Clinical Endocrinology (2015) **83**, 861–865 doi: 10.1111/cen.12860

ORIGINAL ARTICLE

Clinical outcomes in patients with nonfunctioning pituitary adenomas managed conservatively

Amir H. Sam*,†, Sachit Shah*, Keenan Saleh†, Jay Joshi†, Federico Roncaroli‡, Stephen Robinson*, Jeremy Cox*, Niamh M. Martin*,†, Nigel Mendoza*, Karim Meeran*,†, Amrish Mehta* and Waljit S. Dhillo*,†

**Imperial College Healthcare NHS Trust, †Section of Investigative Medicine, Division of Diabetes, Endocrinology and Metabolism, Imperial College London, Hammersmith Hospital and ‡Division of Brain Sciences Imperial College London, London, UK*

Summary

Context The natural history and the optimum management of patients with nonfunctioning pituitary adenomas (NFPAs) are unclear.

Objective Our objective was to characterize the natural history of patients with NFPAs managed conservatively.

Design and patients We conducted a retrospective analysis of patients presenting to a tertiary referral centre between 1986 and 2009. Patients with pituitary adenomas and no clinical or biochemical evidence of hormonal hypersecretion were included. Those presenting with apoplexy or a radiological follow-up period of less than 1 year were excluded. The pituitary imaging for all patients was re-examined by two neuroradiologists in consensus.

Outcome measures The outcome measures were change in tumour size and pituitary hormone function.

Results Sixty-six patients were managed conservatively for a mean follow-up period of 4·3 years (range: 1–14·7). Forty-seven (71%) had a macroadenoma, and nineteen (29%) had a microadenoma. Tumour size decreased or remained stable in 40% of macroadenomas and 47% of microadenomas. The median annual growth rate of enlarging macroadenomas and microadenomas was 1·0 mm/year and 0·4 mm/year, respectively. The median annual growth rate of macroadenomas was significantly higher than that of microadenomas ($P < 0·01$). Sixty-eight percentage of patients with a macroadenoma had pituitary hormone deficiency in one or more axes, compared to 42% of those with a microadenoma.

Conclusion Patients with NFPAs without optic chiasm compression can be managed conservatively. All patients need pituitary function assessment, irrespective of tumour size. These findings provide clinically relevant data for the management of patients with NFPAs.

Correspondence: Prof Waljit S. Dhillo, Section of Investigative Medicine, Division of Diabetes, Endocrinology and Metabolism, Imperial College London, Hammersmith Hospital, London W12 0NN, UK.
Tel.: +442083832820; Fax: +442083833142;
E-mail: w.dhillo@imperial.ac.uk

(Received 13 April 2015; returned for revision 27 April 2015; finally revised 18 June 2015; accepted 13 July 2015)

Introduction

Nonfunctioning pituitary adenomas (NFPAs) are the second most common type of pituitary tumour after prolactinomas.[1] Large NFPAs may present with headache, hypopituitarism and visual field defects owing to compression of the optic chiasm. Small NFPAs are usually detected incidentally following brain imaging performed for an unrelated symptom.[2]

Patients with NFPAs can be managed either surgically or conservatively (with clinical follow-up, serial radiological imaging, pituitary function tests and regular visual field assessments). Surgery is indicated in patients with visual field defects.[3] There is currently no clear consensus regarding the optimum management of NFPAs.

The natural history of NFPAs appears to be related to their size at presentation. In one study with a mean follow-up of 3·5 years, 50% of nonfunctioning macroadenomas and 12·5% of microadenomas increased in size.[4] Similarly, a more recent systematic review and meta-analysis reported that nonfunctioning macroadenomas have a higher incidence of growth compared to microadenomas.[5]

Knowledge of the natural history of NFPAs remains limited by small sample sizes, short follow-up periods, methodological limitations and heterogeneity between studies.[5,6] The aim of the present study was to investigate the natural history, including growth rate and hormonal profile, of NFPAs managed conservatively.

Methods

We identified patients who were diagnosed with a NFPA between 1986 and 2009. The inclusion criteria were as follows: (i) radiological evidence suggestive of a pituitary adenoma and (ii) no clinical or biochemical evidence of hormonal hypersecretion. Patients who presented with pituitary apoplexy or those who had less than a year of radiological follow-up were excluded from the study. Sixty-six patients were managed conservatively.

The patients had pituitary hormone measurement and visual field assessment using Humphrey perimetry at presentation and regularly during follow-up. Baseline pituitary function tests were carried out every 6–12 months. Pituitary function was assessed using baseline prolactin, insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (in men), oestradiol (in women), free thyroxine (fT4), thyroid-stimulating hormone (TSH) and 9am cortisol, as well as dynamic tests including insulin tolerance, glucagon stimulation and metyrapone tests.

Patients were managed conservatively if there was no evidence of visual field defects. All patients with visual field defects were offered trans-sphenoidal surgery. Patients were monitored every 6–12 months by regular magnetic resonance imaging (MRI), including dedicated high-resolution sagittal and coronal views of the pituitary fossa. All scans were re-examined by two neuroradiologists in consensus, to remove interobserver bias. Maximal tumour dimensions were measured and compared between interval scans. Tumours were classified into two groups depending on their size: macroadenomas (>10 mm) and microadenomas. The follow-up period was defined as the period between the first and the most recent scans. To calculate the average rate of growth, the increase in size between the first and the last scan (mm) was divided by the follow-up period (years).

Statistical analyses were performed using PRISM version 5.1 software (GraphPad Software, San Diego, CA, USA). The student's *t*-test and Mann–Whitney test were used to test differences between groups. Results are presented as mean or median (range). A *P*-value of <0·05 was considered statistically significant.

Results

Sixty-six patients consisting of 28 men and 38 women were managed conservatively. The mean follow-up period was 4·3 years (range: 1–14·7). The median follow-up period was 3·9 years. The patient demographics, presentations and the percentage of macroadenomas and microadenomas are shown in Table 1. Forty-seven (71%) patients had a macroadenoma, and nineteen (29%) patients had a microadenoma.

The changes in tumour size over the follow-up period are shown in Table 2. Overall, tumour size increased in 57·6%, reduced in 33·3% and remained stable in 9·1% of patients. Tumour size decreased or remained stable in 40·4% of macroadenomas and 47·4% of microadenomas. The increase in tumour size, as a percentage of the original tumour largest diameter, did not differ between growing macroadenomas and microadenomas ($P = 0·54$). The overall median annual growth rate was 0·8 mm/year (range: 0·1–7·7 mm/year). The median annual growth rate of enlarging macroadenomas and microadenomas was 1·0 mm/year and 0·4 mm/year, respectively. The median annual growth rate of macroadenomas was significantly higher than that of microadenomas ($P < 0·01$). The median time for the first radiological evidence of growth was 1·4 years for macroadenomas (range: 0·4–7·5 years) and 1·5 years for microadenomas (range: 0·5–4·7 years). The probabilities for enlargement of the macroadenomas and microadenomas during the follow-up period are shown in Fig. 1.

Table 1. Patient demographics, symptoms and initial tumour size

Total patients	66
Median age at presentation (years)	41
Gender (male/female)	28/38
Symptoms	
None (incidental finding)	21 (32%)
Headache	20 (30%)
Oligomenorrhoea/amenorrhoea	15 (23%)
Fatigue/malaise/weakness	9 (14%)
Visual field defects related to pituitary tumour	5 (8%)
Galactorrhoea	6 (9%)
Reduced libido	3 (5%)
Tumour size at presentation	
Macroadenomas	47 (71%)
Microadenomas	19 (29%)

Table 2. Changes in tumour size

	Total	Macroadenomas	Microadenomas
Number of patients (*n*)	66	47	19
Increased in size (%)	57·6	59·6	52·6
Remained stable (%)	9·1	6·4	15·8
Decreased in size (%)	33·3	34·0	31·6

Thirty-three of the forty-seven (70%) macroadenomas were in contact with the optic chiasm at presentation; of these patients, five patients had visual field defects attributed to their pituitary tumour at presentation. The reasons for conservative management in these patients included patients refusing surgery ($n = 2$), presence of co-morbidities ($n = 2$) and patient not attending surgery due to social reasons ($n = 1$). Of the thirty-three macroadenomas contacting the optic chiasm, twenty-four (73%) tumours increased in size. However, only eight (24%) patients developed visual field defects over a median follow-up period of 4 years. Of the fourteen macroadenomas not contacting the chiasm, four (29%) increased in size over the follow-up period. One patient with a macroadenoma not contacting the optic chiasm at presentation developed a visual field defect after a follow-up period of 14·7 years**.** All nine patients who developed visual field defects underwent trans-sphenoidal surgery, which ameliorated the visual field defect in every case. The histology was available for eight patients and was reported as gonadotroph adenoma ($n = 6$), one acidophilic stem cell adenoma and one clinically silent somatotroph adenoma.

The frequency of pituitary hormone deficiency in patients with nonfunctioning macroadenoma and microadenoma is shown in Table 3. Overall forty patients (61%) had hypopituitarism in one or more axes. Thirty-two of forty-seven (68%) patients with a macroadenoma had a deficiency in at least one pituitary hormone, compared to eight of nineteen (42%) patients with a microadenoma (Table 3). Twelve of forty-seven (26%) patients with macroadenomas had lost three or more

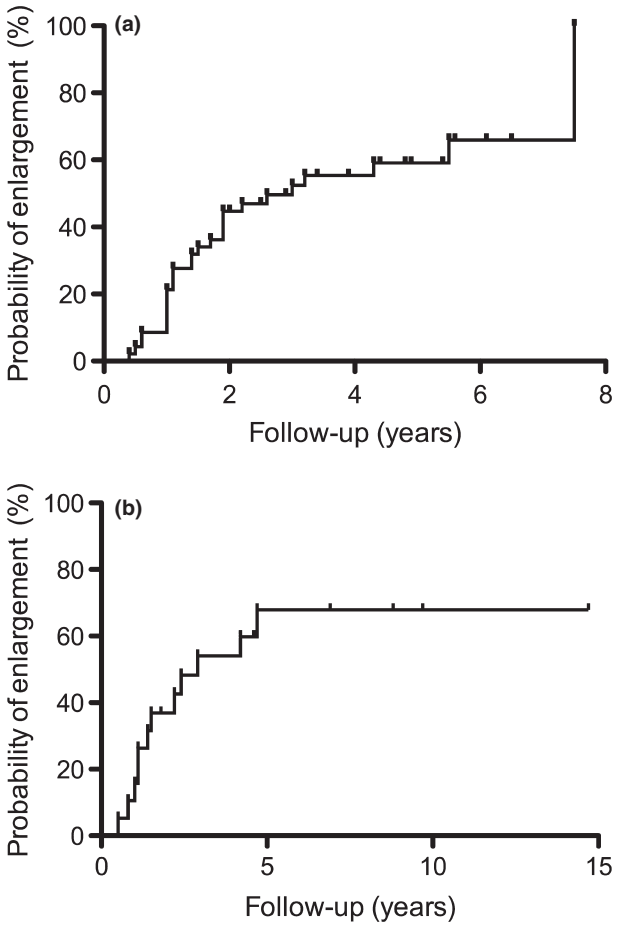

Fig. 1 Probability of macroadenoma enlargement (a) and microadenoma enlargement (b) in patients with nonfunctioning adenomas during the follow-up period.

pituitary hormones, whereas no patients with microadenomas had more than two pituitary hormone deficiencies. The details of pituitary hormone deficiencies in all patients are shown in Table 4.

Discussion

Our study included patients with a NFPA, managed conservatively and followed up over a mean interval of 4·3 years. We found that 60% of macroadenomas and 53% of microadenomas grew in size over the follow-up period. The median annual growth rate of macroadenomas was significantly higher than that of microadenomas. A higher proportion of macroadenomas contacting the optic chiasm (73%) grew in size compared to those not contacting the chiasm (29%) over the follow-up period. Of 33 patients with macroadenomas in contact with the optic chiasm at presentation, eight (24%) developed visual field defects during the follow-up period. Trans-sphenoidal surgery ameliorated the visual field defects in all cases. Other groups have also reported conservative management with close ophthalmological and radiological monitoring in select nonfunctioning pituitary macroadenoma that contact the optic apparatus, without visual dysfunction.[7] This is particularly relevant in patients with

Table 3. Frequency of pituitary hormone deficiency

	Deficiency (%)	
Hormone	Macroadenomas (n = 47)	Microadenomas (n = 19)
GH	22 (47%)	2 (11%)
LH/FSH	24 (51%)	3 (16%)
TSH	12 (26%)	3 (16%)
ACTH	15 (32%)	2 (11%)
Loss of one or more pituitary axes	32 (68%)	8 (42%)

comorbidities and a high perioperative risk. One patient developed a visual field defect requiring trans-sphenoidal surgery after almost 15 years of conservative management, highlighting the importance of long-term follow-up in these patients.

Our observations of the natural history of untreated pituitary macroadenomas are consistent with two other smaller series, reporting growth in 50% of macroadenomas.[4,8] The strengths of our study include the size of the cohort and the follow-up period compared to previous studies. This study reports on the largest cohort of patients with conservatively managed nonfunctioning pituitary macroadenomas observed for a mean follow-up of over 4 years. We found a higher rate of growth in microadenomas than previously reported[4], possibly due to a longer follow-up duration in our study. Another strength of the current study is that each pituitary MRI scan was re-examined by two neuroradiologists to minimize interobserver discrepancies, as opposed to collecting data from reports by different radiologists.

Pituitary hormone deficiency was more common in patients with macroadenomas. However, 42% of patients with microadenomas had at least one pituitary hormone deficiency. In another study, 50% of patients with a nonsecreting pituitary microadenoma were found to be GH-deficient and 50% had at least one other pituitary hormone deficit.[9] Therefore, it is important to assess pituitary function in all patients with pituitary incidentalomas, irrespective of tumour size.

In addition to the negative effects of pituitary hormone deficiency on quality of life, patients with hypopituitarism have increased mortality.[10–13] Therefore, it is important that the risk of hypopituitarism due to surgery with its ensuing morbidity and mortality is weighed against the potential benefits of surgery, when deciding the appropriate management of NFPA patients.

A limitation of this study is that we did not measure tumour volume. However, this information is often not available in routine clinical practice. In addition, as no tumour samples were available from patients in the conservative group, we did not have histological confirmation that these tumours were nonfunctioning. We diagnosed these tumours as NFPAs using clinical and imaging criteria, combined with the lack of hormonal hypersecretion. Finally, the retrospective nature of the study also presents certain limitations to the interpretation of the data.

In conclusion, we have shown that 47% of nonfunctioning microadenomas remained stable or decreased in size and around

Table 4. Pituitary hormone deficiencies in all patients

Patient	Hormone deficiency			
	GH	LH/FSH	TSH	ACTH
1	No	Yes	Yes*	Yes*
2	No	Yes	No	No
3	No	No	No	No
4	Yes	Yes*	Yes*	Yes*
5	Yes	Yes	Yes*	No
6	Yes	Yes*	Yes*	Yes*
7	Yes	Yes*	Yes*	Yes
8	Yes	Yes	No	No
9	No	No	No	No
10	No	Yes*	No	No
11	No	Yes*	No	No
12	No	Yes	No	Yes
13	Yes*	Yes	No	Yes*
14	No	Yes*	Yes*	No
15	Yes	Yes*	Yes*	Yes*
16	Yes	Yes*	Yes	No
17	No	No	No	No
18	Yes	Yes*	Yes	Yes
19	No	No	No	No
20	Yes	No	No	Yes
21	No	Yes*	No	No
22	Yes	Yes	Yes*	Yes*
23	No	No	No	No
24	No	No	No	No
25	No	No	No	No
26	No	Yes	No	No
27	Yes*	Yes*	No	No
28	No	No	No	No
29	No	Yes	No	No
30	Yes	Yes*	Yes*	Yes*
31	Yes	No	No	Yes*
32	No	No	No	No
33	Yes	No	No	No
34	No	No	No	No
35	Yes	No	No	No
36	Yes	Yes*	No	No
37	No	No	No	No
38	Yes	No	No	No
39	Yes	No	No	No
40	No	No	No	No
41	Yes	No	No	Yes
42	No	No	No	No
43	Yes	Yes	Yes	Yes*
44	Yes	No	No	No
45	No	No	No	No
46	No	Yes	No	Yes
47	No	No	No	No
48	No	No	Yes*	Yes*
49	No	No	No	No
50	No	No	No	No
51	No	No	Yes	Yes*
52	No	No	No	No
53	No	No	No	No
54	No	Yes	No	No
55	No	No	No	No
56	No	No	No	No
57	No	No	No	No
58	No	No	No	No
59	No	No	No	No
60	No	Yes	No	No
61	No	No	Yes*	No
62	No	No	No	No
63	Yes	No	No	No
64	No	Yes*	No	No
65	No	No	No	No
66	Yes*	No	No	No

*Detected at presentation. Patients 1–47 had macroadenomas; Patients 48–66 had microadenomas.

40% of nonfunctioning macroadenomas similarly did not grow during the follow-up period. Conservative management with regular surveillance is safe and effective in patients without evidence of optic chiasm compression. These findings provide clinically relevant data for the management of patients with NFPAs.

Disclosure statement

The authors have nothing to disclose.

References

1 Fernandez, A., Karavitaki, N. & Wass, J.A. (2010) Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clinical Endocrinology*, **72**, 377–382.
2 Molitch, M.E. (2012) Management of incidentally found nonfunctional pituitary tumors. *Neurosurgery Clinics of North America*, **23**, 543–553.
3 Wass, J.A., Reddy, R. & Karavitaki, N. (2011) The postoperative monitoring of nonfunctioning pituitary adenomas. *Nature Reviews. Endocrinology*, **7**, 431–434.
4 Karavitaki, N., Collison, K., Halliday, J. *et al.* (2007) What is the natural history of nonoperated nonfunctioning pituitary adenomas? *Clinical Endocrinology*, **67**, 938–943.
5 Fernandez-Balsells, M.M., Murad, M.H., Barwise, A. *et al.* (2011) Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. *Journal of Clinical Endocrinology and Metabolism*, **96**, 905–912.
6 Orija, I.B., Weil, R.J. & Hamrahian, A.H. (2012) Pituitary incidentaloma. *Best Practice & Research. Clinical Endocrinology & Metabolism*, **26**, 47–68.
7 Ryu, W.H., Tam, S., Rotenberg, B. *et al.* (2010) Conservative management of pituitary macroadenoma contacting the optic apparatus. *Canadian Journal of Neurological Sciences*, **37**, 837–842.
8 Dekkers, O.M., Hammer, S., de Keizer, R.J. *et al.* (2007) The natural course of non-functioning pituitary macroadenomas. *European Journal of Endocrinology*, **156**, 217–224.

9 Yuen, K.C., Cook, D.M., Sahasranam, P. *et al.* (2008) Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels. *Clinical Endocrinology*, **69**, 292–298.
10 Rosen, T. & Bengtsson, B.A. (1990) Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet*, **336**, 285–288.
11 Bates, A.S., Van't Hoff, W., Jones, P.J. *et al.* (1996) The effect of hypopituitarism on life expectancy. *Journal of Clinical Endocrinology and Metabolism* **81**, 1169–1172.
12 Tomlinson, J.W., Holden, N., Hills, R.K. *et al.* (2001) Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet*, **357**, 425–431.
13 Schneider, H.J., Aimaretti, G., Kreitschmann-Andermahr, I. *et al.* (2007) Hypopituitarism. *Lancet*, **369**, 1461–1470.