Implications of very high serum prolactin levels associated with pituitary tumors

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Five patients with pituitary tumors associated with unusually high serum prolactin levels are presented. Tumor size and the presence of suprasellar extension were variable, but the finding common to all five cases was invasion of the cavernous sinus. It is proposed that very high serum prolactin levels suggest an invasive tumor, perhaps, specifically, invasion into a cavernous sinus. The surgical significance of this proposition is discussed.

KEY WORDS • invasive pituitary tumor • cavernous sinus • prolactin

The significance of the serum prolactin level associated with pituitary tumors has been discussed in the literature primarily as a predictive value indicating the presence of a true secreting tumor, as opposed to a functional abnormality.1,2,4,6,10 A correlation has been suggested between elevation of serum prolactin and pituitary tumor size.3,8 The great majority of pituitary tumors are associated with serum prolactin levels of less than 1000 ng/ml, and it is unusual for the serum prolactin to be above 2000 ng/ml. Although there are cases reported with serum prolactin levels of greater than 2000 ng/ml, the significance of this finding has received little comment. In a review of 97 patients with pituitary adenomas treated from 1976 to 1979, five patients were found with preoperative prolactin levels greater than 2000 ng/ml (range 2880 to 8120 ng/ml), while no other patient had a value greater than 1000 ng/ml.

In these five patients, tumor size was variable. Two patients had no suprasellar extension and one had minimal suprasellar extension. All five patients had lateral extension of tumor involving a cavernous sinus. Two exhibited clinical signs referable to cavernous sinus invasion, and all five had angiographic or computerized tomography (CT) confirmation of such involvement. Invasion of tumor through the dura into the cavernous sinus could be seen at surgery in two of the patients. In the remaining three, there was tumor growth into the area where the cavernous sinus would normally be, but dural penetration could not clearly be seen. In two of the latter group there were clinical signs suggesting cavernous sinus invasion. Fourteen other patients in the series had prolactin-secreting tumors larger than any in the five cases reported, but none had a serum prolactin level greater than 1000 ng/ml. It is postulated that very high serum prolactin levels (greater than 2000 ng/ml) are related not to tumor size, but to tumor invasion into the bloodstream, perhaps specifically into the cavernous sinus.

Summary of Cases

The pertinent patient data are presented in Table 1. Representative CT scans (Fig. 1), arteriogram (Fig. 2 left), and polytomogram (Fig. 2 right) are also shown. All five cases were treated surgically via a transsphenoidal approach. The histological diagnosis in Case 1 was eosinophilic adenoma. In that case, endocrine evaluation showed a markedly elevated serum prolactin with otherwise normal pituitary function, including normal growth hormone. The histological diagnosis in the other four cases was chromophobe adenoma.

In Cases 1 and 2, tumor could clearly be seen penetrating the dura of the cavernous sinus at surgery. Attempts at manipulation or further removal of the penetrating portion of those tumors were accompanied by significant venous bleeding. In the other three cases, tumor extended more laterally than usual, but the dural covering of the cavernous sinus was either pushed so far laterally or so obliterated that penetration of the dura by tumor could not be identified.

Two of these latter three cases had clinical signs referable to cavernous sinus invasion. One patient

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TABLE 1

Summary of prolactin levels and tumor extension in five patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Suprasellar Extension</th>
<th>Cavernous Sinus Invasion Documentation</th>
<th>Preop Serum Prolactin (ng/ml) at 1 mo</th>
<th>Postop Serum Prolactin (ng/ml) at 6 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37, M</td>
<td>none</td>
<td>CT scan, arteriogram, surgery</td>
<td>2880</td>
<td>2493</td>
</tr>
<tr>
<td>2</td>
<td>38, F</td>
<td>none</td>
<td>CT scan, surgery</td>
<td>3780</td>
<td>1200</td>
</tr>
<tr>
<td>3</td>
<td>23, M</td>
<td>&lt; 5 mm</td>
<td>CT scan, arteriogram</td>
<td>4400</td>
<td>1800</td>
</tr>
<tr>
<td>4</td>
<td>47, M</td>
<td>20 mm</td>
<td>CT scan, arteriogram, clinical signs</td>
<td>8120</td>
<td>5360</td>
</tr>
<tr>
<td>5</td>
<td>22, M</td>
<td>15 mm</td>
<td>arteriogram, clinical signs</td>
<td>4280</td>
<td>2760</td>
</tr>
</tbody>
</table>

*With bromocriptine and no radiation therapy.
†With postoperative radiation therapy and no bromocriptine.

complained of lancinating pain in the right forehead both pre- and postoperatively. His postoperative CT scan showed persistence of tumor in the right cavernous sinus. Postoperative radiation therapy was given, and the episodic pain subsided. In the other patient, there was a mild third nerve paresis preoperatively, manifest by weakness of the medial and superior rectus muscles and a very mild ptosis. Following surgery, the patient had complete third, fourth, and sixth cranial nerve palsies in the left eye, although his visual field and acuity returned to normal. The cranial nerve deficits cleared completely within 3 months. As can be seen in Table 1, none of the patients had return of serum prolactin to normal following surgery or surgery plus radiation therapy. One patient had a dramatic response to bromocriptine treatment without radiation therapy; the decrease in serum prolactin level was associated with CT scan evidence of decreased tumor size.

![Computerized tomography scan showing invasion of tumor into the right cavernous sinus.](Image)

FIG. 1. Computerized tomography scan showing invasion of tumor into the right cavernous sinus.

Discussion

The significance of markedly elevated prolactin levels associated with pituitary tumors has received little attention. In a series reported by Carter, et al., several men had very high serum prolactin levels. The authors state that serum prolactin levels in men with prolactinomas tend to be higher than those in women. Their proposed explanation is that men become symptomatic secondary to the effects of the tumor later than women, so their tumors are larger. They demonstrate a rough correlation between tumor size and serum prolactin level, but not enough specifics, such as tumor size, presence of invasion, or direction of growth, are given to comment any further.

Other patients with marked hyperprolactinemia have been reported, but the invasive nature of the tumors in these cases has not received comment. A 27-year-old man reported by McGregor, et al., had a serum prolactin of 8000 ng/ml, and the CT scan showed a large, widespread tumor with involvement of the right cavernous sinus. Landolt reported two cases with very high prolactin levels. The first was a 48-year-old man with a serum prolactin of 2250 ng/ml, who had a right cavernous sinus syndrome. The second was a 35-year-old woman with a serum prolactin of 2240 ng/ml, described as having an “invasive pituitary adenoma,” but no details are given. In our series, five patients had extremely high serum prolactin levels (> 2000 ng/ml). Tumor size was variable. Three patients had significant suprasellar extension, and two had no suprasellar extension. Fourteen other patients had prolactinomas larger than any of the five reported here, but none had a serum prolactin greater than 1000 ng/ml. Clearly, tumor size and suprasellar extension were not the sole determinants of serum prolactin levels. The serum level of prolactin is a function of three factors: tumor secretory rate, clearance from the blood stream, and rate of entry into the blood stream. In prolactinomas, secretory granules are found completely around the circumference of the tumor cells. It is suggested that when these cells covered with secretory granules invade the cavernous sinus there is an outpouring of prolactin into the blood. In such a situation, tumor size would not be as
important in determining serum prolactin level as the increased interface between secretory granules and the blood stream.

Two postulations are made. First, patients with very high serum prolactin levels (greater than 2000 ng/ml) and no suprasellar extension probably have extrasellar extension into a cavernous sinus. Second, patients with very high serum prolactin levels, even with suprasellar extension, are likely to have invasion into a blood vessel, perhaps, more specifically, invasion into a cavernous sinus.

Management and evaluation of patients with very high serum prolactin levels should take into account that these tumors are probably not curable surgically, and extensive surgical procedures in an attempt to effect a cure (as opposed to decompression) are probably futile and may be hazardous. Preoperative evaluation should include carotid angiography, with particular attention paid to the cavernous portion of the carotid artery. If the early reports of decrease in tumor size with bromocriptine treatment are confirmed, perhaps preoperative treatment with that drug could reduce tumor size enough to make surgical cure feasible.

References

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**Fig. 2.** *Left:* Carotid arteriogram showing stain (arrow) around cavernous portion of artery. *Right:* Polytomogram, anteroposterior view, showing eccentric erosion of sellar floor and extension into the sphenoid bone.