CORTISONE AS AN AID IN THE SURGICAL TREATMENT OF CRANIOPHARYNGIOMAS*

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The surgical treatment of the craniopharyngiomas has been attended by a high mortality rate in the past, especially when total removal was attempted. An operative mortality of 41 per cent, and even higher, has been reported. The close relationship of most craniopharyngiomas to the hypothalamus exposes the latter to operative trauma and in the past, postoperative death has usually been attributed to this cause. Another factor that was thought to contribute to this high mortality, and with good reason we now believe, was the longstanding direct pressure effect of the tumor on the pituitary gland itself.

Patients in whom the anterior lobe of the pituitary gland has been compressed with resultant hypopituitarism are a poor risk for any type of surgical procedure. They may die of adrenocortical collapse either during or shortly after operation. Even in patients without preoperative evidence of hypopituitarism, removal of a craniopharyngioma may necessitate extension of the dissection into the sella turcica with resultant damage to the hypophysis. This may lead to loss of endogenous adrenocorticotrophic hormone upon which survival depends.

At the University Hospital the craniopharyngiomas have been approached for the past 30 years with the idea that total removal would be performed whenever possible. In cases in which the tumor extended beneath the optic chiasm to invade the third ventricle, or when it was densely adherent to the optic nerves or internal carotid arteries, only the accessible portions were removed. In the series reported by Gordy, Peet, and Kahn total removal was believed to have been accomplished in 25 of 51 cases. Recurrence was known to have taken place, however, in 6 of these patients. The operative mortality in the entire series was 41 per cent. The majority of deaths were attributed to severe hypothalamic reactions as a result of operative trauma.

We are reporting a series of 21 patients all operated upon by one of us (E.A.K.) since 1936. Since there has been little change in operative technique over this period of time, it is our opinion that the greatest variable affecting the markedly improved postoperative survival has been the use of

* Presented at the meeting of the Harvey Cushing Society, Quebec, Canada, May 17, 1955.
TABLE 1
Postoperative results, craniopharyngiomas
Definite hypopituitarism
Cortisone not used

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Estimated Removal of Tumor</th>
<th>Maximum Rectal Temperature</th>
<th>Time and Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>M</td>
<td>Incomplete</td>
<td>97.6°</td>
<td>3 hrs. p.o. Circulatory collapse</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>M</td>
<td>Incomplete</td>
<td>106°</td>
<td>1st day p.o. Circulatory collapse</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>F</td>
<td>Incomplete</td>
<td>105°</td>
<td>1st day p.o. Circulatory collapse</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>F</td>
<td>Complete</td>
<td>103°</td>
<td>1st day p.o. Circulatory collapse</td>
</tr>
</tbody>
</table>

cortisone. With this drug it has been possible to prevent postoperative adrenocortical failure and to effectively combat hyperthermia, which in itself may cause death. With the reduction in postoperative complications that the administration of cortisone has permitted, total extirpation of these tumors should be attempted in many more cases. In 1952 Ingraham, Matson and McLaurin⁶ reported good results with the use of cortisone in operations upon 5 patients with craniopharyngiomas and with ACTH in another pa-

Fig. 1. Photograph of the specimen removed from Case 1 of the cortisone series, a 2-year-old child with signs of hypopituitarism preoperatively. Total removal was believed to have been accomplished. Only the irregular solid portion of the tumor contained calcium. Microscopically some pituitary gland substance was attached to the tumor. This child has done well postoperatively but blindness which was present preoperatively has persisted. (Reprinted with permission from Charles C Thomas, Publisher.)
CORTISONE IN SURGERY OF CRANIOPHARYNGIOMAS

Fig. 2. (A) Preoperative roentgenogram of Case 6 of the cortisone series, a 4-year-old child with preoperative signs suggestive of hypopituitarism. Calcification can be seen within the sella turcica. (B) Postoperative roentgenograms taken 2 months later revealed complete absence of calcification in this region. The radiopaque substance seen in the upper portion of the sella is felt to be artifactual since it was not seen in other projections.

Patient. These operations, however, were in general not as radical as those we have attempted.

Raaf, Stainsby and Larson in 1954 reported on 18 consecutive patients with tumors in the region of the sella turcica who were prepared for operation with ACTH. There were no deaths in this series though in the only 2 patients with craniopharyngiomas total removal was not carried out.

CLINICAL DATA

Fourteen patients received no cortisone. Preoperatively at least 4 of these showed definite hypopituitarism and all died postoperatively. Table 1 shows the postoperative results in detail.

Ten of the 14 patients who received no cortisone did not show unequivocal signs of anterior pituitary deficiency prior to surgery. Table 2 shows the break-down in these cases.

The 7 patients who were given cortisone preoperatively had strikingly
TABLE 2
Postoperative results, craniopharyngiomas
Patients without unequivocal signs of hypopituitarism
Cortisone not used

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Date of Operation</th>
<th>Estimated Removal of Tumor</th>
<th>Maximum Rectal Temperature</th>
<th>Time and Cause of Death</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>F</td>
<td>1938</td>
<td>Complete</td>
<td>101°</td>
<td>—</td>
<td>Working as nurse.</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>F</td>
<td>1940</td>
<td>Incomplete</td>
<td>101°</td>
<td>—</td>
<td>Diabetes insipidus 5 mos. Died of recurrence, 2 yrs. 9 mos.</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>F</td>
<td>1940</td>
<td>Complete</td>
<td>108°</td>
<td>2nd day p.o. Circulatory collapse</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>F</td>
<td>1947</td>
<td>Complete</td>
<td>103°</td>
<td>—</td>
<td>Diabetes insipidus 5 yrs. Stormy convalescence; 1 episode of circulatory collapse. Alive and well.</td>
</tr>
<tr>
<td>5</td>
<td>2½</td>
<td>M</td>
<td>1947</td>
<td>Complete</td>
<td>104°</td>
<td>—</td>
<td>Alive and doing well.</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>F</td>
<td>1949</td>
<td>Complete</td>
<td>106.4°</td>
<td>1st day p.o. Circulatory collapse</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>F</td>
<td>1949</td>
<td>Incomplete</td>
<td>103.6°</td>
<td>1st day p.o. Circulatory collapse. Operated upon twice before</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>M</td>
<td>1951</td>
<td>Complete (?)</td>
<td>104°</td>
<td>—</td>
<td>Died 1 yr. p.o. Given ACTH during and after surgery.</td>
</tr>
</tbody>
</table>

uneventful postoperative courses. The maximum temperature was 103° rectally and this subsided within 24 hours (Table 3). One of these patients, however, died with hyperthermia 4 days after reoperation for recurrent tumor in spite of again receiving supplemental cortisone therapy. In addition, a Torkildsen procedure ultimately became necessary in another of these cases. Preoperative cortisone preparation was not carried out at this time and 38 hours after operation the patient suddenly collapsed into irreversible shock from which she never recovered. Death occurred on the 4th postoperative day.
TABLE 3

Postoperative results, craniopharyngiomas
Prepared with cortisone

<table>
<thead>
<tr>
<th>No.</th>
<th>Age Sex</th>
<th>Date of Operation</th>
<th>Estimated Removal of Tumor</th>
<th>Maximum Rectal Temperature</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 M (probable hypopit.)</td>
<td>1951</td>
<td>Complete</td>
<td>101.6°</td>
<td>Diabetes insipidus 1 mo. Alive and well. Preoperative blindness continues.</td>
</tr>
<tr>
<td>2</td>
<td>17 M (hypopit.)</td>
<td>1951</td>
<td>Incomplete</td>
<td>102.8°</td>
<td>Diabetes insipidus 1 mo. Died 3 mos. later. 3 days p.o. recurrence in spite of preparation with cortisone.</td>
</tr>
<tr>
<td>3</td>
<td>2½ F (? hypopit.)</td>
<td>1951</td>
<td>Complete</td>
<td>102.4°</td>
<td>Diabetes insipidus persists. Alive and well.</td>
</tr>
<tr>
<td>4</td>
<td>4 F</td>
<td>1952</td>
<td>Incomplete</td>
<td>103°</td>
<td>Died 2 mos. later in circulatory collapse 4 days p.o. Torkildsen procedure for recurrence. Not prepared with cortisone at this time.</td>
</tr>
<tr>
<td>5</td>
<td>11 M</td>
<td>1954</td>
<td>Complete (?)</td>
<td>102°</td>
<td>Diabetes insipidus. Alive and well.</td>
</tr>
<tr>
<td>6</td>
<td>4 F (probable hypopit.)</td>
<td>1954</td>
<td>Complete</td>
<td>102.8</td>
<td>Diabetes insipidus. Alive and well.</td>
</tr>
<tr>
<td>7</td>
<td>13 M (hypopit.)</td>
<td>1955</td>
<td>Incomplete</td>
<td>101.6°</td>
<td>Diabetes insipidus. Alive.</td>
</tr>
</tbody>
</table>

In summary, all of 7 patients who were prepared for craniotomy with intramuscular cortisone, and who received it throughout the period of surgical stress, survived the initial operative procedure. Of the 5 surviving patients in the series receiving cortisone, it is believed that total removal of the tumor was accomplished in 4. All of these patients require maintenance doses of oral thyroid extract. One patient has complete panhypopituitarism and requires small doses of oral cortisone daily. Only 1 patient in the total series of 21 cases had diabetes insipidus preoperatively. This persisted 5 years postoperatively and then disappeared. In 6 cases diabetes insipidus developed postoperatively requiring intramuscular pitressin tannate in oil every 2 to 12 days to control the polyuria.

ENDOCRINOLOGICAL ASPECTS

Extermination of the anterior lobe of the normally functioning pituitary gland abruptly interrupts secretion of four important hormones, each of which stimulates its specific "target organ": (1) somatotrophic or growth hormone, (2) the gonadotrophic hormones (follicle-stimulating hormone,
luteinizing hormone and luteotrophic hormone), (3) thyrotrophic hormone, and (4) adrenocorticotropic hormone. Lack of trophic hormone secretion is signaled clinically by subnormal function of the target organ, and if all trophic spheres are involved a state of panhypopituitarism exists. It should be noted that one cannot assay the presence or absence of growth hormone in an adult, just as one cannot determine clinically the status of the gonadotrophic sphere in a prepubertal child. In addition, evaluation of adrenocortical status is frequently inconclusive in children because of practical difficulties in obtaining accurate urine collections and because urinary steroid values are low even in normal children. It should also be emphasized that the eosinophil response to a test dose of 25 mg. of intramuscular aqueous ACTH is not a reliable criterion of adrenocortical reserve, since this minimal stimulus may cause an entirely normal eosinopenia even though there actually exists dangerous incapacity of the cortex to respond to the major stress of surgery.

Of practical importance is the fact that, when decrease in anterior lobe function is gradual rather than abrupt—which may occur if a neoplasm either directly invades the adenohypophysis or causes atrophy by external compression—evidence of target organ deficiency usually appears in a selec-
The trophic hormones least necessary for survival disappear first, while the one most vital for survival is the last to go. Thus, growth hormone and gonadotrophic hormones disappear first, thyrotrophic hormone next and adrenocorticotropic hormone last. In patients with craniopharyngiomas, therefore, one frequently finds delayed somatic growth, arrested sexual maturation, and manifestations of hypothyroidism, but with apparently intact adrenocortical function and reserve. On the other hand, if there is evidence of adrenal cortical insufficiency there are usually deficiencies in all other trophic spheres as well.

However, even if all preoperative data indicate entirely normal function of the adenohypophysis, one should not depend upon the continued integrity of the pituitary-adrenal axis in the precarious postoperative period. Preparation with adrenal steroids of patients with suprasellar lesions is still advisable for two reasons:

1. Unless time-consuming tests of adrenocortical reserve are done, one cannot be sure that an apparently intact pituitary-adrenal system will be capable of responding normally to the stress imposed by surgery.

2. In order to achieve gross total removal of the neoplasm it may be necessary to damage the adenohypophysis. Adrenocorticotropic secretion could cease as of that moment and adrenocortical collapse might occur within 24 hours.

No complications from the cortisone itself have been observed before, during or after surgery. Because of the sodium- and water-retaining properties of large doses of 11,17-oxyysteroids, possible aggravation of postoperative cerebral edema was originally accepted as a calculated risk. However, for the past 2 years the same program of cortisone administration has been used at this hospital in virtually all patients undergoing surgery in the pituitary area, and in only 1 instance has the postoperative course been as turbulent as in patients who were not prepared in this manner.

As a matter of fact, it has been consistently noted that the postoperative course in the cortisone-treated patients is impressively benign. Particularly striking is the almost complete absence of the hyperthermic crises which used to routinely follow surgery in the hypothalamic area, and which were attributed to post-traumatic edema and softening in this region. In the present series, the death of 5 of the 13 patients who did not receive cortisone was attributed, at least in part, to hyperpyrexia (rectal temperatures ranged...
from 105° to 108°), whereas in the cortisone-treated patients at primary operation, the highest postoperative rectal temperature was 103°. A reasonable explanation for this property of adrenal steroids in preventing postoperative cerebral edema stems from the fact that brain tissue is predominantly cellular. Elliott and Yrarrazaval have shown in vitro that cortisone reduces hydration of brain tissue; and Streeten demonstrated in studies on human erythrocytes that cortisone induces a loss of intracellular water at the same time that extracellular water is being retained. Thus, by actively preventing retention of intracellular fluid, cortisone may have a specific effect in reducing postoperative cerebral edema.

In the present series cortisone (compound E) was used as the agent of choice, although hydrocortisone (compound F) may ultimately replace cortisone when an intramuscular preparation becomes available. Direct administration of the active adrenocortical compound obviates the risk inherent in using ACTH to stimulate secretion from the patient's own adrenals. As noted by Raaf and coworkers who used ACTH on their patients undergoing parasellar surgery, 3 to 5 days of ACTH administration may be required to restore the involuted adrenal cortices to normal responsiveness. Moreover, it is recognized that the response to intramuscularly administered ACTH, either the aqueous or the gel preparations, is not always predictable because of variation in the rate of absorption or local inactivation in the muscle.

Cortisone administered intramuscularly is absorbed much more slowly than when given orally. Following an intramuscular injection, an effective pharmacologic response is not obtained for more than 24 hours, but steroid activity then persists at least 4 days. Conversely, when cortisone is given orally, its clinical effects are evident 4 hours later but disappear within 12 hours. In patients scheduled for surgery the oral route is neither feasible nor dependable. The intramuscular route is therefore used and the program is begun either 36 or 48 hours preoperatively to ensure the existence of maximal steroid activity at the time of operation. We prepare adolescent and adult patients for surgery by administering 200 mg. of cortisone intramuscularly daily for 2 days preoperatively and on the day of surgery. Postoperatively the dose is usually tapered to maintenance levels, or withdrawn entirely, within a week. In general, small children are given half this dosage. In the weeks or months following cessation of supportive cortisone therapy the patient should be watched carefully for evidences of adrenocortical deficiency. Adrenal insufficiency secondary to pituitary failure is more frequently manifested by symptoms of hypoglycemia than by those of electrolyte loss, whereas the converse is true in primary adrenal failure. This is presumably because of the dual absence in panhypopituitarism of the antinsulin activities of growth hormone and of adrenal corticoids, while only the latter are lacking in Addison's disease. When they occur, symptoms of cortical deficiency usually respond readily to 15 or 20 mg. of oral cortisone in divided doses daily.
If secondary hypothyroidism develops postoperatively, replacement therapy consists of 100 to 130 mg. (1 1/2 to 2 gr.) of desiccated thyroid daily. Hypogonadism in patients past the age of puberty is treated with cyclic oral estrogen (e.g., 1 mg. of stilbestrol daily the first 20 days of each month) or intramuscular depot-testosterone (200 mg. of testosterone cyclopentylpropionate twice a month). There is, at present, no effective replacement for growth hormone deficiency.

Diabetes insipidus of postoperative onset may be transient or permanent, depending upon the reversibility of the surgical trauma to the hypothalamus or the pituitary stalk. Treatment is symptomatic, with 0.5 to 1.0 cc. (5 pressor units per cc.) of pitressin tannate in oil being given intramuscularly as often as necessary to control polyuria. Transient diabetes insipidus usually subsides within 2 or 3 months, but may last a year or longer.

SUMMARY

A series of 21 patients with craniopharyngiomas is presented. Each case has been approached with the idea in mind of total excision of the tumor if it seemed possible from X-ray studies or during operative exposure. Total excision is certainly possible at times, but only a long follow up or autopsy can establish this fact.

Six of the 14 patients who were not given cortisone died within 48 hours of their craniotomy either from hyperthermia or peripheral vascular collapse; 1 patient had persistent hyperpyrexia and expired on the 10th postoperative day, a mortality rate of 50 per cent.

In contrast, all 7 patients who received cortisone recovered uneventfully from their initial craniotomy.

The use of intramuscular cortisone before and after surgery of the craniopharyngiomas reduces postoperative mortality by: (1) preventing postoperative adrenocortical collapse, and (2) preventing postoperative hyperthermic crises, perhaps by minimizing postoperative edema.

No complications attributable to adjunctive cortisone therapy have been observed to date.

CONCLUSIONS

Preoperative and postoperative administration of intramuscular cortisone is recommended in all patients being prepared for surgery of the craniopharyngiomas. The same program is likewise indicated in any patient undergoing surgery in the pituitary-hypothalamic area. Proper preoperative preparation of the patient should lead to many more attempts at total removal of craniopharyngiomas.

REFERENCES