Virchows Arch [Pathol Anat] (1983) 399:277–287

Virchows Archiv A

Pituitary hyperplasia

Definition, light and electron microscopical structures and significance in surgical specimens*

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Summary. Surgical specimens of 15 normal and 106 para-adenomous anterior pituitaries were studied immunocytochemically and in part electron microscopically for the presence of hyperplasia. GH cell hyperplasia was found in 13% of all normal pituitaries, in 6% of the cases with Prolactin secreting adenomas and in 9% of the cases with ACTH secreting adenomas. Prolactin cell hyperplasia occured in nearly equal percentages (17–23%) in normal pituitaries and in areas adjacent to GH-, Prolactin- or ACTH-secreting adenomas or adjacent to inactive adenomas. Previous findings of relatively more frequent Prolactin cell hyperplasia occuring together with Prolactin producing adenomas have to be revised. Prolactin cell hyperplasia as a primary source of hyperprolactinemia is very rare and almost always occurs in conjunction with oncocytic adenomas. ACTH cell hyperplasia was found in 13% of the normal pituitaries, in 14% of the cases with Prolactin secreting adenomas, in 58% of the cases with ACTH producing adenomas and in 40% of the pituitaries with GH secreting adenomas. We have no explanation for the latter result. ACTH cell hyperplasia may be the primary cause of Cushing's disease (18% of all Cushing cases). Hyperplasia of TSH cells in normal pituitaries was rare (7%) and with the exception of Prolactin producing adenomas (22%) was not found near adenomas. Clinical-pathological correlations are discussed.

Key words: Pituitary – Hyperplasias – Immunocytochemistry – Ultrastructure

Introduction

The best definition of hyperplasia in the pitutary, seems to be "a multiplication of one or more cell types". It can take the form either of a diffuse

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* Supported by the Sonderforschungsbereich 34 (Endocrinology) of the Deutsche Forschungsgemeinschaft

formation, if the multiplication exists in areas where the cell type is regularly localized, or a nodular formation, if the multiplying cells form dense foci. Furthermore, two "statistical" types can be differentiated: relative hyperplasia, a multiplication of limited cell types without enlargement of the whole gland, and absolute hyperplasia, involving multiplication of cell types with hyperplasia of the whole gland. Large foci of hyperplasia must be differentiated from microadenomas. These microadenomas show a disrupted or strongly coarsened alveolar basic structure, decreased vessels and a mostly medullary architecture (Saeger, 1981). Hyperplasia has a preserved or slighty disturbed basic alveolar structure. In contrast to adenomas, the surrounding pituitary tissue shows no sign of compression. The identification of pituitary hyperplasia is contraversial since the different cells of the adenohypophysis are not uniformly distributed and the normal numbers of each cell type vary greatly.

Exact data may be obtained only if serial sections are performed and immunohistologically identified cell types are counted in each section. This is nearly impossible and at most limited to a few pituitaries. Investigations of a larger series (of more than 100 cases) for correlations to functional data are not possible using this time consuming method. We are thus dependent on estimations of the relative numbers of cells.

If only small pieces of the peritumoral hypophysis can be obtained it is questionable if these are also representative of the remaining pituitary. Nevertheless, our specimens were obtained from various para-adenomous parts of the pituitaries and are nearly random samples which can at least be compared with one another.

Cell counts of immunohistologically identified cells in the anterior pituitary have not been previously realized. Fowler and MacKeel (1979) counted only histochemically identified pituitary cell types. Estimates of immunohistologically identified cells were reported by Kovacs et al. (1981). They correspond well to numerical data previously reported elsewhere. From these studies, we know that approximately 50% of all cells in the normal pituitary are GH cells, 15–25% Prolactin cells, 15–20% ACTH cells, with less than 5% being TSH cells and approximately 10% being gonadotropic cells.

Hyperplasia or hypoplasia of the pituitary may indicate an altered hormonal balance. When surrounding an adenoma, these changes can be a sign of a hyperplasiogenic tumor development if the adenoma and hyperplasia are composed of the same cell type. On the other hand, hypoplasia adjacent to adenoma may also be the regulative effect of hormonal overproduction of the tumor.

Applying the definition used above, the aim of this study was to demonstrate hyperplasia in the surgical specimens of "normal" pituitary tissue from patients hypophysectomized for metastasizing cancers and in para-adenomous pituitary tissue. We also wished to answer the following questions:

1. How frequent is hyperplasia in the "normal" pituitary and in para-adenomous tissue, and of which cell type does it consist?

2. Are the cells of peritumoral hyperplasia comparable to adenoma cells?
3. Does the hyperplasia have a clinically significant effect and is it related to the hormonal status of the patient?

Material and methods

Fiveteen biopsies were obtained from patients who underwent hypophysectomy for metastasizing cancers of the breast or prostate. 106 specimens were from para-adenomous pituitary tissue in cases of pituitary adenomas (36 GH secreting, 32 Prolactin secreting, 19 ACTH secreting adenomas and 19 inactive adenomas) which were surgically resected by transnasal-transsphenoidal, or, in a few cases, by a transfrontal approach.

Tissue specimens were fixed in Bouin's solution for paraffin embedding. Sections were stained with hematoxylin-eosin, PAS, and performic acid-alcianblue-PAS-orange G (Adams and Swettenham 1958). For immunohistochemical studies, sections were incubated with commercial anti-sera from rabbits (Sternberger et al. 1970) (anti-GH and anti-TSH of the Deutsche Kabi Vitrum GmbH, München, FRG, anti-Prolactin of the Panchem-Gesellschaft für chemische Produkte, Kleinwallstadt, FRG, anti-ACTH of Ferring Arzneimittel, Kiel, FRG) for 24 h at 4°, followed by 10 min with a rabbit anti-gamma-globulin and finally with horseradish peroxidase-anti horseradish peroxidase complex, also for 10 min. A 3.3′-diamino-benzidine-H_2O_2 mixture was applied, for visualizing the peroxidase at the sights of the antigen-antibody-complexes.

Fiveteen biopsies of para-adenomous tissue were available for electron micrscopy. These specimens were fixed in gluteraldehyde and post-fixed in osmium tetroxide. The embedding medium was epon 812. Semi-thin sections, helpful in identifying the type of tissue and in it's differentiation from adenomous tissue, were cut and stained with toluidin blue. Ultra-thin sections were cut on the OmU2 of Reichert. Electron microscopy was done on the $EM9S_2$ of Zeiss.

Immunohistochemically prepared sections were used for identifying the relative numbers of GH-, Prolactin,- ACTH- and TSH cells. The estimated numbers of cells were divided semiquantitatively into 5 stages. An average range of cell numbers, taken from 60% of the normal pituitaries, was calculated and used as the normal range for each of the 4 cell types. A cell number above the normal range was defined as hyperplasia, and a cell number below the normal range, as hypoplasia.

Results

"Normal" pituitaries varied considerably in the estimated number of different cell types. The most frequent cell type was the GH cell, followed by the ACTH cell and the Prolactin cell. TSH cells were the rarest type.

GH cells

GH cells were oval or spherical cells with an oval, mostly central nucleus. The cytoplasm showed immunohistologically dense brown-staining granular deposits, corresponding to secretory granules. The structure of the GH cells is distinctly constant. Variations in granule content or of cell size were not observed. The secretory granules measured 300–500 nm, being mostly spherical and electron dense. The rough endoplasmic reticulum was developed to a medium degree. The Golgi complexes were occasionally enlarged with dilated cisterns. Lysosomes were mostly sparse, small and rich in pigment; in some cells they were numerous and accumulated.

Table 1. Number of GH cells. Percentages in the series of normal pituitaries and associated with different adenoma types

	N	Obviously normal range		Obviously decreased number (hypoplasia)		Obviously increased number (hyperplasia)	
		N	%	*N*	%	*N*	%
"Normal" pituitary	15	12	80	1	7	2	13
Adjacent to GH secreting adenomas	36	4	11	32	89	–	–
Adjacent to Prolactin secreting adenomas	31	19	61	10	32	2	6
Adjacent to ACTH secreting adenomas	11	4	36	6	55	1	9
Adjacent to inactive adenomas	9	2	22	7	78	–	–

80% of the "normal" pituitaries had a number of GH cells which could clearly be defined as normal (Table 1). Consistently fewer GH cells were found in the tissue adjacent to pituitary adenomas, especially in the GH secreting adenomas.

Hyperplasia, mostly of the diffuse type, occured in 2 (13%) of the normal pituitaries, in 2 (6%) cases with Prolactin secreting adenomas and in 1 (9%) case with corticotropic adenoma, but never in cases with GH secreting adenomas.

Prolactin cells

Prolactin producing cells were demonstrable in varying forms and with different granulation. We found densely granulated cells, large in size and having a spherical or polyhedral contour. Other Prolactin cells were medium-sized having an angular or elongated form and an only moderate amount of granulation.

At the electron microscopic level, the densely granulated cells showed an intermediately developed rough endoplasmic reticulum and a small Golgi complex. The secretory granules measured 400–800 nm in diameter. Lysosomes were occasionally numerous. In the moderately granulated Prolactin cells, the rough endoplasmic reticulum was markedly evident, forming long parallel, partly whorled membranes. The secretory granules were smaller, measuring 150–400 nm in diameter. Lysosomes were numerous. The cell membranes were tortuous. The number of Prolactin cells seemed to conform to the norm in 80% of the "normal" pituitaries (Table 2). Just as many (78–83%) of the cases with Prolactin secreting, ACTH producing and inactive adenomas also showed Prolactin cells in a normal range. The number of Prolactin cells adjacent to GH secreting adenomas, was estimated as normal in only 58% of the cases.

Table 2. Number of prolactin cells. Percentage in the series of normal pituitaries and associated with different adenoma types

	N	Obviously normal range		Obviously decreased number (hypoplasia)		Obviously increased number (hyperplasia)	
		N	%	*N*	%	*N*	%
"Normal" pituitary	15	12	80	–	–	3	20
Adjacent to GH secreting adenomas	31	18	58	6	19	7	23
Adjacent to Prolactin secreting adenomas	32	26	81	–	–	6	19
Adjacent to ACTH secreting adenomas	12	10	83	–	–	2	17
Adjacent to inactive adenomas	9	7	78	–	–	2	22

A reduced number of Prolactin cells, or hypoplasia, was observed only adjacent to GH secreting adenomas.

Hyperplasia of Prolactin cells was found to be diffuse or nodular and very extensive in some cases. It occured in nearly equal percentages of 17–23% in normal pituitaries and adjacent to all adenoma types.

ACTH cells

ACTH cells were medium to large in size and oval or polyhedral in shape. Some cells showed paranuclear vacuoles. The granulation was dense, or slightly decreased.

Electron microscopical examination showed these cells to have a moderately developed rough endoplasmic reticulum, medium sized Golgi complexes, and secretory granules varying in size and arrangement. The granules diameter measured from 200–450 nm, but a few granules measured up to 1,000 nm. The lysosomes were numerous in some cells. The number of ACTH cells was estimated to be normal in 74% of "normal" pituitaries (Table 3). Nearly the same range (72%) of normal pituitaries was found in cases with Prolactin secreting adenomas. In the series of GH producing adenomas, cases with normal adjacent ACTH cells had a slightly decreased frequency of 60%. Hypoplasia occured in 2 (13%) cases with normal pituitaries and in 1 (14%) case with Prolactin secreting adenoma.

A hyperplasia of ACTH cells was evident in 13% of normal pituitaries. An increased frequency of ACTH cell hyperplasia was observed in cases with GH (40%) or ACTH (58%) secreting adenomas as well as in cases with inactive adenomas (50%).

Table 3. Number of ACTH cells. Percentage in the series of the normal pituitaries and associated with different adenoma types

	N	Obviously normal range		Obviously decreased number (hypoplasia)		Obviously increased number (hyperplasia)	
		N	%	*N*	%	*N*	%
"Normal" pituitary	15	11	74	2	13	2	13
Adjacent to GH secreting adenomas	10	6	60	–	–	4	40
Adjacent to Prolactin secreting adenomas	7	5	72	1	14	1	14
Adjacent to ACTH secreting adenomas	19	8	42	–	–	11	58
Adjacent to inactive adenomas	6	3	50	–	–	3	50

Table 4. Number of TSH cells. Percentages in the series of normal pituitaries and associated with different adenoma types

	N	Obviously normal range		Obviously decreased number (hypoplasia)		Obviously increased number (hyperplasia)	
		N	%	*N*	%	*N*	%
"Normal" pituitary	15	11	73	3	20	1	7
Adjacent to GH secreting adenomas	9	3	33	6	67	–	–
Adjacent to Prolactin secreting adenomas	9	3	33	4	45	2	22
Adjacent to ACTH secreting adenomas	12	5	42	7	58	–	–
Adjacent to inactive adenomas	4	4	100	–	–	–	–

TSH cells

TSH cells were medium-sized, polyhedral or angular in shape. Immunocytochemistry revealed a weakly diffuse or a cloudy granular positive stain.

In the electron microscope, TSH cells showed very sparse rough endoplasmic reticulum, very small Golgi fields, many free ribosomes and sparse secretory granules measuring 100–200 nm in diameter. They were mostly located along the cell membranes and were only rarely increased in number. Small lysosomes were sparsely distributed.

Thyrotrophic cells were the least numerous cell type, contributing not more than 5% of all cells. Estimated normal numbers of cells were found

Table 5. Hyperplasia of pituitary cells

Cell type	Physiological hyperplasia	Pathological hyperplasia
GH cells	not known	chronic hypoglycemia unstable juvenile Diabetes mellitus
Prolactin cells	pregnancy lactation period	reaction to medication: oestrogens antihistaminics? antihypertensive agents? neuroleptics? lesions of pituitary stalk suprasellar tumors
ACTH cells	frequently in older individuals	hypersecretion of CRH idiopathic hypertension
TSH cells	not known	chronic hypothyroidism
FSH cells and LH cells	post menopause	primary hypogonadism after gonadectomy Klinefelter's syndrome polycystic ovaries

in 73% of all "normal" pituitaries (Table 4). Normal TSH cell counts were also evident adjacent to all inactive adenomas.

Hypoplasia of TSH cells was demonstrable in 20% of "normal" pituitaries and in 45–67% of cases with hormonally active pituitary adenomas.

In one normal pituitary, TSH cells were increased in number. It seems to be remarkable that in two cases a Prolactin secreting adenoma showed adjacent TSH cell hyperplasia.

Discussion

Pituitary hyperplasia is possible under various physiological and pathological conditions which are listed in Table 5 (for references see Saeger 1981).

In our collection, *hyperplasia of GH cells* occurred in 13% of all normal pituitaries and only rarely adjacent to Prolactin or ACTH secreting adenomas. The reasons for these facts are not known and cannot be explained. Local factors may play a role.

We found a reduced number of GH cells in 7% of normal pituitaries and in many specimens of peritumoral tissue. Hypoplysia is frequent especially adjacent to GH secreting adenomas. From the para-adenomous pituitary in these cases, we can assume a regulative suppression of GH which corresponds to the normal or decreased plasma levels of GH after selective adenomectomy (Lüdecke et al. 1976). Otherwise, local factors may also be the cause, as it is possible for peritumoral GH cell hypoplasia occurring in cases with Prolactin- or ACTH secreting or inactive tumors. These results are in good agreement with previously reported findings (Saeger 1977b).

Table 6. Peritumoral prolactin cells in hyperprolactinemia

Postoperative prolactin Plasma levels	Number of cases *N*	Number of prolactin cells			
		Hypo-plastic %	Normal %	Slightly hyper-plastic %	Markedly hyper-plastic %
Decreased	7	14	43	29	14
Slightly decreased	4	–	25	50	25
Normal	1	–	100	–	–
Slightly increased	6	17	17	50	17
Greatly increased	6	Not included because of residual tumor tissue			

Hyperplasia of Prolactin cells in normal pituitaries is not rare, we found it in 20% of all pituitaries. Since many drugs (Table 5) can induce a hyperprolactinemia, probably based on Prolactin cell hyperplasia, many mechanisms may be responsible. We have not found reports on the human hypophysis dealing with this topic. Peritumoral hyperplasia of Prolactin cells in cases with GH secreting or inactive adenomas is just as frequent as hyperplasia adjacent to Prolactin secreting adenomas.

Based on histological and electron microscopical findings, we concluded in a previous report (Saeger 1977a, b) in agreement with Trouillas et al. (1976), that Prolactin cell hyperplasia adjacent to Prolactin secreting adenomas was frequent. Immunohistological studies and correlations with similarily investigated normal pituitaries now show that they are not more frequently adjacent to Prolactin secreting adenomas than to other adenoma types. These findings are in a good agreement with the reports of Girod et al. (1980).

Therefore, certain signs of a hyperplasiogenic development in these adenomas were not present. In cases with para-adenomous Prolactin cell hyperplasia, there was little or no ultrastructural differences from the adjacent Prolactin secreting adenomas. In contrast to this, evident differences were reported by Trouillas et al. (1976).

Correlations with clinical and hormonal data should show an increased Prolactin plasma level after selective adenomectomy of a Prolactin secreting adenoma if para-adenomous hyperplasia of Prolactin cells exists. A small series of such cases were studied in our material (Table 6). Our preliminary clinical and pathological correlations demonstrate that the existence of peritumoral Prolactin cell hyperplasia seems to have no influence on the postoperative Prolactin levels, since cases with slightly or strongly hyperplastic Prolactin cells may have both decreased or increased levels of Prolactin after surgery. An explanation for this may be that the hyperplasia is not representative of the entire gland, but confined to the area around the tumor.

In cases with small cell chromophobe adenomas, having little rough endoplasmic reticulum and showing electron microscopical signs of endocrine inactivity (Saeger 1977a), we come to the hypothesis that partly demonstrable para-adenomous Prolactin cell hyperplasias (Trouillas et al. 1976; Saeger 1977a and 1980) were the source of the elevated Prolactin level. However we now know from our immunocytochemical studies that most of the small cell chromophobe adenomas in hyperprolactinemia contain Prolactin and are the source of the elevated hormone levels. When hyperprolactinemia exists in cases with distinctly oncocytic adenomas which are almost exclusively inactive, or in carniopharyngiomas, the change can be attributed to Prolactin cell hyperplasia.

The ACTH cells in normal pituitaries were just as frequent as in the peritumoral tissue of cases with Prolactin secreting adenomas (13% versus 14%). The reason why 40% of all pituitaries with GH producing tumors showed para-adenomous ACTH cell hyperplasias is hard to explain. A hypothalamic regulated cause cannot be excluded, although elevated plasma levels of ACTH were not found.

Para-adenomous ACTH cell hyperplasia in cases with ACTH secreting adenomas have been demonstrated in other studies (Saeger 1974, 1977b and 1978; Carmalt et al. 1977; Lamberts et al. 1980) and seem to be more frequent in the early stages of hypothalamic hypophyseal Cushing's disease (Saeger 1978). The ACTH cell hyperplasia is usually almost identical in structure to ACTH secreting adenomas. Only one case with an undifferentiated mucoid adenoma showed evident ultrastructural differences to the para-adenomous hyperplasia.

The clinical relevance of para-adenomous ACTH cell hyperplasia in Cushing's disease is doubtful. In vitro studies of human tissue (Lüdecke et al. 1978 and 1980) in concordance with clinical findings (Tyrell et al. 1978; Lüdecke et al. 1981) demonstrate suppression of para-adenomous ACTH secretion in most cases of Cushing's disease.

Diffuse and/or nodular hyperplasia of ACTH cells may be found in cases of Cushing's syndrome without pituitary adenomas. The hyperplasias are the cause of the Cushing's disease only in these cases (Saeger 1974, 1977a and 1978; Carmalt et al. 1977). Our collection of 55 cases with Cushing's disease included 41 ATCH secreting pituitary adenomas and 10 cases in which only ATCH cell hyperplasias could be found. The collection of Carmalt et al. (1977) showed focal hyperplasia in 23% of the cases with Cushing's disease. This hyperplasia frequently develops into an adenoma (Saeger 1978) and must have been the source of the increased ACTH where no adenoma could be found and the ACTH plasma levels returned to normal range after surgery. Nevertheless, we cannot exclude that very small and soft ACTH producing adenomas were removed during surgical dissection and were therefore not histologically demonstrable. According to recent surgical reports, an ACTH secreting adenoma may regularly be identified as the source of ACTH hypersecretion (Bigos et al. 1980; Lüdecke et al. 1981) in clearly defined cases of Cushing's disease.

Hypoplasia of *TSH cells* is more frequent than hypoplasia of other cell types and was demonstrable in about half of all cases with pituitary adenomas. We believe that local phenomena are the cause of this finding.

The reason why TSH cell hyperplasia appears in 22% of all pituitaries with Prolactin producing adenomas is not known. Hyperstimulation by the TRH may be responsable. Further investigation with measurement of the TRH is needed.

In conclusion, pituitary hyperplasia is a frequent and usually a secondary phenomenon, of lesser clinical significance. Pituitary hyperplasia as the cause of primary pituitary hyperfunction is a rare occurance.

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Accepted January 20, 1983

Note added in proof

A very recent report (Asa et al. 1982) of a quantitative immunocytochemical analysis of Prolactin cells showed that Prolactin cells were normal in the nontumerous portion of glands that harbored prolactinomas. However, percentages were slightly elevated in glands with non-prolactin-producing adenomas.

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