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Diagnosis and treatment of craniopharyngioma

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Abstract

Craniopharyngiomas are rare embryonal malformations. Quality of life especially in case of hypothalamic tumor involvement is impaired by hypothalamic obesity, fatigue, and psychosocial deficits. Patients with hypothalamic involvement present with reduced overall survival rates, whereas overall and progression-free survival are not associated with surgical degree of resection. Radiation therapy is effective in prevention and treatment of progression/recurrence. Preliminary experiences with proton beam therapy are promising, offering a more protective radio oncological treatment. Novel insights in molecular pathogenesis of craniopharyngiomas have offered the possibility of targeted therapy and testing treatment in animal models. Treatment options for hypothalamic syndrome are limited. Accordingly, hypothalamus-sparing strategies are recommended. This review summaries novel insights in diagnostics and treatment of craniopharyngioma based on reports published since 2015.

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Craniopharyngioma, Hypothalamus, Pituitary, Surgery, Irradiation, Quality of life, Obesity.

Clinical presentation

Childhood-onset craniopharyngiomas are often diagnosed years after first appearance of symptoms, which are mainly dominated by headaches and visual impairment due to increased intracranial pressure [1]. Hoffmann et al. [2] reported on a median 6 months duration of history (range: 0.1−108 months), which correlated positively with patient age at initial craniopharyngioma diagnosis. Duration of history was not significantly correlated with tumour volume, degree of surgical resection, hypothalamic tumor involvement, and body mass index (BMI) at the time of primary diagnosis. In multivariate analysis, only hydrocephalus at the time of initial diagnosis was associated with shorter duration of history. Neurological deficits and visual impairments were associated with larger tumour volume at initial diagnosis and reduced 10-years overall survival rate. Growth failure and weight gain were observed with longest duration of history [2](see Figure 1).

Diagnostics

The gold standard in diagnostics of craniopharyngioma is magnetic resonance imaging (MRI) and computed tomography (CT) for detection of calcifications. Amelot et al. [3] recently reported on imaging advantages using MRI T2-weighted diffusion sequences for specific neuroradiological diagnosis of craniopharyngioma. Furthermore, in case of neurological symptoms a spinal MRI is advisable due to a recent report on a patient with spinal metastasis [4]. Recent reports of gadolinium chelate deposition in the brain [5] lead to the recommendation to perform routine MRI follow-up monitoring in childhood-onset craniopharyngioma without gadolinium containing contrast medium.

An important step towards standardization of pre and postoperative staging in craniopharyngioma is the definition and grading of hypothalamic involvement/damage with regard to prediction value for severe hypothalamic obesity as one of the major sequelae reducing quality of life with this disease. Mortini et al. [6] analyzed radiological variables associated with hypothalamic involvement on presurgical MRI, and their correlation with clinical features and long-term prognosis. The authors also analyzed the predictive sensitivity of published grading systems for the development of hypothalamic obesity. Hypothalamic hyperintensity in T2-weighted/FLAIR images, involvement of mammillary bodies, unidentifiable pituitary stalk, dislocation of optic chiasm, either infundibular recess or unrecognizable supra-optic recess, and tumor extension to retrochiasmatic areas were major criteria defining hypothalamic invasion. Degree of hypothalamic tumor involvement was the variable with highest prediction value for the development of postsurgical hypothalamic syndrome (see Figure 2). These findings support the hypothesis that disease or treatment-related hypothalamic lesions have strong negative impact on quality of life and long-term prognosis after craniopharyngioma [7,8].

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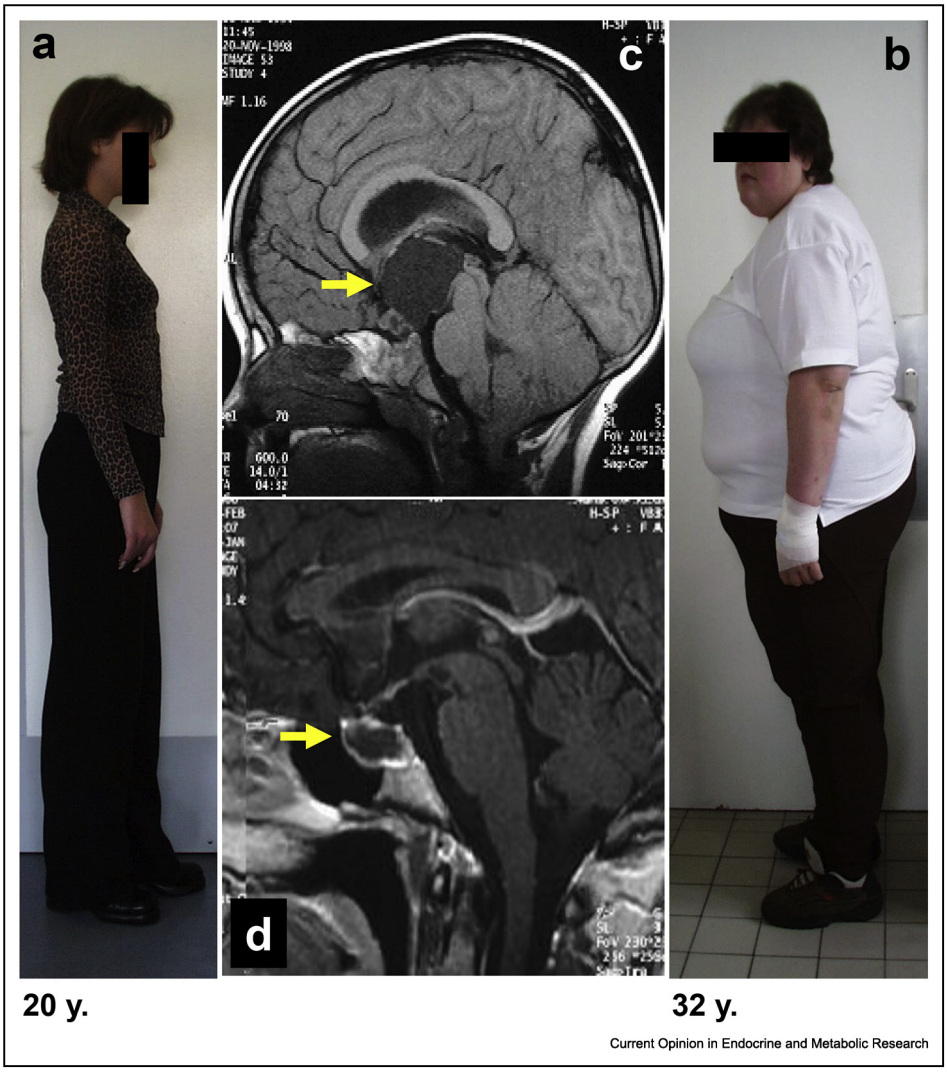
Figure 1



Degree of obesity in relation to the location of craniopharyngioma. In both patients craniopharyngioma (as indicated by arrow on magnetic resonance imaging before surgery) could be completely resected. Both patients presented with complete hypopituitarism after surgery requiring endocrine substitution of all hypothalamic–pituitary axes. The patient depicted in **Figure 1b** developed severe obesity due to hypothalamic lesions of suprasellar craniopharyngioma involvement (**Figure 1c**). The patient depicted in **Figure 1a** presented with a small tumor confined to the sellar region (**Figure 1d**). After complete resection she kept normal weight without any eating disorders (modified from Müller et al.; Monatsschr Kinderheilkd, 2003, with permission of Springer).

Moleculargenetics

Papillary craniopharyngioma

Activating *BRAF* (V600E) mutations were confirmed in papillary craniopharyngioma, using pyrosequencing, whole exome sequencing, next-generation panel sequencing, and Sanger sequencing [9]. The prevalence of these *BRAF* (V600E) mutations ranges from 81% to 100% [10,11]. These findings provide the promising perspective of targeted pharmacological treatment with agents directed against *BRAF* (V600E) mutations.

Pharmacological substances that target and specifically inhibit mutant *BRAF* (V600E) are effective in other malignancies positive for this mutation. Two reports have shown clinically relevant tumor volume reduction in cases of treatment-refractory papillary craniopharyngioma. Aylwin et al. [12] reported on a patient with progressive deterioration of visual capacity due to a recurrent papillary craniopharyngioma previously treated with multiple surgeries and fractionated external irradiation. The papillary craniopharyngioma harbored a *BRAF* (V600E) mutation and the patient was treated with vemurafenib. Stabilization of visual function was achieved within two weeks, along with a significant reduction in tumor volume. Brastianos et al. [13**] reported on a second case of recurrent papillary craniopharyngioma with *BRAF* (V600E). Four surgical decompressions did not result in controlling tumor