CRANIOPHARYNGIOMA - CLINICAL AND THERAPEUTIC OUTCOME DATA IN A MIXED COHORT OF ADULT AND PAEDIATRIC CASES

C. Capatina^{1,2,*}, M. Vintila², I. Gherlan^{1,3}, A. Dumitraşcu², A. Carageorgheopol², C. Procopiuc³, V. Ciubotaru⁴, C. Poiana^{1,2}

¹“Carol Davila” University of Medicine and Pharmacy, Dept. of Endocrinology, ²“C.I. Parhon” National Institute of Endocrinology, ³“C.I. Parhon” National Institute of Endocrinology, Pediatric Endocrinology, ⁴Bagdasar Arseni Hospital - Neurosurgery, Bucharest, Romania

Abstract

Background. Craniopharyngiomas are benign but locally invasive tumours of the sellar region that arise from ectopic embryonic remnants of Rathke's pouch, affecting both children (adamantinomatous type -aCP) and adults (papillary type -pCP) and associated with significant morbidity.

Objective. To study the clinical presentation of CRF as well as the posttreatment evolution of craniopharyngioma in children *versus* adults in a large mixed cohort.

Material and methods. We performed a retrospective review of CRF patients evaluated in the National Institute of Endocrinology in Bucharest between 1990 and 2016.

Results. A total of 107 patients (72 adults, 35 children) with a mean follow-up of 6.2 years were included. The presenting symptoms were mostly headache, visual impairment, symptoms of hypopituitarism, diabetes insipidus. Some symptoms or hormonal abnormalities were significantly more prevalent in the children group ($p < 0.05$): nausea/ vomiting (47.8% vs 16.7%), photophobia (21.7% vs 5.6%), diabetes insipidus (28.5% vs 8.3%), GH deficiency (68.8% vs 17.1%). Impaired visual acuity (67.6% of cases) or visual fields (71.4%) were more frequent in adults compared to children (44.1%; 51.6%). The tumor dimensions were similar in both groups (3.05 ± 1.05 cm in children; 2.7 ± 1.07 cm in adults). Massive suprasellar extension reaching the third ventricle was frequently present in all cases. All cases underwent surgery but only a minority of those not cured received postoperative adjuvant radiotherapy. Frequent postoperative complications were: aggravation of the endocrine deficit (>80% of cases in both groups needed chronic replacement therapy), central diabetes insipidus (68.2% children, 34.3% of adults).

Conclusions. Despite similar tumor dimensions and extension compared to adults, craniopharyngioma in children is more frequently associated with signs of intracranial pressure. The results and complications of treatment are similar in adults and children.

Key words: craniopharyngioma, adults, children, presentation, outcome.

INTRODUCTION

Craniopharyngiomas (CRF) are rare tumors, with an estimated incidence of 0.17/100000 in the general population in a Swedish study (1). They are a rare category of intracranial tumors in adults but represent around 10% of these tumors in children (2).

They are histologically benign (originating in Rathke's pouch remnants), mostly located right above the sella turcica or both intra- and suprasellar. Their usually large dimensions, frequent fibrous, calcified and adherent structure make total surgical removal a challenge. The recurrence rate is very high in cases with subtotal resection but is not negligible in cases with gross tumor removal either. Adjuvant radiotherapy is useful to decrease the recurrence or remnant growth rate but the timing and specific type of radiotherapy are still debated (3).

Anterior pituitary failure (determined by the compression of the normal pituitary by the tumor) is highly prevalent at diagnosis and, as opposed to pituitary adenomas, is also associated with central diabetes insipidus (3). Despite complex management and careful follow-up, the mortality in CRF patients is significantly higher compared to the general population, especially in childhood-onset cases (1).

The histological type is different in childhood-onset cases (the vast majority of tumors are of adamantinomatous type) and adult-onset ones (either papillary type-almost exclusively found in adults or adamantinomatous). Recently, major progresses have been made in the elucidation of the different

*Correspondence to: Cristina Capatina MD, “Carol Davila” University of Medicine and Pharmacy, Dept. of Endocrinology, 34-36 Aviatorilor blvd., Bucharest, 011863, Romania, E-mail: cristina.capatina@yahoo.com

pathogenetic pathways in the two types (4, 5). Since most published studies report on paediatric populations we aimed to study a mixed cohort of adults and children in order to compare and evaluate the differences (if any) that might emerge from the different pathological and histological types in terms of characteristics at diagnosis, treatment results and complications.

OBJECTIVE

To study the clinical presentation of craniopharyngioma as well the outcome of management of craniopharyngioma in children *versus* adults in a large mixed cohort of adult patients with craniopharyngioma (CRF).

METHODS

We retrospectively analysed 107 CRF cases (histologically confirmed) evaluated and followed up in two departments of the “C.I.Parhon” National Institute of Endocrinology in Bucharest (the Pituitary and Neuroendocrine Department and the Paediatric Endocrinology Department) between 1990 and 2016. We studied the presenting symptoms, complications at diagnosis, type of treatment, surgical complications, rate of tumor resection, endocrinological and visual outcome. The vast majority of cases (90%) were operated in the same surgical center in Bucharest, by various surgical teams.

The standard protocol for the follow-up of CRF patients in our department consists of an initial assessment at 6-12 weeks postoperatively and yearly thereafter (or biannually in cases of suspected relapse or tumor growth). These assessments include clinical examination, formal assessment of visual function, evaluation of the pituitary function according to previously published criteria (6), imaging (MRI or CT scanning of the sellar area). We used the measurements of TSH and free T4 as well as FSH, LH and testosterone/estradiol for the assessment of the thyrotrope and gonadotrope axis, respectively. The ACTH reserve was assessed using the standard short synacthen test. The diagnosis of GH deficiency was based on either the results of a GH stimulation test or on the confirmation of multiple pituitary hormone deficiencies, as literature clearly shows that these cases are also GH deficient (7).

The study was approved by the Ethics Committee of our Institution and written informed consent was signed by each patient or legal representative of the patient.

Statistical analysis

The data analyses were performed with SPSS for Windows version 19 software. Descriptive statistics is shown as mean $\pm$ standard deviation or median and range for numerical variables. Significant differences for mean and median values between groups were analyzed using Student's t-test and Mann-Whitney U test, respectively. The results were accepted as statistically significant for p values < 0.05 .

RESULTS

We retrospectively analysed 107 CRF cases: 35 children (age at diagnosis below 18 years old), 72 adults.

In the children-onset (CO) group, the sex distribution was balanced (19 females, 16 males) while in the adult-onset (AO) group there was a slight predominance of male cases (44 males, 28 females) ($p=0.134$). In the AO group the median age at diagnosis was 26.72 years (slightly higher in males 27.8 years compared to 24.67 in females but not statistically significant). The mean and standard deviation for age at onset of the disease was 12.6 ± 4.2 years in the CO group and 39.3 ± 15.4 years in the AO group, respectively. The mean and median height in the AO group were 1.68 and 1.7 meters, respectively. The mean and median follow-up duration were 6.08 and 4.32 years, respectively.

The most frequent symptoms leading to diagnosis were headache, visual problems and anterior pituitary insufficiency symptoms (growth arrest, delayed puberty, hypogonadal symptoms in adults), nausea and vomiting (even in the absence of pituitary insufficiency, probably as a result of increased intracranial pressure). Over 50% of the adults were hypogonadal but infertility was a presenting symptom in only 9 cases (12.5%). Sixteen women from the AO group (57.14%) complained of secondary amenorrhoea.

Figure 1. The most frequent symptoms at diagnosis CN- cranial nerves, GHD- Growth Hormone Deficiency, DI- Diabetes insipidus, VA - Visual acuity, VF- Visual field.

In the CO group nausea, vomiting and photophobia occurred significantly more frequently (Fig. 1).

An important percentage of cases in both groups presented with other neurological symptoms (convulsions, diplopia, loss of conscience, vertigo, problems with memory, concentration, attention, sleep rhythm disturbances) (Fig. 1).

The tumor size was in all cases larger than 1 cm (range 1.4–8.5 cm, mean 2.8 ± 1.06 cm, median 2.55 cm) but there were not significant size differences between the CO (mean tumor diameter 3.05 ± 1.05 cm) and AO group (mean tumor diameter 2.7 ± 1.07 cm). Massive suprasellar extension reaching the third ventricle was frequently present in both groups (AO and CO).

The pituitary function was frequently already affected at the time of the diagnosis. GH deficiency and central diabetes insipidus were significantly more frequent in the CO group (Table 1). In contrast, visual problems were more frequent in adults (Table 1).

After substitution of pituitary failure, the initial treatment was neurosurgical in all cases. Most patients were initially operated by transfrontal route (51 adults and 25 children) and the rest transsphenoidally (7 children, 20 adults). Ventriculoperitoneal shunt was

inserted in 4 adults and 2 children preoperatively; one adult also had a cyst aspiration preoperatively. The results of the initial surgery are presented in Table 2. Unfortunately a detailed pathological description of the surgical specimen was only available in a minority of cases (for the others the pathological diagnosis was craniopharyngioma).

The main postoperative complication was central diabetes insipidus, followed by anosmia. In the whole group studied there was only one perioperative death in an elderly male with significant comorbidities, thus the postoperative mortality rate was 0.9% (Table 2).

After surgery in most cases from both groups the visual deficit (both VA and VF) remained stable while in a significant subset of cases it actually worsened (Fig. 2). The improvement in VF was obtained in approximately 13% of all cases and for VA in 23% of adults and 12% of children (Fig. 2).

The pituitary function was overall worse after surgery (Table 3). The percentage of cases with central diabetes insipidus after surgery was statistically significantly higher in CO compared to the AO group while for the others no statistical significance was

Table 1. Visual and endocrine function at diagnosis

Percentage of cases	CO group	AO group	p
Visual deficit			
Decrease in visual acuity (VA)	44.1	67.6	0.022*
Uni/bilateral blindness	18.8	20.8	0.808
Visual field (VF) impairment	51.6	71.4	0.055
Pituitary function			
GH deficiency	68.8	17.1	0.000*
Gonadotropin deficiency	51.7	54.3	0.817
Central diabetes insipidus	28.57	8.3	0.006*
TSH	21.9	18.6	0.698
ACTH	12.5	10	0.707
hyperprolactinemia	2.9	10	0.207

Table 2. Result of initial surgical resection (no statistical significance for the difference among CO and AO groups for any of the evaluated parameters)

Percentage of cases	CO group	AO group
Tumor resection		
GTR	31.25	38.02
STR	3.1	2.8
IR	68.71	59.2
Complications		
Permanent CDI	68.57	35.21
Transient CDI	11.42	25.35
Anosmia	0	8.45
CSF leak	0	2.81
Convulsions	2.8	1.4
Subdural haematoma	2.8	1.4

Figure 2. The evolution of the visual function after surgery.

Figure 3. The evolution of the tumor remnant after surgery.

Table 3. The anterior pituitary function after surgery (last available)

	Percentage of cases		p
	CO	AO	
Pituitary function			
GH deficiency	74.2	73.6	0.741
ACTH deficiency	82.8	75	0.164
TSH deficiency	85.7	83.3	0.376
Hyperprolactinemia	8.5	16.6	0.294
Permanent CDI	68.2	34.3	0.011*
Visual function			
Impaired VF	96	94.3	0.652
Impaired VA	80.65	97.1	0.164
Other problems			
Sleep disturbances	2.9	23.6	0.008*
Residual headache	8.8	33.8	0.006*
Cognitive impairment	17.14	23.6	0.302
Fatigability	11.7	42.2	0.002*

Figure 4. The type of treatment applied.

reached (Table 3). No hypopituitary case at diagnosis had normal endocrine function after surgery, the overall rate of new endocrinopathies was 37.4% after surgery.

During initial postoperative follow-up of the STR cases, the tumor remnant was stable in most patients. In 17% of cases the tumor remnant grew during follow-up. In 10% of the adults and 5% of the children initially classified as cured the disease relapsed (Fig. 3). Adjuvant radiotherapy was applied in 11.4% children and 18% adults, mostly in cases of relapse. Radiotherapy was applied right after surgery in only 2 STR cases. The majority of the cases with tumor remnant growth received a second surgical intervention (mostly due to the relatively large remnant). 37% of CO cases and 37.5% of AO cases underwent 2 or more surgical interventions (2 adults underwent 4 and 5 operations, respectively). The type of treatments applied in both subgroups are pictured in Figure 4. There was no difference in the number of operations or follow-up duration between the CO and AO groups. In all patients that received radiotherapy tumor control

Figure 5. Weight evolution after treatment.

was obtained. In 56% of cases tumor growth stopped or small shrinkage was noticed, in 33% a significant tumor shrinkage, over 20%, was obtained during follow-up while in 11% of cases only a minimal or completely necrotic remnant remained.

The most striking complication after treatment was weight gain, both in children and in adults (Fig. 5). Weight gain was rapid in the first few months after surgery, associated with increased appetite and food intake. Progressively during follow-up, metabolic complications also occurred. In the AO group diabetes mellitus was newly diagnosed during postoperative follow-up in 26 cases (34.6%) but no such case was registered in the CO group ($p=0.000$). Dyslipidemia occurred in 20 children (57.14%) but in a significantly higher number of adults (50, representing 69.4%; $p=0.015$). Weight gain after treatment was not related to the pretreatment body weight: the body mass index at diagnosis in the patients not gaining weight after surgery (mean 25.2 kg, median 24.6 kg) was not significantly different from that of the patients experiencing weight

gain (mean 23.9 kg, median 24.3 kg; $p=0.879$).

The neuropsychological outcome has not been actively followed in our cohort of patients.

DISCUSSION

CRF are usually large tumors at the time of diagnosis and produce symptoms because of compression on the optical nerves, optic chiasm or hypothalamo-pituitary structures (8). Irrespective of the age at diagnosis, the most frequent onset symptoms are headache, visual problems, endocrine deficiency (especially affecting the GH-more important and clinically relevant in children and the gonadotropin axis). A significant percentage of cases present with neuromotor or psychiatric complaints or with central diabetes insipidus (6, 9), features almost absent in the presentation of more common tumors of the region (pituitary adenomas).

The variable incidence with age (higher in children and in older adults) is misrepresented in our cohort. Possible reasons are the relatively small number of cases and the lack of updated protocols in our country guiding all children with endocrine diseases under paediatric care toward a paediatric endocrinologist. The young mean age of our AO cases might suggest possible misclassification of childhood-onset disease, due to delayed diagnosis. However, the normal height in the AO group (proving normal growth) argues against this possibility in our cohort.

The CO group presented more frequently with nausea and vomiting as well as with photophobia. Similar results indicating more frequent symptoms of raised intracranial pressure in children were reported in other series (10, 11). In our study group hydrocephalus was not more frequent in the CO group, in contrast to other reported results (12). Since the tumor dimension was similar among AO and CO subgroups as well as the frequency of anterior pituitary deficiency at diagnosis, a reasonable putative explanation might be the increased sensitivity of the immature anatomical structures in children to the increased intracranial pressure. Also, the ratio between tumor and skull size, higher in children (at similar tumoral dimensions), is likely to contribute. In the AO group, similar to others, we observed a higher frequency of visual disorders at diagnosis (13). Differences in tumor biology between childhood-onset and adulthood-onset cases could also possibly explain the clinical differences. However, it should be borne in mind that, since almost all studies on CRF are retrospective, the power of the results indicating different clinical

manifestations in different age groups is limited and should be cautiously interpreted.

The frequency of anterior pituitary deficiency at diagnosis was very high in our cohort, as in the studies previously published. In a careful analysis of published data, Karavitaki *et al.* reported that GH deficiency was present in 35–95% of the cases, gonadotropin deficiency in 38–82%, ACTH deficiency in 21–62%, TSH deficiency in 21–42%. (6) In our cohort, GH deficiency was significantly more frequent in children. However, a significant selection bias may have contributed to this result. In our country the GH replacement therapy is only reimbursed in children while in GH-deficient adults, irrespective of the severity of the deficiency, the treatment should be financially supported by the patient. As a consequence, in our cohort children were more likely to have been assessed.

The situation is different with respect to central diabetes insipidus- all symptomatic patients were evaluated. The increased prevalence in children was not observed in other series (12). Therefore, since the increased frequency of CDI in CO group cannot be explained by a selection bias or different tumor characteristics, we argue that the same explanation related to more sensitive intracranial structures in children might be behind these results.

Neurosurgical intervention is the initial treatment of choice but the recommended extent of tumor resection is still debated. CRF remain a surgical challenge because of the tumor dimensions and structure as well as the adherence to neighbouring neurovascular structures. Craniotomy is frequently used in most series, the transsphenoidal approach being reserved for small intrasellar or infradiaphragmatic tumors (14, 15). Gross tumor resection (GTR) rate has significantly increased worldwide in the past decades as a result of significant improvement in neurosurgical techniques and imaging methods. In parallel, perioperative mortality decreased (16). However, recently reported results are still extremely heterogeneous (as a result of variability in tumor dimensions/structure/invasion but also the experience of the neurosurgical team). Reported GTR rate varies from 17 to 89% (17, 18). Most of the remaining cases represent subtotal resection (STR), usually followed by adjuvant postoperative radiotherapy (17). This approach is recommended by some authors as the recurrence rate is significantly lower compared to cases with subtotal resection followed up and monitored conservatively (17). Of course, in the absence of randomized studies these opinions cannot

be translated into clinical guidelines but to date subtotal resection with adjuvant radiotherapy appears to offer a reasonable chance of cure with lower recurrence rates and relatively lower morbidity.

In our cohort radiotherapy was less frequently recommended than in most other published series despite clear literature data supporting its beneficial effect. Plausible explanations are the relatively large tumor remnants in cases not cured surgically as well as a suboptimal implementation of the current evidence into clinical protocols. A further improvement in the neurosurgical results in Romania as well as in the design and widespread use of disease protocols would likely increase the use of radiotherapy in these patients.

The improvement of visual disorders results after surgery were poor (improvement in VF or VA obtained in a minority of cases) and disappointing compared to other reported results. In a small surgical series, 63% of cases had improved postoperative visual function and only 10% worsened (19). In a large series 85.7% experienced visual improvement (21). The pituitary function also worsened after surgery in our cohort, the overall rate of new endocrinopathies was 37.4%, but this result was very similar to other data reported (22). In most series the endocrine outcome is relatively poor. The probabilities of GH, FSH/LH, ACTH, TSH deficiency and diabetes insipidus at the 10-year follow-up were 88%, 90%, 86%, 80% and 65%, respectively (6).

Obesity caused by hypothalamic damage is a major concern in patients treated for CRF, especially in larger tumors, adhering to the floor of the third ventricle. Severe obesity has been reported in about 50% of cases, associated with hyperinsulinemia and insulin resistance (23). Dyslipidemia and diabetes mellitus are diagnosed in a subset of these cases with metabolic complications related to the hypothalamic dysfunction (24). In one study 66% of treated CRF patients were obese, dyslipidaemia was present in 46.9% and diabetes mellitus in 11.5% (25). In our study the percentage of diabetes mellitus was significantly higher, but only in adults.

The mechanisms of hypothalamic obesity in these patients are complex. Larger tumors, affecting hypothalamic nuclei implied in the satiety sensation, are particularly at risk (26). Aggressive surgery or multiple operations increase the risk. Radiotherapy itself was associated with an increased prevalence of posttreatment obesity. In addition to the alteration of the hypothalamic activity, lower energy expenditure and hypopituitarism are also contributing factors

(27). The risk of developing obesity is also higher in children (possibly due to the increased vulnerability of the growing brain) (27), result also present in our study. Further studies to better understand the pathophysiology and to allow the design of specific intervention measures are needed.

In conclusion, craniopharyngiomas are often associated with an ominous prognosis and significant morbidity. Surgery remains the treatment of choice but total resection can be achieved in a minority of patients in our center. Restoration of preexisting hormone deficits after surgical removal, in contrast to anterior pituitary tumors, is absent or uncommon. Hypothalamic damages (especially hyperphagia, obesity, metabolic complications) occur postoperatively in a significant percentage of cases.

Conflict of interest

The authors declare that they have no conflict of interest.

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