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### Pituitary incidentalomas

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Clinically non-functioning pituitary adenomas range from being completely asymptomatic, and therefore being detected either at autopsy or as incidental findings on head magnetic resonance imaging (MRI) or computed tomography (CT) scans performed for other reasons (often referred to as 'pituitary incidentalomas'), to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size. Patients with pituitary incidentalomas should all be screened for hypersecretion (prolactin (PRL), IGF-1, midnight salivary cortisol), and those with macroadenomas should also be screened for hypopituitarism (macroadenomas) and for visual field defects if the tumour abuts the optic chiasm. Growth of non-functioning pituitary adenomas without treatment occurs in about 10% of microadenomas and 24% of macroadenomas. In the absence of hypersecretion, hypopituitarism or visual field defects, patients may be followed up by periodic screening by MRI for enlargement. Growth of a pituitary incidentaloma is an indication for surgery.

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Clinically non-functioning adenomas (CNFAs) of the pituitary, by definition, produce no clinical syndrome related to hormone over-production by the tumour. In fact, however, about three-quarters of CNFAs are actually gonadotroph adenomas, as shown by measurement of gonadotropins or their glycoprotein subunits (alpha and/or beta) in blood, staining on immunohistochemistry, or measurement of the mRNA for these products in the tumours.<sup>1</sup> A few percentage of CNFAs will also be found to stain positively for adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin (PRL) or thyrotropin (TSH) singly or in combinations; as they do not secrete these hormones in sufficient quantities so as to cause clinical syndromes; such tumours are referred to as 'silent' corticotroph, somatotroph, lactotroph, thyrotroph or mixed adenomas.<sup>2</sup>

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Large CNFAs often cause significant hypothalamic/pituitary dysfunction and visual symptoms. However, others may be completely asymptomatic, being detected either at autopsy or as incidental findings on head magnetic resonance imaging (MRI) or computed tomography (CT) scans performed for other reasons. This latter group has been referred to as pituitary incidentalomas. A number of other lesions may be found in the sellar area that may mimic a pituitary adenoma, including aneurysms of the internal carotid artery, craniopharyngeal gliomas, Rathke's cleft cysts, meningiomas of the tuberculum sellae, gliomas of the hypothalamus and optic nerves, dysgerminomas, cysts, hamartomas, metastases, sarcoidosis, eosinophilic granulomas, sphenoid sinus mucocoeles and focal areas of infarction.<sup>3–6</sup> Lymphocytic infiltration of the pituitary can also masquerade as a pituitary adenoma.<sup>7</sup>

Some normal individuals statistically must have pituitaries that exceed the normal size boundary of 9 mm (+ 3 standard deviations in healthy subjects<sup>8–10</sup>). Chanson et al. have reported several such patients.<sup>11</sup> These individuals with 'normal pituitary hypertrophy' had pituitaries that, on MRI, had homogeneous isointense signals and were enhanced homogeneously with contrast.<sup>11</sup> Furthermore, surgical specimens showed normal pituitary tissue in two cases.<sup>11</sup> Artefacts mimicking pituitary lesions include beam-hardening effects with CT and susceptibility distortions with MRI.<sup>4,6</sup> This article reviews the epidemiology and management of patients with pituitary incidentalomas.

## Prevalence of pituitary incidentalomas

### *Autopsy findings*

Pituitary adenomas have been found at autopsy in 1.5–31% of subjects not suspected of having pituitary disease when alive<sup>3,12–42</sup> (Table 1). The average frequency of finding an adenoma for these studies, which examined a total of 18 902 pituitaries, is 10.7%. The tumours are distributed equally throughout the age groups (range: 16–86 years) and between the sexes. In studies in which PRL immunohistochemistry was performed, 22–66% stained positively for PRL.<sup>18,20,21,26,29–31,33–36,38,39</sup> Burman and Saeger provided a detailed immunohistochemical analysis of the 334 pituitary adenomas found in 316 pituitaries of the 3048 autopsy cases they examined, finding that 39.5% stained for PRL, 13.8% for ACTH, 7.2% for gonadotropins or alpha subunits, 1.8% for GH, 0.6% for TSH and 3.0% for multiple hormones.<sup>39</sup>

In these post-mortem studies, all but seven of the tumours were less than 10 mm in diameter. The relative lack of macro adenomas in these autopsy studies suggests that the growth from micro- to macroadenomas must be an exceedingly uncommon event, and/or that virtually all macroadenomas come to clinical attention and, therefore, are not included in autopsy findings. There is a separate report of an additional three macroadenomas being found at autopsy.<sup>43</sup>

### *CT and MRI scans in normal individuals*

Three series have evaluated CT scans of the sellar area in normal subjects who were having such scans for reasons unrelated to possible pituitary disease. Chambers et al.<sup>3</sup> found discrete areas of low density >3 mm in diameter in 10 of 50 such subjects. In our study of 107 normal women, we found seven who had focal hypo-dense areas and five who had focal high-density regions >3 mm in diameter.<sup>44</sup> In a third study, Peyster et al.<sup>45</sup> found focal hypo-dense areas >3 mm in diameter in only eight of 216 subjects.

Two similar studies have been carried out using MRI. Chong et al.<sup>46</sup> found focal pituitary gland hypo-densities 2–5 mm (mean 3.9 mm) in 20 of 52 normal subjects with non-enhanced images using a 1.5-Tesla scanner and 3-mm thick sections. With similar scans but with gadolinium-DTPA enhancement, Hall et al.<sup>47</sup> found that in 100 normal volunteers focal areas of decreased intensity  $\geq 3$  mm in diameter compatible with the diagnosis of adenoma were found in 34, 10 and 2 volunteers, depending upon whether there was agreement on the diagnosis between 1, 2 or 3 independent reviewing neuroradiologists, respectively.

Sellar lesions >10 mm in diameter have not been found in these small studies of consecutive normal individuals, similar to the very limited number found at autopsy. However, Nammour et al.<sup>48</sup> found that of 3550 consecutive CT scans done in men of a mean age of 57 years for the symptoms of change in

**Table 1**  
Frequency of Pituitary Adenomas Found at Autopsy.

Series	Number of Pituitaries Examined Found (%)	Number of Adenomas Found (%)	Frequency (%)	Number of Macroadenomas	Stain+ for Prolactin
Susman (12)	260	23	8.8	–	–
Close (13)	250	23	9.2	–	–
Costello (14)	1000	225	22.5	0	–
Sommers (15)	400	26	6.5	0	–
McCormick (16)	1600	140	8.8	0	–
Haugen (17)	170	33	19.4	0	–
Kovacs (18)	152	20	13.2	2	53
Landolt (19)	100	13	13.0	0	–
Mosca (20)	100	24	24.0	0	23
Burrow (21)	120	32	26.7	0	41
Parent (22)	500	42	8.4	1	–
Muhr (23)	205	3	1.5	0	–
Max (24)	500	9	1.8	–	–
Schwezingger (25)	5100	485	9.5	–	–
Chambers (3)	100	14	14.0	0	–
Coulon (26)	100	10	10.0	0	60
Siqueira (27)	450	39	8.7	–	–
Char (28)	350	35	10.0	0	–
Gorczyca (29)	100	27	27.0	0	30
El-Hamid (30)	486	97	20.0	0	48
Scheithauer (31)	251	41	16.3	0	66
Kontogeorgos (32)	470	49	10.4	0	–
Marin (33)	210	35	16.7	0	32
Sano (34)	166	15	9.0	0	47
Teramoto (35)	1000	51	5.1	0	30
Camararis (36)	423	14	3.2	0	44
Tomita (37)	100	24	24.0	–	–
Kurosaki (38)	692	79	11.4	1	24
Buurman (39)	3048	334	11.0	3	40
Rittierodt (40)	228	7	3.0	0	–
Furgal-Borzych (41)	151	47	31.1	0	21
Kim (42)	120	7	6.7	0	29
Total	18902	2023	10.7	7	–

Each series is identified by the first author and reference number.

Prolactin+ indicates the percentage of tumors that had positive immunostaining for prolactin, indicating that they were prolactinomas.

mental status, headache or possible metastases, seven (0.2%) were found to have pituitary macroadenomas ranging from 1.0 to 2.5 cm in size; all were thought to be CNFAs after hormonal evaluation. Similarly, when non-enhanced MRI scans were performed without specific views of the sellar area in asymptomatic normal subjects, macroadenomas were found in 0.16% of 3672 subjects in a study by Yue et al.<sup>49</sup> and in 0.3% of 2000 subjects in a study by Vernooij et al.<sup>50</sup> Furthermore, macroadenomas have been reported as incidental findings.<sup>51</sup> Clinically, patients with incidental macroadenomas are commonly seen in everyday practice.

## Evaluation and management of patients with pituitary incidentalomas

### *Clinical experience with CNFAs that were not treated*

Ten series of patients have been reported with pituitary CNFAs that were not treated either surgically or medically, thereby giving an indication of their natural history (Table 2)<sup>52–61</sup>; of these 513 patients, 353 (68.8%) had macroadenomas and 260 (31.2%) had microadenomas (Table 2). However, these were not truly all incidentalomas. Several of these patients had tumours 2 cm or more in maximum diameter and many of them were symptomatic, with hypopituitarism or visual field defects,

**Table 2**

Changes in Pituitary Incidentaloma Size.

Series	Macroadenomas				Microadenomas				Years Followed
	Total	Increased	Decreased	No change	Total	Enlarged	Decreased	No change	
Donovan & Corenblum (52)	15	0	0	15	16	4*		12	6–7
Reincke et al. (53)	7	1	1	5	7	2	0	5	8
Nishizawa et al. (54)					28	2*	0	26	5.6
Feldkamp et al. (55)	31	1	1	29	19	5	1	13	2.7
Igarashi et al. (56)	1	0	0	1	22	6	10	6	5.1
Sanno et al. (57)	74	10	7	57	165	20*	22	123	2.3
Fainstein Day et al. (58)	11	1	0	10	7	1	0	6	3.2
Arita et al. (59)	5	2	0	3	37	19*	0	18	5.2
Karavitaki (60)	16	2	1	13	24	12	4	8	3.6
Dekkers (61)					28	14	8	6	7.1
<b>Total</b>	<b>160</b>	<b>17 (10.6)</b>	<b>10 (6.3%)</b>	<b>133 (83.1%)</b>	<b>353</b>	<b>85 (24.1%)</b>	<b>45 (12.7%)</b>	<b>223</b>	<b>(63.2%)</b>

\*A total of 7 cases in these series had tumor enlargement due to apoplexy.

but for a variety of reasons surgery was not carried out. For example, in the series reported by Karavitaki et al.<sup>60</sup>, only one-half of the 24 macroadenomas were incidental findings and 11 had varying degrees of hypopituitarism. In this series, five patients had major visual field defects but did not have surgery either because of major co-morbidities (three patients) or because the patient was “not keen for surgery” (two patients).<sup>60</sup> Similarly, in the series of 28 patients with macroadenomas reported by Dekkers et al.<sup>61</sup> only six (21%) were truly incidentalomas, with 44% having hypopituitarism and 46% having visual field defects. Thus, the proportion of patients with macroadenomas found clinically is much greater than would be expected based on the autopsy findings. This suggests that the mass effects of such tumours may have caused some of the symptomatology, causing the patients to have the scans in the first place, even in those in whom there were no true visual field defects or hypopituitarism.

#### Endocrinological evaluation for pituitary hyperfunction

As the most common lesion in the sella is a pituitary adenoma, it is reasonable to evaluate patients for hormone over-secretion, regardless of the size of the lesion seen. Many of the changes occurring with hormone over-secretion syndromes may be quite subtle and only slowly progressive; therefore, screening for hormonal over-secretion is warranted even in patients with no clinical evidence. ‘Silent’ somatotroph and corticotroph adenomas have been reported many times, but it is not clear whether such patients with minimal clinical evidence of hormone over-secretion are free from the increased risk for the more subtle cardiovascular, bone, oncological and possibly other adverse effects we usually associated with such tumours. Indeed, there is emerging evidence that subclinical Cushing’s syndrome due to adrenal incidentalomas is associated with significantly increased prevalence of diabetes, hypertension, obesity, osteoporosis and cardiovascular risk.<sup>62</sup> Whether there is a similar increased risk for these co-morbidities with ‘silent’ corticotroph adenomas is unknown. Furthermore, there is some evidence that silent corticotroph adenomas have a worse prognosis than those with overt disease with respect to aggressiveness following initial surgery<sup>63</sup> and progression to overt Cushing’s disease over time occurred in four out of 22 (18%) of cases in one series.<sup>64</sup> It is not clear how many of these patients have non-suppressible serum cortisol levels or elevated urinary free cortisol levels, but Lopez et al. have found suppressed ACTH secretion and hypocortisolism in two out of 12 patients following resection of silent ACTH secreting adenomas.<sup>65</sup>

Screening for hormone over-secretion in such patients has been questioned as to its cost-effectiveness.<sup>66–68</sup> However, evidence from the series of Fainstein Day cited above<sup>58</sup> suggests that such screening is worthwhile, as seven of their 46 patients turned out to have prolactinomas, and of the 13 who underwent surgery and immunohistochemistry analysis, two adenomas (15%) were GH positive, three (23%) were gonadotropin positive and four (31%) were plurihormonal adenomas.

A serum PRL should be obtained, but it may be difficult to distinguish between PRL production by a tumour and hyperprolactinaemia from stalk dysfunction in the case of macroadenomas, especially

those with suprasellar extension.<sup>69</sup> For such tumours, PRL levels are usually greater than 200 ng ml<sup>-1</sup> with hormone-secreting tumours, and lower levels suggest stalk dysfunction.<sup>70–72</sup> For very large tumours, the sample should be diluted 1:100 to avoid the ‘hook effect’<sup>73,74</sup>, in which very high PRL levels may saturate the antibodies in two-site assays; however, this is not necessary in all assays. An IGF-1 is probably sufficient to screen for acromegaly, but if this cannot be performed, it may be necessary to demonstrate non-suppression of GH levels by hyperglycaemia during an oral glucose tolerance test.<sup>75</sup> The best screening tests for Cushing’s syndrome have traditionally been the overnight dexamethasone suppression test and the 24-h urinary free cortisol and more recently the assessment of a midnight salivary cortisol.<sup>76,77</sup> An abnormal midnight salivary cortisol has been found to have greater than 93% specificity and sensitivity for diagnosing Cushing’s syndrome.<sup>78</sup> Any abnormality found on such screening would then need to be pursued with more definitive testing. Most clinically non-functioning adenomas are gonadotroph adenomas, as shown by immunohistochemistry.<sup>1</sup> However, as gonadotropin over-secretion rarely causes clinical symptoms and the finding of such hormone over-secretion would not influence therapy, there is no reason to screen for this.

#### *Endocrinological evaluation for pituitary hypofunction*

Microadenomas have generally not been thought to cause disruption of normal pituitary function. Of the 22 patients with suspected microadenomas evaluated in the series of Reincke et al.<sup>53</sup> and Donovan and Corenblum<sup>52</sup>, all had a normal pituitary function. However, recently, Yuen et al. found deficiencies of one or more pituitary hormones in 50% of 38 patients with clinically non-functioning microadenomas.<sup>79</sup> Larger lesions may cause varying degrees of hypopituitarism because of compression of the hypothalamus, the hypothalamic–pituitary stalk, or the pituitary itself. Of the various series reported, between 0% and 41% of patients with macroadenomas were found to have hypopituitarism, depending upon whether the patients were reported from endocrinology or neurosurgery services.<sup>49,50,55,56</sup> Thus, all patients with macroadenomas should be screened for hypopituitarism, but whether all patients with microadenomas should be similarly screened is controversial.

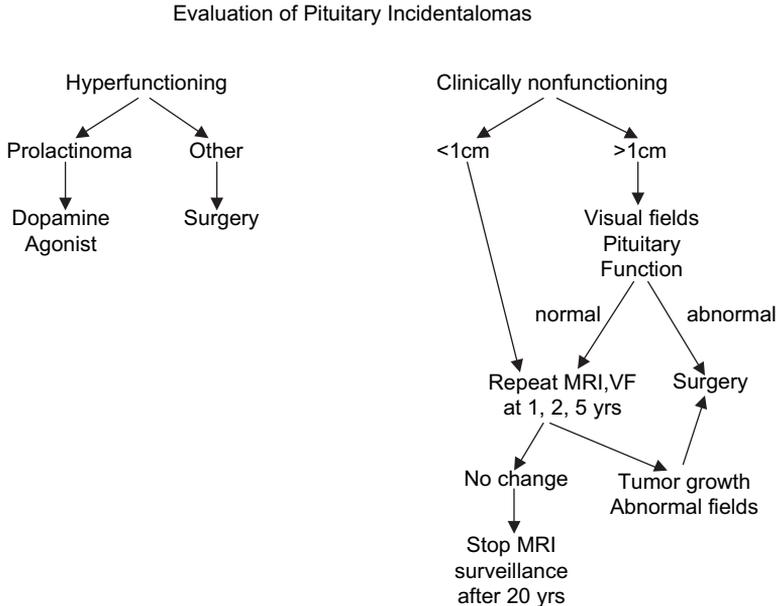
#### *Natural history and follow-up of incidental CNFAs*

Ten separate series have been reported on the follow-up of patients with pituitary CNFA’s that were not treated; as noted above, most were incidentalomas but in many cases the adenomas were symptomatic but not treated for a variety of reasons (Table 2). Of the 160 patients with microadenomas reported in these series, 17 (10.6%) experienced tumour growth, 10 (6.3%) showed evidence of a decrease in tumour size and 133 (83.1%) remained unchanged in size in follow-up MRI scans over periods of up to 8 years.<sup>49–56</sup> Of the 353 patients with macroadenomas, 85 (24.1%) showed evidence of tumour enlargement, 45 (12.7%) showed evidence of a decrease in tumour size and 223 (63.2%) remained unchanged in size on follow-up MRI scans over periods of 8 years.<sup>49–56</sup> The duration of follow-up of these patients was variable and in their analysis, Dekkers et al. suggested that with longer follow-up, up to 50% of patients with macroadenomas will have an increase in tumour size.<sup>80</sup> It should be mentioned that of the 59 macroadenomas with tumour size increase, in seven this was due to a haemorrhage into the tumour (Table 2).

#### *Management of incidental CNFAs*

Therapy is indicated for tumours that are found to be hypersecreting. Therefore, prolactinomas would generally be treated with dopamine agonists and those producing GH or ACTH would be treated with surgery. Treatment guidelines for the management of such tumours are readily available.<sup>69,75,76</sup> For tumours that do not over-secrete these hormones, the indications for surgery are based initially on mass effects of the tumours<sup>80,81</sup> and subsequently on tumour size enlargement.

For patients with microadenomas, the data presented above suggests that significant tumour enlargement will occur in only 10.6% of patients. Therefore, surgical resection is generally not indicated and repeat scanning for 1–2 years is indicated to detect tumour enlargement; subsequently, this can be done at less frequent intervals (Fig. 1). Surgery is performed only in case of significant tumour



**Fig. 1.** Flow diagram indicating the approach to the patient found to have a pituitary incidentaloma. The first step is to evaluate patients for pituitary hyperfunction and then treat those found to be hyperfunctioning. Of patients with tumors that are clinically nonfunctioning, those with macroadenomas are evaluated further for evidence of chiasmal compression and hypopituitarism. Scans are then repeated at progressively longer intervals to assess for enlargement of the tumors.

enlargement. However, the rate of growth is generally quite slow so that the decision and timing of any surgery would depend on the rate and amount of growth as well as any clinical consequences, such as the development of visual field defects.

Tumours greater than 1 cm in diameter have already indicated a propensity for growth. A careful evaluation of the mass effects of these tumours is indicated, including evaluation of pituitary function and visual field examination if the tumour abuts the chiasm. If there are visual field defects, surgery is certainly indicated.<sup>80,81</sup> Because hypopituitarism is potentially correctable with tumour resection, this is also an indication for surgery.<sup>80–82</sup> In my opinion, tumours larger than 2 cm should also be considered for surgery simply because of their already demonstrated propensity for growth. Similarly, if a tumour is found to be abutting the optic chiasm, even though testing shows normal visual fields, consideration should be given to surgery.

If a completely asymptomatic lesion is thought to be a pituitary macroadenoma on the basis of radiological and clinical findings, then a decision could be made to simply repeat scans on a yearly basis, surgery being deferred until there is evidence of tumour growth. As indicated above, significant tumour growth can be expected in approximately one-quarter of patients with macroadenomas. Haemorrhage into such tumours is uncommon, but anticoagulation may predispose to this complication; surgery would prevent such a complication. When there is no evidence of visual field defects or hypopituitarism and the patient is asymptomatic, an attempt at medical therapy with a dopamine agonist or octreotide is reasonable, realising that only about 10–20% of such patients will respond with a decrease in tumour size.<sup>80,81,83</sup> Surgery may be indicated if surveillance scans show evidence of tumour enlargement. As with microadenomas, the decision to proceed with surgery is affected by the rate and extent of growth and any clinical consequences such as compression of the optic chiasm or the development of pituitary hormone deficiencies (Fig. 1).

Attempts have been made to look at the growth rates of those tumours that do grow. Dekkers et al. estimated a growth rate of 0.6 mm per year or 236 mm<sup>3</sup> per year.<sup>61</sup> Of their 14 patients who experienced tumour growth, two showed evidence of growth by 2 years, three more by 3 years and then one

each at 4, 5, 6, 7, 12, 15, 17, 20 and 22 years. In contrast, Karavitaki et al. found that all but four of their 12 patients who experienced macroadenoma re-growth did so by 5 years, although the patients also had evidence of tumour growth at 6 and 8 years.<sup>60</sup> In a statistical evaluation of CNFA growth rates for macroadenomas, Honegger et al. found tumour volume doubling times ranging from 0.8 to 27.2 years, emphasising the tremendous variability in tumour size increases; there was no correlation between initial tumour size and the rate of tumour volume doubling.<sup>84</sup> These data suggest that at least for patients with macroadenomas, surveillance MRI scans should be carried out for at least 22 years, although the frequency of scanning can certainly be reduced after the first few years if there is no evidence of tumour growth.

## Summary

Pituitary incidentalomas are commonly seen in endocrine practice. Although most are either gonadotroph adenomas or truly non-functioning, some may be silent lactotroph, somatotroph or corticotroph adenomas. Hormone hypersecretion, hypopituitarism, visual field defects and evidence of tumour growth are indications for surgery or medical therapy as appropriate for tumours found to be secretory. Growth of non-functioning incidentalomas can be expected in 10.6% of microadenomas and 24% of macroadenomas. Periodic surveillance by MRI may be needed for more than 20 years to detect tumour growth.

### Practice points

- Patients with pituitary incidentalomas should be evaluated for tumour hypersecretion
- Those with macroadenomas should be evaluated for hypopituitarism and other mass effects
- Hypopituitarism, visual field defects and tumour growth are indications for surgery
- Tumour growth can be expected in 10.6% of microadenomas and 24.1% of macroadenomas
- For patients without specific indications for surgery, surveillance MRI scans may need to be performed for up to 20 years

## Conflict of interest

The author has no financial or personal relationships with other people or organisations that could inappropriately influence (bias) the content of this article.

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