Morphological study of clinically nonsecreting pituitary adenomas in patients under 40 years of age

SHOZO YAMADA, M.D., KALMAN KOVACS, M.D., EVA HORVATH, PH.D., AND TADASHI AIBA, M.D.

Department of Neurosurgery, Toranomon Hospital, Tokyo, Japan, and Department of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

Clinically nonsecreting pituitary adenomas removed at surgery from 69 patients under 40 years of age were studied by histological, immunocytochemical, and transmission electron microscopic examination. By morphological analysis, 19 tumors were found to be null-cell adenomas, 17 silent gonadotroph adenomas, 14 silent subtype 3 adenomas of unknown cellular origin, 13 silent subtype 1 or subtype 2 corticotroph adenomas, three oncocytomas, and three silent thyrotroph adenomas. These results indicate that the incidence of null-cell adenomas and oncocytomas, which are known to be the most common types of nonsecreting pituitary adenomas in patients over 40 years of age, is relatively low in younger patients. This trend is even more obvious in patients younger than 30 years of age.

It can be concluded that clinically nonsecreting pituitary adenomas represent a heterogeneous group morphologically, and that the incidence of the different tumor types varies depending on the patient's age. These findings underline the importance of careful morphological studies. It is proposed that, in order for the correct morphological diagnosis to be made, tumors removed surgically from patients with clinically nonsecreting pituitary adenomas (especially younger patients) should be investigated not only by histological means but also by immunocytochemical and electron microscopic examination. The information obtained from such analysis may be useful in assessing prognosis and deciding on the appropriate treatment.

Key Words • pituitary • pituitary neoplasm • null-cell adenoma • oncocytoma • silent adenoma

Approximately 20% to 30% of surgically removed pituitary adenomas are nonsecreting, with no clinical or biochemical evidence of increased release of any known adenohypophyseal hormones.1.18 The majority of these tumors, classified morphologically as null-cell adenomas or oncocytomas,4.10.18 become manifest in older subjects and are rarely diagnosed in patients under 40 years of age.10.13 Recent studies indicate that these clinically nonsecreting adenomas are morphologically heterogeneous tumors composed of cells with immunocytochemical and ultrastructural features of unknown derivation or cells of one of the established adenohypophysyal types.5.8.12 Besides null-cell adenomas and oncocytomas, these tumors include silent subtype 3 adenomas of obscure origin as well as silent gonadotroph, corticotroph, thyrotroph, and somatotroph adenomas.2.5.8.12.16

In this paper, we present the morphology of 69 clinically nonsecreting pituitary adenomas removed surgically from patients under 40 years of age. For comparison, 253 randomly collected morphologically identified null-cell adenomas and oncocytomas removed surgically from patients were analyzed to provide age-related data.

Clinical Material and Methods

Sixty-nine clinically nonsecreting pituitary adenomas removed at surgery from patients under 40 years of age were studied; 22 of the patients were younger than 30 years of age. The tumors were selected from the stored material of the Department of Pathology, St. Michael’s Hospital. The collection at present consists of more than 3000 surgically removed pituitary adenomas.

Fifty-four patients showed no clinical or biochemical evidence of adenohypophysyal hormone excess, and 15 patients presented with mild to moderate hyperprolactinemia. These 15 patients were included in the study since elevations of serum prolactin levels are assumed to be due to stalk section effects and not to hormone...
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secretion from the tumor cells. All tumors were macroadenomas at the time of surgery, with suprasellar extension and/or invasion of parasellar tissues with resultant symptoms of focal compression such as visual disturbances, headache, cerebral nerve palsies, and various degrees of hypopituitarism. All adenomas were investigated by histological, immunocytochemical, and transmission electron microscopic examination. The details of the morphological procedures and the criteria for the morphological diagnosis have been reported in previous papers.3,14 For comparison, 144 morphologically verified null-cell adenomas and 109 oncocytomas were included in the present study to clarify age-related frequencies of these tumor types.

Results

The age distribution of the total group of patients with null-cell adenoma or oncocytoma is shown in Fig. 1. The mean age of patients with null-cell adenoma at the time of surgery was 53 years, whereas that of patients with oncocytoma was 60 years. Only a few patients with null-cell adenoma and none with oncocytoma underwent surgery in their third decade of life. The peak incidence was reached in the sixth decade and the number of cases operated on declined gradually thereafter. There was a male preponderance, however, the relative frequency in women rose gradually as they grew older.

The incidence of various tumor types that were removed surgically from the 69 patients under 40 years of age is shown in Table 1. In contrast to the older age group, in the younger patients null-cell adenomas and oncocytomas were less common. Silent subtype 3 adenomas of unknown derivation, silent subtypes 1 and 2 corticotroph adenomas, and silent gonadotroph adenomas were frequently diagnosed tumor types followed by oncocytomas and silent thyrotroph adenomas. This trend was even more obvious in patients operated on under 30 years of age. In this age group, 68% of the tumors removed were diagnosed as silent subtype 3 adenomas or silent corticotroph adenomas (subtypes 1 and 2), whereas null-cell adenomas were evident in only 14% of cases and there were no oncocytomas.

Discussion

Terminology

Clinically nonsecreting pituitary adenomas account for approximately 25% of all surgically resected pituitary tumors and approximately 50% of these tumors obtained at autopsy.3,10,14,16 The majority of these tumors have been morphologically classified as null-cell adenomas and oncocytomas.3,32 The term “null-cell adenoma” was introduced to designate pituitary tumors that lack immunocytochemical and ultrastructural markers that would allow the recognition of their cellular composition and cytogenesis.11 Many of these tumors contain scattered cells or groups of cells that are immunoreactive for one or more than one adenohypophyseal hormone, most commonly follicle-stimulating hormone and α-subunit, less frequently luteinizing hormone and thyrotropin, more rarely growth hormone and prolactin, and very occasionally adrenocorticotropic hormone.8,9 Based on these immunocytochemical findings, it is believed that these tumors arise in pluripotential precursor cells which are capable of undergoing multidirectional differentiation, most often toward a gonadotroph- or glycoprotein hormone-producing cell line.8,9 Oncocytomas have the same immunocytochemical characteristics and possibly derivation as do null-cell adenomas, with the added feature of mitochondrial abundance.10,16 Oncocytomas are regarded as representing the endstage of gradual oncocytic transformation of null-cell adenomas.20

Silent subtype 3 adenomas were originally classified as one of the histological subtypes of silent corticotroph

TABLE 1

<table>
<thead>
<tr>
<th>Adenoma Type</th>
<th>Cases &lt; 40 yrs</th>
<th>Cases &lt; 30 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Percent (M/F)</td>
</tr>
<tr>
<td>null-cell adenomas</td>
<td>12/7</td>
<td>28</td>
</tr>
<tr>
<td>silent gonadotroph adenomas</td>
<td>9/8</td>
<td>25</td>
</tr>
<tr>
<td>silent subtype 3 adenomas</td>
<td>6/8</td>
<td>20</td>
</tr>
<tr>
<td>silent subtype 2 adenomas</td>
<td>5/1</td>
<td>9</td>
</tr>
<tr>
<td>silent subtype 1 adenomas</td>
<td>3/4</td>
<td>10</td>
</tr>
<tr>
<td>oncocytomas</td>
<td>3/0</td>
<td>4</td>
</tr>
<tr>
<td>silent thyrotroph adenomas</td>
<td>1/2</td>
<td>4</td>
</tr>
<tr>
<td>totals</td>
<td>39/30</td>
<td>11</td>
</tr>
</tbody>
</table>

Fig. 1. Age (years) and sex distribution of 144 patients with null-cell adenomas (N) and 109 patients with oncocytomas (O).
adenomas, and were termed "silent subtype 3 corticotroph adenomas." Subsequent studies have clarified that these tumors show less consistent immunoreactivity for pro-opiomelanocortin-derived peptides and ultrastructurally have no resemblance to corticotroph adenomas, so the term "corticotroph" was deleted. At this time, we have no conclusive evidence as to the cytogensis of this type of tumor.

Other silent adenomas are composed of cells that have immunocytochemical and ultrastructural features of the established adenohypophysal cell types, including silent corticotroph (subtypes 1 and 2), gonadotroph, thyrotroph, and somatotroph adenomas. As demonstrated by immunocytochemistry and in situ hybridization, silent pituitary tumors contain and produce one or more adenohypophysal hormones and express the messenger ribonucleic acid of the related hormone indicating gene expression. The question of why these tumors are clinically or biochemically silent has not been resolved. Several theories have been proposed to explain the discrepancy between morphological features and clinical-biochemical presentation, but conclusive evidence is lacking and the mechanism of silence is still elusive.

Age Relationship

Consistent with previous findings, our results confirm that the incidence of null-cell adenomas and oncocytomas is age-related; these tumors are usually operated on in older patients and only rarely become manifest clinically before the fifth decade. In contrast to the older age group, null-cell adenomas and oncocytomas occur less frequently in patients under the age of 40 years. In the younger subjects, silent subtype 3 adenomas of unknown derivation and silent corticotroph adenomas predominate. This trend is even more obvious in patients under the age of 30 years. In our material, silent subtype 3 adenomas combined with silent corticotroph adenomas accounted for 39% of surgically removed pituitary tumors in patients under 40 years of age and 68% in patients who were younger than 30 years of age at the time of pituitary surgery.

Clinical Implications

All tumors in this study were macroadenomas extending outside the sella turcica in association with visual disturbances. From the clinical standpoint, the fundamental question is whether these various morphologically distinct tumor types differ in relation to biological behavior, pace of growth, invasiveness, recurrence, and therapeutic responsiveness. Although further studies on a large number of cases are required to clarify structure-function correlations, it appears that differences exist in the biological behavior of the various clinically nonsecreting pituitary adenoma types. It has been assumed that null-cell adenomas and oncocytomas are slowly growing tumors, whereas some silent adenomas, particularly silent corticotroph adenomas and silent subtype 3 adenomas, have a more rapid growth rate, are more prone to be associated with apoplexy or invasiveness, and exhibit a more frequent rate of recurrence. However, it has been noted that subtype 3 adenomas appear to be radiosensitive. These findings underline the importance of careful morphological studies of the pituitary tumors of patients who show no clinical or biochemical evidence of hormone excess.

In our view, all clinically nonsecreting pituitary adenomas, especially in younger patients, should be examined not only histologically but also by immunocytochemical and transmission electron microscopic methods. The correct morphological diagnosis may provide useful information to the neurosurgeon and clinical endocrinologist assessing prognosis and making decisions relating to treatment.

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References

13. Martinez AJ: The pathology of nonfunctional pituitary
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Address for Drs. Kovacs and Horvath: Department of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.
Address reprint requests to: Shozo Yamada, M.D., Department of Neurosurgery, Toranomon Hospital, 2-2-2 Toranomon Minato-ku, Tokyo 105, Japan.