RESEARCH ARTICLE
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Characteristics of Patients with Craniopharyngioma and Long-Term Outcomes of Treatment

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ABSTRACT

Objective: Craniopharyngioma (CP) is benign, but its treatment is challenging because of its occurrence in a critical area. Hypothalamic-pituitary dysfunction (HPD) is an important complication that is related to tumour itself or to therapy. This study identified the long-term outcomes of CPs.
Material and Methods: Records of 44 patients with CPs followed up at the Istanbul Faculty of Medicine were retrospectively reviewed.
Results: The mean age of 34 patients (M/F: 19/15) at diagnosis was 24±13.3 years. The most common symptoms were headache (60.3%) and visual impairment (45.5%). The tumour was localised in suprasellar region in 76.6%, in sellar-suprasellar in 16.7%, and in the sellar region in 6.7% of the patients. The mean tumour diameter was 32.7±10.4 mm (n: 19). Surgery was the first line of treatment in all patients except one, and 13 patients underwent more than one operation. Ten patients received radiotherapy. The median duration of follow-up was 6.5 years. Anterior pituitary dysfunction was observed in all patients: hypocortisolism in 88.2%, hypothyroidism in 97%, hypogonadism in 88.2%, growth hormone deficiency in 68.2%, and prolactin deficiency in 20.6% of the patients. Diabetes insipidus occurred in 97% of the patients. Recurrence developed in 2 patients (after 5-6 years). At the end of all treatments, 15 patients had residual disease.
Conclusion: The curative treatment of CP is surgery. HPD is associated with increased mortality and morbidity and decreased quality of life. It is essential to protect the hipothalamo-pituitary axis and to choose the best treatment option for each patient.
Keywords: Craniopharyngioma, hormone, pituitary, hormone deficiency, hypothalamus

INTRODUCTION

Craniopharyngiomas (CPs) are rare and benign epithelial tumours arising along the craniopharyngeal duct and located in the sella turcica or suprasellar area near vital structures like the hypothalamus, hypophysis, optic chiasm, third ventricle, cranial nerves, and major blood vessels. CPs constitute 2-5% of all primary intracranial neoplasms (1). The age-adjusted incidence of CP is 0.19 /100,000 persons in the United States (2). There are two histological subtypes, adamantinomatous (ACP) and papillary (PCP), which also differ in pathogenesis and age distribution. BRAF V600E mutations are detected in up to 95% of the PCP subtypes, and they are typically solid tumours. In contrast, CTNNB1 (encoding β-catenin) mutations are found in up to 96% of ACP subtypes, and these are predominantly cystic tumours (3, 4).

CPs occur equally in males and females and exhibit a bimodal age distribution with the highest incidence rate in children aged 5-15 years and older adults aged 50-74 years (5). CPs are slow-growing tumours, therefore the diagnosis is often delayed. It is diagnosed when the patient develops symptoms due to compression or damage to adjacent structures. Clinical manifestations include headache, visual impairment, endocrine deficiencies, psychiatric disturbances, slowed cognition, nausea, vomiting, and lethargy (6). Although they are benign tumours, their surgical treatment is challenging because they have aggressive behaviour and tend to infiltrate adjacent

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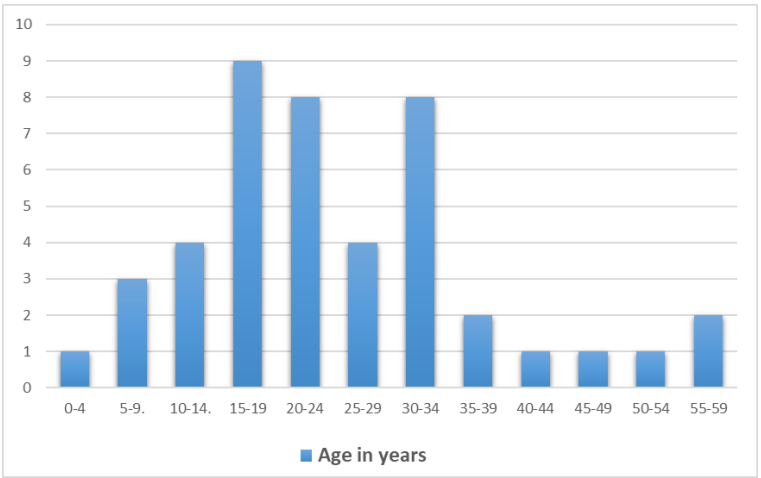

Figure 1: Age distribution of patients with craniopharyngioma

structures. Damage to these critical adjacent structures leads to increased mortality and morbidity (7).

Surgery is the primary treatment, but treatment strategies are controversial. Total gross resection (GTR) is associated with better overall and progression-free survival than subtotal resection alone. Nevertheless, subtotal resection followed by adjuvant radiotherapy (RT) results in similar rates of tumour control as GTR, particularly in tumours with hypothalamic involvement, and is associated with a decreased risk of central diabetes insipidus (DI) (8-11). Surgical complications include bleeding, CSF leakage, infection, and injury to critical structures. Radiation-specific complications include atherosclerosis and vascular anomalies. In addition, endocrine abnormalities can be intensified after treatment due to injury to the hypothalamus and pituitary gland. Isolated hypothyroidism, hypogonadism, adrenal insufficiency, growth hormone deficiency, or panhypopituitarism may develop after therapy because of damage to the pituitary gland. Hypothalamic damage may lead to disturbed hunger-satiety and thirst feelings, disturbances of circadian rhythm and temperature regulation, obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease, hypopituitarism, and central DI.

In this study, we aimed to evaluate the clinical features, presence and type of pituitary-hypothalamic dysfunction (HPD), and long-term treatment outcomes of patients with CP.

MATERIALS and METHODS

This study was designed retrospectively, and patients diagnosed with CP who were followed up in the Department of Endocrinology and Metabolic Diseases of İstanbul Faculty of Medicine between 1980 and 2023 were included. Clinical characteristics, laboratory results, treatment modalities, state of hypothalamic-pituitary axis function, and treatment outcomes were obtained from the patients' medical records. For detailed examination, patients with a follow-up period of at least 1 year were included in the study.

The study protocol was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (Date: 08.09.2023- No: 18). Informed consent was not obtained from the patients because of the nature of the retrospective study.

Statistical analysis

Statistical analyses were performed using the SPSS (IBM SPSS Corp., Armonk, NY, USA) software (version 21.0). Categorical variables are presented as frequency and percentage of occurrence, whereas numerical variables are presented as median, mean, and standard deviation (SD). The Mann-Whitney U test and Student's t-test were performed to compare the groups (non-parametric and parametric data, respectively). Cross-group comparison for categorical variables was obtained using Chi-square/Fisher tests. A "p" value of <0.05 was considered statistically significant.

RESULTS

A retrospective review of the patients' medical records revealed 44 patients with CP. The mean age at diagnosis of CP was 24.4±12 years (range, 2 to 57). The distribution according to age at diagnosis is shown in Figure 1. There were 19 females (43.2%) and 25 males (56.8%), and the male to female ratio were 1.3/1. After excluding 10 patients because of a short follow-up period or lack of follow-up data, 34 CP patients constituted the study group. The mean age at diagnosis of these patients was 24±13.3 years. There were 13 patients under the age of 18 years and 21 patients over the age of 18 years at the time of diagnosis. There were 15 females (44%) and 19 males (56%).

The most common symptoms at presentation were headache and visual impairment, which occurred in 60.6% and 45.5% of patients, respectively. The other symptoms were nausea and vomiting (21.2%), polyuria-polydipsia (12%), seizure (9%), growth retardation (4 /13), delayed puberty (1/13), menstrual irregularities in women, or loss of libido (8/21). Fourteen patients had deficiency of anterior pituitary hormones: hypogonadism in 9 patients, hypocortisolemia in 4 patients, hypothyroidism in 2 patients, and growth hormone deficiency in 2 patients. In 30 patients, data about the localisation of the

CP was available and tumour was localised at the suprasellar region in 23 patients (76.6%), at sellar-suprasellar region in 5 patients (16.7%), and in the sella in 2 patients (6.7%). Data about tumour diameter was available in 19 patients, and the mean diameter was 32.7±10.4 mm (range, 18-60). Only 1 patient had a papillary subtype of tumour.

Surgery was the first line of treatment in all patients except one patient with cystic CP who was treated with endocavitary radioisotopes before surgery. A residual tumour was present in 50% of patients (17/34) after initial surgical treatment. Three of them were re-operated and the tumour was removed completely. In 3 patients, the tumour could not be removed

Table 1: Characteristics of patients, treatment modalities, response to therapy, and presence of hypothalamic-pituitary dysfunction

Patients	Sex	Age at diagnosis	Diameter of tm (mm)	Localisation	No. of surgeries	RT	Presence of residual disease after therapy	Presence of HPD No. of deficient hormone*	Presence of DI
Case 1	M	13	40	Suprasellar	1	+	+	4	+
Case 2	F	12	30	Suprasellar	1	-	-	3	+
Case 3	M	15	60	Suprasellar	3	+	+	3	+
Case 4	M	26	25	Suprasellar	1	-	-	3	+
Case 5	F	30	40	Suprasellar	2	-	-	3	+
Case 6	M	15	NA	NA	1	-	-	5	+
Case 7	M	26	NA	NA	1	+	+	3	+
Case 8	M	24	25	Suprasellar	2	+	+	4	+
Case 9	M	16	NA	Suprasellar	1	-	-	4	+
Case 10	M	38	18	Sellar-Suprasellar	1	-	+	3	+
Case 11	F	30	35	Suprasellar	1	-	-	2	+
Case 12	M	23	40	Suprasellar	4	+	+	5	+
Case 13	M	21	22	Suprasellar	1	-	+	4	+
Case 14	F	34	27	Suprasellar	1	+	-	2	+
Case 15	F	6	NA	NA	1	-	-	1	+
Case 16	F	16	NA	Sellar-Suprasellar	1	-	-	4	+
Case 17	F	57	NA	Suprasellar	1	-	-	2	+
Case 18	F	20	21	Sellar-Suprasellar	2	-	+	4	+
Case 19	F	35	NA	Sellar	2	-	+	2	+
Case 20	M	31	32	Suprasellar	3	+	+	3	+
Case 21	F	15	NA	Suprasellar	2	-	-	2	-
Case 22	M	23	NA	Suprasellar	1	-	-	3	+
Case 23	M	11	25	Suprasellar	1	-	+	4	+
Case 24	F	8	NA	Suprasellar	1	-	-	4	+
Case 25	M	52	NA	Suprasellar	1	-	-	3	+
Case 26	F	5	NA	Suprasellar	3	-	+	4	+
Case 27	M	27	43	Sellar-Suprasellar	3	-	-	5	+
Case 28	M	2	44	Sellar-Suprasellar	4	+	+	5	+
Case 29	F	45	30	Suprasellar	1	-	+	3	+
Case 30	F	42	25	Suprasellar	1	+	-	2	+
Case 31	M	33	NA	NA	2	-	-	5	+
Case 32	M	33	NA	Sellar	1	-	-	3	+
Case 33	F	10	NA	Suprasellar	2	+	+	2	+
Case 34	M	22	39	Suprasellar	1	-	-	5	+

*Anterior pituitary hormones, NA: Not available; Tm: Tumour; No. of surgery: Number of surgery; RT: Radiotherapy; HPD: Hypothalamic-pituitary dysfunction; DI: Diabetes insipidus

completely despite multiple surgeries (total 2 operations in 2 patients, 3 in one patient). Four of the 17 patients with residual tumours were followed up, including a patient who had previously received intracavitary radioisotope therapy. Two patients received only RT. Five of the 17 patients with residual tumours underwent both surgeries plus RT after surgery. CSF leakage developed in 2 patients, haematoma in 2 patients, worsening of vision in 2 patients, and subdural fluid collection in 1 patient. A total of 10 patients received RT, with stereotactic radiosurgery being used in 3 of them (cyber-knife in 2 patients, gamma-knife in 1 patient).

removed after the first operation, 2 patients developed recurrence (after 5 years in 1 patient, and after 6 years in the other). Details are summarised in Table 1.

When the patients were evaluated in terms of disease or treatment-related anterior pituitary dysfunction, five hormone deficiencies developed in six patients, four hormone deficiencies in nine patients, three hormone deficiencies in 11 patients, two hormone deficiencies in seven patients, and one hormone deficiency in one patient. DI occurred in all patients except one. Four of these patients were diagnosed with

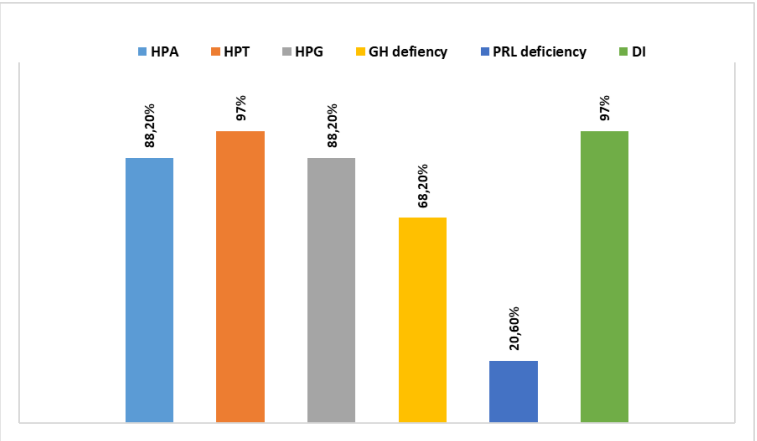

Figure 2: Proportion of patients according to the pattern of hypothalamic-pituitary dysfunction

HPA: Hypothalamic-pituitary-adrenal; HPT: Hypothalamic-pituitary-thyroid; HPG: Hypothalamic-pituitary-gonad; GH: Growth hormone; PRL: Prolactin; DI: Diabetes insipidus

Table 2: Factors influencing hypothalamic-pituitary dysfunction

	All patients n=34	Patients with no. of hormone deficiency** >2 (n=26)	Patients with no. of hormone deficiency** ≤2 (n=8)	p
Age at diagnosis (years) mean±SD	24±13.3	22.6±11.8	28.6±17.3	0.379
Male gender % (n)	55.9 (19)	73.1 (19)	0	**<0.001**
Tumour diameter (mm) at presentation(n=19) mean±SD	32.7±10.4	33.4±11.1 n=16	29±5.3 n=3	0.329
Duration of follow-up (months) Median (IQR)	78 (36-174)*	84 (35-164)*	67 (38.5-208.5)*	0.984
RT % (n)	30.3 (10)	26.9 (7)	37.5 (3)	0.646
Multiple operations % (n)	38.2 (13)	38.5 (10)	37.5 (3)	1.000
Presence of the residue % (n)	44.1 (15)	46.2 (12)	37.5 (3)	1.000

*Median values were used because the data did not comply with the normal distribution. ** anterior pituitary hormone

The mean duration of follow-up from the first surgery to the last visit was 9.75±8.75 years (median 6.5 years; range, one to 34). Among the 17 patients whose tumours were completely

DI at presentation. Details are summarised in Figure 2. The development of more than two hormone deficiencies was not associated with age at diagnosis, tumour size, follow-up time,

number of surgeries, or RT. In contrast, it was associated with male gender (Table 2).

Growth hormone replacement was used in 6 patients (in 5 patients during childhood). One adult patient with no residual tumour had been using growth hormone for 8 years. Eight patients had increased appetite and weight gain after the operation, two of whom developed obesity. Two patients had behavioural disturbances. Diabetes mellitus developed in 8 patients, 5 of whom also had hyperlipidaemia.

DISCUSSION

In this study, the characteristics of patients with CP followed in our centre, their management strategies, the course of their disease, long-term outcomes, and pituitary dysfunction during the follow-up of patients were reviewed.

The incidence of CP is equal in males and females. Bunin et al. reported that the incidence is lowest between the ages of 15 and 34 years, the period defined as late adolescence and early adulthood. A slight male predominance (M/F: 1.2/1) was observed in our study, and in contrast to the study of Bunin et al, the majority of our patients (29/44) were diagnosed between 15 and 34 years of age, and the distribution of age was not bimodal in our patient group (5). The most common symptoms at the presentation of CP are headache and visual impairment. Visual disturbances were observed in 62% of the patients and headache in 43% of the patients in the study of Frič R et al. Tumour location was the suprasellar region in 92% of the patients, the third ventricle and infundibulum in 7% of the patients, and the intrasellar region in 1% of the patients in the study mentioned above. Similarly, the most common symptoms at presentation were headache (60.6%) and visual impairment (45.5%). In addition, the most common location of the tumour was the suprasellar region (suprasellar: 76.6%; sellar-suprasellar: 16.7%) in our patients. However, sellar location was more frequent (6.7% vs 1%) in our study (12). A study that included a total of 666 adult patients with CP reported that 30.3% of the CPs were ACP, 14.1% were PCP, and 55.6% of CPs were reported as histological subtype not otherwise specified (13). In our study, 29.4% of CPs were APC, 3% were PCP, and in the remaining 67.6% of the patients, the subtype was not specified.

Total resection of the tumour is curative for CPs. However, it may not be possible because of the critical location because severe damage to surrounding vital structures increases long-term mortality and morbidity and decreases the quality of life. Therefore, patients may need to undergo reoperation and/or receive RT for residue tumours after the first surgery (8). Damage to the hypothalamic-pituitary region due to surgery or RT or caused by the tumour itself may result with hypothalamic-pituitary dysfunction. It has been reported that the incidence of long-term endocrine hormone deficiencies were significantly increased after the second surgery and/or RT intervention (14, 15).

In addition, Poretti et al. stated that large tumours in the hypothalamic area, young age at diagnosis, and multiple operations for the treatment of recurrent disease were associated with poor functional outcomes (16). In our study, 13 patients (38.2%) underwent multiple operations. The number of surgical procedures was 2 in 7 patients, 3 in 4 patients, and 4 in 2 patients. Panhypopituitarism developed in 6 patients, of whom 4 underwent multiple surgical treatments and 2 of these 4 patients also received RT.

DI was observed in 12% of our patients at presentation. DI was reported in 15% of CP patients at presentation in the literature, which is similar to our finding (17). Although 4 patients had DI preoperatively, almost all patients developed DI postoperatively (29/33). In the study of Frič et al., it was reported that DI developed in 56% of patients and hypopituitarism developed in 74% of patients (panhypopituitarism in 59%, partial hypopituitarism in 15%: growth hormone deficiency in 8%, hypothyroidism in 3% and hypogonadism in 3%) postoperatively (12). Guo et al. demonstrated that suprasellar origin and growth, older age at presentation, transcranial surgery, partial resection or recurrence/progression of the tumour, and ACP type were associated with increased risk of hypothalamic-pituitary dysfunction in patients after surgery. In their study, preoperative and postoperative HPD was observed in 77.5% and 96.9% of the patients, respectively, whereas preoperative and postoperative DI was reported in 24% and 60.1% of the patients, respectively (18). Compared with both studies mentioned above, HPD was observed more frequently after treatment in our study.

In the study of Kiliç et al, it was stated that 3 of the 45 patients (6.6%) whose tumour was resected totally in their first surgery developed recurrence during 15—34 months of their follow-up. In our study, the recurrence rate was similar (2/34, 5.9%), but the time to recurrence was longer (5-6 years) (19). Caldarelli et al. reported that 9 of the 49 patients with CP developed recurrence or regrowth of residue (“true” recurrences in 3 patients), and the overall recurrence rate was nearly 19%, and “true” recurrences were observed between 4 and 6 years after the operation (20).

The limitations of our study include the lack of detailed information about surgical procedures, CP subtype results, and tumour size at diagnosis in all patients. Therefore, we could not assess the effect of surgical methods, tumour size, and subtype on the development of endocrine dysfunction.

CONCLUSION

CPs arise in critical locations and can be life-threatening. Surgery is a curative treatment option, but during surgery, preserving the stalk and hypothalamus is crucial for long-term outcomes, including mortality, morbidity, and quality of life. Targeted therapy options in PCP harbouring BRAF-V600E mutations and advances in surgical and radiotherapy techniques will provide better long-term outcomes for patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (Date: 08.09.2023- No: 18).

Informed Consent: Informed consent was not obtained from the patients because of the nature of the retrospective study.

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