Original Article

Evaluation of Various Modalities of Craniopharyngiomas Management: A Preliminary Study of Twenty Cases

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ABSTRACT

Background: Craniopharyngioma is a histological benign epithelial tumor arising from the remnants of the Rathke’s pouch. Owing to their aggressive infiltrative behavior, the optimal treatment of craniopharyngioma remains a challenge. Objective: The aim of this work is to evaluate indications, efficacy and safety of various modalities used for treatment of craniopharyngiomas. Patients and Methods: This study was conducted on twenty consecutive patients between October 2012 and October 2014 presenting with craniopharyngiomas. The follow-up period ranged from 2 - 24 months. Results: This study included twelve females and eight males, the age ranged from 5-50 years with mean age of 25.45 years. Visual impairment was the most common presenting complaint. Treatment modalities used in this work included; surgical excision, Gamma knife radiosurgery, external beam radiation therapy, and Ommaya reservoir. Visual function improved in three cases without deterioration or improvement in other cases. No change in the pretreatment endocrinological status apart from three surgically treated cases required long-term ADH treatment. Three cases died in the early postoperative period. Conclusion: Analysis of clinical and imaging parameters designated that patients with a worse prognosis are those presented with hypothalamic dysfunction, hydrocephalus, large tumors, peritumoral edema, and calcifications.

INTRODUCTION

Craniopharyngiomas comprise approximately 2.5-4% of all intracranial tumors. Although half of these occur in adults, they account for a greater percentage of childhood tumors. A bimodal distribution by age was noted with peak incidence rates in children of ages 5–14 yr and adults of ages 50–74 yr. Craniopharyngiomas are benign, slowly growing, well-encapsulated tumors of variable consistency (solid and/or cystic with or without calcification) that involve primarily the sellar/parasellar region. Histologically, two primary subtypes have been recognized, the adamantinomatous and the squamous-papillary type.

Pathogenesis is uncertain; according to one hypothesis they arise from neoplastic transformation of embryonic squamous cell rests of the craniopharyngeal duct. A second theory suggests that they result from metaplasia of adenohypophysial cells in the pituitary stalk or gland. Craniopharyngiomas are still regarded to be one of the most challenging intracranial lesions requiring multimodal approach regarding their uncertain behavior and tumour’s proximity to vital neurovascular structures.

This work highlights the clinical, radiological and laboratory features of craniopharyngiomas and analyzes their relation to outcome of the therapeutic option.

MATERIALS AND METHODS

This study was conducted in the Department of Neurosurgery, Benha University during the period from October 2012 to October 2014. This work was done on twenty patients with craniopharyngioma. The patients were evaluated according to the modality of treatment used, and follow-up (by clinical, ophthalmological and radiological assessment) were done two months after the intervention for assessment of the results of each treatment modality. The surgical procedures included tumor removal (total, subtotal, cyst evacuation and biopsy or biopsy only), CSF diversion (shunting), or Ommaya reservoir placement. External Beam Radiation Therapy (EBRT) or Gamma Knife Radiosurgery (GKS) were done for selected patients. The outcome was classified into good and bad according to the criteria of Duff et al as shown in (Table 1).
Table 1: The outcome of management was graded according to the following criteria.8

<table>
<thead>
<tr>
<th>Good</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alive at follow-up examination.</td>
<td>Patients not meeting the &quot;good&quot; criteria</td>
</tr>
<tr>
<td>2. No major motor deficit related to operation or tumor progression.</td>
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<tr>
<td>3. Functional vision.</td>
<td></td>
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<tr>
<td>4. Katz Grade A (able to perform basic activities of daily living &quot;ADLs&quot;).</td>
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<td>5. Karnofsky Performance Scale score ≥80.</td>
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<td>6. No more than 1 year behind in expected school grade.</td>
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<tr>
<td>7. Employability for adults of working age.</td>
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<tr>
<td>8. Absence of debilitating psychological or emotional problems.</td>
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</table>

RESULTS

This study included twelve females and eight males, with age range 5-50 years. Ten cases were children (≤ 16 years) and ten were adults (>16 years). The mean age was 25.45 years. This study was conducted on twenty cases; twelve primary cases and eight recurrent cases. All cases presented with gradual onset and progressive course, the duration of symptoms ranged from 2-36 months. The mean duration was 11.85 months.

Visual impairment was the most common presenting complaint (all the twenty cases). Headache was the second most common complaint (seventeen cases). Endocrinological symptoms come third (eight cases). Hypothalamic regulatory symptoms were encountered in four cases. Neurobehavioral disorders were present in three cases. Only one case in this study was complaining of seizures, three cases were presenting with vomiting and one case with symptoms suggestive of autonomic disturbance. (Figure 1) shows the clinical presentation relative to the age group.

Examination revealed deteriorated visual acuity in all patients. Fundus examination revealed papilledema in eight cases (40%), atrophic papilla in nine cases (45%), and normal in three cases (15%). Field assessment revealed bitemporal hemianopia in seven cases (35%), left temporal hemianopia in three cases (15%), concentric field in one case (5%), and can't be assessed in nine cases (45%); either due to marked diminution of vision or uncooperative patient. Left abducent palsy was present in one case (5%). Cognitive functions were impaired in four cases. Four patients were obese while one patient was underweight. Hormonal abnormalities were frequent in this series as shown in (Figure 2).

Routine laboratory investigations were within normal range in most cases in this work.

![Fig. 1: Clinical presentation relative to age group.](image1)

![Fig. 2: Hormonal abnormalities according to age group.](image2)

All cases in this work were studied with MRI, nineteen cases with CT brain, and three cases with plain x-ray. Imaging features obtained in these cases are summarized in (Table 2).
Table 2: Imaging features relative to tumor type.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Imaging features</th>
<th>Number of cases</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Primary tumor</td>
<td>Recurrent tumor</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>Oval</td>
<td>6</td>
<td>3</td>
<td>9</td>
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<tr>
<td></td>
<td>Lobular</td>
<td>5</td>
<td>5</td>
<td>10</td>
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<tr>
<td></td>
<td>Bilobed</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>Calcifications</td>
<td>-</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td></td>
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<tr>
<td></td>
<td>+</td>
<td>2</td>
<td>6</td>
<td>8</td>
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<td>Cysts</td>
<td>-</td>
<td>1</td>
<td>0</td>
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<td></td>
<td>+</td>
<td>11</td>
<td>6</td>
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<td>0</td>
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<td>Solid parts</td>
<td>-</td>
<td>2</td>
<td>0</td>
<td>2</td>
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<td></td>
<td>+</td>
<td>10</td>
<td>8</td>
<td>18</td>
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<tr>
<td>Enhancement</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td></td>
<td>+</td>
<td>11</td>
<td>8</td>
<td>19</td>
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<tr>
<td>Surrounding edema</td>
<td>-</td>
<td>11</td>
<td>5</td>
<td>16</td>
<td></td>
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<td></td>
<td>+</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>-</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td></td>
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<tr>
<td></td>
<td>+</td>
<td>3</td>
<td>4</td>
<td>7</td>
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</table>

Treatment modalities used in this work included; surgical excision utilized in sixteen cases (ten primary cases and six recurrent), GKR was used as adjuvant therapy in four primary cases for postoperative residual, one recurrent case, and as sole treatment in one primary case, EBRT was used postoperatively in one recurrent case. Ommaya reservoir was inserted in the cystic part of three primary and four recurrent cases, and V-P shunt was used to treat hydrocephalus in three primary and four recurrent cases.

Surgical approaches used in this work included; transsphenoidal in two cases, lateral supraorbital approach "via eye brow skin incision" in three cases, subfrontal approach in six cases, pterional approach in four cases, and combined transcallosal and subfrontal approach in one case. Choice of the surgical approach was based on the surgeon’s preference and experience, location, consistency, degree of calcification, shape, size, and whether the tumor is primary or recurrent.

The goal of treatment was to relieve the raised ICP, optic nerve compression, preserve hypothalamic function, provide long-term tumor control and avoid repeat surgery.

The follow-up period was ranged from 2-24 months with mean period 9.7 months.

Visual function evaluation during follow-up period revealed improvement in three cases. Other cases showed no change in the pretreatment visual function (acuity and field), and no case developed deterioration of vision.

No change in the pretreatment endocrinological status (whether improvement or deterioration) apart from three surgically treated cases requiring long-term ADH treatment. Patients with preoperative hormone dysfunction continued their follow-up with the endocrinologist.

Complications were infrequent in these cases; only one case developed transient CSF rhinorrhea after transsphenoidal approach and resolved with conservative measures, another case developed acute subdural hematoma after attempted excision of recurrent tumor but was not sizable and was managed expectantly.

Poor outcome were absence of functional vision in the four cases plus loss of employability in one case and poor school performance in one case, but it is worth noting that poor vision and cognitive impairment were pretreatment presentations. Three cases died in the early postoperative period (two recurrent and one primary).

Ordinal logistic analysis was performed to determine the impact of age at surgery and tumor size (continuous variable), sex, presence of hydrocephalus, and prior treatment (dichotomous) on the ultimate outcome after treatment, namely mortality as no new morbidity was faced in this series. Each model was tested for significance by using Cox and Snell pseudo-R2 testing and model-fitting chi-square testing with p values. Averages are expressed as the mean ± SD. The Student t-test was used to compare the following parametric variables: age at time of surgery, maximal tumor diameter, and follow-up duration. A p value of < 0.05 was considered statistically significant.

Our results revealed no statistically significant correlation between age, sex, or pre-treatment duration of symptoms and outcome.

Correlation between the presenting symptoms and outcome were statistically significant regarding; the presence of obesity, fatigability & decreased activity, polyuria & polydepsia, autonomic disturbance, and previous surgery to poor outcome.

Analysis of imaging features of the tumor revealed no significant relationship between outcome and shape, cystic component, solid parts, or enhancement. There were statistically significant relationships between outcome and presence of hydrocephalus, peritumoral edema, and calcification. Also, there was statistically significant relationship between outcome and tumor size. The relationship was highly significant between outcome and presence of heavy calcification. Some illustrative cases are shown in (Figures 3-6).
Fig. 3 a-c: A sixteen years old male patient presented with gradually worsening headache accompanied by blurring of vision. Visual examination revealed bilateral papilledema, bitemporal hemianopia. MRI brain with contrast showed large sellar/suprasellar heterogenously enhanced mass. b: Patient was operated via subfrontal approach and pathological examination proved craniopharyngioma. Postoperative MRI brain with contrast performed one week after surgery revealed radical subtotal resection. c: Follow-up MRI brain with contrast performed one year after surgery revealed good tumor control.

Fig. 4 a-i: A five years old girl, with history of V-P shunting and craniopharyngioma surgery, presented by severe headache, vomiting and visual deterioration. b: MRI brain with contrast showed hydrocephalic changes and tumor recurrence. c: There was significant peritumoral edema "moustache sign" in FLAIR. d: A contralateral V-P shunt and direct tumor attack were done with adequate tumor debulking and improvement of hydrocephalus. e: Six months later patient developed new deterioration of vision and follow-up MRI with contrast revealed tumor regrowth as shown in axial T2WI. f: and sagittal T1WI with contrast. Patient was operated by combined subfrontal and transcrallosal approach with subtotal excision as shown in post-operative MRI, axial T2WI. g: and sagittal T1WI with contrast. h&i: Then patient received EBRT, and follow-up 1 year proved satisfactory tumor control.
Fig. 5 a-c: A forty five years old male patient presented with chronic headache accompanied by mild diminution of vision. Clinical and laboratory assessment was unremarkable. MRI brain with contrast showed sellar/suprasellar mass (a). Gamma knife radiosurgery was performed and follow-up MRI brain after one year proved good tumor control (b) and (c).

Fig. 6 a-d: A five years old girl with history of V-P shunting and craniopharyngioma surgery, presented by severe headache, vomiting and visual deterioration. MRI brain revealed tumor recurrence with a solid suprasellar part and large retrostellar - parasellar cysts compressing the brain stem and effacing the 4th ventricle (a) and (b). Cyst evacuation via Ommaya reservoir was performed. Patient improved clinically, follow-up CT brain showed satisfactory cyst evacuation and decompression of the brain stem and fourth ventricle.

DISCUSSION

This work was done on twenty patients with craniopharyngioma over a period of two years, and subjected to one of the modalities of treatment. About 55% of our cases were younger than 20 years conforming well to the first peak incidence in the literature.1,2 No second peak was faced. Sex distribution in this work (females>males) is quite similar to other series, but is different from most case series with equal sex distribution and the large English series in which males were more than females.9,10

The duration of symptoms ranged from 2 months to 36 months in the range described in most series.8,11 The median duration was 9.0 months, which is very close to the median duration in the literature (10 months).12

Visual disturbances were the most common presenting symptom in this work corresponding to other series and most series from developing countries.13 Headache was the second most common complaint and was associated with vomiting in 15% of cases; this was close to other results.11 Endocrine disturbances were evident in 40% of cases in the order of decreasing frequency were gonadal insufficiency, growth failure in children, hypothalamic dysfunction, Diabetes insipidus, hypothyroidism and hypocortisolemia; this was more or less similar to the findings in the literature.1,3,14,15

Imaging studies performed in this work declared the following features; no difference in tumor consistency either between primary and recurrent lesions or between children and adults compatible with other findings.6,7 Calcifications were evident in 50% of cases, and hydrocephalus was evident in 35% of cases approaching other studies.8,11

All pathologically proven craniopharyngioma (nineteen cases) were of the adamantinomatous subtype apart from one case that was of the papillary variety representing 5.26% of all cases, and 11% of adult cases in comparison to the series in which papillary variety was reported in 14–50% in adult patients, and in less than 2% of pediatrics.16,17

The goal of treatment was to relieve the raised ICP and optic nerve compression, preserve existing hypothalamic function and vision, provide long-term tumor control, avoid repeat surgery and minimize neurotoxic effects from surgery and radiotherapy.

The degree of resection was graded according to the parameters of Jane et al.18 Gross-total resection (residual tumor at surgery but not evident in postoperative MRI) was achieved in 6.25%, radical subtotal resection (95%
tumor removal) in 56.25%, subtotal resection (at least 50% tumor removal) in 31.25%, partial resection (<50% tumor removal) in 6.25% of cases. Incomplete surgical eradication of the tumor tissue was intentional for tumors involving hypothalamus following the concept of intentional subtotal/ partial excision and radiotherapy for tumors involving hypothalamus 19 and obligatory in many cases because of complex relationship or firm adherence of the tumor to surrounding structures and its large size. Some authors agree that size has no effect on extent of resection 11, 20, while others believe that tumors larger than 4 cm are less likely to be totally resected. 4, 21

Subfrontal approach was used in six cases; four primary and two recurrent cases. It is the preferred approach for excision of craniopharyngiomas according to some authors 4, 22 while others believed that it causes significant frontal lobe and visual perception dysfunction. 23

Pterional approach was tried in four cases; three primary and one recurrent case. Pterional approach is favored by as it provides the shortest, most direct route to the suprasellar region. 24 This approach minimizes frontal and temporal lobe retraction. On the other hand it carries a not-negligible risk of postoperative visual worsening. 13, 25

Transciliary lateral supraorbital approach was used in two primary cases and one recurrent case without technique related complications. The procedure was appealing because of minimal dissection and smaller but strategic bone opening with less exposure of the brain surface. Its limitations include severe brain swelling and purely intraventricular lesions. Moreover, it is technically demanding and requires well trained surgeon on this approach. Our findings are compatible with the findings of other series. 26

Transsphenoidal approach was used in two cases, one recurrent case after previous transsphenoidal surgery; in which cyst evacuation and tumor debulking was performed. The other case was predominantly cystic and gross total removal was achievable. Transsphenoidal approach is an efficient route for intrasellar and suprasellar craniopharyngiomas except dumbbell or multinodular tumors. 27, 28

A combined transcallosal- subfrontal approach was used in one case because the tumor was recurrent, large, retrochiasmatic and reaching the roof of the 3rd ventricle causing hydrocephalus. These criteria were classified as indications of combined approach. 29 This combined approach facilitated radical subtotal resection with adjuvant postoperative external-beam radiation therapy as recommended by some authors. 29 Being only one case it is insufficient for comparison with the work of others. 29

Craniopharyngioma is highly radiosensitive to either fractionated therapy or radiosurgery and is effectively treated with a low marginal dose ≈ 10 Gy which is tolerated by the optic nerve. GKS was introduced as primary therapy for one case (predominantly solid lesion) according to the recommendation for using GKS as initial therapy for solid craniopharyngioma. 31 GKS was introduced as secondary treatment for: residual tumor in four cases and recurrent tumor in one case as family refused redo surgery. Ommaya reservoir was inserted in two cases before GKS aiming to reduce cyst volume to reduce the risk of radiation-induced injury and allow more effective targeting of the solid portion of the tumor. Analysis of results obtained with GKS revealed; tumor shrinkage was achieved in two cases, and four cases experienced tumor stabilization over a period of approximately 24 months. After considering limited number of cases and short follow up period, this can be compared with results of others as. 32 No complications or treatment related morbidity were faced in these cases after GKS.

Three cases died in the early postoperative period, representing about 15.7% of surgically treated cases. Overall perioperative mortality rate in other studies ranged between 0% and 5%. 35 Data on the treatment-related survival are inconsistent, lack statistical evaluations and affected by the applied therapeutic option resulting in significant heterogeneous results. 2

There was modest improvement of visual function in three cases. It can be accepted that visual function only occasionally improves after surgery. 13 No recorded improvement of preoperative endocrinological status with post-operative diabetes insipidus in 30% of cases; compatible with the believes that restoration of preexisting hormone deficits is absent or uncommon, and reported diabetes insipidus within the range of 25–86%. 7

The outcome of the management was graded according to the criteria adopted by Duff et al. 8 It is simple and can be applied in spite of our limitations in forming true team work and lack of neuropsychological and social partners with significant loss of functional data and inadequate assessment.

No statistically significant correlation was found between age, sex, or duration of symptoms and outcome. The impact of age at diagnosis as a prognostic factor of survival is controversial; some studies suggest better outcome in younger patients 6, others in older age groups 2, while others have found no difference between children and adults. 29

Correlation between hypothalamic dysfunction and poor outcome was statistically significant consistent with other results. 24

Correlation between recurrence and poor outcome was statistically significant. A review of the literature indicated increased morbidity and mortality at reoperation. 24 This may be explained by loss of arachnoid plane with more adhesions to surrounding structures. Most recurrences happen in the first postoperative 3–4 years, this create the need for
frequent surveillance imaging during this time period. Some authors recommend MR imaging at 3-month intervals for the 1st year, 4-month intervals in the 2nd year, and 6-month intervals for the next 3–5 years.\textsuperscript{24}

Analysis of imaging features of the tumor revealed no significant relationship between outcome and shape, consistency, or enhancement, compatible with other studies.\textsuperscript{3} There were statistically significant relationships between outcome and presence of hydrocephalus, consistent with some series\textsuperscript{24} and contrary to others.\textsuperscript{7} Also, there was statistically significant relationship between outcome and tumor size, consistent with some series,\textsuperscript{24} and contrary to others.\textsuperscript{35}

The relationships between outcome and presence of peritumoral edema, and calcifications were statistically significant in this study. The P value was <0.05 for the presence of peritumoral edema, and <0.01 for the presence of calcifications Some authors reported high recurrence rate and poor outcome with calcified tumors,\textsuperscript{36} while others proposed that calcifications are not associated with poor outcome.\textsuperscript{35} Review of the literature failed to find any work addressing the relation between outcome and presence of peritumoral edema.

Declaration

The author(s) declare no conflict of interest or any financial support and confirm the approval of the submitted article by the concerned ethical committee.

CONCLUSION

The goal of treatment in craniopharyngioma should focus on long-term tumor control, reduction of the disease and treatment-related morbidity and mortality and preservation of quality of life. Unfavorable prognosticators include hypothalamic dysfunction, hydrocephalus, large tumors, peritumoral edema, calcifications and recurrent tumors so first surgery should be utilized carefully as the best chance. The severity and rarity of craniopharyngiomas mandates central registration, which may provide correlates between treatments and outcomes, guiding us in the future.

REFERENCES


