Serum prolactin in patients with hypothalamus and pituitary disorders

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Serum prolactin concentrations were studied in 115 patients with anatomically defined disorders in the hypothalamo-pituitary region. Fifty of the patients had expansively growing pituitary adenomas; in 17 of them (13 females and four males) the prolactin values were slightly raised (15 to 100 µg/liter), and in 13 (11 females and two males) they were over 100 µg/liter. The frequency of elevated prolactin values was higher for females than for males. Fifteen patients with invasively growing pituitary adenomas had very high serum prolactin levels (range 1230 to 31,500 µg/liter, geometric mean 3150 µg/liter). In a single case of malignant pituitary adenoma, the serum prolactin was at the lower level of detection.

Of 49 further patients with suprasellar meningiomas, craniopharyngiomas, or other expansive or destructive lesions of the hypothalamus and sellar region, 15 had slightly raised prolactin values (maximum 114 µg/liter). Eight of these 49 patients had sellar destruction, with a roentgenological picture similar to that in patients with invasive pituitary adenomas. Among these eight patients, the maximum prolactin value was 67 µg/liter.

It is concluded that moderately raised serum prolactin values (up to 100 µg/liter) in a patient with a sellar tumor does not prove that the tumor is a prolactinoma. A serum prolactin value of 100 to 1000 µg/liter strongly indicates a prolactin-producing tumor. In a patient with sellar destruction, a serum prolactin value of over 1000 µg/liter is proof that the destruction is caused by an invasive pituitary adenoma.

KEY WORDS · prolactin · pituitary tumor · craniopharyngioma · suprasellar tumor · meningioma · sellar destruction

Serum prolactin measurements have become increasingly important in the diagnosis of pituitary tumors. The reason for this is the observation that a considerable number of patients with what previously was regarded as a functionless pituitary adenoma have in fact pituitary hyperfunction, that is, hypersecretion of prolactin. The importance of these measurements is also based on the fact that, in these patients, the hyperprolactinemia can be cured by treatment with bromocriptine. Occasionally, treatment with this drug may also cause a reduction of the tumor growth and sometimes result in disappearance of the tumor.

Most authors seem to conclude that a patient has a prolactin-secreting tumor, a prolactinoma, from the presence of sellar changes and raised serum prolactin values. However, a number of observations have indicated that hyperprolactinemia may also be present in patients with non-adenomatous types of sellar tumors, such as craniopharyngiomas, and also in the empty sella syndrome.

Most pituitary adenomas grow in an expansive way, pushing away adjacent bone and soft tissue: the optic chiasm, for example. A certain type of pituitary adenoma, on the other hand, invades the bone and nervous tissue, causing destruction of the sella turcica. In a previous study, we found that patients with these latter tumors had very high serum prolactin values (over 1000 µg/liter), a finding that has recently been confirmed.

The purpose of the present investigation was to compare the serum prolactin concentrations in a number of patients with expansive (50 cases) or invasive (15 cases) pituitary adenomas with those in a number of patients (50 cases) with other anatomically defined lesions of the hypothalamo-pituitary region, in order
Prolactin in hypothalamo-pituitary disorders
to elucidate the possibility of using serum prolactin
to discriminate between different types of
tumors.

Clinical Material and Methods

Patients

The total number of patients was 115. Patients on
drugs that might have influenced the prolactin levels
were not included. Most of the patients had more or
less pronounced pituitary insufficiency. Thyroxin and
cortisol substitution was given, but at the time of
blood sampling none of the patients was receiving any
androgen or estrogen replacement therapy. None of
the patients had been treated with bromocriptine be-
fore this study.

Expansively Growing Adenomas. Fifty patients, 34
females and 16 males, had expansively growing ade
nomas. Twenty-eight of them had intrasellar tumors
(mean patient age 42 years, range 20 to 76 years), and
22 had suprasellar expansion of the tumor (mean
patient age 47 years, range 18 to 77 years). An intra
sellar tumor was defined radiologically as having an
intrasellar volume of more than 2000 cu mm and/or
causing sellar floor asymmetry with more than 3 mm
depression of the floor. Patients with less pronounced
sellar changes than these were not included, since
minor sellar changes do not correlate very well to the
presence of a pituitary tumor. The occurrence of
suprasellar expansion of the tumor was determined
from pneumoencephalographic (PEG) findings or, in
some cases, from computerized axial and coronal
tomography (CT). All tumors with suprasellar expan
sion and most of the intrasellar tumors were con
firmed by microscopic examination after surgery.

Invasively Growing Pituitary Adenomas. Pituitary
adenomas occasionally grow in an invasive manner,
destroying adjacent bone structures. They may extend
into the petrous apices and down into the sphenoidal
sinus and the clivus bone, and may also invade the
cranial nerves and the temporal lobes of the brain.
These tumors differ in many aspects from the more
common expansively growing adenomas and have,
therefore, been regarded as a particular type of pitui
tary tumor and called "invasive pituitary ade
nomas." The present series included 15 such pa
tients (six females and nine males), aged 25 to 74 years
(mean 57 years). The tumors were diagnosed from
radiological criteria (skull x-ray films and CT), and
the diagnosis was confirmed in all cases by means of a
transnasal aspiration biopsy.

Malignant Pituitary Adenoma. Only one case of
malignant adenoma, in a 65-year-old man, was found
during the period of investigation. The tumor was
diagnosed by biopsy at open surgery.

Other Hypothalamo-Pituitary Disorders. A group of
49 patients, 26 females and 23 males, suffered from
other hypothalamo-pituitary disorders. Fourteen of
the 49 (eight females and six males), with a mean age
of 58 years (range 42 to 76 years), had suprasellar
meningiomas, and 12 (eight females and four males),
with a mean age of 35 years (range 17 to 69 years),
had craniopharyngiomas. All these tumors were di
agnosed by PEG and/or CT, and confirmed at sur
gery. Six patients (one female and five males) had a
mainly hypothalamic lesion, seen at PEG and/or CT.
Eight patients (three females and five males) had
extensive sellar destruction with a roentgenological
picture similar to that found in patients with invasive
pituitary adenomas (Fig. 1). Radical surgery was not
possible in any of these 14 patients. Their final diag
noses at autopsy, surgical exploration, or transnasal
aspiration biopsy are given in Table 4. Among nine
further patients, PEG revealed an empty sella in five
(two females aged 39 and 71 years, and three males
aged 54 to 77 years), and CT a spontaneously arrested
hydrocephalus, probably caused by a perinatal aque
ductal stenosis, in four (two females aged 17 and 32,
and two males aged 17 and 18 years).

Hormone Assays

Venous blood specimens were taken during the
daytime. Prolactin in serum was measured with a
radioimmunosorbent technique, using rabbit anti-hu
man prolactin antibodies coupled to cyanogen bro
mide-activated ultrafine Sephadex particles. The
reference range for men and postmenopausal women
was 2 to 12 μg/liter, and for women of fertile age 4 to
15 μg/liter. For practical reasons, a serum prolactin
value of less than 15 μg/liter was considered normal
in both sexes.

Results

Expansively Growing Adenomas

Of the 50 patients with expansively growing ade
nomas (Table 1), 20 (10 females and 10 males) had
prolactin concentrations below 15 μg/liter. In 17 (13
females and four males) prolactin levels were between
15 and 100 μg/liter, in 11 (nine females and two
males) between 100 and 1000 μg/liter, and in two

* The prolactin and anti-prolactin preparations were sup
plied by NIAMDD, National Institute of Health, Bethesda,
Maryland, and the ultrafine Sephadex particles were sup
plied by Pharmacia AB, Uppsala, Sweden.

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females over 1000 μg/liter. Thus, in 30 (60%) of the patients the serum prolactin was above normal. The mean prolactin value in these 30 patients was 355 μg/liter. The frequency of raised prolactin values was higher for females than for males (70.6% and 37.5%, respectively). Increased serum prolactin was almost as common among patients with larger tumors and suprasellar expansion (12 of 22 patients) as among those with smaller intrasellar tumors (18 of 28).

**Invasively Growing Pituitary Adenomas**

All patients with invasive pituitary adenomas (Table 2) had very high serum prolactin levels, ranging from 1230 to 31,500 μg/liter, with a geometric mean of 3510 μg/liter. There was no significant difference between males and females (p > 0.05).

**TABLE 1**

<table>
<thead>
<tr>
<th>Prolactin (μg/liter)</th>
<th>Females</th>
<th>Males</th>
<th>Total Cases</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>&lt;15</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>15-100</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>100-1000</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>16</td>
<td>50</td>
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</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Prolactin (μg/liter)</th>
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<tr>
<td></td>
<td></td>
<td>At First Symptoms</td>
<td>At Study</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>73</td>
</tr>
<tr>
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<td>60</td>
<td>71</td>
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<td>M</td>
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<tr>
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<tr>
<td>15</td>
<td>F</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

**Malignant Pituitary Adenoma**

In the patient with malignant pituitary adenoma, the serum prolactin value was very low (0.4 μg/liter).

**Other Hypothalamo-Pituitary Disorders**

The serum prolactin levels for patients with disorders other than pituitary adenomas are given in Table 3. Among the 14 patients with suprasellar meningiomas, 12 had serum prolactin values under 15 μg/liter.

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**Fig. 1.** Plain lateral roentgenographic view of the sellar region in two 58-year-old women, one with an invasive pituitary adenoma (left) and the other with a malignant chordoma (right). There is extensive destruction of the walls of the sella and sphenoid sinus. In both patients, the visual fields were normal and there was a moderate pituitary insufficiency. Serum prolactin in the patient on the left was 4000 μg/liter, and in the patient on the right it was 28 μg/liter.
Prolactin in hypothalamo-pituitary disorders

TABLE 3
Serum prolactin in 49 patients with hypothalamo-pituitary disorders other than pituitary adenomas

<table>
<thead>
<tr>
<th>Disorders</th>
<th>No. of Cases with Serum Prolactin:</th>
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</thead>
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<tr>
<td></td>
<td>&lt;15 µg/liter</td>
</tr>
<tr>
<td>suprasellar meningiomas</td>
<td>12</td>
</tr>
<tr>
<td>craniopharyngiomas</td>
<td>5</td>
</tr>
<tr>
<td>mainly hypothalamic lesions</td>
<td>4</td>
</tr>
<tr>
<td>extensive sellar destruction</td>
<td>5</td>
</tr>
<tr>
<td>empty sella</td>
<td>4</td>
</tr>
<tr>
<td>spontaneously arrested hydrocephalus</td>
<td>4</td>
</tr>
</tbody>
</table>

and two females aged 60 and 51 years had slightly increased values, the highest value being 83 µg/liter. Of the 12 patients with craniopharyngiomas, seven patients, two of the four males and five of the eight females, had serum prolactin values between 15 and 100 µg/liter. One patient had a value over 100 µg/liter (114 µg/liter) on a single occasion. Among the six patients with mainly hypothalamic lesions, two had elevated serum prolactin values (Table 4). One male with a reticulum cell sarcoma had a value of 60 µg/liter, and one female with an undetermined hypothalamic lesion had a 26 µg/liter concentration.

The eight patients with extensive sellar destruction similar to that found in patients with an invasive pituitary adenoma, but with a different pathology, are of particular interest. One female with a reticulum cell sarcoma had a serum prolactin of 28 µg/liter, one female with a metastasis from a carcinoma had a value of 20 µg/liter, and one male with a neurinoma had a 67 µg/liter level. In the other five patients the serum prolactin values were quite normal. Thus, in all these eight patients the serum prolactin levels were very much lower than in the 15 patients with invasive pituitary adenomas.

No differences in serum prolactin were found on comparison between patients with mainly hypothalamic lesions (range 4.3 to 60 µg/liter) and those with extensive sellar destruction (range 0.37 to 67 µg/liter), a suprasellar meningioma (range 0.72 to 83 µg/liter) or a craniopharyngioma (range 0.34 to 114 µg/liter).

None of the patients with spontaneously arrested hydrocephalus and only one of those with an empty sella had serum prolactin values above 14 µg/liter. In this patient, a female aged 39 years old, the values were between 19 and 40 µg/liter.

Discussion

It is well known that both experimental hypothalamic and pituitary stalk lesions and corresponding lesions caused by tumors in humans may result in elevated concentrations of serum prolactin. Of particular interest in this respect is a recent study by Vaughan, et al. They performed a pituitary stalk section in nine rhesus monkeys and placed a Silastic barrier between the proximal and distal stumps of the cut stalk. The prolactin concentrations rose rapidly within the 1st week after surgery from a basal range of 5.0 to 12.5 µg/liter to a mean peak value of 48.6 ± 4.9 (SE) µg/liter at 7 weeks. The prolactin values were significantly above the basal level in all nine animals throughout the observation period of 28 weeks. One monkey was observed for 20 months, and at the end of that time it still had a prolactin value of about 30 µg/liter. In four other monkeys in which the portal vessels regenerated through the transected area, the increase in prolactin did not last for more than 3 weeks.

In patients, elevated serum prolactin values and/or galactorrhea have been reported in a number of hypothalamo-pituitary disorders besides pituitary adenomas. Such disorders are craniopharyngioma, meningioma, ectopic pinealoma, metastasis from carcinomas, sarcoidosis, histiocytosis-X, and empty sella.

Results of hormone assays from different laboratories using different methods are often difficult to compare. However, hyperprolactinemia is usually reported to be modest in patients with hypothalamo-pituitary disorders lacking signs of a pituitary adenoma. Balagura, et al. found an increased serum prolactin concentration of three of five patients with tumors of the third ventricle, in two of 10 patients with cranio-
pharyngiomas, and in two women with parasellar meningiomas. In none of these patients was the serum prolactin level over 90 μg/liter. In 11 patients with tumors involving the hypothalamus, most of them craniopharyngiomas, the serum prolactin was never above 60 μg/liter. These findings are thus very similar to those of the present investigation. Fifteen of our 49 patients with hypothalamo-pituitary disorders other than pituitary tumors had elevated serum prolactin levels but, apart from a single value of 114 μg/liter, none had a value over 100 μg/liter.

Although it cannot be proven without serial sectioning of the sellar region at autopsy that these patients did not have a pituitary adenoma besides the other lesion, this is not likely to be the explanation for the results in more than an occasional patient. Thus, moderately raised serum prolactin levels can probably be explained in humans in the same way as in monkeys, that is, they are caused by disrupted hypothalamic regulation of the pituitary. A finding of a moderately increased serum prolactin level in a patient with symptoms of hypothalamic-pituitary dysfunction, such as amenorrhea and galactorrhea, and sellar changes on skull x-ray films does not prove that this adenoma is actually prolactin-secreting, that is, a prolactinoma. On the other hand, prolactin values of several hundred μg/liter or more are highly suggestive of a tumor that is endocrinously active.

Some authors, such as Klijn, et al., have reported a positive correlation between tumor volume and serum prolactin value. This might be true for patients with hyperprolactinemia. However, when patients without hyperprolactinemia are also included (as in the present study, where 20 of the patients had normal serum prolactin values, many of them with large tumors), no such correlation is found.

The most obvious result of the present investigation was that all 15 patients with diffusely invasive pituitary adenomas constantly had very high serum prolactin values (over 1000 μg/liter). The present case material is an extension of a previously reported series including nine such patients. Such high serum prolactin values are rare among noninvasive expansively growing adenomas (4% in the present investigation). In a study by Shucart, the serum prolactin in five patients with pituitary adenomas that showed invasive growth ranged from 2880 to 8120 μg/liter. This author postulated that these very high serum prolactin levels are related not to tumor size but to tumor invasion into the cavernous sinus. However, the explanation may be quite different. Prolactin has been shown to suppress leukocyte chemotaxis in vitro. Therefore, the invasive growth of the pituitary tumor cells in patients with very high prolactin levels might be explained by an altered host response in these cases.

No matter how the relationship between invasive growth and high serum prolactin may be explained, this relationship has great differential diagnostic importance. Destruction of the sellar region is not unusual in patients who are investigated for endocrine insufficiency, oculomotor malfunction, visual defects, temporal lobe epilepsy, or other neurological disorders. The present material included 23 such patients. Fifteen of them (Table 2) had very high serum prolactin values (over 1000 μg/liter). Eight (Table 4) had normal or slightly raised values (under 70 μg/liter). Microscopic examination of aspiration biopsy material showed the tumor to be an invasive pituitary adenoma in all the former 15 patients, and other types of tumors, such as carcinomas or malignant chordomas, in the latter eight. Thus, in a patient in whom a destructive lesion of the sellar region is found on skull x-ray film or CT, a serum prolactin assay should be performed. A value of more than 1000 μg/liter is pathognomonic for an invasive pituitary adenoma. Since these tumors constitute great surgical risks and preferentially should be treated with bromocriptine and/or radiotherapy, further diagnostic procedures are usually not necessary after the finding of such a high serum prolactin concentration.

References
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