An Overview of Pituitary Tumors

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ABSTRACT

Tumors arising in and around the hypophyseal fossa can cause symptoms by compression of surrounding structures or, in the case of adenomas arising from the adenohypophysis, by hypersecretion of hormones. Until recently, adenomas of the hypophysis have been classified on the basis of light microscopy into chromophobe, eosinophilic and basophilic. Presently available methods of histochemistry, immunocytology, electron microscopy and hormone assays make available a biological classification of these adenomas into two groups: (I) adenomas without secretory activity and (II) adenomas with secretory activity. Amongst the latter are included somatotroph adenomas, prolactin cell adenomas, melanocorticotroph adenomas and thyrotroph adenomas. Many of the large group of tumors formerly called “chromophobe” can now be reclassified amongst the secretory adenomas.

Introduction

Tumors of the hypophysis and its environs constitute an important portion of the clinical experience of the neurologist, neurosurgeon, ophthalmologist, endocrinologist and radiotherapist. Hypophyseal adenomas themselves account for from 7 to 17 percent of brain tumors. The rather mundane classical descriptive histopathology of hypophyseal adenomas has been replaced in the past decade or so by a fascinatingly sophisticated approach combining histochemistry, electron microscopy and immunochemical techniques. The result is a better correlation of endocrine activity with the cell types involved. This was based upon the isolation of the individual hormones of the hypophysis and of releasing and inhibiting factors of the hypothalamus. The ability of the endocrine laboratory to measure blood levels of these hormones and even to measure hormone production from tumor cells in vitro has enhanced the understanding of the clinician. At the same time, refined neurosurgical techniques using microsurgery, coupled with radiological diagnosis of small lesions by polytomography, have benefited the patient with microadenomas, thought once to be pathological curiosities.

The present paper will survey the highlights of pituitary tumors from an historical perspective, first mentioning some of the parapituitary lesions of concern to the clinician in diagnosing hypopituitary function. A review of the development of the hypophysis follows to aid in under-
standing the origin of adenohypophyseal cells and their neoplastic counterpart. The cytology of the normal gland will lead to a description of the classical concepts of adenomas of the hypophysis. Finally, some highlights of recent developments toward a functional classification of adenomas will complete this overview.

Parahypophyseal Tumors

The hypophysis resides in a unique position below the hypothalamus, within the sella turcica of the sphenoid bone. It is connected by a short stalk or infundibulum with the hypothalamus. Thus it is anatomically related to brain, rostral cranial nerves, anterior cerebral blood supply, cavernous sinus and nasopharynx. Expanding tumors of hypophyseal origin can cause symptoms by compression of these structures. By the same token, neoplasms of surrounding tissues can mimic the suprasellar pituitary tumor, with resulting endocrine symptoms from compression or destruction of hypophysis, stalk or hypothalamus. These lesions include gliomas of optic nerve, chiasm and hypothalamus. They are usually juvenile astrocytomas and most frequently occur at a younger age than hypophyseal adenomas. More rarely encountered are ectopic pinealomas or germinomas and other teratoid neoplasms. In an adult, meningiomas arising from the dura surrounding the sella turcica and occasionally aneurysms of the internal carotid artery must be considered.

Lastly, there are three groups of lesions arising from hypophyseal structures or anlage and metastatic carcinomas to be mentioned.

Craniopharyngiomas are suprasellar, occasionally also intrasellar, neoplasms usually of childhood and adolescence but ranging in our series from newborn to 69 years. Male patients predominate. The incidence is about 3 percent of brain tumors. Symptoms arise from compression of surrounding structures and are more frequently visual in nature with associated headache. Signs of hypothalamic and hypophyseal stalk destruction are often observed. Their origin was at one time considered to be from cell rests of the developing Rathke's pouch. The argument, however, for including them as epidermoid cysts is advanced by Russell and Rubinstein. They are composed of stratified squamous epithelium with transition to columnar cells which are arranged in a characteristic trabeculated pattern.

Rathke cleft cysts are rare cystic lesions of cuboidal to pseudocolumnar, often ciliated epithelial cells. They arise within the sella and may cause symptoms of hypopituitarism or extend into the suprasellar region compressing the optic chiasm. Such lesions are presumed to arise from expansion of residual microcysts of Rathke’s pouch origin.

Gliomas arising from the pars nervosa of the gland are rarely reported but an occasional neoplasm called a granular cell myoblastoma presumably arises from pituicytes of the neurohypophysis or stalk. Metastatic tumors to the hypophysis usually occur in the pars nervosa and may be present in as many as 26.6 percent of cancer patients. Most frequently the primary lesion is in the breast.

Development of the Hypophysis

The posterior half of the organ is derived from neuroectodermal tissue as a downward extension of the floor of the forebrain to become the floor of the third ventricle. The inferior and lateral walls of this ventricle contain the neurosecretory cells of the hypothalamus. The hypophyseal stalk or infundibulum contains the axons of these neurosecretory cells in passage to the posterior hypophysis or
pars nervosa. The hormones secreted by the pars nervosa from the hypothalamic cells are oxytocin and vasopressin.

Since the late 19th century, the derivation of the epithelial glandular anterior lobe of the hypophysis has been assumed to be ectodermal derivatives of the primitive stomodeum as Rathke’s cleft which, when closed at its buccal end, becomes Rathke’s pouch. Recent embryological data by Pearse and Takor Takor in the chick cast doubt on its origin in the stomodeum and suggest a neuroectodermal derivation of the adenohypophysis also. Be that as it may, the cells derived from Rathke’s pouch become the hormone producing cells of the adenohypophysis. From these cells arise the most frequent neoplasms of the hypophysis, the pituitary adenomas.

Cytology of the Adenohypophysis

The tinctorial and morphological characteristics of the adenohypophyseal cells with the limited techniques available in the first three or four decades of this century resulted in the classification of the cells into those containing granules with an affinity for basic dyes or for acidic dyes, the chromophil cells, basophilic or acidophilic (eosinophilic), respectively. The largest group of cells containing varying amounts of cytoplasm but no appreciable granulation was referred to as chromophobic. The goal of the morphologist has been to correlate the known hormone production of the human gland with the cytology. Hyperplasia of the eosinophilic cells had long been associated with gigantism or acromegaly and thus with growth hormone. The basophilic cells were apparently related to adrenal gland function, but the large group of cells without granules, the chromophobes, presented an enigma. Small cells with little or no cytoplasm scattered throughout the gland were considered “chief cells” or “stem cells” from which the chromophil storage cells were derived and from which the larger non-granulated chromophobe cells also arose.

The larger cells with no granules remained largely unidentified until Pearse, using the periodic acid Schiff (PAS) stain, related many of these to the basophil series and called the PAS+ cells “mucoid” cells because of their glycoprotein content. Growth hormone and prolactin are simple proteins with affinity for acidic dyes. The more complex glycoproteins of thyrotrophic, luteinizing hormone and follicle stimulating hormone were stained with PAS and were classified amongst the mucoid series. The cell secreting ACTH was originally thought to be a follicle cell but these latter cells are now considered to be phagocytic, related to the breakdown of parenchymal cells. The corticomelanotrophs, polypeptides perhaps combined with protein, may be agranular or be PAS+. The probability has been advanced that the chromophobe stem cell does not exist; all cells as they develop carry secretory potential.

Thus, the goal of relating a single cell to a single hormone awaited the combined techniques of electron microscopy, histochemistry and, especially, immunofluorescent cytology. These are well summarized in recent publications. The outcome is tabulated as follows:

A. Simple Proteins (Eosinophilic) (Orange G+)
   1. Growth hormone (GH) (STH)
      Orange G+\(^4,10,12\)
      Electron microscopy (EM);
      350 nm abundant
      PAS negative
   2. Prolactin (PRL) (LTH)
      Erythrosin (carmoisine)+\(^4,12\)
      EM: 200 to 900 nm (sparse)
      PAS negative

B. Mucoproteins (Basophilic) (PAS+)
   1. Gonadotroph
      a. Follicle stimulating hormone (FSH)
b. Luteinizing hormone (LH)  
EM: 200 to 250 nm

2. Thyroid stimulating hormone (TSH)  
EM: 150 to 200 nm

C. Polypeptides (Basophilic) (PAS +)  
1. Cortic melanotrophs  
a. Adrenocorticotropic hormone (ACTH)  
b. Melanocyte-stimulating hormone (MSH)  
EM: 300 to 400 nm.

D. "Chromophobes" (no hormone production)  
1. Follicle cells  
EM: No granules

2. Those cells with no visible granules by light microscopy can be demonstrated by proper techniques, including electron microscopy, to belong to one of the other categories. That adenomas composed of these cells lack endocrine activity may be due to the inability to measure the hormone output, perhaps subtly altered by the neoplastic condition of the cell or by its effect on surrounding parenchyma.

Adenomas of the Hypophysis

Until recently it has been routine to classify adenomas of the hypophysis according to the predominant cell type as demonstrated by the light microscope and using hematoxylin and eosin or trichrome stains, supplemented by PAS and orange G. Thus, they were either chromophobic, eosinophilic, basophilic or mixed. An occasional malignant variety was observed. They varied in size from incidental occult adenomas (microadenomas), as seen in up to 22.5 percent of autopsy specimens, to massive encapsulated structures extending beyond the confines of the sella superiorly, inferiorly or into the cavernous sinus. The vast majority of these adenomas were classified as chromophobic because specific granules were either not demonstrated or were missed. The presenting complaints were usually the result of suprasellar extension. Hormone secreting adenomas, such as those in acromegaly, were less common.

Most series of hypophyseal adenomas show a high proportion of nonsecreting "chromophobic" tumors. In 131 biopsy cases of pituitary adenomas studied by us since 1960, the presenting symptoms were ophthalmologic in 92 (70 percent) and endocrine dysfunction in 20 (15 percent). The remainder complained of both endocrine and visual dysfunction. Of the 20 patients with primarily endocrine symptoms, 60 percent were seen between 1972 and 1978. The close association with an eye hospital explains much of the bias, but the fact remains that most of the patients presented with signs of supracellular extension of a tumor which begins within the confines of the sella. The recent increase in hormone secreting adenomas presumably reflects refined clinical laboratory techniques to measure circulating hormones, x-ray polytomography of the sella and an awareness on the part of the physician. The demonstration that microadenomas can cause early endocrine symptoms before routine skull x-rays are abnormal is well documented by Wilson and Dempsey in whose recent series the proportion of secreting to nonsecreting adenomas is reversed.

In hypophyseal adenomas, the tinctional qualities, even cytoarchitecture, vary with fixation and with such intravitum degenerative changes as cysts and hemorrhage. The degree of granulation varies with the secretory phase of the cell, as does the appearance of the nuclei. In a phase of active secretion, there is not only nuclear and nucleolar enlargement, but there is a decrease in cytoplasmic granulation whereas in the less active phase, granulation increases and nuclear size decreases. Dense granulation occurs
in the storage phase. Cells of an adenoma may thus appear to be agranular or chromophobe, depending on their secretory activity when examined by the light microscope without special stains to accentuate easily missed dispersed granules.

Pasteels et al have shown that no single method of investigation alone will give adequate information on the functional status of adenohypophyseal cells within adenomas; electron microscopy, immunofluorescence and hormone assays must be combined with histochemistry. Landolt warns that it is a mistake to believe that neoplastic cells must be identical with the hormone producing cells of the normal adenohypophysis and electron microscopy confirms the impression that they are not identical. Hormone assays are now possible on tissue culture of tumor cells which continue to secrete hormone in vitro, at least in respect to growth hormone.

Chromophobe Adenomas

In past years the chromophobe adenomas constituted the largest percentage of hypophyseal tumors. These neoplasms are encapsulated. They vary in size from microscopic structures to massive lesions which can compress frontal or temporal lobes and may extend into the sphenoid or even the nasopharynx.

Classically, they are considered to lack secretory function, although occasional tumors, without light microscopic evidence of specific granules, are associated with clinical evidence of hormonal hypersecretion. Hypopituitarism is more common, owing to compression of the adenohypophysis. Presenting symptoms are most frequently visual.

Many variations are found in the microscopic appearance both amongst different tumors and amongst cells of any one. The structural subdivision into diffuse, sinusoidal and papillary seems to serve no useful purpose biologically and more often than not there is a mixture of these types. The individual cells comprising the adenoma vary from small, round, dark nucleated structures with minimal cytoplasm and no granules ("chief cells") to larger polygonal and even columnar cells with varying amounts of cytoplasm. Although the criterion for diagnosis of a chromophobe adenoma is the lack of granules within the cytoplasm of the cells, all former large series noted occasional cytoplasmic staining with trichrome dyes and even sparse granules in some cells.

Pearse on the basis of PAS techniques indicated many so-called chromophobe tumors were indeed "mucoid cell" adenomas. McCormick and Halni denied the existence of chromophobe adenomas when definitive histochemical stains are used, alleging that many of the chromophobe cells seen by light microscopy are degranulated eosinophils or basophils. The electron microscope has demonstrated secretory granules in the cells of these neoplasms with the exception of those composed of follicle cells and oncocyes. Specific immunohistochemical techniques have confirmed the electron microscopic evidence. For the reasons, present day classifications of large series of pituitary tumors tend to avoid the term chromophobe and substitute nonsecretory or nonfunctioning adenomas.

Eosinophilic Adenomas

Eosinophilic adenomas, associated with the hypersecretion of growth hormone as expressed in acromegaly, were less common than the chromophobe variety in most of the older series, varying from 10 percent to 30 percent or thereabouts of hypophyseal tumors. The prolactin secreting cell is the second member of the eosinophilic series, and the galactorrhea-amenorrhea syndrome of Forbes-Albright is another clinical manifestation.
of eosinophilic adenomas. The eosinophilic adenoma is less likely to extend above the sella than the "chromophobe" variety. When small it lacks a capsule, but with growth a capsule develops from the compressed stroma. The component cells contain abundant to sparse cytoplasmic granules which stain with orange G. By differential staining using erythrosin or carmoisine, these orange G cells can be divided into somatotrophs and prolactin (erythrosin positive) cells. As noted previously, the combined histochemical, immunochemical and electron microscopic analysis of the adenomas formerly classified as "chromophobe" has demonstrated cytological evidence of secretory activity in many. McCormick and Halni found eosinophilic adenomas to comprise 59 percent of their series, but only 3 percent had acromegaly. Wilson and Dempsey demonstrated 33.2 percent growth hormone and 23.6 percent prolactin producing adenomas for a 56.8 percent total in their series of 250 cases. Other recent authors find from 30 percent to 40 percent of the adenomas to be "eosinophilic."

**Basophilic Adenomas**

Adenomas of the basophilic series were rarely encountered before the modern era. When present they were usually intrasellar. Some of these patients had Cushing's disease. Kernohan and Sayre found none with clinical symptoms in their series of about 600 adenomas. The clinical picture of Cushing's syndrome was more frequently associated with adrenal hyperplasia or neoplasm and with Crooke's changes in the basophilic cells of the hypophysis. The frequency of hypophyseal tumors in patients with Cushing's disease can now be established at about 50 percent; microadenomas occur in 40 percent, the remaining 10 percent are macroscopic. The cell types in these tumors have varied with light microscopy from densely granulated cells of the mucoid (PAS+) series to "chromophobe," but electron microscopy has demonstrated corticotrophic granules, and immunohistochemical studies show they contain adrenocorticotropic hormone and/or melanocyte stimulating hormone. Recent series have shown adenomas in Cushing's disease to comprise from 6 percent to 14 percent of the total hypophyseal adenomas.

Nelson's syndrome is another condition associated with corticomelanotroph adenoma formation. In these patients subsequent to Cushingoid symptoms, there is a progressive pigmentation with evidence of an enlarging pituitary tumor following adrenalectomy. These tumors are frequently invasive. They were as frequent as Cushing's disease and comprised 7 percent of Wilson and Dempsey's series.

**Invasive and Malignant Adenomas**

Very rarely have hypophyseal adenomas been reported to metastasize through the blood stream to extra-cranial locations; the liver is most often the site of metastasis. The term carcinoma, if used at all, should be reserved for these, but metastatic adenomas usually have failed to show cytological malignancy. Occasional adenomas spread in the subarachnoid space. Large adenomas which break through their capsule and invade adjacent tissues such as the cavernous sinus or cerebral hemispheres have sometimes been called pituitary carcinomas, a designation which should be avoided. The frequency of invasive tumors is about 2 to 3 percent. These cases, which may show rapid growth and cellular atypism, are usually agranular by light microscopy. They have been reviewed by Martins et al. It is agreed with those authors that a better term is invasive rather than malignant adenoma and that the designation malignant...
adenoma be reserved for those which metastasize.

**Oncocytoma**

Adenomas with faint, finely granular eosinophilic cytoplasm, which on electron microscopy exhibit abundant mitochondria and correspond to oncocytes, have been described in the hypophysis. With light microscopy they are usually considered to be composed of chromophobe cells or degranulated eosinophils. Their final definition depends on electron microscopy. The oncocytes apparently arise from any pre-existing adenohypophyseal cell type, but as adenomas the cell is uniform. They may be associated clinically with hypopituitarism, no secretory activity, or acromegaly.

**Biological Classification**

In several patients in any series which depended on former techniques of morphological identification, there were anomalous and even contradicting findings. Some patients with Cushing's syndrome showed chromophobe adenomas; some patients with eosinophilic adenomas showed no sign of acromegaly. The combined methods of investigation and the new surgical approaches make it clearly advisable to replace the inadequate and outmoded chromophobe-chromophil morphological categories by a biological classification, even though in some adenomas more than one hormone can be produced. Several authors have followed a scheme that divided the tumors into (A) endocrine inactive adenomas (mostly "chromophobe" follicular cell tumors and oncocytomas) and (B) endocrine active adenomas. Amongst the latter are included adenomas in (1) acromegaly, (2) galactorrhea-amenorrhea syndrome, (3) Cushing's disease and (4) thyrotropic adenomas.

The following tentative outline collates some of these recent series and may serve as a working model for classifying hypophyseal adenomas on a practical basis, using light microscopy and limited electron microscopy, correlated with endocrine activity.

I. Adenomas with endocrine activity:
   A. Somatotroph adenomas
      (adenomas with acromegaly)
      1. Heavily granulated cell (orange G+)
      2. Mixed granular cell and agranular or sparsely granulated cell
      3. Agranular cell, including
         a. Oncocyte
   B. Prolactin cell adenoma
      1. Erythrosinophilic granules (adenomas with Forbes-Albright galactorrhea-amenorrhea syndromes)
      2. Adenomas with Peillon-Racadot syndrome (amenorrhea without galactorrhea)
      3. Adenomas with neither 1 or 2
   C. Melanocorticotroph adenoma
      (adenomas with Cushing's disease)
      1. Heavily granulated cells PAS+
      2. Poorly granulated cells and agranular cells
      3. Agranular cells
   D. Thyrotroph adenomas
      1. Type I—Primary, associated with hyperthyroidism
         a. Agranular cell
         b. PAS+ granular
         c. Orange G+ granular cell
      2. Type II: ? secondary, associated with long standing hypothyroidism
         a. Agranular cell
         b. PAS+ granular cell
         c. Orange G+ granular cell

II. Adenomas without endocrine activity
   A. Agranular
      1. Oncocytoma
      2. Follicle cell adenoma
      3. "chromophobe" (chief cells)
B. Granular
1. Adenomas resulting in hypopituitarism
2. Granular adenomas
   a. Too small to be secretory
   b. Secretion too weak to be biologically significant

Such a system implies a close collaboration between clinician and laboratory and the use of laboratory techniques that are not universally available. It further implies that tissue is adequate in amount and fixation for analysis. It eliminates a large group of tumors that the pathologist and clinician were content to consider “chromophobe,” a term which constituted a common meaning to each. The dilemma facing a morphologist concerning the existence of chromophobe adenomas when chromophobe cells do not exist must be reconciled to the benefit of the patient and his clinician as well as to the integrity of scientific advance. A pragmatic approach could be to use the functional biological classification for all applicable neoplasms and to retain the word “chromophobe” (in quotation marks) under nonsecreting adenomas as a frank expression of our lack of sufficient data from whatever cause.

The majority of patients with hypophysal adenomas, even in most recent series, present with symptoms due to expansion beyond the sella turcica. Endocrine symptoms, if any, this late in the disease are those of hypopituitarism. We must continue to ask: Were earlier signs present that would hint at a hypersecretion stage? The early detection of these “chromophobe” or endocrine inactive adenomas must depend on the primary physician. It is well documented\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) that in experienced hands microsurgery through the transsphenoidal approach results in decreased morbidity. In endocrine secreting tumors, refined x-ray techniques can demonstrate microadenomas in many cases. The goal to be attained is thus the early diagnosis also of the nonsecreting adenomas.

Summary
Neoplasms in and around the sella turcica cause symptoms by compression or invasion of surrounding structures, especially the optic pathways, and including the hypothalamic-hypophysal axis and the adenohypophysis. Adenohypophysal tumors can also present with symptoms due to hypersecretion of their component cells. It is no longer adequate or accurate to rely simply on light microscopic morphology to classify these adenomas. Combined techniques of histochemistry, immunofluorescent chemistry and electron microscopy can identify the hormones secreted and their cells of origin thus allowing a functional, biological classification of hypophysal adenomas into (I) endocrine active adenomas: (a) somatotroph, (b) prolactin, (c) melanocorticotroph and (d) thyrotroph and (II) endocrine inactive tumors. Early diagnosis of small endocrine active adenomas allows removal by refined neurosurgical techniques with minimal morbidity. The endocrine inactive tumors present with signs of expansion and create a challenge to search for early diagnostic criteria.

References


