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Craniopharyngioma – a chronic disease

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Craniopharyngiomas are rare embryonal malformations of the sellar/parasellar region [1]. Novel insights into the molecular pathogenesis of adamantinomatous and papillary craniopharyngiomas have offered the possibility of pharmaceutical therapy targeting pathogenic pathways and of testing these treatment options in animal models [2]. Hypothalamic involvement and/or treatment-related hypothalamic lesions result in severe neuroendocrine sequelae and impaired social and physical functionality. Quality of survival after craniopharyngioma, especially in case of hypothalamic tumour involvement, is impaired by severe hypothalamic obesity, physical fatigue, and psychosocial deficits [3]. Patients with craniopharyngioma involving hypothalamic structures present with reduced 20-year overall survival, whereas overall and progression-free survival rates are not associated with the degree of surgical resection [3]. Radiation therapy is effective in prevention of progression and recurrence. Preliminary experiences with proton beam therapy in craniopharyngioma are promising, offering a more protective radio-oncological treatment option than conventional external photon radiation, especially for tumours located close to the optic nerve or chiasm, pituitary gland, or hypothalamus [2, 4].

For favourably located craniopharyngiomas, i.e., without hypothalamic involvement, the treatment of choice is an attempt at radical resection with preservation of visual, pituitary, and hypothalamic function. For unfavourably located tumours with close proximity to hypothalamic and optical structures, a surgical approach attempting gross-total resection is not recommended for prevention of severe sequelae [2, 5]. The implantation of an intracystic catheter with a subcutaneous omaya reservoir provides the possibility of repeated cyst decompression and instillation of sclerosing substances, preferably interferon alpha [6].

Clinical improvement in childhood and adult-onset craniopharyngioma patients requires radio-oncological and neurosurgical treatment strategies developed in a multidisciplinary setting so that both medical and psychosocial support for these patients can be provided. For decades, radical approaches in terms of gross-total resection were the preferred treatment strategies in craniopharyngioma, assuming that gross-total at the time of primary diagnosis would result in cure of disease. Recent reports on long-term prognosis with regard to novel neurosurgical and irradiation treatment approaches provide novel insights into risk-adapted treatment strategies in craniopharyngioma in order to prevent hypothalamic syndrome and severe obesity as major sequelae after craniopharyngioma [1, 7–9].

Furthermore, recent follow-up studies on treatment outcome after craniopharyngioma have provided important insight into sequelae of this disease. Currently in *Swiss Medical* Weekly, Andereggen et al. [10] have published 10-year follow-up results of a single-institutional craniopharyngioma cohort. Hypothalamic obesity and long-term pituitary deficiencies had substantial negative prognostic impact, with postoperative diabetes insipidus being a potential marker for the development of severe obesity as a major clinical manifestation of hypothalamic syndrome. The authors conclude that, besides hypothalamus-sparing strategies, risk-adapted early interventions for patients at risk for hypothalamic sequelae are recommended. Such interventions should also aim at early treatment of neuropsychological sequelae, which could not be analysed in the study of Andereggen et al. [10]. Memory deficits, behavioural abnormalities, and psychosocial impairment frequently occur early after diagnosis and impair quality of survival after craniopharyngioma.

Pharmaceutical treatment options for hypothalamic obesity with glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, somatostatin analogues, methylphenidate, modafinil, dextroamphetamine and other substances have been tested, mostly in small heterogeneous cohorts with mixed results [1]. Even though bariatric procedures, mainly gastric bypass, has been shown to be effective in weight reduction [11] irreversible bariatric surgeries such as roux-en-Y gastric bypass are controversial in the paediatric age group from legal and ethical considerations. The severity of hypothalamic obesity in craniopharyngioma survivors and its chronic, devastating effect on their quality of survival and psychosocial status were confirmed in a recent retrospective analysis of long-term survivors of childhood-onset craniopharyngioma [3]. However, further investigation of psychosocial outcome and specific adult outcome, such as length of schooling, occupation, marriage, and ability to live independently, are warranted.

Based on the mentioned impact of initial hypothalamic involvement and treatment-related lesions of optic structures and hypothalamic-pituitary axes on long-term morbidity, mortality and quality of survival, craniopharyngioma is indeed a chronic, incurable disease. Whereas 20-year overall survival rate is high (0.88 ± 0.03) in childhood-onset craniopharyngioma, low progression-free survival (0.58 ± 0.05) [3] and low disease-free rate (<1%) in childhood-

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onset craniopharyngioma support the concept of craniopharyngioma as a chronic disease with a long course before [12] and after diagnosis [3].

A total of 567 patients with childhood-onset craniopharyngioma were recruited in the German Craniopharyngioma Registry between 1998 and 2010. Only 5 of 567 recruited patients (<1%) presented without confirmed signs of relapse/progression, visual impairment, and (neuro)endocrine deficiencies during longitudinal follow-up of more than 5 years. The craniopharyngiomas in this small subgroup of patients with beneficial prognosis (i.e., without obvious symptoms indicating a chronic state of disease) were characterised by a small nonrecurrent tumour confined to the sellar area and without hypothalamic involvement, which therefore could be resected completely, preserving the integrity of the pituitary gland/stalk and visual and hypothalamic structures [13].

There are only a few studies published in the literature analysing the prognosis of craniopharyngioma patients with regard to the neurosurgeons' experience [14–18], and reporting on clinically relevant prognostic differences according to the neurosurgeons' experience with the condition. Degree of obesity and quality of survival were analysed in a recent report based on reference-confirmed assessment of tumour location and postsurgical hypothalamic damage [17]. Treatment was also analysed regarding neurosurgical strategies in terms of intended degree of resection and the neurosurgical centre sizes (based on patient load) as an indicator of surgical experience with the condition. Surgical damage of anterior and posterior hypothalamic areas was associated with postsurgical obesity, negatively impacting long-term quality of survival in patients with surgical posterior hypothalamic lesions [16, 17]. Treatment strategies in large centres (based on patient load) were less radical and the rates of gross-total resections and hypothalamic surgical lesions were lower than those of middle and small-sized centres [15–17]. However, in multivariable analysis, preoperative hypothalamic involvement was the only independent risk factor for severe obesity [17]. As surgical expertise has a proven impact on post-treatment morbidity, medical societies should establish criteria of adequate professional expertise for surgical treatment of craniopharyngioma. Based on these criteria, health authorities should organise the certification of centres of excellence authorised for treatment and care of patients with this chronic disease.

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