Childhood-onset craniopharyngioma – a life-long family burden?

Short title: Family burden in craniopharyngioma

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Craniopharyngiomas are rare, benign (WHO grade 1) tumors of the sellar/parasellar region, with an annual incidence of 0.5 to 2 new cases per million persons (1). In pediatric patients, the tumor is of adamantinomatous type and the most frequent non-neuroepithelial intracranial tumor, accounting for 5–11% of brain tumors in this age group, whereas the papillary type is more common in adults. The age distribution is bimodal, with a peak incidence in children aged 5–15 years and adults aged 50–70 years. Due to the close proximity to hypothalamic structures, the pituitary gland and the visual pathways, hypothalamic infiltration as well as treatment-related surgical lesion to hypothalamic pituitary axes can result in severe long-term neuroendocrine morbidity (2). These hypothalamic injuries can lead to hypothalamic syndrome, which is characterized by morbid obesity, multiple endocrine deficiencies and behavioral abnormalities (3). On the other side, long-term functional capacity and event-free survival rates have been shown to be associated with age at childhood-onset craniopharyngioma diagnosis (4). When compared with survivors of other tumors, childhood-onset craniopharyngioma survivors face decades of survival and need individualized treatments and a multidisciplinary approach to reduce the risk of long-term morbidity and sequelae (4).

Due to these observed sequelae, the "pendulum of treatment strategies" in childhood-onset craniopharyngioma patients has shifted over the last decades from gross-total resection to more hypothalamus-sparing strategies combined with local irradiation for treatment of residual tumor and prevention of recurrences. Event-free survival rates and relapse rates as parameters of successful treatment became less important, as the recurrence rate remains high in spite of gross-total resection and because local irradiation is highly effective in treatment of residual tumor and

recurrences. The role of quality of life has gained more importance in research and care. Several risk factors such as treatment-related anatomical lesions, neuroendocrine deficits, visual impairments, neuropsychological problems and hypothalamic syndrome have clinically relevant negative impact on quality of life (5). Based on multivariable analyses, Beckhaus *et al.* observed that age at craniopharyngioma diagnosis and surgical lesions of posterior hypothalamic structures had major independent adverse effects on quality of life in long-term survivors (4). Looking at different domains of quality of life, Bogusz *et al.* reported on specific reductions in the quality of life domain of social functionality with regard to family 5 years after craniopharyngioma diagnosis in patients with surgical lesions of posterior hypothalamic structures (6). Their analyses of quality of life in long-term survivors of craniopharyngioma have also shown that self-assessment and parental assessment of quality of life after craniopharyngioma led to different results (4, 6). Parental assessment of quality of life three years after childhood-onset craniopharyngioma diagnosis was different and showed lower scores for the autonomy, emotional stability, physical function and social functionality in the family domain in patients with hypothalamic damage (6). These differences were not found in self-assessment of patients (6).

Whereas patients' quality of life after craniopharyngioma diagnosis and treatment has been studied extensively during the past years, Kayadjanian *et al.* analysed for the first time caregiver burden and its relationship to health-related quality of life in craniopharyngioma survivors (7). Altogether, the authors could show that caregiver burden in craniopharyngioma is significantly associated with the survivor symptomatology impacting health-related quality of life, not the caregiver's characteristics or caregiving duration. They showed that caregiver assessment of survivor quality of life is a valuable parameter to estimate the overall impact faced by caregivers of craniopharyngioma survivors. The results of their study also underline the clinical impact of

the polysymptomatology induced by the craniopharyngioma itself and / or tumor treatment and the long-term effect of clinical manifestations on both survivors of craniopharyngioma and their caregivers. Furthermore, the study analysed obesity and hyperphagia as distinct manifestations of hypothalamic syndrome. Hyperphagia was identified as a critical symptom impairing quality of life in a large subgroup of craniopharyngioma survivors. Moreover, this result supports research not only focusing on hypothalamic obesity but also on the broad range of symptoms of hypothalamic syndrome including sleep problems, fatigue, psychiatric problems, temperature dysregulation, behavioral and social impairments (2). The Kayadjanian *et al.* study also shows that clinically relevant determinants of health, quality of life, and disease burden can be successfully collected by analyzing both patients and caregivers (7). Accordingly, future studies should include caregivers and survivors, with special focus on caregiver perceptions of health-related quality of life in long-term survivors of craniopharyngioma. Health care support should acknowledge the challenging task in daily care and the special parental responsibility in many survivors with hypothalamic syndrome caused by craniopharyngioma.

These findings are even more important, as reduced capabilities in terms of autonomy and social function as well as neuroendocrine and neuropsychological handicaps in childhood-onset craniopharyngioma patients with hypothalamic syndrome lead to problems with regard to self-sufficiency and impaired detachment from parental home during adolescence. Patients with severe sequelae frequently stay in and stick to their (parental) family for many decades and even life-long. Frequently, this also results in life-long parental responsibility for monitoring clinical condition and requirements for immediate modifications of medication in their children with craniopharyngioma.

Currently, many efforts such as the definition of criteria for centers of excellence aim at improving quality of treatment provided by experienced multidisciplinary teams. Based on the

above-mentioned novel results, the perspective of caregivers who take responsibility and provide daily care and treatment for these patients sometimes over decades should also be considered as a major field for research and for potential improvement and support. The perspective of patients revealed the need for an holistic treatment of hypothalamic dysfunction (8). Psychosocial and financial support for caregivers and parents to relieve burden and impaired quality of life should be considered. Together with novel perspectives on medication for hypothalamic syndrome, on targeted therapy, and on hypothalamus-sparing treatment strategies, improvements of daily care by supporting caregivers would be beneficial for patients and their families.

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