Pituitary tumours in the elderly: a 20 year experience

Helen E Turner¹, Christopher B T Adams² and John A H Wass¹

Departments of ¹Endocrinology and ²Neurosurgery, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

(Correspondence should be addressed to J A H Wass)

Abstract

The proportion of the elderly in the population is increasing, and the appreciation and management of medical problems in this age group will therefore become more important. We therefore decided to determine the clinical features and types of pituitary tumour presenting in the elderly, and to examine the treatment and outcome in this group. We conducted a retrospective case-note review from a specialist endocrine and neurosurgical unit in a tertiary referral centre. Eighty-four patients aged 65 years and over on diagnosis of a pituitary tumour were referred to the unit between 1975 and 1996. There were 45 males and 39 females, and the mean age was 72.4 years (range 65–86). Over half of the pituitary lesions were non-functioning adenomas (NFAs) (60.7%). GH-secreting tumours were present in 11 (13.1%) and macroprolactinomas in 7 (8.1%). Four patients had microadenomas and 17 had miscellaneous pituitary-related lesions. Visual deterioration was the commonest mode of presentation in 33 (39.3%), but 54 (64.3%) had evidence of visual impairment on detailed examination. Despite the majority of patients (80.8%) having coexisting medical conditions, trans-sphenoidal surgery was performed in 60 (71.4%) and was well tolerated with a zero peri- and post-operative mortality rate, and post-operative complications in 11 (13.1%).

Pituitary tumours in the elderly are most frequently NFAs that present with visual deterioration and hypopituitarism. The fact that 46.5% were pan-hypopituitary on diagnosis and that 64.3% of patients had visual impairment suggests a delay in diagnosis in this age group. Despite significant coexisting medical pathology in this large series of patients, surgery was safe and successful in the majority.

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Introduction

By the year 2035, the proportion of elderly in the population will have increased from 16 to 24%. An appreciation of the presentation and management of medical conditions in this age group will therefore be increasingly important.

Pituitary tumours may be discovered at all ages, and in an unselected autopsy series of patients aged 16–91 years, the age distribution of patients with pituitary tumours (microadenomas) did not differ from the age distribution of the population as a whole (1). Pituitary microadenomas were found in 20/152 (13%) of pituitaries taken from an autopsy series of patients aged over 80 years (2). Over half (53%) of the tumours in this series where immunostaining was performed stained for prolactin (PRL), and with the exception of one tumour that immunostained for growth hormone (GH) and PRL, the remainder (41%) were negative. This is similar to the autopsy series reported by McComb *et al.* (3), where there was no specific age range quoted and 50% of pituitary adenomas were negative on immunostaining and 42% were PRL positive. It is likely that tumours secreting GH and adrenocorticotrophin (ACTH)

present earlier with syndromes of hormone excess and this might explain their under-representation in autopsy series.

There are two published clinical series of elderly patients with pituitary tumours – one of 22 patients aged 70 years and over (4) and one including 44 patients aged 65 years and over (5). Both of these studies show that in contrast to the autopsy studies, the majority of tumours were non-functioning macroadenomas (NFAs). In the first series there was only one (4.5%) prolactinoma and this was a macroadenoma. Three (13.6%) patients had GH-staining tumours and one patient had Cushing's disease. Visual deterioration was the commonest mode of presentation of elderly patients, with predominantly macroadenomas in both the reports. Approximately two-thirds of the patients underwent trans-sphenoidal surgery (TSA), which was well tolerated in the majority and usually associated with visual improvement.

The literature has little information regarding management and outcome of different types of pituitary tumours in the older age groups. There is a paucity of data on the outcome of the management of prolactinomas because microprolactinomas in the elderly are less

likely to be diagnosed in life. There is a suggestion that acromegaly in older patients may be a milder disease when compared with younger patients, associated with lower GH values at presentation as well as smaller tumours (6–8). Both TSA and octreotide have been shown to be effective and associated with little morbidity in older patients with acromegaly (8, 9). Cushing's disease may also be milder in the elderly (10), although it is a rare diagnosis in this age group and can be difficult to differentiate from the abnormalities of cortisol secretion seen in dementia and depression. It has not been specifically studied in the elderly.

The lack of data in this age group prompted us to look at our own patients who presented with pituitary tumours. An arbitrary age of 65 and over was used to define 'elderly' in this study.

Patients and methods

Patients were selected from our database, which contains information on patients seen in the Endocrinology Department over the last 20 years (1975–1996). Records regarding diagnosis and management were available for 84 patients aged 65 and over, out of a total of 1155 (7.3%) with pituitary tumours listed in the database. There were 45 (53.6%) males and 39 females. Notes were unavailable in seven cases. Data regarding method of presentation, pituitary pathology, pituitary function, documented coexistent medical problems, management, rationale for treatment, outcome and complications were recorded. ACTH reserve was assessed using the insulin tolerance test, glucagon test, depot synacthen test or morning cortisol. Thyroid function was measured using thyrotrophin and thyroxine.

Results

Presentation

The commonest reason for presentation was visual impairment in 33 (39.3%) patients. Hypopituitarism was the second commonest presentation in 17 (20.2%). Eight of these patients were hyponatraemic with a mean sodium of 117.9 mmol/l (range 109–125 mmol/l) (Table 1). In ten patients a pituitary tumour was an incidental finding on imaging performed for other reasons (Table 2). All these patients had macroadenomas detected following skull X-ray (SXR) (four), MRI (three) or CT (three). Pituitary apoplexy with sudden headache, nausea and vomiting and visual disturbance was the mode of presentation of six (7.1%). Thirteen patients (15.5%) were diagnosed as having pituitary tumours on the basis of clinical features – ten with GH-secreting tumours and three with ACTH-secreting tumours. Headaches were the initial presentation in three patients (one GH, one PRL and one NFA), and *Haemophilus influenzae* meningitis secondary to a CSF leak the reason in one patient. One patient (with a meningioma en

Table 1 Primary presenting features of pituitary tumours in the elderly.

Presentation	Number of cases (percentage)
Visual symptoms	33 (39.3%)
Hypopituitarism	17 (20.2%)
Hyponatraemia	8 (9.5%)
Incidental finding on imaging	10 (11.9%)
Apoplexy	6 (7.1%)
Appearance due to hormone excess	13 (15.5%)
Mass effect (headache and meningitis)	4 (4.4%)
Diabetes insipidus	1 (1.2%)

plaque surrounding the optic nerves) presented with diabetes insipidus.

Although 33 patients had visual impairment as their primary presentation, 54 cases (64.3%) had evidence of visual impairment at presentation after formal visual field examination. Of these, 37 patients (68.5%) had either uni- or bitemporal hemianopia, 7 (12.1%) III nerve palsies and 2 had a VI nerve palsy. Hypopituitarism was the presenting feature in 17 patients (20.2%) (Table 3). There were three patients with secondary hypothyroidism which had been incorrectly ascribed to primary – one of these patients had a NFA, one had metastatic carcinoma of the breast and one had Cushing's disease. Of the remaining six, two were diagnosed as cortisol deficient when investigated for possible hypoglycaemia (glucose <3 mmol/l) and the remaining four had symptoms of lethargy and weight loss.

Pituitary pathology

Only four patients with pituitary adenomas had microadenomas, three were ACTH-secreting tumours and one a GH-secreting tumour (Table 4). The commonest type of pituitary tumour was an NFA (immunostaining either negative, luteinising hormone, follicle-stimulating hormone (FSH), α subunit or silent ACTH) in 45 cases (53.6%). Eleven (13.1%) had GH-secreting tumours causing acromegaly, seven (8.3%) had macroprolactinomas and four (4.8%) had pituitary-dependent Cushing's disease. One male patient had an

Table 2 Incidentally detected tumours in the elderly.

Reason for imaging	Number
Leg weakness	1 (MRI)
Head injury	3 (SXR)
Seizures	2 (CT, SXR)
Alzheimer's disease	1 (MRI)
Subdural haematoma	1 (CT)
Tremor, poor balance	2 (CT, MRI)

Table 3 Hypopituitarism as the primary presentation of the pituitary mass.

Presenting feature	Number	Pituitary pathology
Hyponatraemia (mean 117.9 mmol/l)	8	NFA (7); lymphocytic hypophysitis (1)
Secondary hypothyroidism	3	NFA (1); Cushing's disease (1); metastatic carcinoma of the breast (1)
Hypocortisolaemia	6 (hypoglycaemia (2); fatigue and weight loss (4))	NFA (5); lymphocytic hypophysitis (1)

FSH-secreting tumour, with an FSH of >40 IU/l and one patient had a pituitary metastasis from a breast carcinoma. Other histologically confirmed diagnoses included lymphocytic hypophysitis in two, chordoma in two, developmental abnormality of Rathke's pouch, meningioma en plaque and craniopharyngioma (one each). In addition there was an aneurysm confirmed on cerebral angiography in one patient.

Coexisting medical problems

There was information regarding other medical problems in 78 patients, of whom the majority (80.8%) had coexistent medical conditions and only 16 (19.2%) had no medical problems. Twenty-one (26.9%) patients were hypertensive, 18 (21.4%) had ischaemic heart disease or heart failure, 7 (8.3%) had chronic obstructive airways disease and asthma and 5 had a coexisting malignancy diagnosed (bladder, lung or breast). In the group with pituitary apoplexy, three (42.9%) had hypertension or ischaemic heart disease.

Pre-operative pituitary function

Data regarding pituitary function were available for 58 patients. Twenty-seven (46.5%) were pan-hypopituitary,

and nine (15.5%) were gonadotrophin deficient only (inappropriately low or not detected gonadotrophins).

Management

Over 70% of the patients (60 patients) underwent TSA. Three patients had craniotomies performed – for a craniopharyngioma, a meningioma en plaque and a NFA (Table 5).

Post-operative complications

Of the patients who underwent TSA, there were complications in 11, and 6 developed diabetes insipidus. Three patients had post-operative deterioration in vision to no perception of light in one patient, and bitemporal hemianopia in two patients. There was no evidence of haemorrhage on imaging in any of these patients. The presumed aetiology was ischaemic although none of the patients had particular risk factors for the development of ischaemic complications, such as hypertension, ischaemic heart disease or diabetes mellitus. CT scans showed post-operative sellar haematomas in a further two patients – one of whom required repeat surgery. One patient had a peri-operative myocardial infarction, as judged by asymptomatic ECG changes, from which there was good recovery, one had a post-operative chest infection and one had a small gastrointestinal bleed with a drop in haemoglobin of 1 g/dl, which did not require transfusion. Diabetes insipidus was temporary in two patients and permanent in four (6.7%). One patient developed post-operative meningitis in addition to the deterioration in vision described above. Six patients died during follow-up at 2 (four patients), 3 and 4 years post-operatively.

Non-functioning pituitary tumours (NFAs)

In the group of patients with NFAs, 37 (82.2%) underwent TSA and 1 underwent craniotomy. All patients presenting with pituitary apoplexy underwent TSA and were found to have functionless tumours. The reason for not operating was either the age of the patient (three cases – aged 83, 81 and 71), lack of supra-sellar extension (two patients who had coexistent significant illness (multiple sclerosis and Alzheimer's

Table 4 Types of pituitary tumour.

Pituitary tumour type	Number of cases (percentage)
Non-functioning tumour (NFA)	45 (53.6%)
Prolactinoma	7 (8.3%)
ACTH secreting	4 (4.8%)
GH secreting	11 (13.1%)
Apoplexy	6 (7.1%)
Gonadotrophin secreting	1 (1.2%)
Lymphocytic hypophysitis	2 (2.4%)
Infarcted pituitary tumour ? type	1 (1.2%)
Meningioma en plaque	1 (1.2%)
Developmental abnormality of Rathke's pouch	1 (1.2%)
Aneurysm	1 (1.2%)
Metastasis	1 (1.2%)
Craniopharyngioma	1 (1.2%)
Chordoma	2 (2.4%)

Table 5 Management of pituitary tumours.

Management	Number of cases (percentage)
TSA	60 (71.4%)
NFA (37 patients)	
Apoplexy (6 patients)	
Acromegaly (6 patients)	
Cushing's disease (2 patients)	
Macroprolactinomas (2 patients after BCR did not lead to significant shrinkage)	
Chordoma (2 patients)	
Lymphocytic hypophysitis (2 patients)	
Gonadotrophinoma (1 patient)	
Craniotomy	3 (3.7%)
Functionless (1 patient)	
Meningioma en plaque (1 patient)	
Craniopharyngioma (1 patient)	
Drug treatment	
Somatostatin agonist	One patient with acromegaly
Trilostane	One patient with Cushing's disease
BCR	Three patients with macroprolactinomas received treatment leading to some reduction in PRL levels but normalisation in only one; two with macroprolactinomas required TSA due to lack of shrinkage with BCR

disease)), previous radiotherapy (one case) or significant anaesthetic risk due to chronic obstructive airways disease, despite sight-threatening tumour (one case). There was post-operative improvement in vision in 23 (71.9%) patients who had pre-operative impaired vision in association with an NFA. Six (18.8%) patients showed no improvement and three (9.4%) had unexplained deterioration post-operatively as already described. There were no data available for nine patients with pre-operative visual impairment. Follow-up ranged from 1 month to 13 years with a mean of 3.3 years. Follow-up after surgery usually consisted of a post-operative scan, a repeat scan at 1 year, then scans every 3–5 years. There was one documented increase in tumour size within 2 years in a patient who had not received post-operative radiotherapy. There were follow-up data on five patients who were not operated on. Four of these patients followed for 2–4 years showed no deterioration in vision. Only one patient who was followed for 5 years with scans required surgery for deteriorating vision.

Acromegaly

The patients with acromegaly had mean basal GH levels of 46 mU/l (range 2.7–200 mU/l). One patient had a microadenoma and eight had macroadenomas with no supra-sellar extension. There was evidence of both supra-sellar and lateral tumour extension in two patients, one of whom underwent TSA. Six patients who underwent TSA had mean post-operative GH levels <5 mU/l or GH suppression to less than 2 mU/l on a 100 g oral glucose tolerance test for a mean of 3.7 years

follow-up (range 1–7 years). One patient was treated with octreotide, and four patients received no treatment, two because their tumours were not sight threatening (aged 74 and 79), and two because of coexisting medical conditions (aortic valve replacement and chronic obstructive airways disease).

Cushing's disease

There were four patients with pituitary-dependent Cushing's disease, with a mean urinary free cortisol level on diagnosis of 1011 nmol/l (range 700–1320 nmol/l). Three of the patients had pituitary microadenomas, and one had a large invasive macroadenoma, which was treated with trilostane and radiotherapy with no normalisation of cortisol levels before the patient's death 3 years after diagnosis. Two patients underwent TSA for Cushing's disease, but neither patient was cured (post-operative midnight cortisol 183–165 nmol/l). One patient underwent bilateral adrenalectomy.

Macroprolactinomas

The mean PRL level in the seven patients with macroprolactinomas was 149 726 mU/l (22 786–513 000). Three received bromocriptine (BCR) therapy with shrinkage of the tumour and lowering of PRL levels (e.g. 44 200 falling to 6300 mU/l) but normal levels were achieved in only one patient (102 500 falling to 54 mU/l). Two underwent surgery and radiotherapy following unsuccessful BCR therapy with lack of tumour shrinkage. Post-operative PRL was still elevated

in both these patients (63 000 mU/l). Two received no treatment – one because he stated that he was asymptomatic and the other because it was felt that BCR might worsen his postural hypotension.

Discussion

This study is the largest reported clinical series of elderly patients with pituitary lesions and shows that, despite the lack of data in the literature, pituitary mass lesions in patients aged 65 and over comprised 7% of the total number of patients with pituitary tumours seen in our department over 20 years. A comparison of the number of elderly patients seen during 1981 to 1985, and the number seen during 1991 to 1995 shows an increase, although this is clearly not a true reflection of incidence, as bias in terms of investigation and referral are likely to play a role. It is likely that this trend will continue, because the number of elderly in the population is increasing and because imaging techniques are more widely used to investigate, for example, cerebrovascular disease and dementia, and so might be expected to incidentally detect more pituitary tumours.

In contrast to the autopsy data, where microadenomas are the commonest pituitary tumour found and immunostaining for PRL is common (2), our review shows that NFAs are the commonest tumour detected in this age group during life. There were no microprolactinomas found in our series. It is perhaps not surprising that microprolactinomas are not detected clinically in this group of patients as their presentation in younger patients is typically with menstrual disturbance, reduced sexual function and infertility. Craniopharyngioma and lymphocytic hypophysitis are classically lesions seen in young people, lymphocytic hypophysitis occurring typically in post-partum women, although there are rare reports of both occurring in older patients (11, 12). Perhaps they will be detected more commonly as more elderly patients are investigated. One male patient had an FSH-secreting pituitary tumour.

The commonest mode of presentation in our series was with visual impairment – either uni- or bitemporal hemianopia due to supra-sellar extension of the tumour, third or sixth nerve palsy due to lateral extension of tumour, or reduced visual acuity. This had often been mis-attributed to cataracts or macular degeneration, leading to delay in diagnosis. Over 60% of patients had visual impairment at diagnosis, confirming the classical relatively late presentation of functionless tumours and macroprolactinomas. The delay in diagnosis in these patients is not only important in terms of visual deterioration but also as almost 50% of the patients were pan-hypopituitary at diagnosis. Other reported series of younger patients with NFAs confirm the high frequency of visual field defects at presentation, but show that pan-hypopituitarism is less common. For example, 75% of patients (mean age 55 years) with NFAs had visual impairment but only 7% were pan-hypopituitary

(13), and out of 126 patients with functionless tumours, mean age 50 years, where 74% had pre-operative deterioration of vision, only 36% were ACTH deficient (14).

Six patients presented with classical features of pituitary apoplexy in probable NFAs. This is higher than might be expected and may reflect a higher prevalence of risk factors such as hypertension in this group, although there was no significant difference between the medical problems in the group with apoplexy and those without. Hypopituitarism was not uncommon as a presentation, with secondary hypothyroidism that had been mis-diagnosed as primary in three patients. Hyponatraemia was surprisingly common as the initial presentation of a pituitary lesion, and therefore hypopituitarism should always be considered in elderly patients with hyponatraemia (15).

There was, as expected, a high incidence of other medical conditions in the patients, with only 19.2% having no documented coexisting pathology. This is obviously higher than found in younger patients. These results may have been subject to selection bias of only the fitter patients being referred for assessment and consideration of surgery. Despite this, surgery was effective and well tolerated with zero mortality in a group with significant medical problems. Eleven patients (13.1%) had post-operative complications, and six developed diabetes insipidus, which was temporary in two and permanent in four (6.7%). The deterioration in vision in three patients (5%) with no evidence of haemorrhage, may reflect the higher incidence of ischaemic complications in this age group, although none of these patients had known cerebrovascular or ischaemic heart disease. A review of significantly younger patients, with a mean age of 46 years, undergoing TSA for acromegaly at our institution demonstrated post-operative complications in 5.8%, temporary diabetes insipidus in 12.9% and permanent diabetes insipidus in 5.8% (16). The incidence of permanent complications in the form of diabetes insipidus and visual loss following TSA in younger patients is quoted by other groups at 3 and 4% respectively (17) or 5–10% (18). The series of younger patients with NFAs undergoing TSA reported by Harris *et al.* (13) showed that permanent diabetes insipidus occurred in 11% and no patients had deterioration in vision. In a large series of patients (714) undergoing TSA for pituitary adenomas, the majority showed improvement in vision, but in 17 (2.4%) patients vision worsened post-operatively (19). Harris *et al.* (13), showed that patients with only partial recovery in vision were significantly older (mean age 63 years) than the group with complete recovery of vision (mean age 47 years). This may be related to later diagnosis, slower recovery and coexisting diseases in the older group. Thus despite the older age and their associated morbidity the results in our patients compare well with other series.

The majority (71%) of patients showed improvement in vision, which is similar to the figures quoted from other series – 75% (14) and 79% (20). Surgery was effective for the patients with acromegaly, who all had GH levels which suppressed normally on oral glucose tolerance testing, but was not curative for the two patients with Cushing's disease who underwent TSA, both of whom had detectable post-operative cortisol. It is perhaps surprising that during follow-up there was tumour enlargement in only one patient with a surgically treated NFA, but it is possible that the post-operative scanning protocol may not have detected tumour regrowth in others.

It is difficult to find data regarding management of macroprolactinomas in the elderly. Several reviews of surgery include no elderly patients, for example a maximum age of 48 years in one series or 54 years in another (21, 22) and studies of dopamine agonists contain occasional patients aged over 65 with no comment of any different responses in these elderly patients (23, 24). The potential side-effects of the dopamine agonists including dizziness may make them less well tolerated in the elderly. In our series, the tumours were associated with markedly elevated PRL levels and were poorly responsive to BCR – normalising PRL in only one patient and failing to shrink the tumour in two. TSA was also non-curative as the tumours were invasive. It certainly does not appear that prolactinomas are a milder condition in the elderly, but this may be related to the relatively late presentation of these tumours.

This study was too small to consider whether acromegaly is a milder disease in the elderly (6, 7). The mean GH was modest at 46 mU/l, and only two patients had supra-sellar or lateral extension of their tumours on imaging. A review of TSA for acromegaly in patients aged over 64 years showed it to be well tolerated, and effective – lowering GH to <9 mU/l in all patients, with no evidence of recurrence in 13 patients followed for a mean of 4.2 years (9). Our patients confirm the authors' view and TSA led to normal GH suppression on oral glucose tolerance testing in all patients post-operatively. It is likely that the previously held view – that in older patients with acromegaly treatment should be conservative if given at all (25) – will change with the increasing availability of the effective and well-tolerated somatostatin agonists.

The suggestion that Cushing's disease might be a milder disease in the elderly is not borne out by our data, as treatment in three patients was unsuccessful, with bilateral adrenalectomy providing the only curative procedure, but putting the patient at risk of Nelson's syndrome. Clearly it is difficult to draw conclusions from a small number of patients, and it is possible that since the majority of the tumours causing Cushing's syndrome are microadenomas the clinical features might not be diagnosed until relatively late in the disease course, as hypertension, depression, thinning skin, glucose intolerance and osteoporosis are all seen

commonly in the elderly. There are few data on outcome in older patients with Cushing's syndrome. A lower post-operative recurrence rate has been suggested (10, 26) and there is a report of metyrapone as successful treatment in the elderly (27).

In conclusion, a pituitary adenoma should be considered in an elderly patient not only with classical features of acromegaly or Cushing's disease, but with visual impairment, hyponatraemia, or sudden onset headache and vomiting. TSA is an effective and well-tolerated treatment. Further data are required in this age group, particularly regarding therapy with drugs such as the longer acting dopamine agonists and somatostatin analogues. In order to determine the most effective therapy for different conditions, it may be helpful to perform randomised prospective studies of different modalities of treatment, for example TSA and somatostatin agonists for acromegaly. It is likely that the incidentally detected pituitary tumour will become a commoner 'dilemma' in this age group, as not all lesions detected will be clinically relevant, and it may be possible, for example, to simply follow up incidentally detected microadenomas and perhaps some macroadenomas. As more data accrue on the genetic features of these tumours it will be interesting to see whether there are any differences between those seen in younger patients, and whether this information can be used to determine the optimal treatment for these patients.

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