Endocrine aspects and sequel in patients with craniopharyngioma

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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.

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
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 influ-
ence 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]. Fur-
thermore, 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 popula-
tions 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 conven-
tional hormone therapy but without growth hormone
(GH) therapy. Conventional hormone therapy in these
historical cohorts included somewhat higher hydrocor-
tisone 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 child-
hood 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 cardiovascu-
lar 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 cer-
ebrovascular) mortality was enhanced (SMR 3.21, 95% CI
1.29–6.61), but no specific analysis was made for cerebro-
vascular 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 mortal-
ity 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 dif-
ference has also been shown among patients with hypo-
pituitarism 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 mor-
tality. The sex difference for cardiovascular and cerebro-
vascular events possibly results from the fact that women
with hypopituitarism not only have un-substituted hypo-
gonadism 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 recur-
<table>
<thead>
<tr>
<th>Cox regression models</th>
<th>No age stratification</th>
<th>With age stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI p-Value</td>
<td>HR 95% CI p-Value</td>
</tr>
<tr>
<td>All patients (n=60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence (time dependent: yes vs. no)</td>
<td>2.7 (1.0–7.3) 0.05</td>
<td>4.4 (1.4–14) 0.01</td>
</tr>
<tr>
<td>Radicallity at surgery (subtotal vs. total)</td>
<td>2.0 (0.9–4.5) 0.09</td>
<td>1.1 (0.5–2.5) 0.9</td>
</tr>
<tr>
<td>Radiotherapy (yes vs. no)</td>
<td>0.5 (0.2–1.2) 0.1</td>
<td>0.3 (0.1–0.8) 0.01</td>
</tr>
<tr>
<td>Patients surviving the first 6 months after surgery (n=50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence (time dependent: yes vs. no)</td>
<td>1.6 (0.5–4.7) 0.4</td>
<td>2.2 (0.6–7.6) 0.2</td>
</tr>
<tr>
<td>Radicallity at surgery (subtotal vs. total)</td>
<td>1.6 (0.6–4.5) 0.4</td>
<td>0.9 (0.3–2.5) 0.8</td>
</tr>
<tr>
<td>Radiotherapy (yes vs. no)</td>
<td>1.4 (0.4–4.1) 0.6</td>
<td>0.7 (0.2–2.4) 0.6</td>
</tr>
</tbody>
</table>
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, adrenocorticotropic 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](image_url) 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).

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 BMD 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 $\leq -2.0$ 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 $\mu$g (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 $\leq -2.0$ 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 ($> 30$ 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.
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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.

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Conflict of interest statement

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

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