

Childhood craniopharyngioma in Macedonia: incidence and outcome after subtotal resection and cranial irradiation

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Background: Craniopharyngioma is a frequent tumor in children with challenging surgical, endocrine, and visual consequences. We evaluated our experience in treating craniopharyngioma and its incidence in Macedonia.

Methods: Thirteen children (9 male and 4 female) with craniopharyngioma (age 9.55 ± 3.74 years; range 2.90-15.11) who had been treated between 1989 and 2008 in Macedonia were reviewed.

Results: Initial signs were vision disturbances (10 children), seizures (1), growth retardation (13), and diabetes insipidus (DI) (2). All children were subjected to subtotal surgical removal. Cranial irradiation was performed in 12 of the 13 children, and intracystic bleomycin was given to one child. The patients were followed up for 6-229 months (mean \pm SD: 107.00 ± 74.04 months). All children had multiple pituitary deficiencies after surgical removal of the tumor. Body mass index increased from 16.93 ± 6.34 standard deviation scores (SDS) at diagnosis to 26.33 ± 5.91 SDS ($P > 0.005$) at the last follow-up. DI was permanent in 9 of the 13 children, and multiple pituitary deficiencies were seen in all children. Treatment with growth hormone resulted in normalization of adult height from -1.27 ± 1.52 SDS at the start of the treatment to -0.13 ± 1.39 SDS at the last follow-up. The final height was not significantly lower than the genetic target height ($P > 0.005$). The permanent deficit was visual impairment: blindness in one or both eyes in 4

children, bitemporal hemianopsia in 4, and other defects in 2. Recurrence of the disease was ruled out in one child after 31 months. No mortality was observed in the observation period of 104.92 ± 76.11 months.

Conclusions: The overall incidence of craniopharyngioma in the period of 1989-2008 in Macedonia was 1.43 per 1 000 000 person-years. Subtotal resection and systematic irradiation showed good life quality of survivors.

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Key words: craniopharyngioma; growth; incidence; outcome; partial resection

Introduction

Craniopharyngioma accounts for 5%-15% of intracranial neoplasms in children.^[1] The tumor may be detected at any age including the prenatal and neonatal period.^[1] Hormonal deficiency, growth failure, visual and neurologic deficits can be the presenting signs.^[2-4] The mortality of the patients is low, and the survival rate varies between 80% and 91% at 5 years^[5,6] and 83%-92.7% at 10 years of age.^[7-10] Nevertheless, visual, neurologic and hormonal deficiencies can significantly affect the patient's quality of life. We report the growth, endocrine and neurologic outcomes of 13 children with craniopharyngioma treated during 1989-2008, and also estimate the disease frequency.

Methods

Thirteen children with craniopharyngioma who had been treated between 1989 and December 2008 in Skopje, Macedonia were reviewed retrospectively

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concerning the medical records in Departments of Pediatrics and Neurosurgery. In addition, children and their parents were interviewed and the patients were additionally examined.

Height, weight and parental height of the children were measured at diagnosis and at 6-month intervals until the final adult height using standard auxological techniques. The final height was reached when epiphyses were fused and growth velocity was less than 2 cm per year.

Anterior pituitary function was measured by serum growth hormone (after L-dopa, propranolol or glucagon), thyroid-stimulating hormone, thyroxine, prolactin, follicle stimulating hormone, luteinizing hormone, testosterone, estradiol, adrenocorticotropic hormone, cortisol, and sometimes an luteinizing hormone-releasing hormone or adrenocorticotropic hormone test was performed. Diuresis, plasma and urine osmolalities were measured to assess the vasopressin function.

Thyroxin, hydrocortisone and intranasal desmopressin were given as maintenance doses. Human growth hormone was injected subcutaneously every day at recommended doses. Ethynil estradiol was used to induce puberty in girls, and human chorionic gonadotropin or testosterone was used for pubertal induction in boys. Radioimmunoassay or enzyme-linked immunosorbent assay methods were used to determine hormone levels.

All the 13 children were followed up by means of telephone inquiry, direct examinations, scheduled CT and MRI, and endocrinological and ophthalmological examinations. Relapse was defined by clinical (changes in ophthalmological, endocrinological, or neurological status) or imaging criteria (reappearance or progression of the disease).

Measurements of height were expressed as standard deviation scores (SDS^[11]) for age and sex, using the

WHO normative data^[12,13] since there were no data for Macedonian children. Body mass index (BMI: w/h^2 ; w: weight in kg, h: height in cm) was expressed in terms of SDS. One sample *t* test was used to analyze the final height and genetic target height, as well as the BMI values before and after treatment. Paired samples statistics and *Z* scores were used in data analysis. The Kaplan-Meier method for event free survival was also used. The SPSS 6.0.1 was used for analysis.

The incidence of craniopharyngioma was calculated as follows: incidence rate = number of disease onsets/sum of person-time. Two last censuses of the population in Macedonia from 1994 to 2002 were used (The number of children under 14 years was 483 923 and 426 280 respectively). The denominator was the open population, in which the person-years are the product of the average number of people in the population times for duration of the study.

Results

The 13 children were aged 9.55 ± 3.74 years (range: 2.90-15.11 years) including 9 males and 4 females. The overall incidence of craniopharyngioma in the period was estimated to 1.43 per 1 000 000 person-years. Initial presenting signs included vision disturbances (10/13): blindness in one or both eyes in 4 children, bitemporal hemianopsia in 4, and other visual defects in 2. Seizures were observed in one child, nystagmus in one, and ataxia in one. Growth retardation was seen in all the children (relative to the target parental height), delayed puberty was found in a girl, and diabetes insipidus (DI) developed at the onset of the disease in 2 children. Headache was present in all children, sometimes lasting months before its diagnosis.

With tumor characteristics shown by CT/MRI (Fig. 1), the children were categorized into three

Table. The characteristics of the patients

Patients	Sex	Age at DG/OP (y)	Duration of follow-up (mon)	Recurrence	BMI at diagnosis	BMI at control	School
1	M	11.2	111	-	19.2	18.6	Graduated high school
2	M	14.1	48	-	16.6	21.9	Graduated high school
3	M	2.9	56	-	21.6	17.8	Special school
4	M	7.6	220	157	14.2	30.1	Graduated high school
5	M	7.5	214	89	18.6	25.8	Graduated faculty
6	M	12.2	125	-	23.9	33.2	Faculty student
7	M	11.3	115	30	18.0	23.1	Graduated high school
8	F	7.3	78	-	24.7	28.0	Primary school
9	F	15.11	82	35	18.4	21.0	Faculty student
10	F	12.2	91	-	16.6	26.4	Primary school
11	M	11.8	229	-	16.8	21.1	Primary school
12	M	6.5	16	-	20.2	18.3	Primary school
13	F	4.5	6	-	20.9	21.0	Pre-school

DG: diagnosis; OP: operation; BMI: body mass index; M: male; F: female.

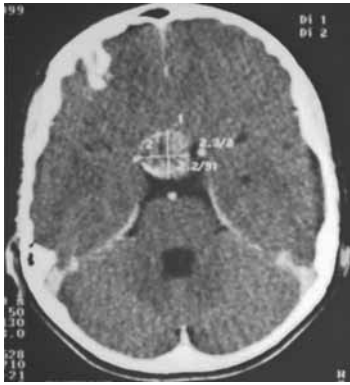


Fig. 1. Computerized tomography of the brain of a 11.5-year-old boy: a large suprasellar tumor mass with calcifications and cysts.

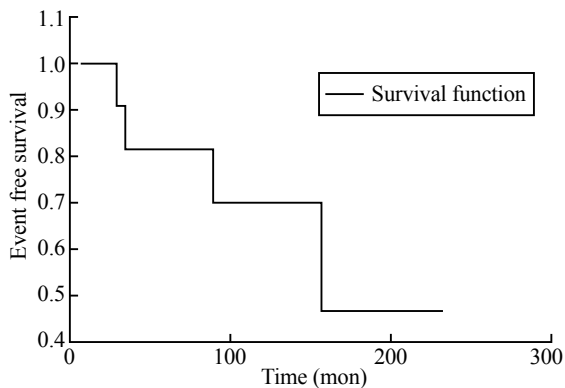


Fig. 2. Kaplan Meier event free survival chart.

groups:^[1] those with predominantly cystic lesions with an insignificant solid part (type I, $n=5$); those with polycystic tumors with appreciable solid portion (type II, $n=7$); and those with usually small, predominantly solid tumors (type III, $n=1$). Regarding the tumor grade,^[14] eleven children had tumor of grade 0, and two had tumor of grade 1.

Gross tumor removal (GTR) was attempted in all children. In 6 children craniotomy with a subfrontal pteryonal approach was performed, and in 7 children the transcallosal/transcortical approach was performed. Two children required a second craniotomy for GTR. Two children were subjected to additional surgery for the nasal liquor fistula. Radiosurgical option or gamma knife was not available. Twelve children received a total radiation dose of 50-55 Gy (28-30 fractions of 180 cGy) 4-6 weeks (35.17 ± 4.95 days) after surgery. Bleomycin was given to the other one child.

Follow-up duration ranged from 6 to 229 months (mean 107.00 ± 74.04 months). One child with chronic seizures was treated with antiepileptic drugs. There were no operative deaths within 30 days after surgery, nor during the follow-up. Local tumor recurrence was

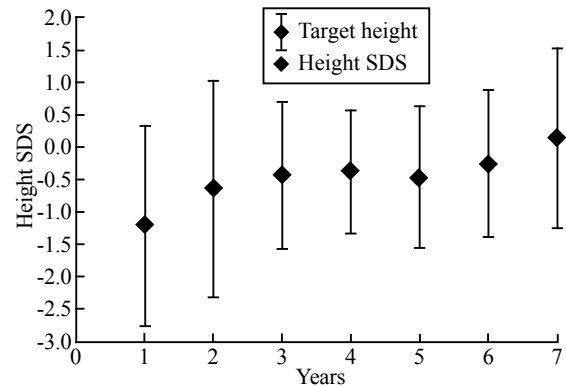


Fig. 3. Height SDS for chronological age from the onset of treatment (13 children) to the final height (8 children).

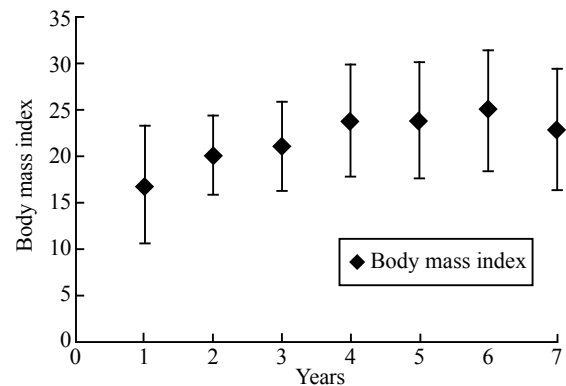


Fig. 4. Body mass index SDS for chronological age from the onset of treatment (13 children) to the final height (8 children).

shown by CT/MRI in 4 children (Table, Fig. 2).

Before treatment growth hormone deficiency (GHD) was diagnosed in 5 children, and DI in 2. All of the 13 children had multiple pituitary deficiencies after the surgical removal of the tumor. After surgery they were treated with thyroxin and cortisone. Among the children of pubertal age, one girl received estrogen and 7 boys received chorionic gonadotropin followed by testosterone. Eleven children were treated with growth hormone, resulting in normalization of the adult height to -0.13 ± 1.39 SDS from -1.27 ± 1.52 SDS before the treatment (Fig. 3). The final height was not lower than the genetic target height ($P>0.05$). Parental heights were obtained from 11 parents (-0.22 ± 1.05 SDS). Since only 4 girls with insufficient follow-up or had adult height, the growth was not compared between boys and girls. DI was permanent in 9 of the 13 children. Obesity was not found before treatment, but BMI increased from 16.93 ± 6.34 to 26.33 ± 5.91 ($P<0.05$) (Fig. 4). The Z test ($z=3.909$, $DF=12$, $P<0.05$) showed significantly higher BMI after surgery and irradiation. Before surgery, 6 children were underweight and 7 had a normal weight. After surgery 2 children were still underweight, 6 had

a normal BMI, 3 were overweight, and one had obesity (1st degree). No extreme obesity was observed.

Blindness in one or both eyes was found in 4 children, bitemporal hemianopsia in 4, and other visual defects in 2. Surgical treatment failed to change the initial visual status of those children.

Discussion

The incidence of craniopharyngioma is reported to be 0.13 per 100 000 per year in the USA, 1.4 per million in Piedmont, Italy and 0.5 per million.^[15-18] The estimated incidence in Macedonia is 1.43 per 1000 000 as revealed in the present study.

The most frequent initial symptom was headache, followed by visual disturbances.^[1] Increased intracranial pressure is also seen frequently.^[19,20] Visual defect is detected in 79% of the patients,^[4] and blindness in one or both eyes is frequent (9%-36%) and did not improve after surgery.^[1] There are high frequency of blindness in our patients. This might be attributed that the children were not able to pinpoint the actual date of occurrence of the visual disturbances because of their age and the fact that the vision on the other eye or in a part of visual field(s) was preserved.

Diabetes insipidus was found in 7%-52% (15.38% in our series) of the patients before treatment.^[21-23] Antidiuretic hormone deficit after surgery is present in 25%-86% (69.23% in our patients).^[1] Obesity before treatment was found in 26%-67% of the children.^[5] BMI in children with suprasellar craniopharyngioma^[24] and in children with higher tumor volume was significantly greater than that in patients with intrasellar craniopharyngioma. In our patients BMI increased significantly at the end of the follow-up. Postoperative obesity was reported in 26%-61% of the patients,^[1] but it was not a particular problem in our patients.

Short stature prior to surgery was found in 7%-53%.^[21,22] Growth deceleration is often overlooked. Mean height SDS at admission was significantly lower than mean target height SDS, while mean final height SDS was similar.^[23] In our group all patients were growth delayed and short for the target height, indicating probably a delay in diagnosis.

Growth hormone deficiency and hypotalamo-pituitary dysfunction before treatment vary between 35%-100%.^[1,3,6,21,25] Endocrine disorder was the principal reason for medical referral in 16/57 patients.^[26] In our group of patients growth hormone deficiency was found in 5 (38.46%) children, which situates this group in the lower end of the published data.^[1,2,3,6,25] Adolescents are frequently referred because of delayed puberty.^[23] Only one child in our group had a late puberty as a presenting

sign. Growth hormone deficiency after treatment varies between 88%-100%.^[21,22] Final height in 25 patients was significantly lower than genetic target height.^[27] Our patients realized normalization of the adult height, nevertheless, the final height was below the genetic target height ($P>0.05$).

Recent reports show that survival has dramatically improved.^[5,16,19,28-31] Operative mortality was reported at 2.4%,^[32] 3.7%,^[30] and 7.4%.^[33] In addition, more postoperative deaths (9/51 children; 2 following the relapse procedure) were also reported.^[19] It is of note that no deaths were reported in our patients. Both long-term cure rate and long-term recurrence rate were reported high (82% and 18% respectively^[10,28,33]). Somewhat lower rates are also observed: the ten-year-survival, progression-free and event-free survival rates were 65%, 39% and 29%, respectively.^[33] Favorable rates were also reported for recurrences. Vinchon and Dhellemmes^[34] reported a 5-year survival rate of 49.9%, and a 10-year survival rate of 40%. Recurrence free rate of 63% at 10.3 years was also reported.^[35] We found a recurrence free rate of 9/13 patients.

The choice of radical versus subtotal tumor removal is still the matter of controversy. It seems that data collected show that GTR brings the risk of severe and more frequent neurologic and endocrine sequelae, while offering fewer recurrences.^[20,30,32,36,37] Some authors recommend a less aggressive, multi-staged and personalized treatment.^[37] For the surgeon the greatest dilemma is to determine intraoperatively whether the better option for the patient is to stop or to continue the attempt at GTR.^[38] Transsphenoidal approach is favored wherever possible.

The degree of resection is not significantly associated with progression-free survival (PFS),^[10] while the absence of calcifications is associated with improved PFS.^[28] Female sex is an independent predictor of increased cardiovascular, neurological and psychosocial morbidity.^[9] Poor outcome was significantly associated with tumor dimension,^[18] the age of the patient, and the size of the tumor.

In conclusion, we found no mortality in the patients treated. Subtotal resection and irradiation resulted in a good quality survival. The incidence rate for childhood craniopharyngioma for the period of 1989-2008 in Macedonia was 1.43 per 1 000 000 person-years.

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