 ISSN 0172–780X **www.nel.edu**

ORIGINAL ARTICLE

Gender-related differences in non-functioning pituitary adenomas

Bernhard Schaller

Department of Neurology, Freiburgstrasse 10, CH-3010 Berne, SWITZERLAND.

Correspondence to: Dr. B. Schaller,
Department of Neuroscience,
Karolinska Institute, Retzius vaeg 8
17177 Stockholm, SWEDEN
E-MAIL: Bernhard.Schaller@neuro.ki.se

Submitted: *May 6, 2003*
Accepted: *July 23, 2003*

Key words: **pituitary; gender; outcome; clinically non-functioning adenoma**

*Neuroendocrinol Lett 2003; **24**(6):425–430 NEL240603A06 Copyright © Neuroendocrinology Letters **www.nel.edu***

Abstract

OBJECTIVES: Clinically non-functioning pituitary adenomas are common tumors of the pituitary gland. No studies have yet documented gender-related differences in the growth and presentation of these tumors and nothing is known about their effects on their subsequent surgical outcome and prognosis.
SETTING AND DESIGN: Twenty-eight patients with non-functioning pituitary adenoma, that met strict inclusion criteria, and that underwent surgical treatment between January 1990 and June 1997, were retrospectively reviewed.
METHODS: The patient charts, as well as histological (incl. immunohistochemistry) and electron microscopic findings were analyzed. Tumor invasiveness was classified according to the modified Hardy criteria.
MAIN FINDINGS: Eleven patients were women and seventeen were men; the female-to-male-ratio was 1:1.5. Men were significantly older, both at diagnosis and surgery. Visual field defect and visual acuity deficit were the most common presenting symptoms with similar occurrence both in women and men, whereas blindness predominated in women. Microadenomas and invasive adenomas did not differ significantly in MIB-1 index, but patients less than 35 years old had higher MIB-1 indices (n=4, 1.72+/–1.15), than did patients over 45 years (n=11, 0.63+/–0.42) (p: n.s.). MIB-1 labeling indices were higher in adenomas of female compared to male patients (1.5 +/–1.2 vs. 0.8+/–1.8; $p < 0.003$). The overall outcome was significantly worse in women than in men.
CONCLUSION: The biology and the clinical course of clinically non-functioning pituitary adenoma seem to differ in women and men. In men, tumors are smaller and less invasive at surgery, and the outcome is better than in women. The present findings may justify a more aggressive therapeutic approach to clinically non-functioning pituitary adenomas in women than in men, especially to improve the availability of viable pituitary cells at the time of surgery.

Introduction

Clinically non-functioning pituitary adenomas (NFAs) do not produce clinically active anterior lobe hormones [1,2]. Their progressive mass effect may cause symptoms and signs of anterior lobe hormone deficiency or of prolactin hypersecretion of the surrounding adenomatous lactotroph cells mimicking the presence of a prolactinoma. Before the 4th decade of life, they are 2–3 times more common in women, and thereafter they are 2–3 times more common in men [3]. Gross invasion of neighboring anatomic structures is present in approximately 40% [4] and represent a formidable challenge in therapeutical management. Null cell adenomas and oncocytomas represent 17% and 6% of all

pituitary tumors, respectively; these two pathological subgroups collectively compromise the most common surgically resected type of pituitary tumors [5].

Transsphenoidal surgery remains the mainstay therapy for NFAs [6]. However, craniotomy may be necessary in the occasional lesions with extreme lateral intracranial or suprasellar extension, which could not be resected by transsphenoidal surgery, and in which effective radiation therapy would be difficult to obtain without considerable morbidity. Whereas gross total tumor removal remains an intuitive surgical goal for all pituitary tumors and should certainly be attempted to the extent that is safely possible, it will not be a realistic expectation, nor will it be an absolute necessity for many NFAs [7]. The goal of surgery in NFAs remains to decompress cranial nerves and to preserve of normal pituitary function. Therefore surgical outcome is quite satisfactory with postoperative clinical improvement in 87% and stabilization in 9% [8,9] Among patients without preoperative hypopituitarism, 97% retained normal pituitary function postoperatively [8,9].

For other tumors of the pituitary, there seems to be a gender-related difference, in clinical presentation, tumor characteristics and surgical outcome [10–14]. For NFAs, such data are not available so far. To determine the nature and extent of gender-related differences in NFAs, a series of surgically treated NFAs was retrospectively reviewed with special reference to differences in surgical outcome and prognosis.

Patients and Methods

Patient Population

The charts of patients who underwent surgical treatment for pituitary adenoma between January 1990 and June 1997 at the University Hospitals of Basel, Switzerland, were retrospectively reviewed. Patients who had multiple surgical pituitary procedures were included only if the first operation was performed at the University Hospitals of Basel; these patients were counted only once. NFAs were diagnosed solely on the basis of immunohistochemical or electron microscopic findings. NFAs were defined as pituitary adenomas that met the following criteria: (i) presence of a sellar mass detected by magnetic resonance imaging or high-resolution CT scans, (ii) absence of signs or symptoms of pituitary hyperfunction, (iii) presence of serum levels of pituitary hormones in the normal or low range, with the exception of mild hyperprolactenima attributable to hypothalamic pituitary discconection in patients with large tumors, (iv) immunostaining criteria as established by Wilson [15], and (v) ultrastructural, morphologic, and cytogenetic criteria as established by Kovacs and Horvath [16].

Pituitary function in patients with NFAs was assessed by means of basal and dynamic testing. Measurement of serum levels of free thyroid hormones, thyrotropic stimulating hormone (TSH), prolactine (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone in men and estradiol in premenopausal women, cortisol, and urinary free cortisol level. A more thorough evaluation of adrenal function was necessary in patients with borderline normal serum and urinary cortisol levels. In this case the insulin hypoglycemia test, the metyrapone test, or the ACTH test have been shown to identify the majority of patients with subnormal adrenal function. Assessment of stimulated growth hormone (GH) secretion and basal insulin-like growth factor I (IGF-I) level were used, because of the recognized importance of the adult GH deficiency syndrome.

All patients underwent preoperative neuroradiological examinations, including cerebral high-resolution computed tomography (CT), cerebral magnetic resonance (MR) imaging, digital subtraction arteriography, or MR arteriography. Preoperatively, none of the patients had been treated with radiation therapy. Tumors were graded according to Hardy's classification [17] as modified by Wilson [18]. Tumor size and invasiveness were evaluated on the basis of preoperative MR imaging scans or on intraoperative findings. Tumors were classified as micro- and macroadenoma when 1 cm or less in dimension or greater than 1 cm, respectively. For all operations, a standard transsphenoidal approach by use of a surgical microscope was performed and the surgical opinion on the success of tumor resection was obtained from the operative records.

Tumors were judged as recurrent if preoperative signs normalized within 12 weeks after surgery, but with documented tumor regrowth by increased tumor size in the follow-up MR-imagines compared with the initial postoperative scan used as baseline imaging.

Neuropathological Examination

All specimens were fixed in 10% buffered formalin, routinely processed, embedded in paraffin, and stained by the haematoxlin-eosin method. Immunohistochemistry for prolactin, GH, ACTH, FSH, LH, TSH and alpha-and/or beta-subunits of the glycoproteins was performed using commercial kits [19].

The histological diagnosis of pituitary adenoma was confirmed, and the mitotic index was assessed semiquantitatively and expressed as 0, 1 or more than 1 mitoses per 10 high-power (x400) fields.

Measurements of cell proliferation were based on MIB-1 (monoclonal antibody, Dianova Hamburg, Germany, lot 006, dilution 1:1000) labeling indices. Sections were systematically examined on high-power fields (x400) for the presence of immunoreactivity and expressed as percentage positive nuclei. The areas with the highest density of MIB-1 labeling index (LI) were assessed by counting at least 1000 adjacent cells in the selected areas. Cells were considered positive when unequivocal nuclear staining could be identified.

Statistical Analysis

Data are reported as the mean±SD unless otherwise indicated. The nonparametric Wilxon two-sample rank sum test was used to compare the geometric mean of the study groups. The frequency of observations between men and women was compared by the unpaired t test and the Fischer's exact probability

where appropriate. The level of significance was set at $p < 0.05$.

Results

Twenty-eight patients met the inclusion criteria. Eleven (39%) were women, and 17 (61%) were men; the female-to-male ratio was 1:1.5 (Table 1). Men were older, both at diagnosis (58±12 (range 18–70) versus 47±18 (range 16–65) years; p: n.s.) and at surgery (59±12 (range 18–70) versus 47±18 (range 16–66) years; p: n.s.). Before the fourth decade of life, the adenomas were 2 times more common in women (8 women vs. 4 men; p: n.s.), and thereafter 4.3 times more common in men (13 men vs. 3 women; p: n.s.). 82% of the patients were between the ages of 30 and 59 years. Two (7%) of the tumors were microadenomas, and 26 (93%) were macroadenomas. The mean tumor size was 19±09 mm overall. The mean suprasellar extension was 14±7 mm. Age at diagnosis did not correlate with tumor size in men or women.

Clinical Features

Of the 23 patients (82%) who demonstrated visual field defects, 12 (52%) showed bitemporal and 5 (22%) temporal hemianopsia, whereas 3 (13%) revealed bitemporal and 3 (13%) temporal quadranopsia (Table 1). Visual acuity reduction was found in 14 (50%) of cases. Blindness of one eye was noticed in 6 patients (21%), and blindness of both eyes in none. Of the 5 patients who presented with an ophthalmoplegia, 3 (60%) had a third nerve palsy and 2 (40%) fourth or sixth cranial nerve palsy. Visual field defects (100% vs. 71%; p: n.s.), visual acuity reduction (72% vs. 35%; p: 0.03) and ophthalmoplegia (36% vs. 6%; p: n.s.) all were more common in women compared to men. Headache was more common in women compared to men (7 of 11 (64%) vs. 4 of 17 (24%); p: n.s.). At presentation, pituitary apoplexy occurred in 2 patients (7%).

At the time of initial pituitary function test, 8 (29%) had no deficiency, and 3 (11%) had simultaneous deficiencies in FSH-LH, ACTH, and TSH (Table 3). Women predominantly had hypogonadism (82% vs. 65%; p: n.s.), whereas men showed more common adrenal hypofunction (47% vs 27%; $p < 0.002$). Female patients had higher PRL level than male patients (37±16 vs. 20±14 μg/L; $p < 0.03$). In 2 of the 7 cases where initial serum PRL was less than 10 μg/L, a pituitary apoplexy was found during surgery. There was a positive correlation between tumor size and hypopituitarism.

Tumor Characteristics

Of the overall 28 patients, 15 (54%) had null-cell adenoma, 8 (29%) an alpha-subunit producing adenoma and 5 (18%) oncocytoma (Table 2).

The release of alpha-subunit in NFAs differed not significantly between the sexes; however it was seen slightly more often in men (35% vs. 18%). Eighty three per cent of men (5 of 6) with alpha-subunit producing adenoma had decreased testosterone levels; both women were over 50 years of age and did not have the expected elevation of gonatropins found in postmenopausal women. Null-cell-adenomas occurred predominantly in men (11/17 (65%) vs. 4/11 (36%); $p < 0.002$). Fifty five per cent of men (6 of 11) with null-cell-adenomas had testosterone deficiency; 75% of women (3 of 4) demonstrated a diminished gonadotropic function. *Oncocytomas* were exclusively seen in women. Of this patient subpopulation, 80% had altered gonadotropic function. Overall, women had larger tumors (22±7 versus 17±11 mm; p: n.s.) and more frequently presented with invasive tumors (55% versus 13%; p: n.s.) than men. Microadenomas were exclusively seen in men, and macroadenomas were more common in women than men (100% versus 85%; p: n.s.).

TABLE 1: Gender-related differences in preoperative clinical features.

Clinical Feature	Female (n = 11)	Male (n = 17)	Overall (n = 28)
Mean age at onset (yr±SD)	47±18	58±12	54±9
Endocrine signs			
Diminshed libido	2 (18%)	7 (41%)	9 (32%)
Adrenocorticotropic function			
Normal	8 (73%)	9 (53%)	17 (61%)
Diminished	3 (27%)	8 (47%)	11 (39%)
Thyrotropic function			
Normal	8 (73%)	14 (82%)	22 (79%)
Diminished	3 (27%)	3 (18%)	6 (21%)
Gonadotropic function			
Normal	2 (18%)	6 (35%)	8 (28%)
Diminshed	9 (82%)	11 (65%)	20 (72%)
Normal endocrine function	2 (18%)	6 (35%)	8 (29%)
Focal neurological signs and symptoms			
Headache	7 (64%)	4 (24%)	11 (39%)
Visual field defect	11 (100%)	12 (71%)	23 (82%)
Visual acuity deficit	8 (72%)	6 (35%)	14 (50%)
Blindness	4 (36%)	2 (12%)	6 (21%)
Other cranial nerve palsies	4 (36%)	1 (6%)	5 (18%)

Yr, year; n, number; SD, standard deviation; NA, not applicable.

TABLE 2. Gender-related differences in classification of non-functioning adenomas according to the modified Hardy criteria [17,18] and other tumor characteristics

Tumor Characteristic	Female (n = 11)	Male (n = 17)	Overall (n = 28)
Microadenoma	NA	2 (12%)	2 (7%)
Macroadenoma	11 (100%)	15 (88%)	26 (93%)
Grade I (<10 mm)	NA	2 (12%)	2 (7%)
Stage 0	NA	2 (12%)	2 (7%)
Grade II (>10 mm)	6 (55%)	13 (76%)	19 (68%)
Stage 0	3 (27%)	5 (29%)	8 (29%)
Stage A	1 (9%)	4 (24%)	5 (18%)
Stage B	2 (18%)	4 (24%)	6 (21%)
Grade III (locally invasive)	3 (27%)	2 (12%)	5 (18%)
Stage B	1 (9%)	1 (6%)	2 (7%)
Stage C	2 (18%)	1 (6%)	3 (%)
Grade IV (diffusely invasive)	2 (18%)	NA	2 (7%)
Median tumor size (mm±SD)	22±7	17±11	19±9
Null-cell adenoma	4 (36%)	11 (65%)	15 (54%)
Alpha-subunit producing adenoma	2 (18%)	6 (35%)	8 (29%)
Oncocytomas	5 (45%)	NA	5 (18%)

n, number; SD, standard deviation; NA, not applicable.

TABLE 3. Gender-related difference in long-term outcome in patients with non-functioning micro- or macroadenomas as documented by serial MR imagines.

	Female/Male [n (%)]		
Outcome	Microadenoma (n = 0/2)	Macroadenoma (n = 11/15)	Total (n = 11/17)
Remission	0 / 2 (100%)	9 (81%)/ 14 (93%)	9 (81%)/ 16 (94%)
- invasive adenoma 1)	NA	3 (27%)/ 2 (13%)	3 (27%)/ 2 (12%)
- postoperative radiation	NA	2 (18%)/ 2 (13%)	2 (18%)/ 2 (12%)
Recurrence	NA	2 (18%)/1 (7%)	2 (18%)/ 1 (6%)
- invasive adenoma 1)	NA	2 (18%)/1 (7%)	2 (18%)/1 (6%)
- postoperative radiation	NA	2 (18%)/ 0	2 (18%)/ 0

1) invasivness was classified according to the modified Hardy criteria[17,18]
n, number.

TABLE 4. Gender-related differences of postoperative clinical features in non-functioning adenomas.

Clinical Feature	Female (n = 11)	Male (n = 17)	Overall (n = 28)
Endocrine signs			
Adrenotropic function			
Normal	8 (73%)	11 (64%)	19 (68%)
Diminished	3 (27%)	6 (36%)	9 (32%)
Thyrotropic function			
Normal	5 (45%)	15 (88%)	20 (71%)
Diminished	6 (55%)	2 (12%)	8 (29%)
Gonadotropic function			
Normal	3 (27%)	8 (47%)	11 (39%)
Diminished	8 (73%)	9 (53%)	17 (61%)
Normal endocrine function	3 (27%)	8 (47%)	11 (39%)

n, number; SD, standard deviation; NA, not applicable; GH, growth hormone; IGF-1, insulin-like growth factor 1.

The following mean MIB-1 index values +/–SD were found; microadenomas (n=2), 1.58+/–0.93%; expansive adenomas (n=19); 0.67+/–0.43%; invasive adenomas (n=7), 0.75+/–0.86%. Microadenomas and invasive adenomas did not differ significantly in MIB-1 index, but patients less than 35 years old had higher MIB-1 indices (n=4, 1.72+/–1.15%), than did patients over 45 years (n=11, 0.63+/–0.42%) (p: n.s.). MIB-1 labeling indices were higher in adenomas of female compared to male patients (1.5 +/–1.2% vs. 0.8+/–1.8%; $p < 0.003$).

Outcome

The mean duration of follow-up was 21±9 months and was not significantly different in men and women (19±8 versus 22±12 months, respectively). No patient with a microadenomas had a symptomatic relapse during the follow-up period (Table 3). However, the overall outcome was slightly better in men than in women: The overall symptomatic recurrence rate was 11% (3 of 28), with 6% in men (one of 17) and 18% in women (2 of 11; p: n.s.). Symptomatic recurrence was observed more frequently with invasive tumors (100% vs. 22%; p: n.s.). After surgery, vision was normalized or improved in 75% (15 of 20 patients) with a slightly better outcome in men (p: n.s.). Postoperatively, thyroid, adrenal, and gonadal functions were normalized in 16% (1 of 6), 36% (4 of 11), 15% (3 of 20), unchanged in 82% (23 of 28), 79% (22 of 28), 89% (25 of 28), and worsened in 14% (4 of 28), 7% (2 of 28), 0% (0 of 28), respectively (Table 4). Four of 11 women (36%) and two of 17 men (12%) underwent radiation therapy three to six months after operation, because of incomplete intraoperative tumor resection (p: n.s.). Men showed no recurrence after radiation therapy, whereas a symptomatic recurrence was seen in 50% of women after radiation therapy (p: n.s.). There was no relationship between symptomatic recurrence and age, suprasellar extension, and hormonal deficiency. Null-cell-adenomas showed a significantly better outcome compared to other histological subtypes. In cases of persistent remission, age less than 45 years was a beneficial factor in women.

Discussion

For other tumors of the anterior pituitary than NFAs, there is a tendency to gender-related difference, not only in clinical presentation and other incidences, but also in surgical outcome [10–14]. As an underlying pathological source of this phenomenon, the tumor biology and the clinical course seem to differ in some pituitary adenomas between women and men [10,11]. As a consequence of these findings, a tailored therapeutic approach according to gender may be adequate in pituitary adenomas [9,12]. For NFAs, such data are not available so far. Here, it could be shown that there are gender related differences not only in overall surgical outcome but also in the duration of symptoms, tumor biology and in restoration of normal pituitary function.

Clinical Features

In the present series, a typical clinical syndrome could be described for patients harboring a NFA differing between the two genders. In agreement with previous studies, the lesion usually was large enough to produce subjective and objective loss of vision and often loss of libido [20,21]. This more severe clinical symptomatic in women compared to men at presentation may be related to a gender-related difference in growth potential with a more pronounced invasive tumor growth in women compared to men. Most of these tumors occurred in middle-aged patients. The growth of pituitary adenomas, especially the NFA subtype, is extremely slow [22]. Theoretical evaluations based on tumor growth rates have shown that the average volume doubling time of remaining adenoma tissue is approximately 230 days but amount to 3–4 years in many NFAs [22]. Partial or complete hypopituitarism can often accompany NF macroadenomas [2]. Loss of normal somatotroph, and corticotroph function can occur when there is destruction of the normal residual pituitary gland by the tumor or a compressive effect by the tumor on either the normal pituitary or the pituitary stalk [2]. As previously hypothesized by the author [10,11], the normal residual pituitary gland may show a gender-related difference on compression by pituitary adenoma. Somatotroph loss is invariably seen, and evidence of gonadotroph insufficiency is the second most common endocrine abnormality observed in these patients: men have low serum testosterone and women have relatively low gonadotropin levels. Postmenopausal women with low gonadrotropins may have evidence of gonadotroph insufficiency [2]. However, it is difficult to distinguish between elevated gonadotropins due to menopause versus tumor gonadotroph hypersecretion. In addition to gonadotroph insufficiency secondary to tumor mass effect, patients with NFAs may also have gonadotroph insufficiency due to the mild degrees of hyperprolactinemia that are caused by pituitary stalk compression by the tumor [2]. The present data suggest that the mechanism of hypopituitarism is often compression rather than destruction of normal pituitary tissue by the underlying tumor. According to data of Arafah et al. [12] elevation of intrasellar pressure may be the dominant mechanism contributing to the development of mild hyperprolactinemia or hypopituitarism in patients with pituitary adenomas. Portal blood flow is likely to be diminished in these patients, accounting for the decreased delivery of hypothalamic-releasing hormones to the anterior pituitary. Cell viability, however, is likely to be maintained in the majority of patients through increased blood supply form the arterial circulation. Therefore, depending on the size of the tumor, preoperative pituitary function, and the extent of surgery, a postoperative return of one or more anterior pituitary hormones may occur, as seen in the present series. The availability of viable pituitary cells at the time of surgery can limit the potential recover of pituitary function postoperatively. However, in the light of the high rate of unexpected histological findings among patients with probable NF macroadenomas [23], it may be advocated early exploration, especially in women, to establish diagnosis and to effect removal.

Clinical Features

The present results confirm that the incidence of null-cell adenomas and oncocytomas is gender related. However, previous findings could show an age-related dependence as these tumors only rarely become manifest clinically before the fifth decade [24]. The suggested monoclonal nature of these tumors makes unlikely the possibility that circulating factors (hypothalamic or others) alone can transform pituitary cells and lead to neoplasia [25]. Therefore, somatic mutation of pituitary cells is at least one of the necessary "hits" that invoke neoplasia; if external factors play a role, then they affect pituitary cells that have undergone somatic changes potentiating their transformation [25]. 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. From the present data, it appears that differences exists in the biological behavior of the various clinically NFA subtypes and therefore may explain the gender-related differences. According to the present results, the growth potential of macroprolactinomas seems greater in women than in men, given the preponderance of aggressive forms of the disease in women. Besides the direction of adenoma expansion, the rate of adenoma growth may be an important factor of the viability of pituitary function that is essential for every specific treatment.

Medical and Surgical Characteristics

Medical treatment of NFAs with bromocriptine, whether preoperatively or as primary therapy, is a matter of controversy. Both the long-acting synthetic somatostatin analog octreotide and the dopamine agonist bromocriptine have been used for the medical treatment of NFAs. Octreotide seems to decrease tumor size, visual field deficits, and serum-alpha-subunits levels in some patients with gonadotrophic or pure alpha-subunit-secreting pituitary adenomas [26,27], some of these tumors were shown to have somatostatin receptors [26]. Neither from the present data, nor from the literature [26,27], there is a clear gender-related difference after medical treatment. However, the difference in biological behavior in the present series, may implicate also a potential gender-related difference in medical treatment.

Outcome

The symptomatic recurrence rate of only 12% in the present study is comparable with the 12–24% reported in previous series and indicates that further treatment may not be needed in some patients with residual adenoma [21,28–30]. The gender-related difference in outcome may be influenced by the different biological behavior with a more invasive growth potential in women. Certainly, progressive clinical and/or

radiographic evidence of tumor growth can also be demonstrated many years after initial treatment [31]. Although total removal of pituitary adenomas with the transsphenoidal technique is not always possible, prolonged symptom-free intervals can frequently be achieved. Earlier work by MacCarty et al. [31] suggest that radiation therapy decreases the recurrence rate, but the present series would not attempt to confirm this hypothesis because all patients with known or suspected residual adenoma were advised to have radiation therapy. The present small number of patients with or without radiation therapy does no allow a clear answer on gender differences on postoperative radiation therapy in the long-term outcome. In the present study, the strongest prognostic factor appeared to be the invasiveness of the tumor. However, Ciric reported a recurrence rate of 42% when suprasellar extensions exceeded 20 mm [28]. The present recurrence rate was not associated with the volume of the adenoma. This could be because pituitary adenomas that invade the bone may be more aggressive than those that expand and induce only compression. An alternative explanation is that complete surgical removal is more difficult in invasive than in enclosed adenomas.

Conclusion

The biology and clinical course of NFAs appear to differ in women and men. In women, the preoperative duration of symptoms is shorter, the tumors are larger and more invasive, and the clinical outcome is worse than in men. From the present data, it cannot be determined if these gender-related differences reflect a less symptomatic disease course at an earlier stage or significantly faster tumor growth in women. The histological background of gender-related differences warrants further investigation. However, the present findings seem to justify a more aggressive therapeutic approach to NFAs in women than in men, especially to improve the availability of viable pituitary cells at the time of the time of surgery that can limit the potential recovery of pituitary function postoperatively.

REFERENCES

1 Kovacs K, Horvath E, Ryan N, Ezrin C. Null cell adenoma of the human pituitary. Virchows Archiv A Pathol Anat Histol 1980; **387**: 165–74.
2 Klibanski A. Nonsecreting pituitary tumors. Endocrinol Metab Clin North Am 1987; **16**:793–804.
3 Mindermann T, Wilson CB. Pediatric pituitary adenomas. Neurosurgery 1995; **36**:259–69.
4 Selman WR, Laws ER Jr, Scheithauer BW, Carpeneter SM. The occurrence of dural invasion in pituitary adenomas. J Neurosurg 1986; **64**:402–7.
5 Mindermann T, Kovacs K, Wilson CB. Changes in immunophenotype of recurrent pituitary adenomas. Neurosurgery 1994; **35**:39–44.
6 Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C. Intraoperative magnetic resonance imaging during transsphenoidal surgery. J Neurosurg 2001; **95**:381–90.
7 Thapar K, Laws ER Jr. Pituitary tumors. In : Kaye AH, Laws ER Jr. Editors. Brain tumors. Edingburgh: Churchill Livingstone, 1995, pp 759–73.
8 Trautmann JC, Laws ER Jr. Visual status after transsphenoidal surgery at the Mayo Clinic, 1971–1982. Am J Ophthalmol 1983; **96**: 200–8.
9 Laws ER, Trautmann JC, Hollenhorst RW Jr. Transsphenoidal decompression of the optic nerve and chiasm: Visual results in 62 patients. J Neurosurg 1977; **46**:717–22.
10 Schaller B, Kirsch E, Tolnay M, Mindermann T. Symptomatic granular cell tumor of the pituitary. Case report and review of the literature. Neurosurgery 1998; **42**:166–71.
11 Schaller B. Gender-related differences in growth hormone releasing pituitary adenomas. A clinicopathological study. Pituitary 2002; **5**: 247–53.
12 Arafah BM, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. J Clin Endocrinol Metab 2000; **85**:1789–93.
13 Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex related difference in the growth of prolactinomas: Clinical and proliferation marker study. J Clin Endocrinol Metab 1997; **82**: 2102–7.
14 Calle-Rodrigue RDP, Giannini C, Scheithauer BW, Lloyd RV, Wollan PC, Kovacs KT, et al. Prolactinomas in male and female patients: A comparative clinicopathologic study. Mayo Clin Proc 1998; **73**: 1046–52.
15 Wilson JD, Forster DW, Kronenberg HM, Larsen PR. William`s Textbook of Endocrinology, 9th edn,, Chapter 9, Philadelphia, USA: Saunders.
16 Kovacs K, Horvath E. Tumors of the pituitary gland, in Atlas of Tumor Pathology, Second series, Fascicle 21. Washington, DC: Armed Forces Institute of Pathology. 1986.
17 Hardy J. Transsphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg 1969; **16**:185–217.
18 Wilson CB, Mindermann T. Pituitary neoplasms. In: Cancer Medicine. Holland JF, Bast RC, Morton DL, Frei E, Knufe DW, Weichselbaum RR. Editors. ed 4. Baltimore: Williams and Wilkins. 1997. 1539–50.
19 Friend KE, Chiou YK, Lopes MB, Laws ER Jr, Hughes KM, Shapnik MA, et al. Estrogen receptor expression in human pituitary: correlation with immunohistochemestry in normal tissue, and immunohistochemestry and morphology and macroadenomas. J Clin Endocrinol Metab 1994; **78**:1497–504.
20 Black PM, Hsu DW, Klibanski A, Kliman B, Jameson L, Ridgway EC, et al. Hormone production in clinically non-functioning pituitary adenomas. J Neurosurg 1987; **66**:244–50.
21 Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall R Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. J Neurosurg 1986; **64**:713–9.
22 Landolt AM, Shibata T, Kleihues P, Tuncdogan E. Growth of human pituitary adenomas: Facts and speculations, in Landolt AM, Heitz PU, Zapf J, Girard J, del Pozo E. editors. Advances in Pituitary Adenoma Research: Advances in the Bioscience. Oxford Pergamon Press, Vol 69, 1988, 53–62.
23 Mindermann T, Staub JJ, Probst A. High rate of unexpected histology in presumed pituitary adenomas. Lancet 1998; **352**:1445.
24 Yamada S, Kovacs K, Horvath E, Aiba T. Morphological study of clinically nonsecreting pituitary adenomas in patients under 40 years of age. J Neurosurg 1991; **75**:902–5.
25 Alexander JM, Biller BMK, Bikkal H, Zervas NT, Arnold A, Klibanski A. Clinically nonfunctioning pituitary tumors are monoclonal in origin. J Clin Invest 1990; **86**:336–40.
26 de Bruin TW, Kwekkeboom DJ, Van't Verlaat JW, Reubi JC, Krenning EP, Lamberts SW, et al. Clinically nonfunctioning pituitary adenoma and octreotide response to long term high dose treatment, and studies in vitro. J Clin Endocrinol Metab 1992; **75**:1310–7.
27 Katznelson L, Oppenheim DS, Coughlin JF, Kliman B, Schoenfeld DA, Klibanski A. Chronic somatostatin analog administration in patients with alpha-subunit-secreting pituitary tumors. J Clin Endocrinol Metab 1992; **75**:1318–25.
28 Ciric I, Mikhael M, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. J Neurosurg 1983; **59**:395–401.
29 Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J. The clinical and endocrine outcome to transsphenoidal microsurgery of nonsecreting pituitary adenomas. Cancer 1991; **68**:860–6.
30 Van Linder EJ, Grotenhuis JA, Meijer E. Results of follow-up after removal of non-functioning pituitary adenomas by transcranial surgery. Br J Neurosurg 1991; **5**:129–33.
31 Mac Carty CS, Hanson EJ Jr, Randall RV et al. Indications for and results of surgical treatment of pituitary tumors by the transfrontal approach. In: Kohler PO, Ross GT (eds): Diagnosis and Treatment of Pituitary Tumors. International Congress Series, No. 303. Amsterdam: Excerpta Medica, 1973, pp 139–45.