in comparison to the general population. Much is known of the causes of these problems but more needs to be discovered. The management of the tumour is

complex and life-long surveillance by a multidisciplinary team (experienced neurosurgeon, endocrinologist, neuro-oncologist and neuro-ophthalmologist) is required for better prognosis. Careful surgery to prevent further complications from the hypothalamus is essential. Indeed, cardiovascular risk factors need up front therapy. In addition, pituitary hormone deficiencies need balanced replacement therapies. Early postoperative intervention with strict dieting and physical activity is essential if hypothalamic damage is obvious pre- or post-operatively. Continuous surveillance of BMD is recommended in patients with a history of CP, particularly among patients with a hypothalamic tumour involvement.

Acknowledgments: This work was supported by the Swedish Children's Cancer Foundation, the South Medical Research Council and the Medical Faculty, Lund University, Sweden.

Conflict of interest statement

Author conflict of interest disclosure: There is no conflict of interest to declare.

References

1. Bülow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH, et al. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumour recurrence. *J Clin Endocrinol Metab* 1998;11:3897–904.
2. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, et al. The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 1998;89:547–51.
3. Müller HL. Childhood craniopharyngioma. *Pituitary* 2013;16:56–67.
4. De Vile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. *Arch Dis Child* 1996;75:108–14.
5. Müller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004;89:3298–305.
6. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, et al. Association between premature mortality and hypopituitarism. *Lancet* 2001;357:425–31.
7. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev* 2006;27:371–97.
8. Van Effenterre R, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. *J Neurosurg* 2002;97:3–11.
9. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)* 2005;62:397–409.

10. Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, et al. Morbidity and mortality in patients with craniopharyngioma after surgery. *Clin Endocrinol (Oxf)* 2010;73:516–21.
11. Visser J, Hukin J, Sargen M, Steinbok P, Goddard K, et al. Late mortality in pediatric patients with craniopharyngioma. *J Neurooncol* 2010;100:105–11.
12. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Int J Radiat Oncol Biol Phys* 2004;58:714–20.
13. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, et al. Craniopharyngioma—a long-term results following limited surgery and radiotherapy. *Radiother Oncol* 1993;26:1–10.
14. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, et al. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005;62:197–204.
15. Rosén T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990;336:285–8.
16. Bülow B, Hagmar L, Mikoczy Z, Nordström CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf)* 1990;46:75–81.
17. Erfurth EM, Bülow B, Svahn-Tapper G, Norrving B, Odh K, et al. Risk factors for cerebrovascular deaths in patients operated and irradiated for pituitary tumours. *J Clin Endocrinol Metab* 2002;87:4892–9.
18. Barrett-Connor E. Clinical review 162: cardiovascular endocrinology 3: an epidemiologist looks at hormones and heart disease in women. *J Clin Endocrinol Metab* 2003;88:4031–42.
19. Anderson, GL Anderson GL, Limacher M, Assaf AR, Bassford T, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *J Am Med Assoc* 2004;14:1701–12.
20. Kalapurakal JA. Radiation therapy in the management of pediatric craniopharyngiomas—a review. *Childs Nerv Syst* 2005;21:808–16.
21. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1587–609.
22. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, et al. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a meta-analysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2004;89:2192–9.
23. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, et al. ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. *J Clin Endocrinol Metab* 2009;94:4216–23.
24. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab* 2006;91:4849–53.
25. Owen PJ, Lazarus JH. Subclinical hypothyroidism: the case for treatment. *Trends Endocrinol Metab* 2003;14:257–61.
26. Klose M, Marina D, Hartoft-Nielsen ML, Klefter O, Gavan V, et al. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. *J Clin Endocrinol Metab* 2013;98:3802–10.
27. Bray GA, Gallagher TF Jr. Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. *Medicine (Baltimore)* 1975;54:301–30.
28. Holmer H, Ekman B, Björk J, Nordström CH, Popovic V, et al. Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy. *Eur J Endocrinol* 2009;161:671–9.
29. Bray GA, Inoue S, Nishizawa Y. Hypothalamic obesity. The autonomic hypothesis and the lateral hypothalamus. *Diabetologia* 1981;20(Suppl):366–77.
30. Verhelst J, Kendall-Taylor P, Erfurth EM, Price DA, Geffner M, et al. Baseline characteristics and response to 2 years of growth hormone (GH) replacement of hypopituitary patients with GH deficiency due to adult-onset craniopharyngioma in comparison with patients with nonfunctioning pituitary adenoma: data from KIMS (Pfizer International Metabolic Database). *J Clin Endocrinol Metab* 2005;90:4636–43.
31. Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, et al. Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. *Clin Endocrinol (Oxf)* 2004;61:273–9.
32. Griffiths AP, Henderson M, Penn ND, Tindall H. Haematological, neurological and psychiatric complications of chronic hypothermia following surgery for craniopharyngioma. *Postgrad Med J* 1988;64:617–20.
33. Crowley RK, Woods C, Fleming M, Rogers B, Behan LA, et al. Somnolence in adult craniopharyngioma patients is a common, heterogeneous condition that is potentially treatable. *Clin Endocrinol (Oxf)* 2011;74:750–5.
34. van der Klaauw AA, Biermasz NR, Pereira AM, van Kralingen KW, Dekkers OM, et al. Patients cured from craniopharyngioma or nonfunctioning pituitary macroadenoma (NFMA) suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls. *Clin Endocrinol (Oxf)* 2008;69:769–74.
35. Rehman HU, Atkin SL. Sleep disturbances and cardiac arrhythmia after treatment of a craniopharyngioma. *J R Soc Med* 1999;92:585–6.
36. Mong S, Pomeroy SL, Cecchin F, Juraszek A, Alexander ME. Cardiac risk after craniopharyngioma therapy. *Pediatr Neurol* 2008;38:256–60.
37. Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, et al. Long-term outcomes for surgically resected craniopharyngiomas. *Neurosurgery* 2000;46:291–302.
38. Cabezudo Artero JM, Vaquero Crespo J, Bravo Zabalgoitia G. Status of vision following surgical treatment of craniopharyngiomas. *Acta Neurochir (Wien)* 1984;73:165–77.
39. Harris JR, Levene MB. Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. *Radiology* 1976;120:167–71.
40. Drake WM, Carroll PV, Maher KT, Metcalfe KA, Camacho-Hubner C, et al. The effect of cessation of growth hormone (GH) therapy on bone mineral accretion in GH-deficient adolescents at the completion of linear growth. *J Clin Endocrinol Metab* 2003;88:1658–63.
41. Boot AM, van der Sluis IM, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and body composition in adolescents with childhood-onset growth hormone deficiency. *Horm Res* 2007;1:364–7.
42. Sävendahl L. Hormonal regulation of growth plate cartilage. *Horm Res* 2005;64(Suppl 2):94–7.

43. Wark JD. Osteoporotic fractures: background and prevention strategies. *Maturitas* 1996;23:193–207.
44. Holmer H, Svensson J, Rylander L, Johannsson G, Rosén T, et al. Psychosocial health and levels of employment in 851 hypopituitary Swedish patients on long-term GH therapy. *Psychoneuroendocrinology* 2013;38:842–52.
45. Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res* 1993;8:567–73.
46. Hamrick MW, Ferrari SL. Leptin and the sympathetic connection of fat to bone. *Osteoporos Int* 2008;19:905–12.
47. Roth C, Wilken B, Hanefels F, Schröter W, Leonhardt U. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *Eur J Endocrinol* 1998;138:89–91.
48. Do Prado WL, de Piano A, Lazaretti-Castro M, de Mello MT, Stella SG, et al. Relationship between bone mineral density, leptin and insulin concentration in Brazilian obese adolescents. *J Bone Miner Metab* 2009;27:613–9.
49. Müller HL, Schneider P, Bueb K, Etavard-Gorris N, Gebhardt U, et al. Volumetric bone mineral density in patients with childhood craniopharyngioma. *Exp Clin Endocrinol Diabetes* 2003;111:168–73.
50. Holmer H, Popovic V, Ekman B, Follin C, Siversson AB, et al. Hypothalamic involvement and insufficient sex steroid supplementation are associated with low bone mineral density in women with childhood onset craniopharyngioma. *Eur J Endocrinol* 2011;165:25–31.
51. Guo Y, Zhao LJ, Shen H, Guo Y, Deng HW. Genetic and environmental correlations between age at menarche and bone mineral density at different skeletal sites. *Calcif Tissue Int* 2005;77:356–60.
52. Finkelstein JS, Neer RM, Biller BM, Crawford JD, Klibanski AN. Osteopenia in men with a history of delayed puberty. *N Engl J Med* 1992;326:600–4.
53. Almstedt Shoepe H, Snow CM. Oral contraceptive use in young women is associated with lower bone mineral density than that of controls. *Osteoporos Int* 2005;16:1538–44.
54. Saag KG. Glucocorticoid-induced osteoporosis. *Endocrinol Metab Clin North Am* 2003;32:135–57.
55. Mora S, Saggion F, Russo G, Weber G, Bellini A, et al. Bone density in young patients with congenital adrenal hyperplasia. *Bone* 1996;18:337–40.
56. Karsenty G, Oury F. The central regulation of bone mass, the first link between bone remodeling and energy metabolism. *J Clin Endocrinol Metab* 2010;95:4795–801.
57. Poretti A, Grotzer MA, Ribl K, Schönle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. *Dev Med Child Neurol* 2004;6:220–9.
58. Friedman MA, Meyers CA, Sawaya R. Neuropsychological effects of third ventricle tumour surgery. *Neurosurgery* 2008;62(6 Suppl 3):1093–100.
59. Donnet A, Schmitt A, Dufour H, Grisoli F. Neuropsychological follow-up of twenty two adult patients after surgery for craniopharyngioma. *Acta Neurochir (Wien)* 1999;141:1049–54.
60. Carpentieri SC, Waber DP, Scott RM, Goumnerova LC, Kieran MW, et al. Memory deficits among children with craniopharyngiomas. *Neurosurgery* 2001;49:1053–7.
61. Anderson CA, Wilkening GN, Filley CM, Reardon MS, Kleinschmidt-DeMasters BK. Neurobehavioral outcome in pediatric craniopharyngioma. *Pediatr Neurosurg* 1997;26:255–60.
62. Ondruch A, Maryniak A, Kropiwnicki T, Roszkowski M, Daszkiewicz P. Cognitive and social functioning in children and adolescents after the removal of craniopharyngioma. *Childs Nerv Syst* 2011;27:391–7.
63. Kawamata T, Amano K, Aihara Y, Kubo O, Hori T. Optimal treatment strategy for craniopharyngiomas based on long-term functional outcomes of recent and past treatment modalities. *Neurosurg Rev* 2010;33:71–81.
64. Honegger J, Barocka A, Sadri B, Fahlbusch R. Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. *Surg Neurol* 1998;50:19–28.
65. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, et al. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. *Int J Radiat Oncol Biol Phys* 2002;53:533–42.
66. Schubert T, Trippel M, Tacke U, van Velthoven V, Gump V, et al. Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? *Childs Nerv Syst* 2009;25:1419–27.
67. Hofmann BM, Höllig A, Strauss C, Buslei R, Buchfelder M, et al. Results after treatment of craniopharyngiomas: further experiences with 73 patients since 1997. *J Neurosurg* 2012;116:373–84.
68. Pedreira CC, Stargatt R, Maroulis H, Rosenfeld J, Maixner W, et al. Health related quality of life and psychological outcome in patients treated for craniopharyngioma in childhood. *J Pediatr Endocrinol Metab* 2006;19:15–24.
69. Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg* 2011;114:1350–9.
70. Dekkers OM, Biermasz NR, Smit JW, Groot LE, Roelfsema F, et al. Quality of life in treated adult craniopharyngioma patients. *Eur J Endocrinol* 2006;154:483–9.
71. Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, et al. Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. *J Neurosurg* 2005;103(Suppl 4):302–11.
72. Bengtsson BÅ, Edén S, Lönn L, Kvist H, Stokland A, et al. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab* 1993;76:309–17.
73. Burman P, Broman J, Hetta J, Wiklund I, Erfurth E, et al. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. *J Clin Endocrinol Metab* 1995;80:3585–90.
74. Rosilio M, Blum W, Edwards D, Shavrikova E, Valle D, et al. Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab* 2004;89:1684–93.
75. McGauley G. The psychological consequences and quality of life in adults with growth hormone deficiency. *Growth Horm IGF Res* 2000;10(Suppl B):S63–8.
76. Gilchrist FJ, Murray RD, Shalet SM. The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. *Clin Endocrinol (Oxf)* 2002;57:363–70.
77. Baum H, Katznelson L, Sherman J, Biller B, Hayden D, et al. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficit. *J Clin Endocrinol Metab* 1998;83:3184–9.