ISSN 2472-1972

Presenting Features in 269 Patients With Clinically Nonfunctioning Pituitary Adenomas Enrolled in a Prospective Study

Pamela U. Freda,[1] Jeffrey N. Bruce,[2] Alexander G. Khandji,[3] Zhezhen Jin,[4] Richard A. Hickman,[5] Emily Frey,[1] Carlos Reyes-Vidal,[1] Marc Otten,[2] Sharon L. Wardlaw,[1] and Kalmon D Post[6]

[1]Departments of Medicine, Columbia University, Vagelos College of Physicians and Surgeons, New York, 10032 New York, [2]Departments of Neurosurgery, Columbia University, Vagelos College of Physicians and Surgeons, New York, 10032 New York, [3]Departments of Radiology, Columbia University, Vagelos College of Physicians and Surgeons, New York, 10032 New York, [4]Departments of Biostatistics, Mailman School of Public Health, Columbia University, New York, 10032 New York, [5]Departments of Pathology and Cell Biology, Columbia University, Vagelos College of Physicians and Surgeons, New York, 10032 New York, [6]Departments of Neurosurgery, Mount Sinai School of Medicine, New York, 10021 New York

ORCiD numbers: 0000-0002-1818-0762 (P. U. Freda); 0000-0002-6844-0286 (J. N. Bruce); 0000-0002-8329-6083 (R. A. Hickman); 0000-0003-1587-9479 (K. D. Post).

Context: Clinically nonfunctioning pituitary adenomas (CNFPAs) typically remain undetected until mass effect symptoms develop. However, currently, head imaging is performed commonly for many other indications, which may increase incidental discovery of CNFPAs. Since current presentation and outcome data are based on older, retrospective series, a prospective characterization of a contemporary CNFPA cohort was needed.

Objective: To determine the prevalence of incidental presentation and hypopituitarism and its predictors in a CNFPA cohort that spanned 6 to 9 mm micro- to macroadenoma included observational and surgical therapy.

Methods: At enrollment in a prospective, observational study, 269 patients with CNFPAs were studied by history, examination, blood sampling, and pituitary imaging analysis and categorized into incidental or symptoms presentation groups that were compared.

Results: Presentation was incidental in 48.7% of patients and due to tumor symptoms in 51.3%. In the symptoms and incidental groups, 58.7% and 27.4% of patients had hypopituitarism, respectively, and 25% of patients with microadenomas had hypopituitarism. Many had unappreciated signs and symptoms of pituitary disease. Most tumors were macroadenomas (87%) and were larger in the symptoms than incidental and hypopituitary groups than in the eupituitary groups. The patients in the incidental group were older, and males were older and had larger tumors in both the incidental and symptoms groups.

Conclusions: Patients with CNFPAs commonly present incidentally and with previously unrecognized hypopituitarism and symptoms that could have prompted earlier diagnosis. Our data support screening all large micro and macro-CNFPAs for hypopituitarism. Most patients with CNFPAs still have mass effect signs at presentation, suggesting the need for more awareness of pituitary disease. Our ongoing, prospective observation of this cohort will assess outcomes of these CNFPA groups.

Abbreviations: AI, adrenal insufficiency; CFNPA, clinically nonfunctioning pituitary adenoma; GH, growth hormone; GHD, GH deficiency; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; PI, pituitary incidentaloma; VF, visual field.

Received 3 January 2020
Accepted 14 February 2020
First Published Online 18 February 2020
Corrected and Typeset 27 March 2020

Key Words: pituitary tumor, incidentaloma, hypopituitarism

Clinically nonfunctioning pituitary adenoma (CNFPA) is the presumptive diagnosis in a patient presenting with a sellar mass consistent with a pituitary adenoma on imaging and no clinical or laboratory evidence of hormone excess. Traditionally, patients with CNFPAs remained undiagnosed until they present due to symptoms of tumor mass effect. As a result, nearly all CNFPA studies are surgical series [1], and the few that are not are limited to patients not requiring surgery [2–4]. In addition, guidelines addressing the evaluation of CNFPAs are based on retrospective series [5, 6]. Therefore, a prospective characterization of a modern CNFPA cohort encompassing the full spectrum of clinically relevant tumors was lacking. Whether delayed detection of CNFPAs remains the norm was also unknown.

Less commonly, CNFPAs are reported to come to medical attention incidentally. Given the widespread use of MR imaging, incidental detection of pituitary lesions on head imaging done for unrelated indications is likely to increase. Accordingly, the Endocrine Society proposed guidelines for the evaluation of pituitary incidentalomas (PIs) [7]. Although most PIs are pituitary adenomas, these guidelines address the broadly defined PI that includes all types of sellar masses, so their applicability to the incidental CNFPA specifically has not been tested. The true prevalence of incidentally presenting CNFPAs and to what extent they harbor unrecognized, clinically significant endocrine or other abnormalities is unknown. Investigation of these questions is warranted to inform recommendations for CNFPA evaluation.

Therefore, we began a prospective, observational study of patients presenting with apparent CNFPAs that aims to characterize a large cohort at presentation and in follow-up, the natural history of these tumors followed conservatively without surgery, and the outcomes of those treated with surgery or radiotherapy. We modeled aspects of our assessment after the Endocrine Society PI guidelines, in particular with regard to screening for hypopituitarism. In this report, we analyze the presenting features of our study cohort of 269 patients with CNFPAs in order to define the prevalence of incidental presentation, the prevalence and predictors of hypopituitarism, especially among those presenting incidentally, and to profile a contemporary cohort illustrative of the full spectrum of clinically relevant CNFPAs.

1. Methods

A. Study Participants

We prospectively recruited consecutive patients aged ≥ 18 years presenting to our centers with an apparent CNFPA, defined as a pituitary lesion most consistent with a pituitary adenoma on imaging in a patient with no clinical or available biochemical evidence of a hormone-secreting tumor. Radiographic features considered consistent with a pituitary adenoma included a lesion in the sella turcica with or without enlargement of the bony sella. The lesion may have extended into the suprasellar or parasellar cavernous sinus region or inferiorly through the floor of the sella into the sphenoid sinus. The lesion appeared iso or hypointense relative to brain parenchyma on T1-weighted spin echo images and typically hypointense on postcontrast T1-weighted images relative to the enhancing pituitary gland. We included cystic lesions that were relatively bright and fluid-like in signal intensity on T2-weighted spin echo images and, therefore, most consistent with a cystic adenoma. Inclusion criteria included a pituitary lesion maximal diameter ≥ 6 mm.

Initial screening for a hormone-secreting tumor was based on a general physical examination and review of endocrine data obtained by the referring physician that was available at the patient's presentation. Inclusion criteria included normal prolactin level for lesions 6 to 9 mm or a prolactin level < 100 ng/ml for lesions ≥ 10 mm in maximal tumor diameter.

We screened 554 patients meeting our inclusion criteria. From the screening, 306 were enrolled and 248 declined participation, typically due to insufficient time and/or traveling

distance to participate in study visits. The screened but not enrolled patients were similar to those enrolled in gender distribution, median and range of ages, presentation reason, and proportion of macro- and microadenomas. Of the 306 enrolled, 6 were excluded from further study after the baseline visit testing showed evidence of hormone excess: 3 had elevated 24-hour urinary free cortisol levels, 2 had an elevated insulin-like growth factor 1 (IGF-1) level, and 1 had a prolactin level > 100 ng/ml. Also excluded from the current analysis were 31 patients with CNFPAs who had prior pituitary surgery that pathologically confirmed a nonsecreting pituitary tumor and who entered the surgery/radiotherapy arms of our study (Study Design below).

Of enrolled participants, 84.3% were recruited from patients presenting to our study neurosurgeons, 14.7% were referred by endocrinologists, and 1.5% came to the study by ClinicalTrials.gov referral. The study was approved by the Institutional Review Board of Columbia University Medical Center. All participants gave written informed consent before participation.

B. Study Design

Participants participated in a baseline study visit at which we obtained a comprehensive history and structured review of systems, including questioning about signs or symptoms potentially due to tumor mass effect or hypopituitarism. We collected details of the events that led to each participants' pituitary tumor coming to medical attention, and their presentations were categorized as incidental, defined as discovery of a pituitary lesion on imaging done for a reason other than suspected pituitary disease, or due to symptoms related to the tumor. A physical examination including confrontation visual field (VF) was performed. The results of formal VF testing were collected and reviewed.

Participants underwent morning peripheral blood sampling for measurement of prolactin, cortisol, free thyroxine, thyroid-stimulating hormone, growth hormone (GH), IGF-1, luteinizing hormone, follicle-stimulating hormone, and testosterone in men. Samples were centrifuged and stored in multiple aliquots at –80°C until assay. Hormones were measured by chemiluminescent immunometric assay from IMMULITE (Siemens) and compared with the manufacturers' established reference intervals [8]. Results were used to re-screen participants for hormone hypersecretion, confirm inclusion criteria, and evaluate, in conjunction with review of existing endocrine data, for hypopituitarism. For participants on replacement therapy at the baseline visit, pretherapy data were used to confirm deficiencies. Prolactin levels were categorized as normal or elevated (males: >17 ng/mL; females: >25 ng/mL). Participants with examination features within the spectrum seen in Cushing syndrome (n = 42) were screened by 24-hour urine free cortisol [7]. Criteria for hypopituitarism included secondary adrenal insufficiency (AI): morning cortisol level ≤ 5 μg/dL and clinical response to glucocorticoid replacement (81% of AI cases) or morning cortisol level < 8 μg/dL and peak cortisol after cortrosyn stimulation <19 μg/dL (19% of AI cases); secondary hypothyroidism with free thyroxine < 0.89 ng/dL with a normal or low thyroid-stimulating hormone (normal range 0.40- 4 μIU/mL) and no history of primary hypothyroidism; secondary hypogonadism with male testosterone level <286 ng/dL for patients aged 20 to 49 years and < 212 ng/dL for patients aged > 50 years with normal or low luteinizing hormone/follicle-stimulating hormone; premenopausal females with amenorrhea with normal or low gonadotropins; and postmenopausal females with gonadotropins below menopausal range. IGF-1 levels were characterized as normal or low, that is, below the lower limit of normal for age. Patients were categorized as being hypopituitary if they had a deficiency of 1 or more pituitary axis.

Pituitary MRIs were reviewed initially by a study neurosurgeon and endocrinologist and confirmed by the neuroradiologist to meet imaging entry criteria. Images were also uploaded encoded into an image analysis software (Osirix MD, v. 11.0, Bernex, Switzerland) for later neuroradiological review. The suspected pituitary adenomas were best visualized on the T1-weighted coronal and sagittal postcontrast images. Lesion size in the anterior/posterior, cranial/caudal, and left to right dimensions were measured directly from the T1-weighted

postcontrast images. T2-weighted coronal views were also used to determine the relationship of the lesion to the optic chiasm and assess for its compression.

Following the baseline visit, participants entered into a no-surgery, surgery, or radiotherapy arm (as outlined below) based on the treatment plan decided upon by the patient and the treating physician. Study enrollment did not determine a treatment plan, but the rationale for this decision in each participant was recorded. An observational follow-up was then initiated according to PI guidelines [7] and is ongoing.

C. Statistical Analysis

Continuous variables were compared by unpaired *t* test, and the Fisher exact test was used to compare group proportions. Logistic regression models were used to examine the relationship between the outcome of hypopituitarism and potential predictors, which included a set of 7 symptoms of hypopituitarism that were considered representative of a spectrum of pituitary axes deficiencies. Multivariable logistic regression models were built with symptoms that were significant at the 0.1 level in univariable logistic regression models. Participant ages and pituitary tumor sizes were recorded as mean ± standard deviation (SD; range). *P* values < 0.05 were significant. Data were analyzed with GraphPad Prism 8.0 (La Jolla, CA).

2. Results

A. Presentations

The study cohort consisted of 269 patients presenting with a CNFPA. None had prior pituitary surgery or radiotherapy. The cohort was 50.6% male and 49.4% female (Fig. 1), with males older than females (Fig. 1A). Causes of tumor presentation are listed in Table 1. Participants were categorized based on why their pituitary tumor came to medical attention into a group of 131 (48.7%) patients whose tumor was detected incidentally (incidental group) and 138 (51.3%) whose tumor was diagnosed because of tumor-related symptoms (symptoms group). A wide spectrum of complaints led to incidental presentation. Tumor-related symptoms that led to diagnosis were those related to mass effect (vision disturbance, headache, neurologic symptoms, n = 78) and signs or symptoms of pituitary dysfunction (n = 60)(Table 1). Headache was included as a symptom related to the tumor unless it was clearly transient or due to another, identifiable cause. The incidental group was older than

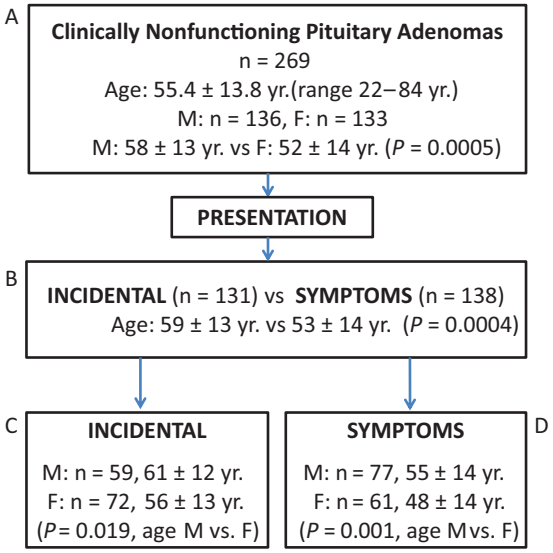

Figure 1. Flow diagram of the participant ages and genders in the cohort overall (**A**), in the incidental group compared with the symptoms group (**B**), and within these 2 groups (**C** and **D**). M, male; F, female; yr., years.

Table 1. Primary Reasons for Presentation in Incidental and Symptoms Presentation Groups of the Cohort

INCIDENTAL (n = 131)		SYMPTOMS (n = 138)
Head/Neck Complaint (n)	**Neurologic (n)**	**Mass Effect (n = 73)**
Head injury (17)	Syncope (4)	**Vision-related (n)**
Sinus disease (7)	Gait abnormality (2)	Vision disturbance (30) and headache (4)
Tinnitus (5)	Bell palsy (2)	Cranial neuropathy (4)
Neck pain or swelling (5)	Hand/arm numbness/tingling (3)	**Headache (n)**
C-spine disease (4)	Dystonia (1)	Headache (28) and cranial neuropathy (5)
Head pain, transient (5)	Seizure disorder (1)	**Neurologic (n)**
Hearing loss (3)	Guillain Barré evaluation (1)	Seizure (2)
Otitis (2)	Parasellar aneurysm (1)	Syncope (2)
Dental x-rays (1)	Parkinson disease (1)	Apoplexy symptoms (2)
Skull lesion (1)	Subdural hematoma (1)	**Pituitary dysfunction (61)**
Throat infection (1)	Hydrocephalus (1)	Panhypopituitarism symptoms (15)
Deviated septum (1)	Acoustic neuroma (1)	Hypogonadism symptoms (17) (not menstrual)
Jaw pain (1)	Leg numbness (1)	Adrenal insufficiency symptoms (2)
Nosebleed (1)	**Other (n)**	Hyponatremia, symptomatic (4)
Palate lesion (1)	Health screening (4)	Galactorrhea (9)
Eye complaint (n)	Elective MRI (4)	Menstrual irregularity (5) and galactorrhea (4)
Primary eye disorder (8)	MRI study volunteer (3)	Secondary amenorrhea (3) and galactorrhea (1)
Orbital pseudotumor (1)	Cushing's phenotype evaluation (2)	
Neurologic (n)	2^{o} adrenal insufficiency/steroid use (1)	
Vertigo (10)	Fatigue (1)	Secondary hypothyroidism evaluation (1)
Dizziness (6)	Groin pain (1)	
Memory complaint (6)	PET scan for breast cancer evaluation (1)	
CVA (5) or TIA (3)	Lyme disease symptoms (1)	

n = number of participants.
CVA, cerebrovascular accident; MRI, magnetic resonance imaging; PET, positron emission tomography; TIA, transient ischemic attack.

the symptoms group (Fig. 1B). Males were older than females in both groups (Fig. 1C, D). There was a trend for predominance of males in the symptoms group compared with the incidental group (57% vs 46.7%; $P = 0.09$). Of the symptoms group, participants presenting due to symptoms of mass effect did not differ in age or gender distribution from those presenting due to symptoms of pituitary dysfunction.

B. Hypopituitarism

As expected, hypopituitarism was more common at tumor presentation in the symptoms group than in the incidental group (58.7% vs 27.4%; $P < 0.0001$)(Table 2). Overall, hypopituitarism was more common in males; 64.7% of males had hypopituitarism compared with 21.8% of females ($P < 0.0001$). Secondary hypogonadism was the most common deficiency in both the incidental and symptoms group and among males and females. Secondary hypogonadism was isolated in 33.3%, occurred with 1 other deficiency in 10%, and with 2 to 3 other deficiencies in 56.6% of patients. Secondary hypothyroidism was isolated in 2% of patients, occurred with 1 other deficiency in 34%, and occurred with 2 to 3 other deficiencies in 64%. Secondary adrenal insufficiency was isolated in 2.6% of participants, occurred with 1 other deficiency in 13%, and occurred with 2 to 3 other deficiencies in 87%. Low IGF-1 was isolated in 8%, occurred with 1 or 2 other deficiencies in 29%, and occurred with 3 other deficiencies in 34% of patients.

Table 2. Number (%) of Patients in Incidental and Symptoms Presentation Groups With Hypopituitarism or Hyperprolactinemia

	INCIDENTAL GROUP (N = 131)	SYMPTOMS GROUP (N = 138)	*P* Value[a]
HYPOPITUITARY	27 M/9 F (27.4%)	61 M/20 F (58.7%)	<0.0001
Secondary hypogonadism	30(22.9%)	72(52%)	<0.0001
Secondary hypothyroidism	13(9.9%)	42(30%)	<0.0001
Secondary adrenal insufficiency	9(6.9%)	33(24%)	0.0002
Low IGF1 level	13(9.9%)	25(18%)	0.06
Symptoms of hypopituitarism[b]	23(64%[c])	55(68%[c])	*P* = 0.67
EUPITUITARY	32 M/63 F (72.5%)	16 M/41 F (41%)	
Symptoms of hypopituitarism[b]	35(37%[d])	22(38.5%[d])	*P* = 0.73
HYPERPROLACTINEMIA	20(15.3%)	37(26%)	0.026

[a]*P* value for comparison of proportions in incidental and symptoms groups.
[b]Symptoms of hypopituitarism: sexual dysfunction/reduced libido, unintentional weight loss, weakness, low blood pressure, body hair loss, cold intolerance, menstrual abnormalities (irregular menses or amenorrhea).
[c]Percent of hypopituitary participants in incidental or symptoms groups.
[d]Percent of eupituitary participants in the incidental or symptoms groups.
F, female; M, male.

Patients were categorized by presence or absence of one or more of a set of symptoms of hypopituitarism (sexual dysfunction/reduced libido, weakness, unintentional weight loss, low blood pressure, cold intolerance, body hair loss, and menstrual abnormalities [irregular menses or amenorrhea]) within the hypopituitary and eupituitary groups and the concordance been hypopituitarism and its symptoms was assessed (Table 2). As expected, the proportion of patients with symptoms of hypopituitarism was higher in the symptoms group (55.8%) than in the incidental (36.6%) ($P = 0.0022$) group overall, but within the hypopituitary and eupituitary groups these did not differ (Table 2). The results of multivariable logistic regression analysis (Table 3) showed that the risk of hypopituitarism was significantly increased in patients with a history of sexual dysfunction/reduced libido compared with those without this symptom. The negative predictive value of lack of symptoms was high, 92%, in the incidental group, but only moderate, 71%, in the symptoms group. In the full cohort model, receiver operating characteristic area under the curve was 0.67, which was not high enough to provide assurance that the presence or lack of these symptoms can guide the need to test or not test for hypopituitarism, respectively.

Hyperprolactinemia was more common in the symptoms group than in the incidental group (Table 2). Hyperprolactinemia was accompanied by symptoms (galactorrhea, hypogonadism symptoms, or menstrual abnormalities) in 40% of the incidental group and 65% of the symptoms group ($P = 0.1$). Prolactin measurement at the baseline visit found asymptomatic hyperprolactinemia in 9.2% of patients of the cohort overall. Posterior pituitary dysfunction was rare. No patients presented with diabetes insipidus, and syndrome of inappropriate antidiuretic hormone secretion was present in 1 patient in the symptoms group (0.72%) who also had adrenal insufficiency, hypogonadism, and low IGF-1 level. None was present in the incidental group.

C. Signs and Symptoms of Pituitary Disease

The prevalence of a broader group of signs and symptoms in the incidental and symptoms groups, including some of hypopituitarism and others of the tumor mass, are shown in Table 4. Although the incidental group came to medical attention for a reason unrelated to the tumor, many of these patients, when questioned, gave the history of a symptom that could have prompted recognition of the tumor. For example, in the incidental group, 55% of

Table 3. Logistic Regression Models for Predicting Hypopituitarism Based on Symptoms of Hypopituitarism

	Symptoms	Odds Ratio (95% CI); *P* Value	ROC AUC (95% CI); *P* Value	Sensitivity	Specificity	PPV	NPV
Incidental group model	Sexual dysfunction/ reduced libido	8.373 (3.022 to 25.89); <0.0001	0.6855 (0.5769 to 0.7941); 0.0008	78.2%	71.4%	38.5%	93.5%
	Weakness	2.151 (0.6428, 6.972); 0.2016					
Symptoms group model	Sexual dysfunction/ reduced libido	3 (1.334, 7.173); 0.0099	0.6672 (0.5784, 0.7561); 0.0008	52.5%	70.7%	51.9%	71.3%
	Weight loss	2.258 (0.8832, 6.323); 0.1003					
	Amenorrhea	0.523 (0.1969, 1.337); 0.1803					
Combined groups model	Sexual dysfunction/ reduced libido	4.283 (2.371, 7.974); <0.0001	0.6688 (0.6028, 0.7348); <0.0001	66.8%	63.8%	50.8%	77.5%
	Weakness	1.997 (0.9773, 4.160); 0.0597					
	Amenorrhea	0.6774 (0.2745, 1.558); 0.3744					

AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator curve.

participants reported symptoms of tumor mass effect (headache or visual symptoms), and 29.8% had symptoms of pituitary dysfunction (sexual dysfunction/reduced libido, amenorrhea, and/or galactorrhea). Headache constituted a large portion of symptoms in the incidental group, reported in 42.7% of participants. Of the symptoms group, 37% of participants had VF deficits that were accompanied by visual symptoms in all cases. Of the incidental group, 8.4% had VF deficits, but 33% of these participants did not report visual symptoms, suggesting that they underappreciated the visual compromise.

D. Pituitary Tumor Imaging

Pituitary tumor imaging data were compared in the incidental and symptoms groups and separately in the hypopituitary and eupituitary groups (Table 5). The majority of tumors (87%) in our cohort were macroadenomas. Tumors were larger in the symptoms group than in the incidental group, and males had larger tumors than females in both these groups. Hypopituitarism was more common among macroadenomas than microadenomas in the cohort overall (46.5% vs 26.8%; $P = 0.025$) and in the symptoms group (62.7% vs 35%; $P = 0.03$) but not in the incidental group (29% vs 20%; $P = 0.58$). Tumors were larger in the hypopituitary than eupituitary group. In the eupituitary group, males had larger tumors and were more likely to have a macroadenoma than females, but there was no gender difference in tumor size among hypopituitary participants.

E. Treatment Plan and Prospective Study Arms

After the baseline visit, patients entered into 1 of 3 treatment arms of the observational study. The 141 (52.4%) participants who planned surgery for their tumor entered the surgery arm. Reasons for surgery included optic chiasm compression without VF deficit (49.3%) or with visual field deficit (39.7%), both VF deficit and cranial nerve abnormality (3%), cranial nerve abnormality alone (1.9%), hypopituitarism (3.5%), unremitting headache (1.4%), or patient preference (0.7%). The surgery group included 49 macroadenomas that presented incidentally and planned surgery because of tumor impinging on the chiasm (n = 44) (11 had VF deficits, 2 of whom also had a partial third cranial nerve palsy), hypopituitarism (n = 3), unremitting headache (n = 1), or patient preference (n = 1). Participants who did not plan surgery for their tumor, 128 (47.6%), entered the no-surgery, observation-only arm.

Table 4. Prevalence of Signs or Symptoms Potentially Related to Hypopituitarism or Tumor Mass Effect Elicited on History at Study Enrollment in the Incidental and Symptoms Presentation Groups

	Incidental Group (n = 131) (% of Patients)	Symptoms Group (n = 138) (% of Patients)	*P* Value
Symptoms			
Mass effect symptoms			
Headache	42.7	56.5	0.015
Visual symptoms[a]	5.9	37.0	<0.0001
Pituitary dysfunction			
Sex dysfunction/ reduced libido	16.0	26.8	0.038
Cold intolerance	17.0	24.0	0.07
Excess thirst	8.4	18.5	0.02
Generalized weakness	12.9	13.7	ns
Menstrual abnormalities	5.3	12.3	0.054
Unintentional weight loss	8.4	11.6	0.42
Body hair loss	8.0	7.8	ns
Skin changes[b]	9.0	7.4	ns
Galactorrhea	8.2	6.9	0.81
Low blood pressure	0.8	2.2	0.62
No symptoms	35.0	0	<0.0001
Other endocrine disorders			
Hyperlipidemia	54.2	48.6	0.39
Hypertension	41.2	34.8	0.315
Type 2 diabetes mellitus	14.5	9.4	0.26
Osteoporosis	12.2	7.2	0.22
Primary hypothyroidism	12.2	9.4	0.556
Graves disease	3.1	0	0.055
Primary hyperparathyroidism	1.5	0.7	0.61

[a]Visual symptoms considered likely related to the tumor.
[b]Skin changes: dry or thin skin, change in skin color.
ns, not significant.

In the no-surgery arm, 86 presented incidentally, and 42 presented due to tumor-related symptoms. Follow-up of these groups is ongoing and will be the subject of future reports.

3. Discussion

This study, by design, included only patients with radiographic and endocrine characteristics most consistent with a CNFPA [2]. Although many studies have described the clinical features of nonfunctioning pituitary adenomas, nearly all have been retrospective analyses of surgical cohorts [1], in which the majority of patients presented due to symptoms of mass effect and likely represented the most symptomatic CNFPAs [1, 2]. However, other small studies have limited their populations to patients not requiring surgery [2–4]. Guidelines addressing management of CNFPAs, including those presenting incidentally, also have a drawback of being based on retrospective series [5, 6]. Our prospectively studied cohort, however, is illustrative of the broader spectrum of contemporary CNFPAs, and thus our analysis of presentations and clinical features at diagnosis provides robust data that can inform decisions about the evaluation and treatment of these patients.

Table 5. Pituitary Tumor Imaging Results

	Presentation Groups		Pituitary Function Groups	
	Incidental	**Symptoms**	**Hypopituitary**	**Eupituitary**
All Participants				
Macroadenomas # (%)	111 (84.7%)	118 (85.5%)	106 (90.6%)	122 (80.3%)
Microadenomas # (%)	20 (15.3%)	20 (14.8%)	11 (9.4%)	30 (19.7%)
Maximal tumor diameter				
Mean ± SD, mm	16.6 ± 7.6[a]	21.8 ± 11[a]	23.1 ± 9.9[b]	16 ± 8.4[b]
Median (range), mm	16 (6–56)	20 (6–60)	23 (6–48)	15 (6–60)
Males				
Macroadenomas #	56[c]	71[d]	80	47[e]
Microadenomas #	3	6	8	1
Maximal tumor diameter				
Mean ± SD, mm	18.6 ± 7.9[f]	24.1 ± 10.4[g]	23.4 ± 10	18.3 ± 7.6[h]
Median (range), mm	17.7 (6–56)	23 (6–56)	23 (6–48)	17 (9–56)
Females				
Macroadenomas #	55[c]	47[d]	26	75[e]
Microadenomas #	17	14	3	29
Maximal tumor diameter				
Mean ± SD, mm	14.8 ± 7[f]	18.8 ± 10.8[g]	22.14 ± 8.8	15 ± 8.6[h]
Median (range), mm	14.5 (6–47)	15.6 (6–60)	20 (8–40)	14 (6–60)

[a] $P < 0.0001$, tumor size: incidental vs symptomatic.
[b] $P < 0.0001$, tumor size: hypopituitary vs eupituitary.
[c] $P = 0.0033$, proportion macroadenoma vs microadenoma, males vs females, incidental group.
[d] $P = 0.015$, proportion macroadenoma vs microadenoma, males vs females, symptoms group.
[e] $P < 0.0001$, proportion macroadenoma vs microadenoma, males vs females, eupituitary group.
[f] $P = 0.004$, tumor size: males vs females, incidental group.
[g] $P = 0.005$, tumor size: males vs females, symptoms group.
[h] $P = 0.027$, tumor size: males vs females, eupituitary group.

A primary finding of our study is that a large percentage of our cohort, 48.7%, presented incidentally. This prevalence of incidental presentation is much higher than that reported in 3 older nonfunctioning tumor surgical cohorts of 8.7% [9–12], higher than the 26.4% found in a more recent surgical series, and higher still than the 21% to 37% prevalence in 3 small studies of CNFPAs followed conservatively without surgery [2–4]. We considered whether aspects of our study design could have influenced the high prevalence we found. It is not likely due to our definition of incidental presentation since our definition is that used by most other studies [5, 13]. Since we selected for CNFPAs, it is unlikely to be higher due to the inclusion of other types of pituitary lesions, as is typical for PI studies [13–15]. Although the reasons for incidental presentation in our cohort were similar to those in many PI studies, we and others included headache as a tumor symptom unless it was clearly unrelated to the tumor [16, 17] whereas some included headache as a frequent incidental cause [13, 17, 18]. Given the difficulty in identifying the nature of a headache, we took a conservative approach and classified patients undergoing head imaging for a headache in the symptoms group, but this might have decreased, not increased, the prevalence of incidental presentation in our cohort. We considered that most of our cohort was recruited from patients referred to our neurosurgeons for an opinion about the need for pituitary surgery, but this more likely selected for symptomatic patients with larger tumors. Our cohort was not skewed toward smaller tumors less likely to present due to symptoms since we enrolled patients across a wide spectrum of sizes, with 87% being macroadenomas. In addition, at our centers, only a small percentage of pituitary surgery cases are admitted emergently and would have been unavailable for us to recruit. Also, our screened but not enrolled patients were very similar to our study cohort with regard to percentage with incidental presentations. We conducted detailed questioning of our cohort about presentation, which could have resulted in more

being classified as incidental compared with other studies that typically made this determination based on chart review. It seems most likely, therefore, that the high prevalence of incidental presentation in our cohort is an accurate representation of how CNFPAs currently come to medical attention. Today's common use of head imaging for other indications may be responsible for the increased incidental discovery of these tumors.

Another focus of our study was to determine the prevalence of hypopituitarism at tumor presentation in our cohort. As expected, a large percentage of the symptoms group had hypopituitarism, similar to that reported in nonfunctioning tumor surgical cohorts, which consist of symptomatic patients [1]. Clearly, all CNFPAs with mass effect symptoms require a full pituitary function evaluation [7, 19]. We also found that a substantial proportion of the incidental group, 27.4%, had hypopituitarism. This is particularly notable given that it was undiagnosed prior to incidental tumor detection. Our results cannot readily be compared to PI studies, in which rates of hypopituitarism varied from 14.9% to 61% [13, 18, 20, 21] since they included other lesion types and different definitions of hypopituitarism. Our data could have been influenced by the practical clinical approach we took to evaluate for hypopituitarism, following Endocrine Society guidelines [7]. For example, low IGF-1 level has been used as a marker of growth hormone deficiency (GHD) in other CNFPA cohorts, but since our participants with low IGF-1 had a variable number of other hormone deficiencies, GHD cannot be assured [22, 23]. Although it is likely that GH stimulation testing would have diagnosed more GHD, it is our practice to perform GH stimulation testing only on patients for whom it is clinically appropriate to initiate GH therapy. Although studies have demonstrated that GH replacement therapy does not increase the risk of nonfunctioning tumor regrowth/recurrence in patients previously treated with surgery/radiation [24–27], to our knowledge the safety of GH replacement therapy with regard to tumor growth has not been tested in patients with a newly diagnosed macroadenoma who did not have surgery. In addition, the utility of preoperative GH stimulation testing is unclear since it would need to be repeated because changes in pituitary function are likely after surgery. With regard to tumor size and hypopituitarism, we found, not unexpectedly, larger tumors in hypopituitary than eupituitary patients, and hypopituitarism was more likely to be present in patients with a macroadenoma than microadenoma. Overall, in our study, 46.5% of patients with macroadenomas had hypopituitarism, similar to the 45% rate of this in one study of CNFPAs followed without surgery [3], but lower than the >70% prevalence of hypopituitarism reported in most surgical series [3, 11, 28]. Although normal pituitary function is found in most patients with micro-PIs [4, 16, 29], one study found deficiencies in 50% of microadenomas [30]. In our study, there was no size cutoff below which participants did not have hypopituitarism. We found that 25% of participants with tumors 6 to 9 mm in size had some degree of hypopituitarism, supporting the need to test all lesions this size for hypopituitarism.

Our data also suggest that symptoms of hypopituitarism do not assuredly predict the need for testing. Although sexual dysfunction and reduced libido were most associated with increased risk of hypopituitarism, likely because secondary hypogonadism was the most common deficiency, receiver operator curve analysis did not identify a symptom set that was highly discriminating for hypopituitarism. Many symptoms of hypopituitarism are nonspecific, which likely explains the low sensitivity and specificity of them. A limitation of our analysis is that we selected a small set of symptoms and signs that we considered most suggestive of pituitary disease since, to our knowledge, no such set has been previously validated. Also, it is unknown whether our patients having been interviewed about pituitary-related symptoms by 1 or more physicians prior to us changed their reporting of them. Notwithstanding, in contrast to other guidelines suggesting screening of only macroadenomas [5, 6], our data support recommendations that all patients with an incidentally presenting large micro- or macro-CNFPA, with or without symptoms, should undergo clinical and laboratory evaluations for hypopituitarism [7].

We also found that incidentally presenting participants harbored unappreciated signs and symptoms of their tumor. For example, one-third of those with VF deficits had visual symptoms, and 16% had symptoms of hypogonadism, yet these did not lead to an endocrine

evaluation or tumor detection. Had they been recognized by the patient or physician, diagnosis might have been earlier and hypopituitarism and other signs prevented. These data do support recommendations for VF testing in all incidentally diagnosed pituitary lesions abutting or compressing the optic chiasm on MRI [7]. Headache was common and could have been clinically underevaluated in the incidental group, but since its relationship to the tumor is uncertain, it may be too nonspecific a sign to be classified as a missed symptom. It has been suggested that symptoms may have actually led to the imaging that identified many macro-PIs [31], but this is not likely to be the case in our series since we questioned our participants carefully about the events leading to tumor recognition.

We also found gender and age-related differences in reason for presentation and tumor size in our cohort. Incidentally presenting tumors were significantly smaller than those presenting due to symptoms, possibly because they had not yet grown to a size likely to present with symptoms. Alternatively, since the incidental group was older, smaller tumors could reflect a lesser potential for tumor growth. Our ongoing follow-up study of those incidental tumors undergoing observation-only treatment may provide insight. In both the incidental and symptoms groups, males were older and had larger tumors than females at tumor presentation. Consistent with our findings, a Surveillance, Epidemiology, and End Results database analysis found a higher incidence of pituitary adenomas in men than in women aged >50 years, and tumors were larger in males across all ages [32]. Our data do not suggest that higher tumor incidence in older men [32] is due to men presenting incidentally more often than women. Rather, we observed a trend for more males than females in the symptoms group. This and the older age and larger tumors at diagnosis in males suggest a delay in diagnosis, which may explain more hypopituitarism in males than females. Whether this is due to less recognition or less seeking of medical care or a biological difference in the tumors of males is unknown. Interestingly, average tumor size was similar in male and female patients with hypopituitarism, suggesting that tumor size may be more explanatory of hormone deficiencies than gender or age.

After the baseline visit described in this report, each participant entered a treatment arm they and their physician agreed on, not by protocol of the prospective study they had entered. Of the 269 participants, 61.6% of the symptoms group and 34.4% of the incidental group participants planned surgery for their tumor. In line with accepted indications for pituitary tumor surgery [7], most patients in both the incidental and symptoms groups who opted for surgery did so because their tumor was abutting or compressing the optic chiasm. Given that a number of incidentally presenting patients had unrecognized VF deficits, our data also support guiding the need for surgery by the presence of clinically significant signs and symptoms of the tumor, rather than the cause of presentation itself [17]. Since, by design, our study excluded tumors < 6 mm in size, and most of our cohort was referred to the study from among patients referred to our neurosurgeons, most tumors in our cohort were macroadenomas, which is more than might be expected were it a population survey of CNFPAs. Thus, although only about half of our cohort went on to surgery, our cohort may consist of only the more clinically significant tumors and is not necessarily representative of all CNFPAs.

In conclusion, our study shows that incidentally presenting CNFPAs are more common than previously recognized. Our data illustrate the importance of complete endocrine and vision investigations of these patients since we found that incidental diagnosis does not necessarily indicate lack of unrecognized, yet clinically significant, endocrine abnormalities or signs of tumor compression. Our data support guidelines recommending the need to evaluate all large micro- and macro-CNFPAs for hypopituitarism, both those with and without symptoms, since these are not assured to predict the need for testing. The profile of our cohort also shows that many patients with CNFPAs still present with vision abnormalities and large tumors, evidence that considerable delay in diagnosis persists today. Our data also highlight the fact that signs and symptoms of pituitary disease are often unrecognized by the patient and/or physician and suggest the need for greater awareness and education

about this diagnosis. Given the likelihood that incidental CNFPA diagnoses will increase, our data can help inform guidelines about their evaluation. Through our ongoing, prospective, observational study of this cohort, we hope to address additional questions about the outcomes of treatment of both incidentally and symptomatically presenting tumors with observation alone or surgical therapy.

Acknowledgments

Financial Support: Funded by grants R01NS070600, R01DK110771 to PUF, and in part from NIH grant No. UL1 TR000040 from NCATS/NIH.

***Clinical Trial Information*:** Clinical trials #: NCT01556230 (registered March 16, 2012).

Additional Information:

Correspondence: Pamela U. Freda MD, Department of Medicine, Columbia University, Vagelos College of Physicians & Surgeons, 650 West 168th Street, Rm.1014, New York, NY 10032. E-mail: puf1@cumc.columbia.edu.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

References

1. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. *Endocrinol Metab Clin North Am*. 2008;**37**(1):151–71, xi.
2. Dekkers OM, Hammer S, de Keizer RJ, et al. The natural course of non-functioning pituitary macroadenomas. *Eur J Endocrinol*. 2007;**156**(2):217–224.
3. Karavitaki N, Collison K, Halliday J, et al. What is the natural history of nonoperated nonfunctioning pituitary adenomas? *Clin Endocrinol (Oxf)*. 2007;**67**(6):938–943.
4. Sam AH, Shah S, Saleh K, et al. Clinical outcomes in patients with nonfunctioning pituitary adenomas managed conservatively. *Clin Endocrinol (Oxf)*. 2015;**83**(6):861–865.
5. Galland F, Vantyghem MC, Cazabat L, et al. Management of nonfunctioning pituitary incidentaloma. *Ann Endocrinol (Paris)*. 2015;**76**(3):191–200.
6. Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S; French Endocrinology Society non-functioning pituitary adenoma work-group. Management of clinically non-functioning pituitary adenoma. *Ann Endocrinol (Paris)*. 2015;**76**(3):239–247.
7. Freda PU, Beckers AM, Katznelson L, et al.; Endocrine Society. Pituitary incidentaloma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;**96**(4):894–904.
8. *Antibody Registry Numbers: AB_2756880, AB_2811291, AB_2827375, AB_2756389, AB2756388, AB_2756391, AB_2810257,AB_2827386, AB_2827385*. 2020. www.antibodyregristry.org.
9. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas – a study on 721 patients. *Acta Neurochir (Wien)*. 2004;**146**(1):27–35.
10. Chang EF, Zada G, Kim S, et al. Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. *J Neurosurg*. 2008;**108**(4):736–745.
11. Greenman Y, Stern N. Non-functioning pituitary adenomas. *Best Pract Res Clin Endocrinol Metab*. 2009;**23**(5):625–638.
12. Losa M, Mortini P, Barzaghi R, et al. Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. *J Neurosurg*. 2008;**108**(3):525–532.
13. Day PF, Guitelman M, Artese R, et al. Retrospective multicentric study of pituitary incidentalomas. *Pituitary*. 2004;**7**(3):145–148.
14. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y. A survey of pituitary incidentaloma in Japan. *Eur J Endocrinol*. 2003;**149**(2):123–127.
15. Vaninetti NM, Clarke DB, Zwicker DA, et al. A comparative, population-based analysis of pituitary incidentalomas vs clinically manifesting sellar masses. *Endocr Connect*. 2018;**7**(5):768–776.

16. Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W. The 'incidentaloma' of the pituitary gland. Is neurosurgery required? *JAMA*. 1990;**263**(20):2772–2776.
17. Losa M, Donofrio CA, Barzaghi R, Mortini P. Presentation and surgical results of incidentally discovered nonfunctioning pituitary adenomas: evidence for a better outcome independently of other patients' characteristics. *Eur J Endocrinol*. 2013;**169**(6):735–742.
18. Esteves C, Neves C, Augusto L, et al. Pituitary incidentalomas: analysis of a neuroradiological cohort. *Pituitary*. 2015;**18**(6):777–781.
19. Fleseriu M, Bodach ME, Tumialan LM, et al. Congress of neurological surgeons systematic review and evidence-based guideline for pretreatment endocrine evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery*. 2016;**79**(4):E527–E529.
20. Feldkamp J, Santen R, Harms E, Aulich A, Mödder U, Scherbaum WA. Incidentally discovered pituitary lesions: high frequency of macroadenomas and hormone-secreting adenomas - results of a prospective study. *Clin Endocrinol (Oxf)*. 1999;**51**(1):109–113.
21. Anagnostis P, Adamidou F, Polyzos SA, Efstathiadou Z, Panagiotou A, Kita M. Pituitary incidentalomas: a single-centre experience. *Int J Clin Pract*. 2011;**65**(2):172–177.
22. Dekkers OM, Pereira AM, Roelfsema F, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab*. 2006;**91**(5):1796–1801.
23. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ; HyposCCS Advisory Board; U.S. HypoCCS Study Group. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab*. 2002;**87**(2):477–485.
24. Arnold JR, Arnold DF, Marland A, Karavitaki N, Wass JA. GH replacement in patients with nonfunctioning pituitary adenoma (NFA) treated solely by surgery is not associated with increased risk of tumour recurrence. *Clin Endocrinol (Oxf)*. 2009;**70**(3):435–438.
25. Hartman ML, Xu R, Crowe BJ, et al.; International HypoCCS Advisory Board. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *J Clin Endocrinol Metab*. 2013;**98**(3):980–988.
26. Shen L, Sun CM, Li XT, Liu CJ, Zhou YX. Growth hormone therapy and risk of recurrence/progression in intracranial tumors: a meta-analysis. *Neurol Sci*. 2015;**36**(10):1859–1867.
27. Olsson DS, Buchfelder M, Schlaffer S, et al. Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy. *Eur J Endocrinol*. 2009;**161**(5):663–669.
28. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *J Clin Endocrinol Metab*. 2008;**93**(10):3717–3726.
29. Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. *Arch Intern Med*. 1995;**155**(2):181–183.
30. Yuen KC, Cook DM, Sahasranam P, et al. Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels. *Clin Endocrinol (Oxf)*. 2008;**69**(2):292–298.
31. Molitch ME. Pituitary incidentalomas. *Endocrinol Metab Clin North Am*. 1997;**26**(4):725–740.
32. McDowell BD, Wallace RB, Carnahan RM, Chrischilles EA, Lynch CF, Schlechte JA. Demographic differences in incidence for pituitary adenoma. *Pituitary*. 2011;**14**(1):23–30.