The pathogenesis of acromegaly

Clinical and immunocytochemical analysis in 75 patients

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A series of 75 patients with acromegaly and immunocytochemically characterized pituitary adenomas has been analyzed. Tumors secreting growth hormone (GH) only were found in 21% of cases. The remainder had tumors immunoreactive for more than one pituitary hormone: GH and prolactin in 31%; GH, prolactin, and glycoprotein in 40%; and GH and glycoprotein in 8%. Microadenomas were surgically treated in 17 patients with a success rate of 82%. Overall, normalization of basal GH secretion (to ≤ 5 ng/ml) was achieved in 54% of cases. The implications of these findings for the pathogenesis and neurosurgical management of acromegaly are discussed.

KEY WORDS • acromegaly • pituitary adenoma • immunocytochemistry • growth hormone

T he pathogenesis of acromegaly was a matter of controversy for many years after the syndrome was first described by Pierre Marie in 1886. Many authors, including Harvey Cushing, initially thought that the enlargement of the pituitary gland might merely be part of a generalized hypertrophic process affecting many endocrine glands and other organs. It was not until 1905 to 1910 that the intrasellar abnormality was generally recognized as a neoplasm actually responsible for the entire clinical syndrome.

Currently, acromegaly is one of the clearest endocrine abnormalities. It is relatively straightforward in diagnosis and is usually responsive to therapy directed toward the eradication of the pituitary tumor. A critical histological and immunocytochemical review of the pathology associated with acromegaly has, however, revealed a spectrum of etiologies that reflects a number of facets of the disease, and invites speculation as to the basis of the pathological process involved. We present our findings in a study of 75 patients with acromegaly associated with pituitary adenomas.

Clinical Material and Methods

A retrospective review of all patients evaluated at the Mayo Clinic between 1972 and 1984 with the diagnosis of acromegaly was accomplished, with particular regard to the presumed etiology of acromegaly. For this purpose, tumors were characterized as microadenomas, diffuse adenomas, and invasive macroadenomas. Microadenomas are focal lesions, 10 mm or less in diameter, clearly separable from the adjacent normal gland. Some of these focal lesions are also focally invasive, macroscopically involving dura or bone. Diffuse adenomas are nonfocal lesions generally involving the sellar contents, and enclosed by dura and diaphragma sellae. Suprasellar and lateral extensions may occur, but lack of invasion of macroscopic dura or bone is assumed. Invasive macroadenomas are large tumors which grossly invade dura and/or bone, and may have suprasellar or parasellar extensions. This classification is different from that proposed by Hardy and his associates, which was based on radiological features. It is thought that a biological classification is more pertinent to the assessment of the stage of disease and the analysis of outcome than a system based on radiographic studies which are no longer routinely performed.

A prospective study was undertaken, starting in 1980, in which the tumor tissue from all patients with acromegaly treated by transsphenoidal microsurgical removal of a pituitary adenoma (100% of surgically managed acromegalic patients) was subjected to immunocytochemical analysis. All of these patients underwent systematic evaluation, which included recording the stage of the tumor, an assessment of serum growth hormone (GH) values before and after surgery.
and on follow-up examination, the nature of subsequent adjunctive therapy, and the state of the patient's health at follow-up examination.

Fresh tissues obtained at surgery were fixed in 10% formalin, routinely processed, and embedded in paraffin. Microsections of pituitary tissues were histologically stained by the hematoxylin and eosin (H & E), periodic acid-Schiff (PAS), and Gomori's reticulin methods.

Immunocytochemical tests were performed, utilizing the modified peroxidase-antiperoxidase technique of Sternberger, et al., and commercially available antisera to GH, prolactin, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, and thyrotrophic hormone. Adenomas of known type as well as pituitary glands obtained at autopsy served as positive controls, whereas substitution of specific primary antiserum with normal rabbit serum served as negative controls. In selected cases, tissues fixed primarily in Trump's solution (4% formalin, 1% glutaraldehyde) were routinely processed for ultrastructural study, and were examined on a Phillips 400 electron microscope.

**Results**

The analysis of the two major areas of study is presented in Tables 1 to 3. Table 1 reviews the presumed etiology of acromegaly in the entire patient population. Table 2 details the results of the immunocytochemical analysis, correlating the cell type of the tumor with the patient's sex, preoperative basal serum GH values, the stage of tumor, and postoperative success as defined by basal GH values at the most recent follow-up evaluation. Values for basal GH of 5 ng/ml or less were considered to indicate successful treatment. Table 3 correlates these findings with the type of tumor.

Preoperative bromocriptine therapy was administered to five patients and six were treated with bromocriptine postoperatively. Postoperative radiation therapy was given to 10 patients, all with macroadenomas (eight invasive). One patient with an invasive tumor refractory to multiple attempts at therapy is being treated with a combination of bromocriptine and tamoxifen. Follow-up periods in the patients considered in Table 2 ranged from 1 to 256 months, with a mean follow-up period of 24 months, obviously too short a time to make any definitive comment about recurrence. Four patients had acromegaly treated by craniotomy a number of years prior to their transphenoidal operation. Five other patients with initially normal postoperative GH levels (≤ 5 ng/ml) subsequently developed recurrent pathological GH elevations at intervals ranging from 18 months to 3 years postoperatively.

**Discussion**

It is evident that pituitary adenoma is overwhelmingly the most common cause of the clinical syndrome of acromegaly. Approximately 25% of our reported cases were associated with microadenomas, 40% with diffuse (nonfocal) adenomas involving the entire intrasellar contents, and 25% to 30% with invasive macroadenomas (using gross criteria). Some 10% of the microadenomas had obvious invasive characteristics at surgery, and a higher percentage of these tumors showed microscopic invasion of adjacent dura. The incidence of microscopic invasion of the dura in all types of adenomas is currently being subjected to systematic prospective analysis, and will be greater than 50%. Multiple microadenomas have been reported, and two cases of multifocal GH-secreting microadenomas were found in our series.

Of great interest is the minority of cases not associated with pituitary neoplasms. In three patients, somatotroph hyperplasia was clinically suspected but pathologically unproven as the apparent cause of acromegaly, although there was no evidence of a neoplastic source of growth hormone-releasing factor (GHRF). Three patients in this series had documented GHRF-induced...
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adenomas due to hypothalamic-type neuronal hamartomas. One of these had a hypothalamic neuronal hamartoma with an associated intrasellar GH-secreting microadenoma. This patient had been reported previously, both as a single case and as one of a group of similar patients, from this and other institutions, with intrasellar neuronal hamartomas secreting GHRF, associated both with somatotrophic pituitary adenomas and with somatotroph hyperplasia.25

Several patients with peripheral sources of GHRF have been reported; all had neuroendocrine neoplasms.5,10,24,27 One patient had a pulmonary carcinoid tumor producing GHRF. The sellar enlargement and elevated GH level both reverted to normal following removal of the carcinoid tumor. Although the sella was not explored in this case, the pathology was presumed to be somatotroph hyperplasia. A clinically similar patient had a pancreatic islet cell tumor which has been immunocytochemically shown to produce GHRF.5 The acromegaly in this instance also resolved following removal of the pancreatic tumor. The sella was not explored but the process likely represented somatotroph hyperplasia. The latter has been demonstrated in other reported cases.27 Although such ectopic sources of GHRF are rare, they should be considered in acromegalic patients who have any symptoms or signs pointing to lesions elsewhere than the sella, and in patients with poor response to standard therapy.

A genetic cause for the tumor may be assumed in acromegalic patients who have the multiple endocrine neoplasia syndrome, type I (Wermer's syndrome). Seven such patients were encountered in this review. Our studies indicate that there are no distinctive clinical, immunocytochemical, or ultrastructural characteristics of these tumors.17 The prepubertal patients with acromegaly in this series had gigantism, as expected, and a review of the somatic growth characteristics of one of these patients strongly suggests the presence of elevated levels of GH in utero.

Of interest in this series is the high proportion of adenomas demonstrating immunoreactivity for more than one pituitary hormone. It has previously been assumed that the majority of pituitary tumors elaborate only one hormone. The most frequent form of pituitary tumor producing two hormones is the mixed-growth hormone cell-prolactin cell adenoma, a tumor composed in varying proportion of mature growth hormone and prolactin cells.6 The association of growth hormone and prolactin cells reflects the recognized histogenetic relationship between lactotrophic and somatotrophic cells. Plurihormonal adenomas have been described in laboratory animals23 but until recently were not characterized in the human; nearly every pituitary hormone combination has been reported.13 A surprising feature in our study of acromegalic adenomas is the frequency with which glycoprotein hormone components are demonstrated. This association has only recently been reported.13 The most frequent glycoprotein element appears to be thyrotrophic hormone, a feature particularly interesting in view of the rarity of thyrotrophic adenomas. Interestingly, the glycoprotein production of such adenomas is not expressed in the form of serum elevations of target hormones nor in clinical symptoms. Such lack of biological activity may be due to 1) hormone production but ineffective secretion, 2) structural peculiarities of the molecule permitting immunoreactivity but no bioactivity, or 3) the operation of a physiological feedback mechanism whereby low levels of tumor-secreted hormones offset endogenous or tumoral glycoprotein hormone production. It is evident that the immunohistochemical profile of plurihormonal adenomas is not necessarily reflected in their endocrinological effects.

It was remarkable that only 21% of the patients in this series had "pure" GH-secreting adenomas. This indicates the existence of a spectrum of pathogenesis, selective in the case of the tumors that secrete GH only and more generalized in the tumors that are immunoreactive for two or more pituitary hormones. This is particularly intriguing because the mechanisms of hypothalamic control of GH, prolactin, and glycoprotein hormones are in most instances basically different. In the case of the plurihormonal tumors in particular, one can speculate that a stem-cell neoplastic transformation has occurred, with multiple lines of differentiation as the tumor evolves. It is clear that serum PRL and other pituitary hormone measurements and immunocytochemical analysis of the tumor tissue should be part of the routine evaluation of patients with acromegaly.

There is no obvious correlation of success of surgical management with the type of tumor (Table 3). The goal of gross total surgical removal remains reasonable, and adjunctive therapy for invasive tumors or those incompletely removed remains advisable.

TABLE 3
Characteristics of pituitary adenomas in acromegaly

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>No. of Cases</th>
<th>Mean Preop Basal GH (ng/ml)</th>
<th>Postop GH ≤ 5 ng/ml (% Cases)</th>
</tr>
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<tbody>
<tr>
<td>GH only</td>
<td>16</td>
<td>78.6</td>
<td>50</td>
</tr>
<tr>
<td>microadenoma</td>
<td>4</td>
<td>50.0</td>
<td>50</td>
</tr>
<tr>
<td>diffuse adenoma</td>
<td>6</td>
<td>26.2</td>
<td>66</td>
</tr>
<tr>
<td>invasive adenoma</td>
<td>6</td>
<td>150.1</td>
<td>33</td>
</tr>
<tr>
<td>GH &amp; PRL</td>
<td>23</td>
<td>68.2</td>
<td>45</td>
</tr>
<tr>
<td>microadenoma</td>
<td>4</td>
<td>26.7</td>
<td>100</td>
</tr>
<tr>
<td>diffuse adenoma</td>
<td>13</td>
<td>83.5</td>
<td>42</td>
</tr>
<tr>
<td>invasive adenoma</td>
<td>6</td>
<td>83.4</td>
<td>17</td>
</tr>
<tr>
<td>GH, PRL, &amp; glycoprotein</td>
<td>30</td>
<td>71.8</td>
<td>60</td>
</tr>
<tr>
<td>microadenoma</td>
<td>8</td>
<td>22.0</td>
<td>75</td>
</tr>
<tr>
<td>diffuse adenoma</td>
<td>11</td>
<td>107.8</td>
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<td>11</td>
<td>71.0</td>
<td>55</td>
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<tr>
<td>GH &amp; glycoprotein</td>
<td>6</td>
<td>35.4</td>
<td>67</td>
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<tr>
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<td>32.7</td>
<td>100</td>
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<tr>
<td>diffuse adenoma</td>
<td>3</td>
<td>40.3</td>
<td>67</td>
</tr>
<tr>
<td>invasive adenoma</td>
<td>1</td>
<td>40.0</td>
<td>0</td>
</tr>
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* GH = growth hormone; PRL = prolactin; glycoprotein = glycoprotein pituitary hormones: follicle-stimulating hormone, luteinizing hormone, thyrotrophic hormone, alpha subunit.
Summary

This study demonstrates considerable diversity in the pathogenesis of acromegaly, and in the nature of the associated pituitary pathology. Further study of the genetic basis of the neoplastic transformation involved in pituitary adenomas and of the biology of the "normal" pituitary gland should clarify further this intriguing disease.

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References