Childhood Craniopharyngioma

Recent Advances in Diagnosis, Treatment and Follow-Up

Hermann L. Müller

Department of Pediatrics, Pediatric Hematology and Oncology, Klinikum Oldenburg GmbH, Oldenburg, Germany

Key Words

Craniopharyngioma • Obesity • Quality of life • Irradiation • Hypothalamus

Abstract

Background: Craniopharyngioma are embryogenic malformations of the sellar area. With an overall incidence of 0.5–2 new cases per million population per year, 30–50% of all cases occur in childhood. Overall survival rates are high. However, quality of life (QoL) is substantially reduced in many survivors due to sequelae such as extreme obesity caused by hypothalamic lesions. **Methods:** Based on retrospective analysis of 306 patients with childhood craniopharyngioma (HIT ENDO), we found that QoL was negatively related to hypothalamic involvement, tumor size and the number of neurosurgical interventions. **Results:** Irradiation had no significant impact on long-term QoL. The prospective surveillance of 98 patients in KRANIOPHARYNGEOM 2000 revealed frequent and early events in terms of tumor relapse after apparently complete resection (EFS: 0.60 ± 0.09 at 3 years) and tumor progression after incomplete resection (EFS: 0.22 ± 0.09). **Conclusion:** We conclude that radical surgery in patients with hypothalamic involvement has a major negative impact on long-term QoL. Innovative treatment strategies are warranted to improve QoL in these patients at risk. Accordingly, the appropriate time point of irradiation after incomplete resection will be analyzed in KRANIOPHARYNGEOM 2007.

Copyright © 2008 S. Karger AG, Basel

Craniopharyngioma are rare embryogenic malformations of the sellar area with low-grade histological malignancy. Despite high survival rates, the quality of life (QoL) is frequently impaired in long-term survivors due to sequelae caused by the anatomical proximity of craniopharyngioma to the optic nerve, pituitary gland, and hypothalamus [1]. An improvement in its prognosis will require earlier diagnosis and the development of risk adapted neurosurgical and radiotherapeutic treatment strategies in a multidisciplinary approach. Recent multicenter cooperation in this area has led to beneficial results.

Epidemiology and Pathology

Craniopharyngioma is a nonglial intracranial tumor derived from a malformation of embryonal tissue. There are controversial hypotheses on the embryonal origin: originating from ectodermal remnants of Rathke's pouch versus originating from residual embryonal epithelium of the anterior pituitary and of the anterior infundibulum. Its incidence is 0.5–2 cases per million persons per year. 30–50% of all cases become apparent in childhood and adolescence [2]. Craniopharyngioma represent 1.2–4% of all childhood intracranial tumors. In childhood and adolescence, its histological type is usually adamantinous, with cyst formation [3]; it also arises in adulthood, with peak incidence between the ages of 50 and 75, most often with a papillary histological type. Cases of craniopharyngioma are systematically documented by the German Paediatric Cancer Registry (Deutsches Kinderkrebsregister) in accordance with international guidelines [4]. The degree of

case capture by this registry is not yet high enough, however, to permit the calculation of valid incidence figures. From 1980 to 2001, data were obtained on 385 patients in whom a craniopharyngioma was diagnosed at age ≤ 18 years. 345 of the patients were younger than 15 years of age at the time of diagnosis. In the latter group, the sex ratio was 1:1 and the median age at diagnosis was 8 years und 3 months. The survival rate was 95% at 3 years, 91% at 5 years, und 87% at 10 years from the time of diagnosis. Patients who developed the disease in the 1980s had a lower survival rate than those diagnosed in the 1990s (survival at 5 years, 88% vs. 96%; $p < 0.05$) [1].

Clinical Manifestations

The diagnosis of craniopharyngioma is often made late, sometimes years after the initial appearance of symptoms. The clinical picture at the time of diagnosis is often dominated by non-specific manifestations of intracranial hypertension, such as headache and nausea. Further leading manifestations include visual impairment (62–84%) and endocrine deficits (52–87%). The latter involve the hypothalamic-pituitary axis and affect the secretion of growth hormone (75%), gonadotropins (40%), adrenocorticotrophic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%). Neurohormonal diabetes insipidus is present preoperatively in 17% of patients. A study of the history of craniopharyngioma patients before diagnosis (fig. 1) reveals that the initial symptoms often occur long before the diagnosis is made [1]. An analysis of anthropometric data obtained in routine checkups before the diagnosis of craniopharyngioma in 90 children [5] revealed that a pathological growth rate is already demonstrable at age 12 months as an early manifestation of the disease (fig. 2a). An increase in weight, in contrast, tends to occur as a later manifestation, shortly before diagnosis (fig. 2b). The clinical combination of headache, visual impairment, decreased growth rate, and polydipsia/polyuria should arouse suspicion of craniopharyngioma in the differential diagnosis [1].

Imaging Studies

Both computerized tomography (CT) and magnetic resonance imaging (MRI) reveal craniopharyngioma as a usually cystic tumor of the intra- and/or suprasellar region. CT may be better at revealing calcification, which is found in approximately 90% of tumors. The signal in-

Fig. 1. Manifestations before diagnosis of craniopharyngioma in children and adolescents: frequency of occurrence of each manifestation before diagnosis (red) and frequency of occurrence as an initial manifestation (blue). The median time from the appearance of each initial manifestation until diagnosis (in months) is indicated above each blue column. In the overall group, the median time from the initial manifestation of disease until diagnosis was 12 months, with a range of 0.01 to 96 months. Modified from Müller et al. [1] with kind permission from Springer Verlag.

tensity of craniopharyngioma in MRI is highly variable, as it depends on the protein content of the cysts. Solid tumor portions and cyst membranes appear isointense in T_1 -weighted images, often with a mildly heterogeneous structure. The most common localization is suprasellar, with an intrasellar portion. 20% of tumors are exclusively suprasellar, 5% exclusively intrasellar [6]. The combination of solid, cystic, and calcified tumor components is an important radiological clue to the diagnosis (fig. 3). MRI before and after gadolinium application is the standard imaging for detection of craniopharyngioma. A sellar or parasellar mass detected on MRI should be further imaged by native CT for detection of calcifications [6].

Operative Treatment

Before surgery, a tumor-related disturbance of cerebrospinal fluid (CSF) flow often causes hydrocephalus, which can be of varying severity. The resection of the tumor is the treatment of first choice for restoration of normal CSF flow, but a shunt operation may also be required. For a craniopharyngioma with a large cyst, particularly in infancy or early childhood, a further valuable treatment option is the stereotactic or open implantation of an

Fig. 2. Body height/length [52] **(a)** and BMI [53] **(b)** expressed as standard deviation scores (SDS) at birth (U1), at routine check-ups before diagnosis (U2 – 3rd to 4th day of life; U3 – 3rd to 4th week; U4 – 3rd to 4th month; U5 – 6th to 7th month; U6 – 10th to 12th month; U7 – 21st to 24th month; U8 – 3.5 to 4 years; U9 – 5th year), at time of diagnosis (Dx), at annual intervals after the diagnosis of craniopharyngioma, and at the time of the last visit (n = 90). Modified from Müller et al. [5] with kind permission from the Endocrine Society Press.

Fig. 3. Development of obesity and localization of craniopharyngioma. Postoperatively, both patients had panhypopituitarism. The patient seen in (a) had a small tumor revealed by MRI (d), which was removed trans-sphenoidally. Postoperatively, she continued to have normal eating behavior, and her weight developed normally (BMI: + 1 SD according to Rolland-Cachera et al. [53]). The patient whose preoperative MRI (b) showed a large tumor extending to the suprasellar region and infiltrating the hypothalamus went on to develop an eating disorder and, consequently, obesity (BMI: +14 SD [53]) (c). Modified from Müller et al. [1] with kind permission from Springer Verlag.

intracystic catheter, both for the relief of pressure and, in some cases, for the instillation of sclerosing substances (bleomycin).

In children with craniopharyngioma, the stereotactic or open surgical implantation of an intracystic catheter with a subcutaneous reservoir can be a useful means of reducing the volume of the cyst to prolong the interval until radiotherapy or surgical resection. In particular, for patients with large cysts exerting mass effect and, in consequence, marked preoperative visual impairment, a two-staged approach has been proposed, with cyst drainage to relieve pressure and improve vision, followed by resection [7]. The operative approach is generally dictated by the localization and extent of the craniopharyngioma. A right frontotemporal approach is standard, but purely intrasellar tumors can be operated on by the trans-sphenoidal route. Craniopharyngioma arising in childhood usually extend to the suprasellar area and must be removed through a transcranial approach. For topograph-

ical-anatomical reasons, transsphenoidal surgery has the advantage of not disturbing hypothalamic function [8].

For favorably localized tumors, the treatment of first choice is an attempt at complete resection with preservation of visual, hypothalamic, and pituitary function [7]. For unfavorably localized tumors, there is controversy over whether this should still be attempted or whether a planned limited resection (biopsy, partial/subtotal resection) should be performed instead. Many authors take a critical view of planned radical resection because of the risk of surgically induced deficits (mainly hypothalamic) and the high rate of recurrence (23%) in infants and small children despite apparently complete resection [7]. After subtotal resection, the residual tumor shows progression in 71–90% of patients. The rate of progression after incomplete resection followed by radiotherapy is 21% [9, 10]. If the tumor progresses after incomplete resection and radiotherapy, scarring may make reoperation more difficult than it would have been if radiation therapy had

not been performed. Ultimately, whatever the preoperative intention, the final decision regarding the extent of the surgical resection can only be made intraoperatively by the neurosurgeon.

The data in the published literature [11–17] to date have not settled the controversy over the best treatment strategy for craniopharyngioma in childhood and adolescence (intended primary radical resection, versus biopsy/partial resection followed by radiotherapy). At present, there is no clear way to make a well-founded determination of the optimal strategy because of the lack of prospectively acquired data. KRANIOPHARYNGEOM 2000 [18], a German multicenter, prospective observational study of children and adolescents with craniopharyngioma, was designed to answer this question.

Any discussion of this issue must take account of the late sequelae and QoL experienced by the patients after treatment. A follow-up study of QoL in children after complete resection of craniopharyngoma revealed that QoL depended to a statistically significant extent on the experience of the operating neurosurgeon [19]. The author conducted a multicenter cross-sectional study on the functional capacity of children and adolescents after treatment for craniopharyngioma using the Münster-Heidelberg Skills Rating Scale ('Fertigkeitenskala Münster-Heidelberg,' FMH) [20]. This study revealed no significant dependence of functional capacity on the intended or achieved degree of resection.

Irradiation

Optimal techniques must be used. The target volume should be defined according to the visible tumor in the CT and/or MRI images. The resolution of current medical imaging techniques permits the use of a small safety margin, which may be no greater than 5 mm, depending on the precise configuration of the tumor. A smaller safety margin may be chosen in the vicinity of important structures, such as the optic chiasm, as long as the less than perfect precision of radiological localization as well as possible difficulties in the interpretation of images, of both physical and medical nature, are taken into account. A larger safety margin is required if the hypothalamus is involved, even when MRI-based planning is used. Three-dimensional planning and multifield techniques with individual field configurations (collimation) should be used to protect radiosensitive structures and to provide a maximal dose fall-off between the tumor and the adjacent normal structures.

Only limited experience has been gained to date with stereotactic gamma-radiotherapy (Gamma Knife) in the treatment of primary or recurrent craniopharyngioma. For reasons relating to radiation biology, single-dose convergence irradiation seems to be of little value in the treatment of craniopharyngiomas. Another experimental treatment option, the stereotactic instillation of radioisotopes, is mainly applicable to monocystic recurrences of craniopharyngioma. This method can only be used for cystic tumors and should only be considered for tumors that recur after both surgery and percutaneous radiation therapy.

Treatment in Case of Recurrence or Progression of a Residual Tumor or Cyst

The site and rate of progression of the tumor, as well as the patient's age, are important considerations for the decision whether reoperation and/or radiotherapy should be performed. The implantation of an intracystic catheter with a subcutaneous reservoir affords the possibility of repeated decompression of the cyst and often relieves pressure only transiently. The radical resection of a recurrent craniopharyngioma can be rendered more difficult by local postoperative changes from the first operation that make the tumor less easily separable from the adjacent vessels, nerves, and brain tissue. The instillation of sclerosing substances such as bleomycin through an intracystic catheter implanted by a stereotactic or open procedure is a useful method of treatment mainly for cystic recurrent tumors whose anatomical configuration makes them difficult to resect [18].

Late Sequelae and Quality of Life (QOL)

Ophthalmological Findings

In a French case series [7], 42% of patients were visually impaired at the time of diagnosis of craniopharyngioma; the impairment was moderate in 17% and severe in 25%. Ophthalmoscopy at the time of diagnosis reveals papillary atrophy in 35–45% of cases and papilledema somewhat less frequently, in 20–35% of cases. According to a meta-analysis of 23 published series, the visual fields were impaired (bitemporal hemianopsia) in 36% of patients at the time of diagnosis. Vision was normal in 30% of patients [5]. Visual acuity improved postoperatively in 66% of patients with preoperative visual impairment treated with complete resection and in 46% of those treated with subtotal resection of the tumor.

Neuropsychological Deficits

Hypothalamic lesions are frequently associated with emotional lability, rage attacks, abnormal sexual behavior, and deficits of memory and intellectual capacities. Figures found in the literature on the intelligence quotient (IQ) of persons operated on in adulthood for craniopharyngioma are mostly normal. A number of studies [21, 22] of children with craniopharyngioma, however, have revealed disturbances of memory, attention, impulse control, motivation, and socialization resulting from tumor infiltration into the hypothalamus. Longitudinal studies on the development of functional capacities in craniopharyngioma patients have revealed marked deficits as a function of tumor size and hypothalamic involvement [23–25].

Endocrine Deficits

Most patients (85–95%) suffer from multiple deficits of hypothalamic-pituitary function, ranging to panhypopituitarism [26, 27]. A full restoration of preoperatively deficient hormonal function occurs after craniopharyngioma resection only in exceptional cases [28]. Irreversible diabetes insipidus follows 80–93% of all complete resections [19], and growth hormone deficiency occurs in 75% of cases. The effectiveness of a substitution therapy with recombinant growth hormone is documented [29]. However, long-term follow-up of growth hormone substituted patients is necessary in order to monitor for adverse late effects, relapse rates and secondary malignancies. Morbidly obese patients frequently present with normal growth rates despite growth hormone deficiency. The pathogenesis of this observation, known as ‘growth without growth hormone’, is still debated. Hyperinsulinemia in morbidly obese patients could increase the circulating (and tissue) levels of free IGF-I due to a decreasing effect on IGF binding proteins. The substitution of growth hormone in these patients is controversial because growth hormone can increase insulin resistance [30]. Sklar et al. [31] recently reported on an apparently higher risk of second neoplasms in childhood cancer survivors treated with growth hormone in comparison with survivors not so treated. However, the elevation of risk resulting from growth hormone treatment appeared to decrease with increasing length of follow-up, and the overall risk remained small. These findings indicate the need for long-term surveillance in patients with childhood craniopharyngioma.

Obesity and Eating Disorders

Obesity and eating disorders are observed in 40–50% of craniopharyngioma patients [5, 32–36]. A disturbance of hypothalamic structures, particularly the ventrome-

dial hypothalamus, by the tumor and its treatment is considered to be the major pathogenetic factor for hyperphagia and obesity. De Vile et al. [37] assessed the extent of hypothalamic involvement with the aid of imaging studies. The body mass index (BMI) of the affected patients was positively correlated with the degree of hypothalamic damage.

Roth et al. [38] measured serum leptin levels in craniopharyngioma patients and found significantly elevated leptin concentrations, in relation to BMI, in patients with a suprasellar tumor component. They proposed that the normal inhibition of appetite fails to occur because of disruption of the negative feedback loop in which leptin, formed in adipocytes, binds to hypothalamic leptin receptors. Accelerometric measurements show that craniopharyngioma patients have a markedly lower than normal level of physical activity. Based on self-assessment using nutritional diaries, caloric intake was similar in craniopharyngioma patients and BMI-matched controls [39]. Marked daytime sleepiness and disturbances of the day-night rhythm have been demonstrated in obese craniopharyngioma patients [40]. Daytime sleepiness and obesity in these patients were both correlated with low nocturnal melatonin levels; the proposed pathogenetic mechanism involves impaired hypothalamic regulation of melatonin rhythmicity in patients with suprasellar craniopharyngioma. First experiences with melatonin substitution in patients with childhood craniopharyngioma, reduced melatonin levels and daytime sleepiness were promising [41]. Polysomnographic studies in patients with craniopharyngioma and severe daytime sleepiness revealed sleeping patterns pathognomonic for secondary narcolepsy [42]. Reports on a beneficial effect of treatment with central stimulating agents (modafinil, methylphenidate) supported the hypothesis that secondary narcolepsy should be considered as a rare cause for severe daytime sleepiness in these patients [42]. Mason et al. [43] also reported on a significant weight loss in patients with childhood craniopharyngioma treated with central stimulating agents. Lustig et al. [44] postulated hypothalamic disinhibition of vagal output as a cause of increased beta-cell stimulation, leading to hyperinsulinism and obesity. In a randomized, double-blinded study, treatment with a somatostatin analog (octreotide) to suppress beta-cell activity resulted in weight reduction. Roth et al. [45] hypothesized that decreased physical activity and severe obesity in patients with childhood craniopharyngioma could be related to decreased central sympathetic output. Reduced concentrations of catecholamine metabolites in the urine of patients with childhood cra-

Fig. 4. Kaplan-Meier analyses of event-free survival rates (EFS) among the 85 craniopharyngioma patients followed prospectively in the KRANIOPHARYNGEOM 2000 study up to March 2006. **a** 3 years EFS depending on the extent of resection. **b** 1 year EFS after radiation therapy for patients treated with radiation. Modified from Müller et al. [49] with kind permission from Thieme Verlag.

niopharyngioma correlated with the degree of obesity and the level of physical activity.

The experience with laparoscopic adjustable gastric banding (LAGB) in obese craniopharyngioma patients is limited. We were surprised to find not only a constant and persisting weight loss but also a profound change in preexisting addiction to food especially sweets in a pilot study on 4 severely obese patients treated with LAGB [46]. We speculate that LAGB may result in altered regulation of gastrointestinal endocrine satiety factors such as ghrelin, PYY and vagal tone. Analysis of these endocrine factors and long-term follow-up of weight development after LAGB is part of the prospective multicenter study KRANIOPHARYNGEOM 2007 in order to test the hypothesis that LAGB might be a therapeutic option in adolescents developing morbid obesity after childhood craniopharyngioma.

Despite the availability of these promising therapeutic approaches, it must be emphasized that there is currently no generally accepted pharmacological therapy for obesity in children and adolescents with craniopharyngioma that has been shown to be effective in controlled studies.

Quality of Life

No prospective studies have yet been published on the QoL of patients who underwent treatment for craniopharyngioma in childhood and adolescence. A retrospective study of functional capacity using the FMH found significantly lower percentile rankings for craniopharyngioma patients than for age-matched controls [47, 48]. The FMH quantifies the ability to perform everyday psychomotor tasks. The patients' marked obesity was responsible for their low self-rating of their functional capacity.

Perspectives

There are no randomized, controlled studies on the treatment of craniopharyngioma. Reports in the literature mainly refer to single-center, heterogeneous groups of patients that were analyzed retrospectively. Because craniopharyngioma is a rare disease, children and adolescents with craniopharyngioma should be documented uniformly in prospective studies. KRANIOPHARYNGEOM 2000 [49] was designed as a prospective surveil-

Fig. 5. Flow chart of the study design of KRANIOPHARYNGEOM 2007. Modified from Müller et al. [49] with kind permission from Thieme Verlag.

lance study within the treatment network of the German working group for brain tumor studies (Hirntumorstudien, HIT). In this observational study, data on chosen treatment strategies and on the postoperative outcome were collected. From May 2001 to September 2005, 88 newly reported patients were entered into the prospective evaluation. An interim calculation of event-free survival rates reveals frequent early events (i.e. tumor progression after subtotal resection and recurrent tumor relapse after complete resection in the first 3 years after primary surgery) (fig. 4a). A high rate of early events after irradiation (tumor progression in 5 patients during the first year after irradiation – three cystic, two mixed solid/cystic) was also seen in the subgroup of patients who received irradiation ($n = 16$) (fig. 4b). Long-term results will be obtained after further observation.

Based on the results of this interim analysis of KRANIOPHARYNGEOM 2000, we conclude that radical surgery is no appropriate treatment strategy in patients with hypothalamic involvement of childhood craniopharyngioma. For patients after incomplete resection innovative treatment strategies are warranted due to high progression rates of residual tumor. Accordingly, in the prospective trial KRANIOPHARYNGEOM 2007 [49] QoL, EFS and overall survival in patients (age ≥ 5 years at diagnosis; incomplete resection) will be analyzed after stratified (according to postoperative QoL) randomization of the

time point of irradiation after incomplete resection (immediate irradiation versus irradiation at progression of residual tumor) (fig. 5). Regular monitoring and imaging is recommended also in patients after complete resection in order to detect and treat relapses at an early stage [50]. All patients with complete resection and patients of an age below 5 years after incomplete resection will be recruited in the surveillance segment of the trial KRANIOPHARYNGEOM 2007. The study will be initiated in 2007 with support of the German working group for Paediatric Endocrinology (APE; section of the German Endocrine Society [DGE]). The schedule of prospective data collection and the set and definition of parameters is based on a European consensus achieved in the craniopharyngioma subgroup of the brain tumor committees of the International Society for Pediatric Oncology (SIOP) [51]. Standardized European data sets on a rare disease such as childhood craniopharyngioma will help to increase cohort sizes and facilitate common data evaluation.

Acknowledgment

Supported by the German Pediatric Cancer Foundation (Deutsche Kinderkrebsstiftung), Bonn (www.kinderkrebsstiftung.de). The author expresses particular thanks to Mrs. Ursel Gebhardt, study assistant of KRANIOPHARYNGEOM 2000/2007 for her help in writing the manuscript.

References

- Müller HL, Kaatsch P, Warmuth-Metz M, Flentje M, Sörensen N: Kraniopharyngeom im Kindes- und Jugendalter: diagnostische und therapeutische Strategien. *Monatsschr Kinderheilkd* 2003;151:1056–1063.
- Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 1998;89:547–551.
- Müller-Scholden J, Lehrnbecher T, Müller HL, Bensch J, Hengen RH, Sörensen N, von Stockhausen HB: Radical surgery in a neonate with craniopharyngioma. *Pediatr Neurosurg* 2001;33:265–269.
- Janzer RC, Burger PC, Giangaspero F, Paulus W: Craniopharyngioma; in Kleihues P, Cavaneer WK (eds): *Pathology and Genetics of Tumours of the Central Nervous System*. International Agency for Research on Cancer. Geneva, WHO, 1999.
- Müller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R, Sörensen N: Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004;89:3298–3305.
- Warmuth-Metz M, Gnekow A, Müller HL, Sörensen N: Differential diagnosis of suprasellar tumors in children. *Klin Pädiatr* 2004;216:323–330.
- Choux M, Lena G, Genitori L: Craniopharyngioma in children. *Neurochirurgie* 1991;37(suppl 1):1–174.
- Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical management of craniopharyngiomas: experience with 168 patients. *J Neurosurg* 1999;90:237–250.
- Becker G, Kortmann RD, Skalej M, Bamberg M: The role of radiotherapy in the treatment of craniopharyngeoma: indications, results, side effects; in Wiegel T, Hinkelbein T, Brock M, Hoell T (eds): *Controversies in Neuro-Oncology*. Front Radiat Ther Oncol. Basel, Karger, 1999, vol 33, pp 100–113.
- Einhaus SL, Sanford RA: Craniopharyngiomas; in Albright AL, Pollack IF, Adelson PD (eds): *Principles and Practice of Pediatric Neurosurgery*. New York, Thieme, 1999, pp 545–562.
- Fischer EG, Welch K, Shillito J, Winston KR, Tarbell NJ: Craniopharyngiomas in children: long-term effects of conservative surgical procedures combined with radiation therapy. *J Neurosurg* 1990;73:534–540.
- Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM, Tarbell NJ: 20-year experience in childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* 1993;27:189–195.
- Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, Lustig RH, Kun LE: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. *Int J Radiat Oncol Biol Phys* 2002;53:533–542.
- Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJG, Marsh H, Brada M: Craniopharyngioma: long-term results following limited surgery and radiotherapy. *Radiother Oncol* 1993;26:1–10.
- Tomita T, Bowman RM: Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. *Childs Nerv Syst* 2005;21:729–746.
- Yasargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P: Total removal of craniopharyngiomas: approaches and long-term results in 144 patients. *J Neurosurg* 1990;73:3–11.
- Müller HL: More or less: treatment strategies in childhood craniopharyngioma. *Childs Nerv Syst* 2006;22:156–157.
- Müller HL, Sörensen N: KRANIOPHARYNGEOM 2000 – Multizentrische, prospektive Beobachtungsstudie von Kindern und Jugendlichen mit Kraniopharyngeom, ed 1. Oldenburg, Verlag Isensee, 2001.
- Sanford RA: Craniopharyngioma: results of survey of the American Society of Pediatric Neurosurgery. *Pediatr Neurosurg* 1994;21(suppl 1):39–43.
- Wolff JE, Daumling E, Dirksen A, Dabrock A, Hartmann M, Jürgens H: Münster Heidelberg abilities scale: a measuring instrument for global comparison of illness sequelae. *Klin Pädiatr* 1996;208:294–298.
- Riva D, Pantaleoni C, Devoti M, Saletti V, Nichelli F, Giorgi C: Late neuropsychological and behavioural outcome of children surgically treated for craniopharyngeoma. *Child's Nerv Syst* 1998;14:179–184.
- Pierre-Kahn A, Recassens C, Pinto G, Thalassinos C, Chokron S, Soubervielle JC, Brauner R, Zerah M, Sainte-Rose C: Social and psycho-intellectual outcome following radical removal of craniopharyngiomas in childhood: a prospective series. *Childs Nerv Syst* 2005;21:817–824.
- Müller HL, Bruhnken G, Emser A, Faldum A, Etavard-Gorris N, Gebhardt U, Kolb R, Sörensen N: Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. *Childs Nerv Syst* 2005;21:975–980.
- Müller HL, Gebhardt U, Faldum A, Emser A, Etavard-Gorris N, Kolb R, Sörensen N: Functional capacity and body mass index in patients with sellar masses: cross-sectional study on 403 patients diagnosed during childhood and adolescence. *Childs Nerv Syst* 2005;21:539–545.
- Fisher PG, Jenab J, Goldthwaite PT, Tihan T, Wharam MD, Foer DR, Burger PC: Outcomes and failure patterns in childhood craniopharyngiomas. *Childs Nerv Syst* 1998;14:558–563.
- DeVile CJ, Grant DB, Hayward RD, Stanhope R: Growth and endocrine sequelae of craniopharyngioma. *Arch Dis Child* 1996;75:108–114.
- Merchant TE, Goloubeva O, Pritchard DL, Gaber MW, Xiong-Xiaoping, Danish RK, Lustig RH: Radiation dose-volume effects on growth hormone secretion. *Int J Radiat Oncol Biol Phys* 2002;52:1264–1270.
- Honegger J, Buchfelder M, Fahlbusch R: Surgical resection of craniopharyngiomas: endocrinological results. *J Neurosurg* 1999;90:251–257.
- Müller HL: Childhood craniopharyngioma: current strategies in laboratory diagnostics and endocrine treatment. *Lab Med* 2003;27:377–385.
- Halac I, Zimmerman D: Endocrine manifestations of craniopharyngioma. *Childs Nerv Syst* 2005;21:640–648.
- Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, Yasui Y, Robison LL, Sklar CA: Growth hormone treatment and risk of second neoplasms in childhood cancer survivor. *J Clin Endocrinol Metab* 2006;91:3494–3498.
- Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kühl J, Gutjahr P, Sörensen N, Calaminus G: Obesity after childhood craniopharyngioma: German multicenter study on preoperative risk factors and quality of life. *Klin Pädiatr* 2001;213:244–249.
- Srinivasan S, Ogle GD, Garnett SP, Briody IN, Lee JW, Cowell CT: Features of the metabolic syndrome after childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004;89:81–86.
- Müller HL, Schneider P, Etavard-Gorris N, Gebhardt U, Kolb R, Sörensen N: Volumetric bone mineral density (BMD) in patients with childhood craniopharyngioma. *Exp Clin Endocrinol Diabetes* 2003;111:168–173.
- Müller HL, Heinrich M, Bueb K, Etavard-Gorris N, Gebhardt U, Kolb R, Sörensen N: Perioperative dexamethasone treatment in childhood craniopharyngioma: influence on short-term and long-term weight development. *J Exp Clin Endocrinol Diab* 2003;111:330–334.
- DeVile CJ, Grant DB, Kendall BE, Neville BGR, Stanhope R, Watkins KE, Hayward RD: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? *J Neurosurg* 1996;85:73–81.

- 37 De Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BGR, Stanhope R: Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. *J Clin Endocrinol Metab* 1996;81:2734–2737.
- 38 Roth C, Wilken B, Hanefeld F, Schröter W, Leonhardt U: Hyperphagia in children with craniopharyngioma is associated with hyperleptinemia and a failure in the down regulation of appetite. *Eur J Endocrinol* 1998; 138:89–91.
- 39 Harz KJ, Müller HL, Waldeck E, Pudel V, Roth C: Obesity in patients with craniopharyngioma: assessment of physical activity and food intake. *J Clin Endocrinol Metab* 2003;88:5227–5231.
- 40 Müller HL, Handwerker G, Wollny B, Faldum A, Sörensen N: Melatonin secretion and increased sleepiness in childhood craniopharyngioma. *J Clin Endocrinol Metab* 2002;87:3993–3996.
- 41 Müller HL, Handwerker G, Gebhardt U, Faldum A, Emser A, Kolb R, Sörensen N: Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. *Cancer Causes Control* 2006;17:583–589.
- 42 Müller HL, Müller-Stöver S, Gebhardt U, Kolb R, Sörensen N, Handwerker G: Secondary narcolepsy may be an underrated cause of increased daytime sleepiness in obese patients after childhood craniopharyngioma. *J Pediatr Endocrinol Metab* 2006;19:423–429.
- 43 Mason PW, Krawiecki N, Meacham LR: The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. *Arch Pediatr Adolesc Med* 2002;156:887–892.
- 44 Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kasten SC, Schreiber RE, Rai SN, Lensing SY, Wu S, Xiong X: Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003;88:2586–2592.
- 45 Roth C, Hunneman D, Gebhardt U, Stoffel-Wagner B, Reinehr T, Müller HL: Reduced sympathetic metabolites in urine of obese patients with craniopharyngioma. *Pediatr Res* 2007;61:496–501.
- 46 Müller HL, Gebhardt U, Wessel V, Kolb R, Sörensen N, Maroske J, Hanisch E: First experiences with laparoscopic adjustable gastric banding (LAGB) in the treatment of obese patients with childhood craniopharyngioma. *Klin Pädiatr* 2007;219:323–325.
- 47 Müller HL, Faldum A, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R, Sörensen N: Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. *Klin Pädiatr* 2003;215:310–314.
- 48 Müller HL, Gebhardt U, Etavard-Gorris N, Korenke E, Warmuth-Metz M, Kolb R, Sörensen N, Calaminus G: Prognosis and sequelae in patients with childhood craniopharyngioma: results of HIT-ENDO and update on KRANIOPHARYNGEOM 2000. *Klin Pädiatr* 2004;216:343–348.
- 49 Müller HL, Gebhardt U, Pohl F, Flentje M, Emser A, Warmuth-Metz M, Kolb R, Calaminus G, Sörensen N: Relapse pattern after complete resection and early progressions after incomplete resection of childhood craniopharyngioma: update on KRANIOPHARYNGEOM 2000 and design of KRANIOPHARYNGEOM 2007. *Klin Pädiatr* 2006;218:315–320.
- 50 Müller HL, Gebhardt U, Etavard-Gorris N, Kolb R, Sörensen N: Current strategies in diagnostics and endocrine treatment of patients with childhood craniopharyngioma during follow-up: recommendations in KRANIOPHARYNGEOM 2000. *Onkologie* 2004;28:150–156.
- 51 Müller HL, Albanese A, Calaminus G, Hargrave D, Garré ML, Gebhardt U, Saran F, Sörensen N, Spoudeas HA: Consensus and perspectives on treatment strategies in childhood craniopharyngioma: results of a meeting of the craniopharyngioma study group (SIOP), Genova 2004. *J Pediatr Endocrinol Metab* 2006;19:453–454.
- 52 Prader A, Largo RH, Molinari L, Issler C: Physical growth of Swiss children from birth to 20 years of age: First Zürich Longitudinal Study of Growth and Development. *Helv Paediatr Acta Suppl* 1988;52:1–125.
- 53 Rolland-Cachera MF, Cole TJ, Sempé, Tichet J, Rossignol C, Charraud A: Body mass index variations: centiles from birth to 87 years. *Eur J Clin Nutr* 1991;45:13–21.