RESEARCH

A comparative, population-based analysis of pituitary incidentalomas vs clinically manifesting sellar masses

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Abstract

Purpose: Sellar masses may present either with clinical manifestations of mass effect/hormonal dysfunction (CMSM) or incidentally on imaging (pituitary incidentaloma (PI)). This novel population-based study compares these two entities.
Methods: Retrospective analysis of all patients within a provincial pituitary registry between January 2006 and June 2014.
Results: Nine hundred and three patients were included (681 CMSM, 222 PI). CMSM mainly presented with secondary hormone deficiencies (SHDs) or stalk compression (29.7%), whereas PIs were found in association with neurological complaints (34.2%) ($P < 0.0001$). PIs were more likely to be macroadenomas (70.7 vs 49.9%; $P < 0.0001$). The commonest pathologies among CMSM were prolactinomas (39.8%) and non-functioning adenomas (NFAs) (50%) in PI ($P < 0.0001$). SHDs were present in 41.3% CMSM and 31.1% PI patients ($P < 0.0001$) and visual field deficit in 24.2 and 29.3%, respectively ($P = 0.16$). CMSM were more likely to require surgery (62.9%) than PI (35.8%) ($P < 0.0005$). The commonest surgical indications were impaired vision and radiological evidence of optic nerve compression. Over a follow-up period of 5.7 years for CMSM and 5.0 years for PI, tumour growth/recurrence occurred in 7.8% of surgically treated CMSM and 2.6% without surgery and PI, 0 and 4.9%, respectively ($P = 1.0$). There were no significant differences in the risk of new-onset SHD in CMSM vs PI in those who underwent surgery ($P = 0.7$) and those who were followed without surgery ($P = 0.58$).
Conclusions: This novel study compares the long-term trends of PI with CMSM, highlighting the need for comprehensive baseline and long-term radiological and hormonal evaluations in both entities.

Key Words
▶ pituitary incidentaloma
▶ adenoma
▶ sellar mass
▶ outcome

Introduction

Sellar masses (SMs) are mostly benign growths of pituitary or non-pituitary origin that are increasingly encountered in clinical practice, accounting for approximately 14–18% of all brain tumours (1, 2). SMs typically present with either clinical manifestations of symptoms related to mass effect and/or hormonal dysfunction ('clinically manifesting sellar masses' (CMSM)) or as incidental abnormalities found during brain imaging performed

for unrelated indications. This latter group is generally referred to as 'pituitary incidentalomas' (PIs) (3). In a population-based study of SM, we previously reported an overall prevalence and standardized incidence rate (SIR) of 107/100,000 and 5.12 for all SMs, and subgroup analysis of PI demonstrated a prevalence and SIR of 24.4/100,000 and 1.62, respectively (5, 6). Similar rates are reported from Scandinavia (7, 8) and Europe (9, 10, 11, 12).

To date, population-based studies examining the epidemiology and natural history of SM have either focused on isolated CMSM or PI but, to our knowledge, there are no population-based studies comparing both entities. Given the prevalence and clinical importance of SM, it is important to characterize the comparative epidemiological trends of these two entities in order to understand their implications on diagnostic strategies and long-term management of these lesions.

Materials and methods

Study population and HNP database

The province of Nova Scotia, Canada has a relatively stable population of almost 1 million based on the 2011 census report. All adult patients (over the age of 16 years) with neuropituitary disorders within the province are enrolled in an interlinked computerized provincial registry since November 2005 called the Halifax Neuropituitary (HNP) database. The HNP database, which currently follows over 1700 patients, prospectively collects clinical, biochemical, radiological and surgical (when applicable) data, and patients are followed according to standardized criteria by a single team comprising an endocrinologist and neurosurgeon as well as specialized nurses from endocrinology and neurosurgery.

Study design

A retrospective analysis was carried out on all patients within HNP database meeting the following inclusion criteria: i) seen between January 1, 2006, and June 30, 2014; ii) have any of the following diagnoses: non-functioning pituitary adenoma (NFA), prolactinoma (PRLoma), growth hormone-producing adenoma (GH adenoma), adrenocorticotrophic-producing adenoma (ACTH adenoma), thyroid-stimulating hormone-producing adenoma (TSH adenoma) or any of the non-pituitary tumours including craniopharyngioma, Rathke's cleft cyst (RCC), pituitary cyst, meningiomas or lipomas and iii) have at least 12 months of follow-up with complete physical and/or biochemical profile. Consent was obtained from each patient after full explanation of the purpose and nature of all procedures used. The Nova Scotia Health Research Ethics Board approved the study.

Diagnostic strategies for pituitary-related growths

Diagnostic assessment of SM by our group has been described elsewhere (5, 6). SMs were categorized based on size into macroadenomas ($\geq$10 mm) or microadenomas (<10 mm), functional status into either NFA or functioning adenomas (FAs) and on the basis of origin into pituitary adenomas (PAs) and other sellar and parasellar tumours (non-pituitary lesions). FAs were further stratified based on the predominant hormonal release pattern as follows: PRLomas were defined as FA associated with detectable PA on imaging, a persistently elevated PRL level and presence of symptoms related to high PRL. A subgroup of patients without a detectable MRI lesion but persistently elevated PRL and absence of secondary causes of hyperprolactinaemia such as hypothyroidism, chronic kidney disease, hepatic cirrhosis and medications known to raise PRL were defined as MRI-negative PRLoma based on previously published analysis (10). GH adenomas were diagnosed on the basis of typical clinical features, an elevated age- and gender-matched serum insulin-like growth factor-1 (IGF-1) and inability to suppress GH to <0.4 µg/L following a 75 g oral glucose load. ACTH adenomas were diagnosed based on clinical and biochemical features of hypercortisolism and evidence of pituitary origin of hypercortisolism based on some or all of the following tests: inappropriate-normal or elevated ACTH, abnormal dexamethasone suppression test, adequate stimulation with a corticotropin-releasing hormone test and inferior petrosal sinus sampling with or without a detectable pituitary tumour. TSH adenoma diagnosis was based on elevated serum-free T4, inappropriately normal or elevated TSH, presence of pituitary tumour and a positive tissue diagnosis. NFA was diagnosed when there was no clinical and/or biochemical evidence of hormonal oversecretion and in cases of macroadenoma in which serum PRL was <150 µg/L (N=2.1–17.7 in males and 2.8–29.2 in females). For non-pituitary lesions, the diagnosis was based on typical clinical and radiological features; the latter was judged either by an experienced neurosurgeon or directly obtained from the radiology report. For all patients who underwent surgery, tissue diagnosis was the primary method for making the diagnosis. Secondary hormone deficiency (SHD) was defined as follows. Secondary adrenal insufficiency was

defined as either basal serum cortisol of <130nmol/L, failure of serum cortisol to rise ≥500nmol/L after an insulin tolerance test or 250µg ACTH stimulation test based on our previously published data (13). Secondary hypothyroidism (SHT) diagnosis was based on low serum free thyroxine with inappropriately normal or subnormal TSH. Secondary hypogonadism (SHG) was defined as low testosterone or oestradiol with inappropriately low serum luteinizing hormones and follicle-stimulating hormone. Diabetes insipidus was diagnosed based on the presence of polyuria and polydipsia in addition to abnormal water deprivation test. We do not routinely perform dynamic testing for GH deficiency unless coverage for GH therapy is available; therefore, GH deficiency was defined as a low IGF-1.

Follow-up strategy

Standardized follow-up protocols are in place for each patient (6). After the initial clinic visit, patients requiring surgery are assessed at 3 (in the case of those requiring immediate surgery) to 6 months (in the case of those not requiring immediate surgery), every 12 months thereafter for 5 years and then every 12–24 months thereafter based on the physicians' discretion. Patients routinely undergo pituitary hormonal assessment and sellar imaging with MRI (or CT in rare cases when patients are unable to undergo MRI) at the time of presentation and at each subsequent visit. Follow-up visual field assessments were routinely performed in patients who had documented visual field abnormalities at baseline or MRI findings concerning for optic nerve involvement.

Significant increase in size of PA was defined as increase of 2mm or more in any dimension. New-onset SHD was defined as pituitary hormonal dysfunction during follow-up in a patient with a previously intact hypothalamic–pituitary axis. Worsening SHD was defined as further loss of one or more hormonal axes during follow-up among patients already meeting the criteria for SHD at baseline. In patients undergoing immediate surgery (within 90 days of presentation), the post-operative sellar imaging and SHD obtained 3 months post-operatively were used as the new baseline to which subsequent imaging and SHD status were compared to identify any significant change. Mean follow-up period was 5.7 years for CMSM and 5.0 years for PI. In this study, we have reported the long-term follow-up and outcomes of NFA and non-pituitary SM only while that of FAs will be reported separately.

Statistical analysis

Population characteristics were summarized as means with standard deviation for continuous variables and frequencies with percentage for categorical data; differences between continuous variables were assessed using the Student's *t*-test. Associations between categorical variables were analysed using Fisher's exact test. Similarly, management strategies, change in tumour size and change in SHD status were compared between clinically manifesting SM and PI using the Fisher's exact test. All statistical comparisons were two-sided using a significance level of $P=0.05$. Statistical analysis was completed using SAS, version 9.4 (The SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Comparison of baseline characteristic between CMSM and PI are summarized in Table 1. Between January 2006 and June 2014, a total of 903 patients meeting inclusion criteria were evaluated, of which 681 (75.4%) presented as CMSM and 222 (24.6%) as PI. Patients with CMSM were younger at the time of diagnosis compared with PI (41.7 vs 53.7 years; $P<0.0001$ and had a higher female preponderance (64.9 vs 54.5%; $P=0.006$). Although both CMSM and PI often present as macroadenomas, a greater proportion of PI presented as macroadenomas (70.7%) compared with CMSM (49.9%; $P<0.001$).

Indications for imaging and diagnostic categories

These data are summarized in Table 1. The most common indications for imaging in the CMSM cohort were symptoms of secondary hormonal deficiency (SHD)/stalk compression (29.7%) and hormonal oversecretion (25%); and PIs were non-specific neurological symptoms (34.2%) and headaches (23%). PA constituted the most common type of SM observed in both groups. PRLomas were the most common SMs in the CMSM cohort, and NFAs were the most common in the PI cohort.

Baseline secondary hormonal deficiencies and visual field abnormalities

As described in Table 1, a significant proportion of both CMSM and PI had evidence of SHD at baseline. Among patients with CMSM, 41.3% had evidence of SHD in at least one axis, whereas 31.1% of PI had SHD

Table 1 Baseline characteristics of CMSM and PI.

	CMSM (*n* = 681)	PI (*n* = 222)	*P* value
Age at diagnosis – mean (s.D.)	41.7 (16.9)	53.7 (16.9)	<0.0001
Gender			
Female	442 (64.9%)	121 (54.5%)	0.006
Male	239 (35.1%)	101 (45.5%)	
Tumour size			
Micro	244 (35.8%)	59 (26.6%)	<0.0001
Macro	340 (49.9%)	157 (70.7%)	
MRI negative	11 (1.6%)	0 (0%)	
Unknown	86 (12.6%)	6 (2.7%)	
Indication for head imaging			
Symptoms of SHD or stalk compression	202 (29.7%)	0 (0%)	<0.0001
Symptoms of hormonal oversecretion	170 (25%)	0 (0%)	
Visual field abnormalities	99 (14.5%)	0 (0%)	
Non-pit related visual dysfunction*	0 (0%)	5 (2.3%)	
Headache	60 (8.8%)	51 (23%)	
Symptoms of apoplexy	31 (4.6%)	0 (0%)	
Neurological symptoms**	7 (1.0%)	76 (34.2%)	
Other***	20 (2.9%)	75 (33.8%)	
Unknown	92 (13.5%)	15 (6.8%)	
Diagnosis			
Non-functioning adenoma	242 (35.5%)	111 (50%)	<0.0001
ACTH-secreting adenoma	29 (4.3%)	5 (2.3%)	
Prolactinoma	271 (39.8%)	32 (14.4%)	
GH-secreting adenoma	49 (7.2%)	9 (4%)	
Craniopharyngioma	32 (4.7%)	9 (4%)	
Rathke's cleft cyst	19 (2.8%)	40 (18%)	
Meningioma	14 (2.1%)	5 (2.3%)	
Other****	25 (3.7%)	11 (5.0%)	
Baseline SHD			
No	218 (32.0%)	138 (62.2%)	<0.0001
Yes	281 (41.3%)	69 (31.1%)	
Unknown	182 (26.7%)	15 (6.8%)	
Baseline VF abnormalities	165 (24.2%)	65 (29.3%)	0.16
Microadenoma (<10 mm)	11 (6.7%)	1 (1.5%)	
Macroadenoma (≥10 mm)	145 (87.9%)	62 (95.4%)	
Unknown	9 (5.4%)	2 (3.1%)	

*Including glaucoma, optic neuritis, macular degeneration; **including dizziness, vertigo, gait abnormalities, cognitive concerns, parasthesias, Transient ischemic attack (TIA)/stroke; ***including imaging done for trauma, sinusitis, seizure disorders, syncope, hearing loss, medication-induced endocrinopathies, screening for genetic or multisystem disorders or as part of clinical trial (cancer/MS/etc.) protocol; ****including arachnoid cysts, histiocytosis, hypothalamic lipomas, germinomas, plasmacytomas, epithelial neoplasms, osteolipomas, TSH secreting adenoma, hypophysitis.

ACTH, adrenocorticotrophic-producing adenoma; CMSM, clinical manifestations of mass effect/hormonal dysfunction; GH, growth hormone; PI, pituitary incidentaloma; SHD, secondary hormone deficiency; TSH, thyroid-stimulating hormone.

at presentation. The most common SHD in both CMSM and PI were SHG followed by SHT. Baseline visual field (VF) abnormalities were common as 24.2% of CMSM and 29.3% of PI had evidence of VF abnormalities on formal testing attributable to a SM.

Management strategies

Management strategies are summarized in Table 2. Median follow-up time was 5.7 and 5.0 years for CMSM and PI, respectively. PRLomas were excluded from this analysis as they were almost exclusively managed medically in both groups. Differences were seen in the management strategies between CMSM and PI (*P* < 0.0001). CMSMs were more likely than PI to be treated with surgery alone (62.9 vs 35.8%) or require both surgery and medical therapy (8.3 vs 1.6%). A total of 388 patients (316 CMSMs and 72 PIs) underwent surgery. The indications for surgery differed among the groups (*P* < 0.0001) and are summarized in Table 2. The most common indication for surgery in both CMSM and PI was impaired vision/radiological evidence of optic nerve compression (32.6 and 29.2%, respectively). In CMSMs, presence of FA was the second most common reason for surgery (23.7%), whereas among PIs, increase in size on follow-up constituted the second most common indication for surgery (20.8%).

Table 2 Management strategies of CMSM vs PI.

	CMSM*	PI*	*P* value
Management*	(*n* = 410)	(*n* = 190)	
Medication only	8 (1.9%)	4 (2.1%)	<0.0001
Surgery only	258 (62.9%)	68 (35.8%)	
Medication and surgery	34 (8.3%)	3 (1.6%)	
Followed without surgery	110 (26.8%)	115 (60.5%)	
Indications for surgery	(*n* = 316)	(*n* = 72)	
Impaired vision/ compressive symptoms	103 (32.6%)	21 (29.2%)	<0.0001
Growth of the tumour in follow-up	16 (5.1%)	15 (20.8%)	
Functioning adenoma	75 (23.7%)	11 (15.3%)	
Contact with optic chiasm	16 (5.1%)	10 (13.9%)	
Diagnostic resection	2 (0.6%)	4 (5.6%)	
Patient preference	1 (0.3%)	0 (0%)	
Not recorded	76 (24.1%)	11 (15.3%)	
Apoplexy	27 (8.5%)	0 (0%)	

*Excluding PRLomas.

Follow-up and outcomes of NFA and non-pituitary SM

Tumour size on follow-up – surgical vs non-surgical cohorts

These data are summarized in Fig. 1. In patients who underwent immediate surgery (within 90 days of initial presentation), post-surgery images were used as the baseline measure to assess subsequent recurrence of tumours. Of the CMSM cohort, follow-up tumour size data were available in 142 patients, of which 64 (45.1%) underwent surgical resection and 78 (54.9%) were managed without surgery. Within the PI group, tumour size follow-up data were available in 132 patients, of which, 30 (22.7%) underwent surgery and 102 (77.3%) were followed without surgery. Due to the overall low risk of tumour enlargement, factors associated with tumour enlargement could not be calculated. The mean and median time to increase in tumour size was pooled for all groups due to the small number of overall events, and was 4 years for CMSM and 3.37 years for PI during the follow-up period.

SHD in follow-up – surgical vs non-surgical cohorts

SHD follow-up was performed on NFA and non-pituitary lesions only, whereas FAs were excluded from the current analysis and will be reported elsewhere. Baseline and consistent follow-up data on SHD were available in 205 CMSM patients (124 who underwent surgery and 81 who were managed non-surgically). Among PIs, similar data on SHD were available for 142 patients (46 who underwent surgery and 96 who were managed non-surgically). In patients who underwent immediate surgery, hormonal function at 3-month post-surgery visit was regarded as the baseline (time '0') measurement. Overall, there were no significant differences in the risk of SHD in CMSM vs PI in those who underwent surgery and those who were followed without surgery (Fig. 2A and B); however, pooled data of CMSM and PI did demonstrate a statistically significant difference in the risk of developing new/worsening SHD in patients who underwent surgery (Fig. 2C). When further subdivided into those with or without pre-existing SHD, there was no significant difference between groups (Fig. 3A, B, C and D). Several factors were associated with
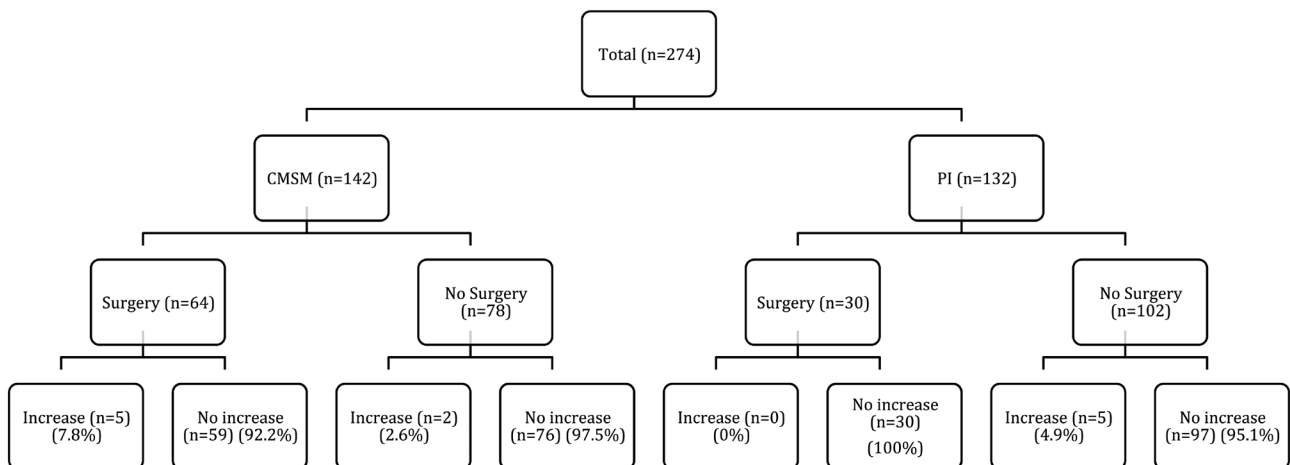

Figure 1

Increase in tumour size (>2 mm) in follow-up. Flow chart showing changes in tumour size in non-functioning pituitary adenomas and non-pituitary sellar masses.
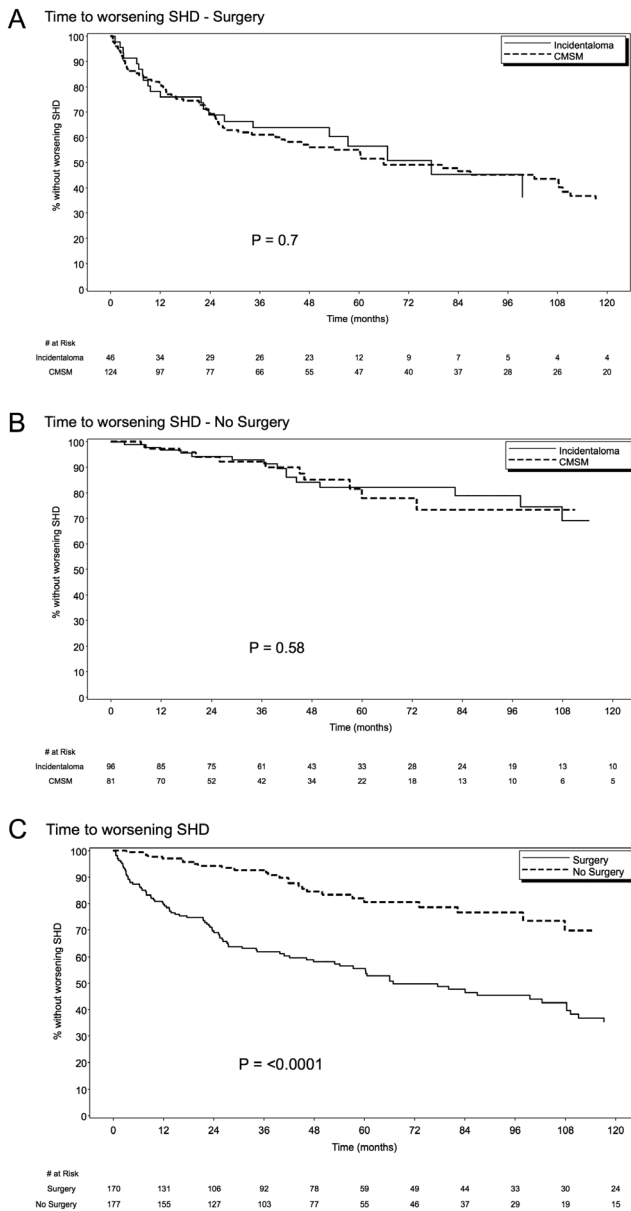
Figure 2
Kaplan–Meier analysis demonstrating risk of new or worsening SHD in follow-up among CMSM and PI in (A) surgically treated patients, (B) non-surgically treated patients and (C) pooled CMSM and PI in surgical and non-surgically treated patients. Among patients undergoing immediate surgery, SHD obtained 3 months post-operatively were used as the new baseline ('time 0'). CMSM, clinical manifestations of mass effect/hormonal dysfunction; PI, pituitary incidentaloma; SHD, secondary hormone deficiency.

Discussion

Given the high prevalence of SM, characterizing the comparative epidemiologic trends and treatment responses of CMSM and PI is important to enable patients and their healthcare team to make informed decisions. Previous studies have primarily focused on either PI or CMSM and most studies did not include non-pituitary lesions in their analyses. To our knowledge, this is the first population-based study comparing the presentation and long-term follow-up of both CMSM and PI.

There were significant differences in the baseline characteristics of the two entities: CMSM patients presented almost a decade (mean age=41.7 years) before PI (mean age=53.7 years). This is similar to the previously reported age range of 47–61 years in PI patients (14, 15, 16). A slight female preponderance was observed in both groups, similar to findings in other studies of PI (14, 15, 16, 20) and NFA (17, 18, 19, 20); however, we were unable to determine a valid physiological explanation for this trend.

SM presenting primarily as macroadenomas is well known (15, 21, 22). However, in our study, we found that tumour size varied between groups with 71% of PI presenting as macroadenomas compared with 50% of CMSM. These findings are in contrast with autopsy studies where microadenomas are more common (4). This difference may be due to the initial imaging modality, particularly in the case of PI being CT scan of the head or non-sella MRI (e.g. MRI brain), where smaller pituitary lesions would be missed. Additionally, small lesions may have been historically under-reported, as demonstrated by more recent studies that have reported slightly higher proportions of microadenomas (23) with increased awareness of the clinical importance of these entities. Selection bias, with referral of nearly all macroadenomas to tertiary referral centres, may also contribute to these findings.

PAs made up the majority in both the CMSM and PI cohorts. In our study, 71.1% of PIs were PAs, which is lower than the reported rates in surgical cohorts of up to 90% (24). The most common lesion type among PI was NFA, followed by RCC, which is consistent with other series (15, 16, 22). The incidence of PA in CMSM was 86.8%, with the vast majority of these being PRLomas or NFAs. It is perhaps intuitive that more patients with PRLomas present as CMSM as these lesions are more likely to present with overt reproductive symptoms than NFA and RCC, which are typically clinically silent until they develop mass effect.

The most common indications for head imaging among the CMSM cohort were features of SHD, stalk
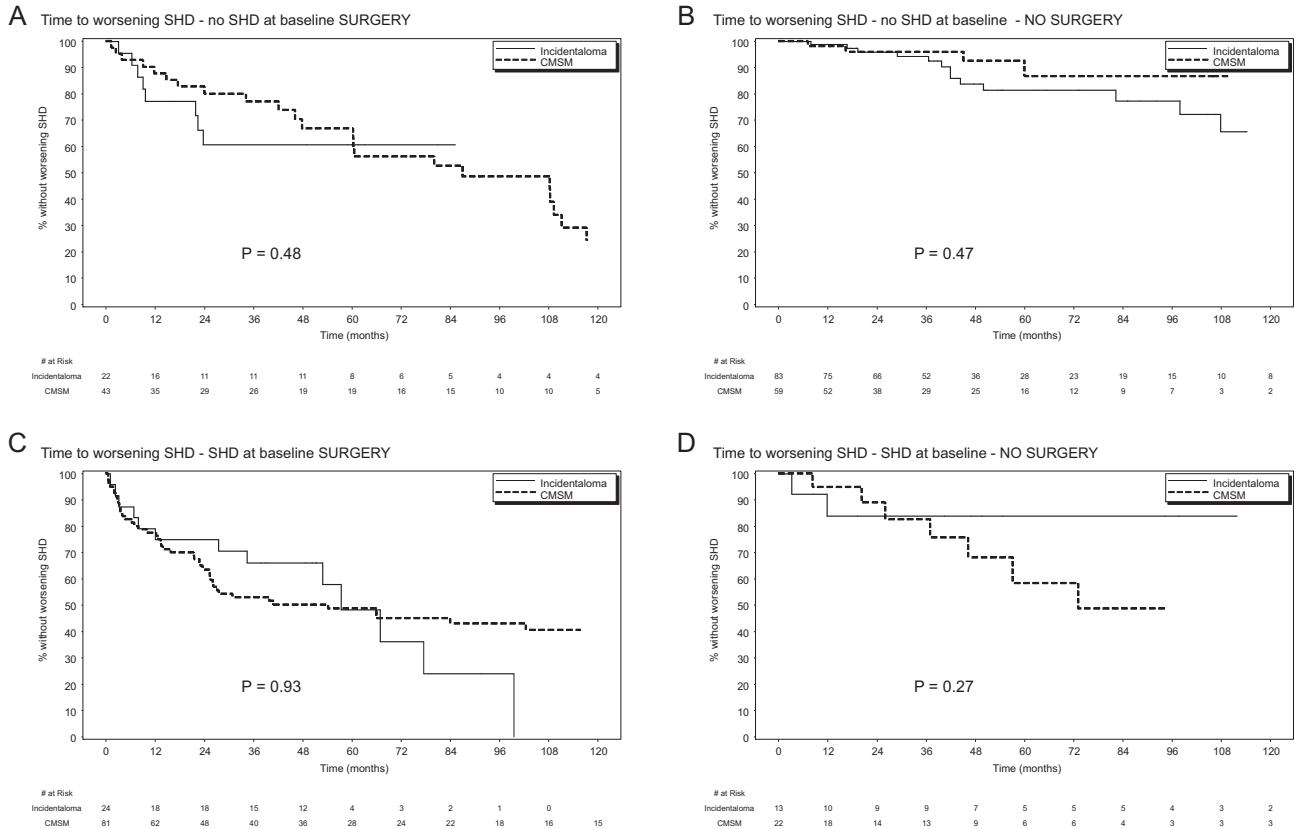
an increased risk of developing new or worsening SHD among pooled CMSM and PI cohorts, including male gender (*P*=0.006), presence of macroadenoma (*P*=0.002), presence of baseline SHD (*P*<0.001) and VF deficits at presentation (*P*<0.001). New-onset or worsening SHD occurred up to 120 months later in both surgery and non-surgery cohorts.

Figure 3

Kaplan–Meier analysis demonstrating risk of SHD in CMSM vs PI in (A) surgical cohort with no pre-existing SHD at baseline; (B) non-surgical cohort with no pre-existing SHD at baseline; (C) surgical cohort with baseline SHD and (D) non-surgical cohort with baseline SHD. CMSM, clinical manifestations of mass effect/hormonal dysfunction; PI, pituitary incidentaloma; SHD, secondary hormone deficiency.

compression and hormonal oversecretion; in contrast, indications for head imaging among PI patients were almost exclusively neurological complaints, including headache, ataxia, dizziness, weakness, parasthesias and cognitive concerns. The association between headaches and SM remains controversial. Headaches are reported to be the most common reason for brain CT in the outpatient setting (25). A multifactorial association between chronic headache and pituitary tumours has been suggested (26), and resolution of headaches has been reported in some post-surgical patients (27), although it remains unclear if this is due to tumour removal or the natural history of headaches and effects of anaesthesia. Further studies are needed to clarify this issue, and if there is truly an association between SM and headaches, then the definition of PI, which also included SM discovered during investigations of headaches, may have to be reconsidered.

The risk of baseline SHD in both CMSM and PI is significant, highlighting the importance of a full hormonal evaluation in all patients presenting with SM. Literature regarding baseline SHD is quite variable.

Previously, a large Japanese study reported no SHD in 506 PI patients (16); however, another study from Greece reported baseline SHD in 61% patients (21). The overall risk of SHD was higher in men, those with larger tumours and those with pre-existing SHD and VF defects. To our knowledge, this is the first study to systematically analyse follow-up risk of SHD and directly compare surgical and non-surgical cohorts. In a small study of 28 conservatively followed patients with macroadenomas, worsening SHD on follow-up was associated with increase in tumour size (17). Similarly, surgery has been shown to increase the risk of hormonal deficiency in NFA (28). In addition, a high proportion of VF abnormalities at presentation is also concerning (24.2% for CMSM and 29.3% in PI) as this indicates many patients with PI are unaware of their VF defects. Whether more widespread utility of VF testing would result in an earlier diagnosis of PI remains a tantalizing research question.

A significant proportion of patients in both groups required either surgery and/or medical intervention. That a large number of CMSM patients required surgical

intervention is not surprising as many patients presented with established indications for surgical resection (i.e. diagnosis of GH or ACTH-secreting adenoma, visual field deficits, apoplexy). However, a significant proportion (36%) of PI also underwent surgery – many for vision changes and tumour growth. Additionally, around 15% of PIs required surgery for hormonal oversecretion thus raising the question of why these patients did not present with clinical manifestations despite the fact that most of these were macroadenomas. It is conceivable that that these tumours are inherently different from those presenting with clinical manifestations and perhaps have a more subclinical course.

Literature on long-term follow-up of tumour size and risk of SHD among surgical and non-surgical cohorts is limited and made up of heterogeneous studies. We limited our analysis in this paper to NFA and non-pituitary SM. FAs were excluded from the analysis as the majority were PRLomas, which were almost exclusively managed with medical therapy to shrink tumour size with associated resolution of SHG. We aim to conduct future studies specifically examining FA. Our study is the first to report the longitudinal trends of SHD in these patients and our data show that the risk of new-onset SHD was similar in both CMSM and PI patients whether or not they had baseline SHD, underwent surgery or were followed without surgery. These data highlight the need for ongoing hormonal assessment in these patients, even those who present incidentally. When CMSM and PI cohorts were pooled together, there was an increased risk of new or worsening SHD among patients who underwent surgery. The overall risk of increase in tumour size in follow-up was low among both CMSM and PI and an even smaller number were clinically relevant in terms of requiring surgical intervention. Due to the small number of overall events, we were unable to identify any specific risk factor for tumour growth. This is an important area for future research, to risk-stratify patients for individualized long-term monitoring strategies. To date, long-term data on the risk of increasing tumour size are quite variable. Small studies of conservatively managed NFAs demonstrated a risk of increasing tumour size to be 12–35% (15, 18, 28, 29). However, surgical expertise varies among different centres, and it has been suggested that risk of recurrence is related to the size of the tumour remnant after initial surgery, with a regrowth rate of 6.9% with complete tumour resection and up to 40% with incomplete resection (28, 30). In our study, the overall risk of increase in tumour size was relatively small within the follow-up period, and our data suggest that rigorous follow-up and frequent imaging may not be required in medium

term. While our data do not allow us to suggest the ideal frequency of follow-up imaging and hormonal testing, we follow a standardized protocol for follow-up assessment. In our centre, patients requiring surgery are assessed at 3 (in the case of those requiring immediate surgery) to 6 months (in the case of those not requiring immediate surgery), every 12 months thereafter for 5 years and then every 12–24 months thereafter based on the physicians' discretion. All non-surgical patients are initially assessed after 6 months and then as surgery patients.

Our study has some limitations. Part of the data (particularly patients diagnosed prior to the initiation of the registry) were collected retrospectively and information on baseline pituitary function, tumour size and radiological characteristics of some patients was not available. Furthermore, diagnostic categorization in non-surgical patients was based on well-established radiological features rather than tissue diagnosis. Finally, surgical outcomes may also vary depending on local neurosurgical expertise, and the results of our study may not be universally applicable. Our study also has several strengths. This is the first study to directly compare the baseline presenting features, management strategies and long-term follow-up trends of CMSM and PI in a large cohort. Additionally, patients were followed in a standardized fashion by the same team.

In summary, this study is the first to directly compare the natural history of certain subtypes of PI with CMSM over a 5-year period. Our results demonstrate the importance of comprehensive radiological and hormonal evaluation, initially and over time. We plan to report the data on FA separately. Longer-term studies are necessary to evaluate how these entities behave over a prolonged period of time.

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