Estrogen-receptor protein in intracranial meningiomas

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The increased frequency of meningiomas in women compared with men, and the rapidly progressive course of these tumors in pregnant patients suggest that hormones may be involved in this disease. Tumor tissue from six patients with meningiomas was analyzed for estrogen-receptor protein. Two patients had tumors with very high concentrations of this protein, approaching that found in hormonally sensitive breast carcinoma. The biochemical and possible clinical significance of these findings is discussed.

KEY WORDS • meningioma • neurochemistry • estrogen • hormone

The tissue concentration of estrogen-receptor protein has been found to correlate well with the response of breast carcinoma to hormonal therapy.1,13 This receptor protein has been found in a number of other benign and malignant tissues including liver,4 pancreas,21 uterus,24 uterine leiomyoma,6 endometrial carcinoma,14,25 ovarian papillary adenocarcinoma,6 malignant melanoma,6 and colon carcinoma.14

The epidemiology and clinical course of some meningiomas suggest that these tumors may be hormonally sensitive and that they may contain estrogen-receptor protein. Two-thirds of all intracranial meningiomas and 80% of all spinal meningiomas occur in women.3,16,19 The relationship between pregnancy and a rapid progression of symptoms in patients with meningiomas was described by Cushing and Eisenhardt in 1929.2 Since that time many authors have reported cases of pregnant patients with meningiomas and an unusually rapid clinical course.1,7,9,12,18,20,28 Interestingly, a majority of these patients improved after delivery, sometimes only to experience a recurrence of their symptoms during their next pregnancy. It has been suggested that this rapid neurological deterioration results primarily from vascular engorgement of the tumor caused by hemodynamic changes during pregnancy.12,18,25 Other authors have postulated that an acceleration in the growth rate of the tumor may also occur, perhaps secondary to hormonal changes.1,28 Finally, a statistically significant association has been reported between meningiomas and breast carcinoma.22

Clinical Material and Methods

In this study, tissue samples were obtained from six patients with meningiomas operated on between February and April, 1978. These samples were analyzed for estrogen-receptor protein and were then correlated with preoperative and intraoperative observations.

A portion of tumor tissue weighing 1 to 2 gm was obtained at the time of operation and was immediately frozen. The samples were stored at -70 °C for up to 2 weeks. At the time of assay the tissue was weighed, immersed in liquid nitrogen, and pulverized. The resulting powder was homogenized and the cytosol protein was extracted as described previously.4 The estrogen-receptor concentration was measured using the sucrose gradient sedimentation procedure of Jensen, et al.11 This method involves incubation of the cytosol protein with radiolabeled 17 β-estradiol, sucrose gradient centrifugation, and scintillation counting. The results were calculated as the total estrogen binding minus the nonspecific binding, and were expressed in Femtomoles per gram (Fmoles/gm) of tumor tissue. Estrogen-receptor protein was clearly present in tumors with concentrations greater than 10 Fmoles/gm, whereas values below this could not be clearly differentiated from experimental error.

Case Reports

Case 1

This 33-year-old premenopausal woman had noted a sudden decrease in vision in her right eye 1 month
before examination, and had been experiencing moderately severe bifrontal headaches for several weeks. The patient was also 10 weeks pregnant with her second child. Past history included very poor vision in her left eye since childhood and coma lasting several days after an automobile accident when she was 18 years old. Examination revealed an uncorrectable visual acuity of 20/60 in her right eye and the ability to detect finger motions at 2 feet in her left eye. There was a right temporal hemianopsia and a large left central scotoma. The remainder of the neurological examination was normal. A computerized tomography (CT) scan demonstrated a strongly enhancing mass 4 X 5 cm in size in the region of the tuberculum sellae. Angiograms showed this lesion to be a highly vascular tumor fed primarily by the right ophthalmic artery. At operation, a large tuberculum sellae meningioma was found in the tuberculum sellae, which invaded bone and encircled the right internal carotid artery. Microscopic examination revealed a benign meningioma with extensive vasculature.

Case 2

This 35-year-old man was seen for evaluation of a slowly expanding nontender bony mass of the upper left forehead, and a 2-year history of dull aching frontal headaches. Examination was normal except for a painless firm mass 4 X 4 cm in size in the left frontal bone. A CT scan revealed an enhancing 5-cm mass protruding from the skull into the left frontal lobe. The angiogram demonstrated a well circumscribed tumor fed from the left external carotid artery. Total removal was easily achieved. Microscopic examination revealed a benign meningotheliomatous meningioma.

Case 3

This 49-year-old perimenopausal woman was admitted 18 months after craniotomy and subtotal removal of a left medial sphenoid ridge meningioma. The patient had had residual mild dysphasia and right arm paresis since her initial operation. She had noted a rapid loss of vision in her left eye 4 months before this admission, and had experienced increasing dysphasia and progression of her right-sided paresis. Examination revealed minimal light perception in her left eye and a right superotemporal quadrantanopsia. A CT scan and angiogram confirmed a recurrence of her tumor and a second operation was performed. Microscopic examination showed the tumor to be a benign meningioma.

Case 4

This 36-year-old premenopausal woman had a 14-week history of progressive cervical and left shoulder pain. Examination was normal except for slightly decreased strength in the left arm and hand. Cervical spine and skull films were normal. A gas myelogram demonstrated an epidural mass extending from the C-2 level into the foramen magnum. A pneumoencephalogram showed that the mass extended approximately 1 cm above the foramen magnum. A faint tumor blush was seen on the angiogram. At operation, a large intradural tumor was found extending from the foramen magnum to the C-1 level, where it became extradural and extended down to the C-2 level. The tumor was noted to be invading both bone and muscle. Microscopic examination revealed a benign meningotheliomatous meningioma.

Case 5

This 33-year-old man experienced two episodes of twitching of his right extremities during the 2 months preceding admission. These episodes were quickly followed by euphoria, right-leg weakness, staggering gait, nausea, and vomiting. Examination was normal except for decreased swing of the right arm when walking. The CT scan demonstrated a strongly enhancing left parafalcine mass extending across the midline in the posterior frontal region. A cerebral angiogram showed that the lesion was supplied by the left internal and by both external carotid arteries. At operation, a large vascular encapsulated tumor was found to be extending into both the left and right posterior frontal lobes. Total removal was achieved. Microscopic examination showed the tumor to be a benign meningioma.

Case 6

This 61-year-old postmenopausal woman was seen after two episodes of left-sided jerking seizures followed by loss of consciousness. The examination was completely normal. An electroencephalogram showed right temporal slowing. A CT scan demonstrated a strongly enhancing lesion 3 X 4 cm in size in the right frontotemporoparietal cortex. At operation, a firm encapsulated tumor was totally resected. Microscopic examination revealed a benign meningioma.

Study Results

As shown in Table 1, significant quantities of estrogen-receptor protein were found in tissue from four of the six patients with meningiomas. Tumor tissue from three of the four women and from one of the two men contained measurable estrogen-receptor protein. The highest estrogen-receptor concentrations were found in tissue from Cases 1 and 4. Common findings in these cases included premenopausal status, prominent tumor vascularity, and adjacent tissue invasion.

Cases 2 and 3 had lower tissue concentrations of estrogen-receptor protein. Case 3, although only 49 years old, was classified as perimenopausal on the basis of a 6-month period of amenorrhea within the previous year. No significant estrogen-receptor ac-
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>4s Receptors (Fmoles/gm)</th>
<th>8s Receptors (Fmoles/gm)</th>
<th>Total Receptors (Fmoles/gm)</th>
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</tbody>
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*Patient was 10 weeks pregnant.

Estrogen receptor protein in meningiomas was found in the tissue samples from Cases 5 and 6. The sedimentation coefficient of the estrogen-receptor protein varied among the tissue samples. In Cases 1 and 3, the receptor protein was present primarily in the 4s fraction, while in Cases 2 and 4, the concentration was greatest in the 8s fraction.

**Discussion**

Estrogen-receptor protein has been extensively studied in both benign and malignant tissues. The receptor activity has been localized to the cytoplasmic protein of the cell. Estradiol entering the cell is bound to this protein and the resulting complex migrates toward the cell nucleus. An increase in ribonucleic acid synthesis has been observed to occur shortly after this complex enters the cell nucleus. The significance of the 4s and 8s receptor fractions is not well understood. Receptors in breast carcinoma are primarily of the 8s variety when measured by the sucrose gradient method.

The concentration of estrogen receptors found in tissue samples from Cases 1 and 4 was very high, approaching that of hormonally responsive breast carcinoma. The actual tissue concentration of receptors in Case 1 was likely to have been even higher because some of the receptor sites were probably occupied due to the increased levels of estrogen present in pregnant women. As the estrogen concentration increases, the number of unbound receptor sites decreases. This is the accepted explanation for the higher average estrogen-receptor concentrations found in breast carcinoma tissue from premenopausal compared to postmenopausal patients.

The discovery of estrogen-receptor protein in meningioma tissue is difficult to explain *a priori*. The meninges are not known to be sensitive to hormones. It has been suggested that the presence of estrogen-receptor protein in malignant tissue is a result of undifferentiation of the cells and derepression of normally inactive genes. The quantity of estrogen-receptor protein in endometrial carcinoma tissue has been reported to increase with the degree of undifferentiation of the tumor. A similar finding was noted in a study of malignant colonic neoplasms. Since meningiomas are almost always histologically benign, this explanation would not seem to apply. Regardless of the reason for the presence of estrogen-receptor protein in meningiomas, an important question is whether these receptors are metabolically active and thereby subject to hormonal manipulation.

The clinical significance of estrogen-receptor protein in meningioma tissue is unknown. On the basis of clinical experience with breast carcinoma, receptor concentrations of greater than 250 Fmoles/gm in premenopausal women and 750 Fmoles/gm in postmenopausal women have been accepted as predictive of tumor response to hormonal therapy. Tissue from two of the patients with meningiomas approached these concentrations.

If hormonal therapy were found to be successful in slowing or halting the growth of some meningiomas, it could have great clinical importance. Preoperative anti-estrogen therapy might be useful in reducing tumor vascularity, thereby facilitating removal. In the case of an incompletely resected meningioma, hormonal therapy might delay recurrence of the tumor. Finally, meningiomas are occasionally found in elderly patients who are poor operative candidates and who might benefit from a non-surgical mode of therapy.

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**References**


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