Acta Neurochir (Wien) (1989) 100: 56–61

Acta Neurochirurgica

Intratumoural Cyst Formation in Pituitary Macroadenomas

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Summary

Twenty-one patients with various types of pituitary macroadenomas underwent hypophysectomy at the Chaim Sheba Medical Centre between 1985 to 1987. Intraoperative fine needle aspiration of the tumoural content was attempted prior to tumour excision. Although none of the patients had a history compatible with pituitary apoplexy, intratumoural fluid suggestive of a cyst within the tumour was found in 57% of the patients. Analysis of the hormones in the aspirated fluid revealed variable elevations in hormone levels, some reaching 3,000 times the equivalent plasma levels. Concomitant elevated levels of other pituitary hormones found in the cyst fluid support the concept of mixed secretory potential of pituitary adenomas, including the apparently non-functioning tumours. Six out of seven patients (86%) who received preoperative treatment with bromocriptine had an intratumoural cyst while only seven out of fourteen patients (50%) who were not treated with this drug prior to surgery had a cyst within the tumour. The implications of these observations on current theories concerning the pathophysiology of pituitary adenomas are discussed.

Keywords: Pituitary adenomas; pituitary infarction; bromocriptine; pituitary hormones; pituitary cyst; pituitary apoplexy.

Introduction

Haemorrhage into pituitary adenomas is well documented[3, 4, 7–9, 18, 20, 22]. While early reports of pituitary haemorrhage emphasized an acute event with altered consciousness, ophthalmoplegia and blindness[2, 3], haemorrhage may occur in patients who do not show the signs of pituitary apoplexy. In one series, 18 of 70 patients with pituitary adenoma had visible haemorrhage within the tumour at surgery, but only three of them presented with symptoms referable to haemorrhage[18].

The pathogenesis of spontaneous haemorrhage and cystic degeneration in pituitary tumours is unclear. In addition, no data could be found concerning the cytological, haematological and endocrinological characteristics of intra-tumoural fluid encountered in pituitary adenomas.

Accordingly, we have evaluated the incidence of pituitary cyst formation by intraoperative aspiration of the sellar contents in 21 patients with pituitary adenoma. The haematological, cytological and hormonal contents of the cysts were determined as well as the possible role of preoperative treatment with bromocriptine in the pathogenesis of cyst formation.

Methods and Materials

Patients: Twenty-one patients with pituitary macroadenoma were studied: 8 had prolactin secreting adenoma, 3 had growth hormone secreting adenoma, 2 had ACTH secreting adenoma, and 8 had non-functioning adenoma. There were 14 males and 7 females with a mean age of 42 years (range: 26 to 72 years).

Seven of the patients with pituitary adenoma received bromocriptine prior to surgery. The presenting symptoms of the patients with pituitary adenoma are listed in Table 1.

The preoperative diagnosis was based on axial and coronal high resolution CT scans. A neuro-ophthalmological evaluation was performed on all patients prior to surgery. Preoperative blood samples for hormone assessment were taken immediately prior to surgery. Postoperative samples were obtained one month later.

Prolactin (PRL), growth hormone (GH), luteinizing hormone (LH) and follicular stimulating hormone (FSH) were measured by radio-immunoassay using kits supplied by Diagnostic Products Corporation (Los Angeles, California).

Aspiration technique and surgery: Pterional craniotomy was performed in nine patients, while the transsphenoidal approach was used in the remaining twelve patients. Upon exposure of the tumour, three attempts at aspirating the pituitary contents were made using a long 23 gauge needle. The tumour was then removed and examined by routine histopathological methods.

Evaluation of the aspirated fluid: Each sample of the aspirated fluid was subjected to haematological, cytological and endocrinological analysis. Haematocrit and haemoglobin levels were determined to exclude gross contamination with blood. The presence of adenoma cells in the fluid was determined by the use of the cytospin

Table 1. *The Major Presenting Symptoms of 21 Patients with Pituitary Adenoma.* The number of patients in whom a pituitary cyst was found is also noted for each of the symptoms

Presenting symptom	No. of patients	Presence of cyst
Visual disturbances:		
Visual field defect	14	8
Visual hallucinations	3	1
Impotence	4	2
Amenorrhea	4	3
Physical changes:		
(acromegaly, Cushing's disease)	5	3
Chronic headache	4	2
Panhypopituitarism	1	1
Acute neurologic signs	0	

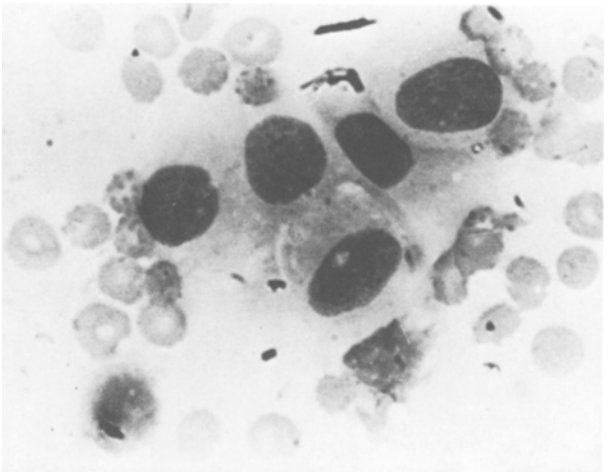

Fig. 1. Micrograph: a cluster of adenoma cells isolated from the cyst fluid of a patient with a non-functioning pituitary adenoma (H & E × 1,200)

technique. Prolactin, GH, LH and FSH levels in the tumoural fluid were measured by radio-immunoassay as previously described.

Statistical analysis: Data were analyzed by the use of non-parametric statistical techniques.

Results

CT-scan failed to identify a cyst in any of the patients. Intraoperative aspiration of the tumour revealed however intra-adenomatous fluid in twelve pituitary adenomas an incidence of 57% for cyst formation in this series. In the remaining nine cases, no fluid was obtained by the three attempts at aspiration during surgery.

In one patient the fluid which filled most of the pituitary fossa was lost during exposure of the tumour. The cytological and haematological characteristics of the fluid samples obtained from the other 11 patients are listed in Table 2.

The volume of the cysts ranged from 0.2 to 2.5 cc (mean 0.85 cc). The colour was dark brown to clear xanthochromic correlating with the haemoglobin content of the fluid. Adenoma cells were found in all samples after isolation by cellofuge (Fig. 1).

The hormone levels in the cyst fluid, as well as the pre- and postoperative plasma hormone levels are listed in Table 3.

Plasma levels of thyroid stimulating hormone were within normal limits in all patients and no measurements of this hormone were made in the cysts fluid.

The ratio between hormone levels in the cyst fluid and the preoperative plasma (i.e. C/P ratio) is illus-

Table 2. *Characteristic of the Aspirated Fluid Samples*

Type of adenoma	Volume (cc)	Hb (g%)	Colour	Presence of adenoma cells
PRL	0.5	1.5	Xanthochromic	+
PRL	1.0	1.0	Xanthochromic	+
PRL	0.5	1.7	Xanthochromic	+
PRL	0.2	1.8	Xanthochromic	+
NFA	0.5	0.7	Clear	+
NFA	0.5	0.8	Xanthochromic	+
NFA	2.5	2.8	Dark brown	+
NFA	0.7	2.5	Dark brown	+
NFA	>2.0	n. d.	Dark brown	n. d.
GH	1.0	2.2	Clear brown	+
GH	0.9	2.0	Xanthochromic	+
GH	1.0	1.0	Xanthochromic	+

(PRL prolactin secreting adenoma, GH growth hormone secreting adenoma, NFA non functioning adenoma, Hb haemoglobin).

Table 3. *Hormone Levels Measured in the Cyst Fluid (when Present) and the Pre and Post Operative Plasma Levels in 21 Patients with Pituitary Adenoma*

Pt. no.	Sex/age	Type of adenoma	Hormone levels												Pre-op. bromo-criptine
			PRL (ng/ml)			GH (ng/ml)			LH (mlU/ml)			FSH (mlU/ml)			
			Pre-op.	Cyst fluid	Post-op.	Pre-op.	Cyst fluid	Post-op.	Pre-op.	Cyst fluid	Post-op.	Pre-op.	Cyst fluid	Post-op.	
1	M/56	PRL	285	900,000	200	n.d.	n.d.	1.0	n.d.	n.d.	1.8	n.d.	n.d.	1.0	no
2	F/27	PRL	7.6	5	65.5	1.0	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	yes
3	M/39	GH	33.0	203	26.0	143	325,000	37.2	1.2	23	1.5	1.2	510	1.1	yes
4	F/38	GH	5.0	424	11.8	16.5	15,000	11.6	32.8	2,630	1.8	5.3	180	1.4	yes
5	M/68	NFA	19.4	208	14.7	1.0	n.d.	1	1.8	n.d.	1.5	1.1	n.d.	1.0	no
6	M/26	NFA	12.7	996	32	1.0	428	1.3	5.4	8.4	6.2	3.2	6.8	3.0	no
7	M/52	NFA	n.d.	n.d.	n.d.	1.0	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	no
8	F/32	PRL	1,420	76,000	120	1.0	722	1.0	2.0	44	1.5	2.1	92	1.7	yes
9	F/27	PRL	730	22,300	600	4.2	238	2.1	38	1,420	22	17	245	9	yes
10	M/29	NFA	32	425	120	1.0	5.0	1.0	6.2	4.2	5.0	3.0	3.4	n.d.	no
11	M/37	NFA	5	<5	5	1.0	1.0	1.0	22	9,000	12	6.7	550	9.0	no
12	M/44	GH	63	403	36	250	7,500	195	1.5	13	1.5	1.2	610	1.1	yes
13	M/41	PRL	1,159		2,400	1.0		1.0	1.8		1.8	1.0		1.0	yes
14	F/66	NFA	38.7		14.5	1.0		1.0	3.4		4.5	12.8		5.5	no
15	M/27	NFA	9.1		11.3	1.0		2.2	4.1		3.8	2.1		3.6	no
16	F/37	ACTH	28.6		9.3	1.0		1.0	7.1		1.8	2.7		1.9	no
17	M/45	PRL	13,000		6,200	1.0		1.0	1.8		2.8	1.3		1.6	no
18	M/72	NFA	9.9		16.9	1.0		1.0	5.2		1.8	2.8		1.3	no
19	M/40	PRL	348		228	1.8		2.6	4.0		3.8	4.5		5.2	no
20	M/51	PRL	5,000		420	1.0		1.0	1.5		1.9	1.0		1.0	no
21	F/30	ACTH	58		33	1.0		1.0	10		4.3	3.1		1.9	no

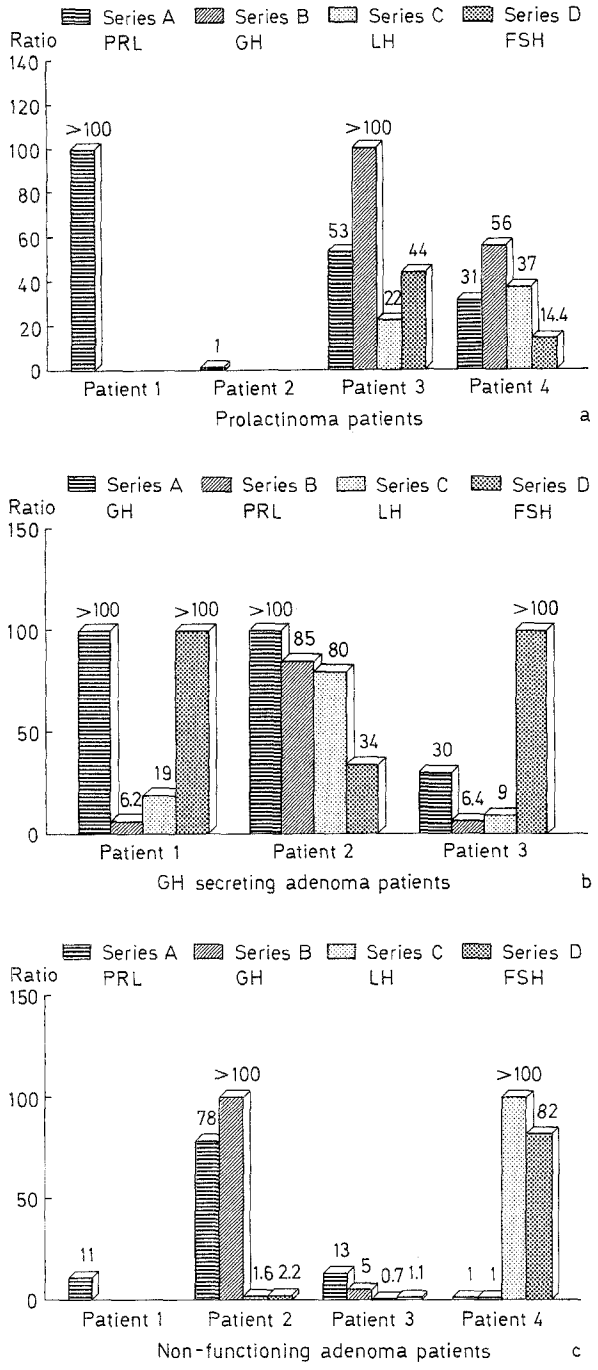

Fig. 2. The ratio between hormone levels in the cyst fluid and the preoperative plasma hormone levels for individual patients. a) Cyst/plasma ratio for patients with prolactin secreting adenoma. b) Cyst/plasma ratio for patients with GH secreting adenoma. c) Cyst/plasma ratio for patients with non-functioning adenoma

trated for individual patients in Fig. 2 (a–c) for the three major adenoma groups.

Six out of seven patients (86%) who received preoperative treatment with bromocriptine had an intratumoural cysts. Only seven of the remaining 14 patients (50%) who did not receive bromocriptine preoperatively had intratumoural cyst. These values did not reach however statistical significance ($p = 0.078$, Fisher exact test). No correlation was found between cyst formation and sex, age, or tumour type.

Discussion

Tumoural infarction and degenerative cyst formation have long been known to occur in patients with pituitary adenoma[7–9]. The reported incidence of this phenomenon varies. Müller and Pia found 19 incidences of haemorrhage in a series of 270 pituitary adenomas[20]. Poppen[22] reported an incidence of 20%, while Mohanty found pituitary haemorrhage in 25% of his patients[18]. Others reported haemorrhage and cyst formation as "a common surgical finding"[4] and the diversity in the reported incidence was explained by Wakai[28] as due to incomplete analysis of the symptomatology and surgical findings as some reports dealt with only severe cases and others included mild or asymptomatic cases as well.

None of our patients had the characteristic symptomatology of pituitary apoplexy. Subacute symptoms such as headache and recent onset of visual disturbances, which were present in 11 of the 12 patients with intratumoural cyst, may have represented a recent haemorrhage into the adenoma. Those complaints are however non-specific and were also present in patients with no intratumoural cyst.

In our series, twelve out of 21 patients had intratumoural cysts suggestive of intra-adenomatous haemorrhage. The aspirated fluid varied in amount, colour and haemoglobin content (Table 2). As expected, the haemorrhagic fluid had higher haemoglobin and haematocrit values than the xanthochromic and clear fluid samples. The volume of the fluid tended to be larger in the former.

The pathogenesis of infarction and cyst formation in pituitary adenomas is unclear. Insufficient blood supply to a growing tumour may lead to infarction of the tumour. The empty sella syndrome has also been associated with silent infarction of pituitary adenomas[4, 21]. Login[16] reported an empty sella in a patient whose acromegaly resolved spontaneously. He speculated that the tumour had undergone silent selective infarction. Similar cases mainly of GH secreting adenomas have also been reported[6, 14].

Other mechanisms may be involved in the formation of intratumoural cysts such as the "misplaced exocytosis" phenomenon. This term was used by Horvath

and Kovacs[5] to describe misplacement of secretory granule extrusion in some forms of pituitary adenomas. Normal anterior pituitary cells extrude hormone containing granules primarily at the interface between the cell membrane and the capillaries of the pituitary capillary plexus[25]. Neoplastic pituitary cells however, can have multiple sites of granule exocytosis remote from the pericapillary space. Such misplaced exocytosis could occur because a tumour outgrows its vascular supply, resulting in fewer available pericapillary exocytosis sites, or as a consequence of abnormal secretory process by the neoplastic cell. Accumulation of such aberrant secretions may lead to formation of intra-adenomatous hormone containing cysts. This process may be the underlying mechanism in some of the cysts found in our patients, especially those containing clear xanthochromic fluid with low haematocrit values.

Pituitary apoplexy may be induced by radiotherapy to a pituitary adenoma, steroid administration, and in the course of long term bromocriptine therapy[19, 28]. Recently, pituitary apoplexy has been described in association with even a single test dose of bromocriptine given to a patient with a GH and prolactin producing adenoma[26].

The effect of the dopaminergic drug bromocriptine on pituitary adenomas has been studied extensively[5, 11, 12, 23, 27]. While cell necrosis is not a manifestation of a bromocriptine effect on adenoma cells, it brings about a marked reduction in the size of the adenoma. Reduction in cell size is evident within a week after initiation of therapy with prominent effects on the cytoplasm, endoplasmic reticulum and nucleoli. A softening effect within the adenoma may appear as early as after 24 hours if the long acting depot-bromocriptine is used. Cell shrinkage caused disruption of the adenoma tissue with enlargement of the perivascular spaces where fluid and tissue debris are accumulated[13]. This disruption may induce haemorrhage and participate in the formation of intra-adenomatous cysts. In our series, six of the seven patients who received preoperative bromocriptine treatment, had a pituitary cyst, as did six patients in the untreated group. Statistical analysis failed to demonstrate a significant correlation between preoperative bromocriptine administration and cyst formation. However, one cannot ignore the apparent effect of the drug associated with cyst formation in 86% of the patients receiving it (as opposed to a frequency of only 50% in the untreated group). Such an effect is perhaps masked by the limited size of our study group.

The hormone levels within the cyst were higher than the preoperative blood levels. However, no consistent pattern of such a ratio (C/P ratio) could be shown (Fig. 2).

The heterogenicity of hormones present in the cyst fluid may indirectly support the hypothesis of mixed secretory potential of pituitary adenomas. This assumption is also supported by studies of adenoma tissue cultures by Lipson *et al.*[15]. They reported a tumour from an acromegalic patient secreting PRL, ACTH, TSH, LH and FSH and two ACTH secreting tumours which contained PRL, GH and LH. Also, one prolactin secreting adenoma released large amounts of all the anterior pituitary hormones. Furthermore, many chromophobe adenomas secreted various combinations of anterior pituitary hormones. Labat reported multihormonal pituitary adenomas in 12 of 77 patients undergoing operation for symptomatic pituitary adenomas[9]. Forty-five out of 66 asymptomatic pituitary adenomas, examined at post mortem also contained several pituitary hormones[10].

In our series, when examining the cyst/plasma hormone ratio of patients with prolactin and GH secreting tumours, the mixed secretory potential of these tumours becomes apparent as illustrated in Figs. 2 a and b.

The possibility that multihormone secreting adenomas represent multiclonal lesions arising from hyperplasia, seems unlikely as the para-adenomatous tissue appeared histologically normal[10]. On the other hand, the Rathke Pouch stem cell common to the adenohypophysis cell lines, favours the concept of pituitary adenoma being a native tumour expressing multiple secretory potentialities, a view which is expressed by Reichlin[24].

Evaluation of the apparently non-functional adenomas presents a unique problem. Some of these patients, who show normal plasma levels of adenohypophysis hormones, appear to have tumours which do secrete a variety of hormones, as shown in vitro by Lipson[15] and Mashiter[17] who used immunocytochemistry and cell culture techniques. As a matter of fact, 66% of 114 functionless tumours studied by Mashiter secreted gonadotropins, as well as other hormones. In a recent report, Black *et al.*[1] evaluated hormone production in 37 clinically non-functioning pituitary adenomas. By the use of immunocytochemical staining techniques, they demonstrated that one or more pituitary hormones were secreted from 73% of these non-functioning tumours.

In our series, two patients with endocrinologically silent adenomas (patients 2, 4, in Fig. 2 c) had markedly

elevated levels of at least two types of hormones within the intratumoural cyst. The other two patients in this category had more moderate elevations of one of the hormones measured in the cyst fluid.

The results of this study should be viewed as a preliminary observation only. They should be verified by studying larger groups of patients together with the use of other laboratory techniques. It may be that measuring hormone levels within a cyst fluid (when present) may serve as a simple alternative to other diagnostic techniques, such as cell cultures and immunocytochemistry in establishing the endocrinological nature of pituitary adenomas.

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