Stereotaxic intracavitary irradiation for cystic craniopharyngiomas

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Stereotaxic intracavitary irradiation with instillation of phosphorus-32 (32P) colloidal chromic phosphate was performed in nine patients with cystic craniopharyngiomas. Serial neurological, ophthalmological, neuroendocrinological, and radiological examinations were performed before and after treatment. Dosimetry was determined based on a computerized tomography (CT) estimation of tumor volume, and was calculated to provide a tumoricidal dose (200 to 300 Gy) to the cyst wall. The follow-up period ranged from 14 to 45 months (mean 27 months). After treatment, all nine patients showed improvement of symptoms and radiological evidence of cyst regression. Because of an expanding solid component producing recurrent symptoms, one patient required a craniotomy 14 months after isotope instillation. Three of five patients with impaired visual acuity before surgery had significant improvement in acuity after treatment. Preoperative visual field defects in eight patients improved in four after 32P therapy. Of seven patients with preoperative endocrine abnormalities, one individual showed almost complete normalization and another had improvement in endocrine function. Patients who exhibited residual neuroendocrine function before isotope instillation developed no significant deterioration in endocrine status during the follow-up period. The findings suggest that stereotaxic intracavitary irradiation is a safe and effective treatment which should be considered as the initial surgery for cystic craniopharyngiomas.

KEY WORDS □ craniopharyngioma □ brain neoplasm □ phosphorus-32 □ cystic neoplasm □ stereotaxy

C RANIOPHARYNGIOMAS are histologically benign but clinically treacherous tumors. Their attachment to critical cerebral, endocrine, and vascular structures makes radical excision often difficult and occasionally hazardous.5,10,13 In patients with solitary cystic or multicystic tumors (30% to 60% of total cases),14,21,22 encouraging postoperative survival rates and a high incidence of cyst regression have been reported after intracavitary administration of radiopharmaceutical agents.2,8,9,11,12 Beta-emitting isotopes such as yttrium-90 (90Y), rhenium-186 (186Rh), and phosphorus-32 (32P) have been most commonly used for intracavitary treatment because of the short penetration of their emitted radiation and their relatively brief half-lives. Only 32P is currently available for intracavitary use in the United States.

Between 1983 and 1986, nine patients with cystic craniopharyngiomas were treated by stereotaxic intracavitary irradiation at the University Health Center of Pittsburgh. Although such surgery has been shown to result in roentgenologically documented cyst involu-

Clinical Material and Methods

Patient Selection

The nine patients (three males and six females) ranged in age from 3½ to 72 years. All had predominantly solitary cystic craniopharyngiomas. Two patients had undergone prior craniotomies with subtotal resection of the solid tumor components followed by external beam radiation therapy. In these two patients, the diagnosis of craniopharyngioma was based on the typical histological features of the tumor tissue removed during the initial open procedure. Histological verification of the diagnosis based on biopsy specimens from the cyst wall was also obtained in two of the seven patients who had intracavitary irradiation as the initial treatment. In the remaining five patients, the diagnosis
of craniopharyngioma was based on the following criteria: 1) preoperative clinical findings typical of a suprasellar mass lesion; 2) roentgenological demonstration of a cystic suprasellar mass with a calcified rim; and 3) the finding of motor oil-like fluid (which in three of the five cases contained cholesterol crystals) within the cyst cavity at the time of stereotaxic cyst puncture.

**Preoperative Assessment**

Prior to surgery, all patients underwent detailed neuroradiological investigation to delineate the size and location of the tumor. This evaluation included high-resolution unenhanced and intravenous contrast-enhanced computerized tomography (CT) scanning performed in the axial and coronal planes through the sellar and suprasellar regions. Eight patients underwent formal testing of visual fields and acuity as part of a thorough neuro-ophtalmological examination. The remaining patient, a 31-year-old child who was unable to cooperate with formal testing, had grossly normal visual function. All patients were subjected to preoperative combined endocrine testing which included determination of fasting baseline serum levels of glucose, cortisol, growth hormone, follicle-stimulating hormone, luteinizing hormone (LH), thyroid-stimulating hormone, and prolactin. Glucose and hormone levels were then measured at 15-minute intervals for 90 minutes after the intravenous administration of arginine hydrochloride (0.5 gm/kg to a total of 30 gm, given over 30 minutes), regular insulin (0.05 to 0.2 units/kg), gonadorelin hydrochloride (synthetic LH-releasing hormone, 100 µg), and protirelin (synthetic thyrotropin-releasing hormone, 7 µg/kg to a total of 400 µg). In addition, thyroxine radioimmunoassay and measurements of triiodothyronine resin uptake and testosterone (in males) were performed. Patients with symptoms suggestive of diabetes insipidus were studied by a water deprivation test.

**Surgical Technique**

Surgery was performed under local scalp anesthesia supplemented by intravenous sedation. After placement of the Leksell stereotaxic coordinate frame, a preliminary contrast-enhanced CT scan was obtained with a dedicated surgical GE 8800 CT scanner. The target stereotaxic coordinates were selected for cyst puncture which was carried out with a fine needle (0.9 mm outer diameter), yielding fluid for microscopic examination. Dosimetry was based on the cyst volume as determined by CT in nine patients and was confirmed in six patients by volumes derived using technetium-99 sulfur colloid isotope dilution methods. In order to enhance the accuracy of dosimetry, colloidal chronic phosphate was mixed with a small quantity of 30% glucose diluent (0.1 to 3.0 ml) prior to instillation to expand the volume of injectate in which the 32P was delivered. A target dose of 200 to 300 Gy (20,000 to 30,000 rads) was administered to the cyst wall. A postoperative CT scan was obtained with the stereotaxic frame in place to reassess cyst size and exclude complications related to the needle puncture.

**Postoperative Evaluation**

Follow-up radiological, neurological, endocrinological, and ophtalmological evaluations were performed 3 months after isotope instillation and at 6-month intervals thereafter. The follow-up period ranged from 14 to 45 months (mean 27 months).

**Results**

**Surgery**

Cyst volumes ranged from 2.8 to 80 ml. The 32P dosimetry based on a CT estimation of the tumor volume proved accurate when compared to results obtained using the isotope dilution technique, and three patients were treated with dosimetry calculated from the CT-derived data alone. Five patients underwent nuclear scintigraphy 1 to 3 days after implantation, and none demonstrated leakage of the isotope from the cyst cavity. Four patients who had large cysts and preoperative signs of increased intracranial pressure or rapidly declining vision underwent stereotactic resection with removal of approximately 50% of the cyst volume 14 to 70 days after initial implantation to diminish local mass effect. Although the need for resection in these four patients was anticipated at the time of initial isotope instillation, the target dose to the cyst wall was kept between 200 and 300 Gy. In these four patients, less than 1% of calculated isotope activity was recovered at the time of repeat puncture, presumably because the isotope adhered to the cyst wall.

Prior to stereotaxic 32P instillation, two patients had undergone open procedures for attempted tumor excision (craniotomy and transsphenoidal explorations). In a third patient (a 31-year-old child, who presented with obtundation, papilledema, and severe hydrocephalus), emergency placement of a ventriculoperitoneal shunt preceded 32P therapy. Fourteen months after isotope therapy, one patient required craniotomy and resection of residual solid craniopharyngioma that was causing progressive optic chiasm compression.

**Clinical Findings**

Table 1 details the clinical symptoms and signs in these nine patients before and after surgery. Before surgery, eight patients reported severe headache, eight complained of bothersome visual loss, two had declining mentation, two had progressive obesity of recent onset, three had decreased libido, and one had diplopia. One patient reported polydipsia; diabetes insipidus was confirmed by water deprivation testing. Two other patients were already receiving desmopressin acetate for...
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### TABLE 1

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs</th>
<th>Preop Status</th>
<th>Postop Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Cleared</td>
<td>Improved</td>
</tr>
<tr>
<td>headache</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>visual impairment</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>declining mentation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>obesity</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>decreased libido</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>diplopia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>thirst</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>sign</td>
<td>visual field &amp;/or acuity deficits</td>
<td>8</td>
</tr>
<tr>
<td>lethargy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>oculomotor palsy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ataxia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>papilledema</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* One of these patients showed late visual deterioration 35 months postoperatively.
† Endocrine replacement instituted, with control of symptoms.

### TABLE 2

Cyst size in nine patients at various times after stereotaxic intracavitary irradiation

<table>
<thead>
<tr>
<th>Interval Postinstillation</th>
<th>Cyst Resolved</th>
<th>Cyst Volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 75% Decrease</td>
<td>25%-75% Decrease</td>
</tr>
<tr>
<td>3 mos</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>9 mos</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>15 mos</td>
<td>2</td>
<td>6†</td>
</tr>
<tr>
<td>&gt; 15 mos</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

* In no patient was the cyst volume increased.
† One of these patients required craniotomy for excision of an enlarging solid tumor component.

### TABLE 3

Status of visual function before and 9 months after ³²P intracavitary irradiation in eight patients

<table>
<thead>
<tr>
<th>Visual Findings</th>
<th>Preop Visual Impairment</th>
<th>Postop Visual Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>visual acuity</td>
<td>5‡</td>
<td>2</td>
</tr>
<tr>
<td>visual fields</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

* Delayed deterioration in visual acuity and fields (12 and 35 months after ³²P therapy) occurred in two patients, one of whom had normal acuity before ³²P therapy (see text for explanation).
† Increase in visual acuity to 20/40 or better and/or resolution of a previous hemianopsia, quadrantanopsia, or central visual field defect. This group includes two patients who regained normal acuity and one who regained normal visual fields after ³²P therapy.
‡ Visual acuity less than 20/40 in either eye.

previously documented diabetes insipidus. Five patients had lost anterior pituitary function before surgery. Neurological examinations demonstrated moderate to severe lethargy in three patients, hemiparesis in one patient, partial oculomotor nerve palsy in one patient, and papilledema and bilateral abducens nerve palsies in one patient. Eight patients had deficits affecting their visual acuity and/or visual fields.

During the follow-up period, headache resolved or improved in all eight patients so afflicted. Subjective improvement in vision was reported by seven patients, and dramatic improvement in mentation was noted by one. The single patient with preoperative hemiparesis regained normal use of the affected side 3 months after isotope instillation. In the patient with diplopia due to oculomotor nerve palsy, the symptom resolved.

**Neuroradiological Findings**

Cyst size after ³²P therapy was assessed by serial CT scans and compared with the preoperative baseline study (Table 2). In all nine patients, cyst size decreased during the 3 to 12 months after isotope instillation, then remained stable or continued to decrease in size thereafter (Fig. 1). In two patients the cyst resolved entirely; in five a minute cavity within a calcified rim remained; and in one a 50% decrease in cyst size was noted. In the ninth patient, significant reduction in cyst volume was noted although the solid tumor component continued to grow.

**Neuro-Ophthalmological Findings**

The effect of treatment on visual acuity and fields in the eight testable patients is seen in Table 3. Before surgery, all eight patients had abnormal visual fields; five had evidence of chiasmal compression and three had predominantly unilateral optic tract compromise. Three patients with chiasmal syndromes and one with optic tract involvement also had associated optic nerve compression (central visual field abnormalities and significant unilateral impairment of visual acuity). At 9 months after treatment, visual fields were improved in four patients (one of whom regained normal fields) and stable in four. Before surgery visual acuity was impaired in five patients (worse than 20/40 in either eye), and at 9 months after treatment acuity was improved in three of these (two of whom regained normal acuity) and stable in two. In six of the eight testable patients, visual function remained stable or continued to improve slowly at further follow-up evaluations. Two patients had delayed deterioration in visual function after treatment. In one patient with normal visual acuity and bitemporal field defects before surgery, declining vision resulting from growth of solid tumor was found 12 months after ³²P therapy. Craniotomy was performed to remove this solid tumor component, but unfortunately vision failed to improve. A second patient, who had only one-half of one visual field preoperatively, became blind 35 months after surgery despite nearly complete resolution of the cyst. Because this patient had undergone two prior operations and external beam radiotherapy, the delayed blindness was likely multifac-
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**Neuroendocrinological Findings**

Assessment of anterior and posterior pituitary function before surgery (Table 4) revealed normal pituitary function in two patients and panhypopituitarism in three patients. Two patients had preservation of only posterior pituitary function, and two had selective impairment of growth hormone and/or gonadotropin function. During the follow-up period, partial improvement in endocrine status was noted in one patient (Case 3) and nearly total resolution of abnormalities was seen in another (Case 5) (Tables 4 and 5). No significant change in endocrine function was recorded in the remaining seven patients. Those individuals with intact endocrine function before treatment retained normal function after isotope instillation. No evidence of late deterioration in endocrine function was noted.

**Morbidity and Mortality**

No complications resulted from the initial isotope instillation. After surgery, no immediate or long-term radiation-related sequelae were confirmed during the follow-up period, except possibly in the one patient with delayed visual loss described above. This patient also manifested signs of a slowly progressive dementia. No other patient demonstrated deterioration in either neurological or endocrinological function, or CT evidence of radiation injury to the surrounding brain. One patient died from a myocardial infarction 2 years after treatment.

**Discussion**

Stereotaxic intracavitary irradiation of cystic craniopharyngiomas using $^{32}$P chromic phosphate was described by Leksell, et al., in 1967. Subsequent application of this technique using a variety of different beta and gamma radiation-emitting isotopes (such as gold-198 ($^{198}$Au), $^{90}$Y, or $^{166}$Rh) has been reported by several authors. As an internal radiation source, beta-emitting isotopes are preferred because of the limited penetrance of the energy released and the greater ease of handling. Of the isotopes listed, only $^{32}$P and $^{90}$Y are pure beta-emitters. As compared to $^{90}$Y, $^{32}$P has a lower mean energy release (0.69 MeV vs. 0.93 MeV) and a shorter tissue penetrance (half value 0.8 mm vs. 1.1 mm; maximum range 7.9 mm vs. 11.0 mm). The short tissue penetrance minimizes damage to surrounding critical vascular and neural structures. The half-life of $^{32}$P is 14.2 days in compari-
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### TABLE 4
Results of pre- and postoperative endocrinological assessment*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Adrenal</th>
<th>Thyroid</th>
<th>Growth</th>
<th>LH/FSH</th>
<th>Pro-lactin</th>
<th>Anterior Pituitary Function</th>
<th>Posterior Pituitary Function: ADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>2</td>
<td>3 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>3</td>
<td>2 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>4</td>
<td>7 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>5</td>
<td>6 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>6</td>
<td>5 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>7</td>
<td>4 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>8</td>
<td>3 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
<tr>
<td>9</td>
<td>2 1/2</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>normal</td>
<td>ADH -=</td>
</tr>
</tbody>
</table>

* Results of baseline and stimulated hormone levels; a postoperative change in status is indicated by an arrow. A = abnormal; N = normal; — = tests not performed. LH/FSH = luteinizing hormone/follicle-stimulating hormone; ADH = antidiuretic hormone. Case numbers correspond to those in Fig. 1.

In an additional 32 patients with recurrent tumor after previous radical surgery, he reported that 84% had good-quality survival. Strauss, et al., 23 reported a decrease in cyst size in six of 11 patients followed for at least 4 months postinstillation. Cyst collapse or significant decrease in volume was documented in all eight patients reported by Kobayashi, et al., 11 who were followed for 13 to 156 months; however, one patient who was treated initially with only 6000 rads required a second isotope instillation.

In the present series, all nine patients had radiographic evidence of cyst regression: complete cyst obliteration was noted in two; greater than 75% decrease in volume in six; and approximately 50% volume decrease in one. Associated improvement of symptoms was noted in eight patients.

Detailed data on the effects of intracavitary irradiation on endocrine and visual function have been provided in comparatively few patients prior to this report. Backlund, et al., 2, 14 noted some improvement in visual acuity and/or fields in six of nine patients presenting initially with visual loss. A single patient had worsening of vision in one eye. Strauss, et al., 23 also reported one case of visual deterioration after treatment. In the nine patients treated by Julow, et al., 23 visual acuity remained stable in eight and deteriorated in one. In a review of 15 patients treated with 199Au, Kodama, et al., 12 noted some improvement in visual function in nine, stabilization in four, and deterioration in two who subsequently required craniotomy for resection of recurrent tumor. In our own experience, visual acuity improved in three of five patients who exhibited preoperative impairment. Of the eight evaluable patients, visual fields improved in four, remained stable in two, and deteriorated in two. In the two patients who had undergone previous surgery and external beam radiotherapy, ongoing visual deterioration was arrested in one patient (although visual function remained impaired) and late visual deterioration developed in another. The most encouraging response to treatment was noted in three patients who had exhibited visual symptoms for less than 1 year. All three maintained or regained nearly normal visual acuity and fields. The less dramatic results of treatment in patients with long-standing visual compromise may reflect the effect of irreversible damage to the optic apparatus from chronic compression.

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=* No change in preexisting endocrine impairment.
In contrast to the dramatic decreases in cyst volume on serial radiographic studies and the generally favorable impact of treatment on visual function, changes in endocrine status were modest. This again may relate to irremediable damage to the hypothalamopituitary axis since radiographic evidence of mass effect was alleviated in all nine cases. Before treatment, five patients had absent anterior pituitary function; four showed no significant changes in replacement hormone requirements after surgery. One patient with absent anterior pituitary function before treatment and one with an incomplete endocrinologic deficit had improvement in function after surgery. Two patients with essentially normal endocrine function before isotope instillation retained normal endocrinologic status during the follow-up period. No patient in the present series developed postoperative diabetes insipidus, a sequela frequently associated with radical surgery.\(^1,2,7,20\) In the series reported by Kodama, et al.,\(^12\) no significant changes in endocrinologic status were noted after treatment, although three patients had mild improvements in growth hormone response to insulin challenge testing. Backlund\(^1\) reported nine patients with preoperative endocrine deficits; four patients showed partial improvements in anterior pituitary function and three in posterior pituitary function.

Complications related to the stereotaxic procedure itself are uncommon. Backlund\(^1\) reported a single case of subarachnoid hemorrhage and subsequent death resulting from inadvertent puncture of the anterior cerebral artery. Sturm, et al.,\(^24\) described a frontal hematoma in one of their patients. Julow, et al.,\(^9\) reported a patient who developed fatal meningitis after cyst puncture. No complications of surgery were encountered in the present series.

New cyst formation, reported by others, has been treated effectively by additional isotope instillation.\(^1,2,8\) Secondary cyst formation has not proved to be a problem in our series, but growth of residual solid tumor led to increased visual loss in at least one patient. Residual solid neoplasm in one other patient (who had also failed two previous operations and external beam irradiation) probably contributed to eventual blindness and dementia.

Stereotaxic intracavitary irradiation is a safe and efficacious treatment which should be considered as a primary surgical modality in cases of solitary cystic or multiloculated craniopharyngiomas. Although the follow-up period in the present series is limited and further studies will be needed to assess the impact of this treatment on long-term survival, disease control, and symptom relief, the initial response to therapy in our patients has been encouraging. Such treatment obviated the need for craniotomy and resection in the majority of patients. It resulted in a significant reduction in cyst size associated with improvement of clinical symptoms and often neuro-ophthalmological deficits, and preservation of endocrinological function.

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