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Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas

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Abstract

Purpose Non-functioning pituitary adenomas (NFPAs) are benign pituitary neoplasms that do not cause a hormonal hypersecretory syndrome. An improved understanding of their epidemiology, clinical presentation and diagnosis is needed.

Method A literature review was performed using Pubmed to identify research reports and clinical case series on NFPAs.

Results They account for 14–54% of pituitary adenomas and have a prevalence of 7–41.3/100,000 population. Their standardized incidence rate is 0.65–2.34/100,000 and the peak occurence is from the fourth to the eighth decade. The clinical spectrum of NFPAs varies from being completely asymptomatic to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size. Most patients present with symptoms of mass effect, such as headaches, visual field defects, ophthalmoplegias, and hypopituitarism but also hyperprolactinaemia due to pituitary stalk deviation and less frequently pituitary apoplexy. Non-functioning pituitary incidentalomas are found on brain imaging performed for an unrelated reason. Diagnostic approach includes magnetic resonance imaging of the sellar region, laboratory evaluations, screening for hormone hypersecretion and for hypopituitarism, and a visual field examination if the lesion abuts the optic nerves or chiasm.

Conclusion This article reviews the epidemiology, clinical behaviour and diagnostic approach of non-functioning pituitary adenomas.

Keywords Non-functioning pituitary adenomas · Incidentalomas · Hypopituitarism · Neuroophthalmological complications

Epidemiology of non-functioning pituitary adenomas

Non-functioning pituitary adenomas (NFPAs) are benign pituitary neoplasms that arise from the adenohypophyseal cells and lack clinical or biochemical evidence of hormone excess except for a mild hyperprolactinaemia in some cases. They account for 14–54% of pituitary adenomas [1–9].

Population studies from UK, Belgium, Switzerland, Northern Finland, Western Sweden, Malta, Iceland, Canada and Argentina have estimated that the prevalence of clinically relevant NFPAs is 7–41.3 cases per 100,000 of population (Table 1) [1–10]. In most epidemiological studies they are the second most common type of adenomas after prolactinomas, when taking into account both micro and macroadenomas but predominate amongst macroadenomas. Data are discordant about gender predominance [1, 2, 4–9, 11, 12]. They have a standardized incidence rate of 0.65–2.34/100,000 [5, 7–9] and the peak occurrence is from the fourth to the eighth decade [1, 2, 4–9, 11, 13].

Non-functioning pituitary incidentalomas

Pituitary incidentalomas are generally described as pituitary lesions without any overt features of pituitary disease, that are found on brain imaging, done for an unrelated indication [14]. Magnetic resonance imaging (MRI) studies in unselected populations report microincidentaloma rates of 10–38% [15, 16] and 0.16–0.3% for macroadenomas [17, 18]. The proportion of macroadenomas is higher in neuroradiological series, where imaging was performed because of non specific symptoms and the majority of them are NFPAs [19–24].

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Table 1 Prevalence and demographics of clinically relevant non-functioning pituitary adenomas in population studies

	Countries	Period	Prevalence per 100,000 population	Clinically relevant NFPAs (%)	Macroadenomas n(%)	Females/males	Age (yrs)
Davis et al. [10]	UK, Stoke-On Trent	1988–1998	7–9				
Daly et al. [1]	Belgium, Liege	2005	13.8	14.7	9 (90)	3/7	Median (range) 61.5 (41–86)
Fontana and Gaillard [3]	Switzerland	2006–2007	23.8	29.5	13 (100)		
Fernandez et al. [2]	UK, Oxford (Banbury)	2006	22.1	28.5	12 (66.7)	6/12	Median (range) 51.5 (19–79)
Raappana et al. [5]	Northern Finland	1992–2007	22.2–26.5	37	126 (82)	1.2	Median (range) 60 (49–70)
Gruppetta et al. [4]	Malta	2000–2011	25.8	34.2	70 (64.8)	119/27	Median (range) 47 (18–84)
Tjörnstrand et al. [7]	Western Sweden	2001–2011	22	54.1	262 (82)	135/185	
Al-Dahmani et al. [8]	Canada	2005–2013	41.3	48	269 (70)	385/215	Mean (SD) 52.1 ± 16.8
Agustsson et al. [6]	Iceland	1955–2012	41.32	43	151 (74.4)	99/104	Median (range) 57 (13–88)
Day et al. [9]	Argentina	2003–2014	21.48	18.8	28 (96.6)	19/10	Mean (SD) 68.7 ± 13.5

A radiological review of 2598 subjects undergoing a pituitary MRI scan from 1999 to 2009 in Cedars Sinai Medical Centers estimated that NFPAs ranked second after prolactinomas. Interestingly, it was the most common entity amongst 282 incidentalomas, defining them as masses identified on imaging procedures before pituitary MRI, for indications unrelated to an endocrinopathy or for visual symptoms consistent with a sellar mass [25].

Autopsy data estimate an average prevalence of pituitary adenomas of 10.7% with the predominance of microadenomas. In studies in which prolactin immunohistochemistry was performed, 22–66% stained positively for prolactin [26]. Furthermore, in an autopsy series of 316 pituitaries Buurman et Saeger found that NFPAs (mostly null cell and gonadotroph adenomas) were the second most common type of pituitary adenoma after prolactinomas and only three amongst them were macroadenomas [27].

The prevalence of incidentally discovered NFPAs in surgical series ranges between 9 and 21% [28–34].

NFPAs in hereditary syndromes

Less than 5% of pituitary tumors occur as a benign component of hereditary syndromes, such as MEN1, MEN4, the Carney complex, and familial isolated pituitary adenomas (FIPAs).

Data from 324 MEN1 patients from a French and Belgian multicenter study showed that among 136 cases of pituitary adenomas, only 20 (14.7%) were non-functioning macroadenomas (10 were invasive) [35]. Interestingly, systematic presymptomatic screening for pituitary tumors in the Dutch MEN1 Study Group predominantly (42.3%) resulted in detection of non-functioning microadenomas [36]. Seven cases were pediatric and patients were older than 15 years old.

NFPAs have not been reported to occur in the context of the Carney complex and they represent less than 20% of patients belonging to FIPA family [37]. They mainly occur in heterogeneous FIPA families and are diagnosed at an average 8 years earlier compared with the sporadic counterparts [37].

Dwight et al. have reported the case of a 30 years old man with a non-functioning pituitary macroadenoma in the setting of germline SDHA mutation [38].

Clinical presentation

The clinical spectrum of NFPA varies from being completely asymptomatic to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size.

The absence of clinical symptoms of hormonal hypersecretion causes a delay in diagnosis. Drange et al. estimated a mean time of delay 1.96 ± 2.9 years [11]. Most patients present with symptoms of mass effect, such as headaches,

visual field defects, ophthalmoplegias, and hypopituitarism [11, 13, 28–32, 34]. Other manifestations are hyperprolactinaemia due to pituitary stalk deviation and less frequently pituitary apoplexy 3.7–14.1(%) [28, 29, 31, 32, 34, 39, 40].

Neurologic manifestations

Headaches are common (19–75)% in patients with pituitary tumors regardless of size [41, 42]. These rates are extracted from what the patients reported on history taking, and it is not always clear whether the presenting headache is an unrelated primary headache, a lesion-induced aggravation of a preexisting primary headache, or is a separate secondary headache related to the lesion. In a series of 121 incidentally discovered NFPAs headache was one of the most frequent reasons to perform a neuroimaging study and was present in 19.8% of the cases [32]. Suprasellar extension can produce headaches. Proposed mechanisms for headache include increased intrasellar pressure and stretching of dural membranes containing pain receptors, or activation of trigeminal pain pathways by tumors affecting the cavernous sinus [43].

Neuroophthalmological complications are caused by the pressure of the tumor on the optic chiasm. The typical visual field defect associated with pituitary tumors is bitemporal hemianopia, occurring when the body of the chiasm (which is comprised of the crossing nasal fibres of each optic nerve) is compressed by the enlarged gland. The different sites of compression account for different patterns of field loss which can be uni-, bilateral or even central. The defect may be complete, involving the whole hemi-field or partial, usually beginning superiorly and progressing inferiorly, depending on the degree of nerve compression. Anterior placed lesions can cause central scotomas and nerve fibre layer pattern visual field defects, while posterior lesions may involve the optic tracts producing a homonymous hemianopia.

Asymmetry is a common finding of visual field testing possibly attributed to a different nerve fiber strain between the nasal and temporal nerve fibers of bilateral eyes. In a series of pituitary macroadenomas, Lee et al. noted and confirmed by qualitative analysis of the visual fields asymmetry in 39 of 49 patients (79.6%) [44]. In another series of patients with pituitary adenoma Ogra et al. reported that although a bitemporal pattern of visual field loss was the most common (41%), a significant proportion of patients had unilateral (33%) and altitudinal defects (16%) [45].

In the case of severe and long-term compression, a decline in visual acuity may develop. Rarely, pupillary abnormalities, optic atrophy and papilledema may occur. Often the onset of the visual deficit is gradual and not noticed by the patient for several months. Median visual symptom duration before diagnosis is 6.5 months and older age is the only factor associated with delayed diagnosis [46].

Ophthalmoplegia is caused by pressure on the abducens or oculomotor nerves in the cavernous sinus. The invasion of the cavernous sinus (parasellar expansion) may affect the cranial nerves, causing a varied clinical profile according to the compromised nerve: eyeball shift out and/or ptosis (III nerve lesion, oculomotor nerve), deviation of the eyeball superiorly and slightly inward (IV nerve involvement, trochlear nerve) and convergent strabismus (lesion VI nerve, abducens nerve). Trigeminal neuralgia (lesion of branches V1 and/or V2 of V nerve, the trigeminal nerve) is rare [47]. Third cranial nerve palsy develops most frequently, followed by sixth, then fourth or fifth cranial nerve palsies in that order. When present, diplopia seems to be caused by either third or sixth cranial nerve palsy alone, or by paralysis of various nerves participating in the movement of the eye. Pituitary apoplexy can provoke or aggravate cranial nerve palsy.

In rare cases the tumor may invade local structures as the cavernous sinus, the dura and adjacent brain and compress other intracranial structures, resulting in symptoms such as temporal lobe epilepsy. Giant tumors defined as $\geq$40 mm in one extension, may rarely obstruct the foramen of Monro, leading to intracranial hypertension and hydrocephalus [48–50]. Cerebrospinal fluid rhinorrhea can occur if the tumor causes erosion to the sellar floor and extends inferiorly (infrasellar extension) to the sphenoid sinus [50]. Rarely occlusion of the internal carotid artery (ICA) has been reported [51]. NFPAs in FIPAs are significantly more frequently invasive than sporadic (84.6 vs. 59.6%, respectively) [37, 52].

Apoplexy is an acute vascular event that presents with acute expansion of tumor volume, manifesting itself by sudden onset of intense headache. It may be associated with neuro-ophthalmologic signs and symptoms, intracranial hypertension and altered levels of consciousness. In addition, it can cause hypopituitarism [53]. NFPAs is the most frequent type of preexisting adenoma [54], accounting for 45–82% of pituitary apoplexy cases [53–59]. In small cohorts of asymptomatic NFPAs observed for a mean period of 5 years, 7–9.5% developed pituitary apoplexy [20, 60]. However, no pituitary apoplexy case was diagnosed in another NFPA cohort (with both micro- and macroadenomas) followed-up for a mean of 42 months, despite significant growth of the macroadenomas included [61].

The progression rate of NFPAs is difficult to estimate. In a retrospective study from Oxford Karavitaki et al. studied 40 patients with presumed NFPAs who were not treated at the time of detection and had regular follow-up. They showed that during a 16-year period in the subjects with macroadenoma, the cumulative probability of enlargement at 4 years' observation was 44%. The vast majority of the macroadenomas with an increase in size (11/12) had chiasmatic involvement with or without visual field defects.

By contrast, subjects with microadenoma had a small probability of tumour growth (19% at 4 years), which was not associated with visual compromise. These data suggest that the 'watch and wait' policy seems reasonable for microadenomas, but is probably not a safe approach for adenomas measuring ≥ 1 cm [61].

Some NFPAs show a slow growth and necessitate a long observation time, while others act more aggressively and invade the neighboring structures, thereby requiring rapid neurosurgical intervention to prevent long-term impairment on visual field or pituitary deficiency [62].

Endocrine manifestations

NFPAs may demonstrate mild elevations in serum prolactin [11, 13, 28, 29, 31, 32, 34, 63] as they have the capacity to cause "disconnection hyperprolactinaemia", where the mass blocks dopamine inhibition of lactotrophs. Notably, a serum prolactin level > 2000 mU/L is almost never encountered in individuals with NFPAs [63]. Values above this limit in a patient with macroadenoma should normally imply—once acromegaly and Cushing disease have been excluded—that prolactinoma is the probable diagnosis, and a dopamine agonist should be considered as the first line treatment.

Mechanical compression of the normal anterior pituitary gland and/or pituitary stalk preventing the passage of stimulatory hypothalamic factors can result in partial or complete hypopituitarism. Hypopituitarism develops slowly and often goes undetected.

The overall prevalence of partial hypopituitarism in patients with NFPAs ranges from 37 to 85% [11, 64–68]. Panhypopituitarism occurs in 6–29% of patients [67, 68]. The most commonly affected pituitary axis is the GH axis, with 61–100% of patients showing laboratory evidence of GH deficiency [70–75]. Central hypogonadism is noted in 36–96% of patients [11, 31, 70–75, 77, 78] and adrenal insufficiency is noted in 17–62% [31, 69–72, 75–77]. Finally, 8–81% exhibit central hypothyroidism [31, 71–78]. The presence of diabetes insipidus at the time of clinical presentation of NFPAs is very rare [8].

Although pituitary incidentalomas are clinically unsuspected at diagnosis, many are finally associated with partial hypopituitarism and some with compression of the optic chiasm. Deficits of gonadotropins (not associated with hyperprolactinaemia) were detected in up to 30% of patients [19, 22, 79], ACTH deficiency in up to 18% [22, 79], TSH deficiency in 28% [22, 79], and GH deficiency in up to 8% [19].

30–42% of patients with microadenomas have at least one pituitary hormone deficiency [80, 81]. In another study, 50% of patients with a nonfunctioning pituitary microadenoma were found to be GH-deficient and 50% had at least one other pituitary hormone deficit [82].

Pituitary adenomas rarely occur in childhood and adolescence. In a series of 44 young patients (9/44) 20% had a non-functioning tumor. At presentation amongst those with a macroadenoma 50% had headache, visual defects and secondary amenorrhea, 25% primary amenorrhea and galactorrhea, and 33% obesity. Amongst those with a microadenoma 67% had headache and secondary amenorrhea [83].

Diagnosis

Pathology

NFPAs include a cluster of pituitary tumors without endocrine manifestations of hormone overproduction. The new fourth WHO classification has abandoned the concept of "a hormone-producing adenoma" and adopted a pituitary adenohypophyseal cell lineage designation of the adenomas with subsequent categorization of histological variants according to hormone content and specific histological and immunohistochemical features. As a consequence, nonfunctioning pituitary tumors include gonadotroph adenomas—with varying degrees of immunohistochemical reactivity for β-FSH, β-LH, and α-subunit or combinations, null cell adenomas—with no immunohistochemical evidence of cell-type-specific differentiation by using pituitary transcription factors and adenohypophyseal hormones- and some plurihormonal adenomas [84]. A very small percentage of tumors that are clinically classified as non-functioning have immunohistochemical characteristics of somatotropinomas or corticotropinomas and consequently are referred to as silent somatotroph and coricotroph adenomas [85].

Radiological investigation

Pituitary microadenomas are measuring less than 10 mm in diameter and are typically small intrasellar lesions. Macroadenomas (tumors ≥ 1 cm) are predominantly localized within an enlarged sella turcica. They may present with extrasellar extension, upwards into the suprasellar cistern, downwards into the sphenoid sinus or laterally into the cavernous sinus. The normal residual pituitary tissue is compressed and pushed laterally, towards one side, and superiorly, but never inferiorly. In the Oxford series of 546 surgically managed NFPAs 252/546 (46%) had suprasellar extension at diagnosis, 194/546 (35.53%) had both suprasellar and cavernous sinus extension, 28/546 (5%) extended suprasellarly up to the level of hypothalamus and ventricles (unpublished data).

For the radiological classification two systems are currently used, the Hardy and the Knosp classification. The Hardy classification divides pituitary adenomas into four grades based on their size and the invasiveness in the sella

Table 2 Investigation of pituitary function in clinically non-functioning pituitary tumors

- Check IGF-1, cortisol (09.00 a.m.), prolactin, FSH/LH, estradiol (females)/testo (males), TSH, FT4

Check for hormone hypersecretion

- If IGF-1 is elevated, further evaluation for GH excess
- Screening for glucocorticoid excess (overnight dexamethasone suppression test, 24 h urinary free cortisol, midnight salivary cortisol) [91, 92] may be considered, regardless of clinical suspicion

Check for hypopituitarism

- If GH deficiency is suspected, GH stimulation testing is recommended. Biochemical testing for GHD can be avoided in patients with clear-cut features of GHD and three other documented pituitary hormone deficits. Insulin tolerance test/GHRH + arginine/glucagon tests may be performed and GH should be > 3–5 µg/L taking into account that cutoffs for GH response are BMI related
- A basal cortisol level < 3 µg/dL is indicative of adrenal insufficiency (AI) and a cortisol level > 15 µg/dL likely excludes an (AI) diagnosis. To check for ACTH deficiency one of the following tests (corticotropin stimulation test/ITT/low dose corticotropin test) may be performed. Peak cortisol levels < 18.1 µg/dL (500 nmol/L) at 30 or 60 min indicate adrenal insufficiency

turcica [86]. The Knosp classification takes into account the tumor invasion of the cavernous sinus according to coronal sections of MRI scans, with the readily detectable ICA serving as the radiological landmark [87].

MRI is the gold standard for the evaluation and differential diagnosis of sellar/suprasellar region. In T1-weighted images, the adenomas can be hypo- or isointense compared to non-tumoral pituitary tissue and take up gadolinium poorly or not at all. In T2-weighted images the adenomas appear isointense compared to the white matter. When there is bleeding into the tumor, as in cases of pituitary apoplexy the hemorrhage appears as hyperintense in the T1-weighted images without contrast. This characteristic hyperintensity may be absent in the early stage because hemorrhage is still in the form of deoxyhemoglobin. Hyperintensity of the optic chiasm on T2-weighted images can indicate a poor prognosis for the visual function even after quick removal of the pituitary adenoma responsible for optic pathway compression. Other non-adenomatous lesions of the sellar region like meningiomas or craniopharyngiomas are more heterogeneous and usually take up gadolinium more avidly [88].

Nishioka et al. retrospectively correlated the histological subtypes of 390 NFPAs with preoperative MRI findings. They found that MRI findings such as giant lesions, marked cavernous sinus invasion and a lobulated configuration of the suprasellar tumor were significantly more common among silent ACTH, GH, TSH and PRL adenomas than among null cell or gonadotroph adenomas [89].

Neuro-ophthalmological investigation

A careful evaluation of the mass effects of the tumor is indicated, including visual field examination if the tumor abuts the chiasm. Guidelines on pretreatment Ophthalmology Evaluation in Patients With Suspected NFPAs have recently been published by the Congress of Neurological Surgeons [90]. They recommend preoperative ophthalmologic evaluation with psychophysical (acuity and visual fields), functional (quantitation of afferent pupillary defect and visual evoked potentials), and anatomic [disc appearance and optical coherence tomography (OCT)] assessment. Ophthalmologic evaluation may also provide prognostic factors for recovery and, when paired with postoperative evaluation, documents postoperative change.

Automated static perimetry is recommended for early detection of visual field deficits. Even with a standard III size test object, it will often pick up subtle bitemporal visual field defects, less commonly homonymous defects, and infrequently arcuate defects characteristic of optic nerve pathology.

Visual evoked potentials may be used to assess the optic nerves in NFPA patients, a manner that may correlate with visual field deficits, but false positives and negatives may limit this testing to cases in which psychophysical testing, such as acuity and visual fields, cannot be assessed.

It is recommended that older patients and patients with longer duration (> 4 months) of vision loss are counselled regarding the reduced chance of postoperative vision improvement [90]. Formal ophthalmologic examination looking for optic nerve atrophy or OCT to measure both retinal nerve fiber layer thickness and the presence of damage to the ganglion cell layer on algorithms that segment the macular cube is recommended to assess a patient's chances of postoperative vision improvement.

Investigation of pituitary function

All patients presenting with a pituitary incidentaloma or an NFPA should undergo laboratory evaluation for hormone hypersecretion and hypopituitarism (Table 2) [14, 90].

Further testing

In patients whose personal or family history suggests the possibility of a multiple endocrine neoplasia syndrome, additional screening and follow-up as appropriate to the

suspected syndrome should be undertaken (e.g., serum calcium). No clinical evidence is available to support the measurement of any biomarkers or routine genetic testing in patients with sporadic NFPAs [91].

Differential diagnosis

The differential diagnosis of an incidentally discovered sellar mass is broad and includes a large number of entities: anterior pituitary tumors, posterior pituitary tumors (e.g., pituicytoma, granular cell tumors), benign parasellar tumors (e.g., meningioma, craniopharyngioma), malignant tumors (e.g., glioma, germ cell tumor), malformative lesions (e.g.,, Rathke's cleft cysts, dermoid cyst, epidermoid cyst, arachnoid cyst), inflammatory and granulomatous lesions (e.g., lymphocytic hypophysitis, granulomatous hypophysitis, Langerhans cell histiocytosis) and vascular lesions (e.g., aneurysms) [94].

When a pituitary macroadenoma is diagnosed it is important to differentiate from a macroprolactinoma as the incidence of hyperprolactinaemia in patients with histologically verified NFPAs is (25–65)% [95]. In this regard, although macroprolactinomas usually result in prolactin levels greater than 21,276 mIU/L (1000 ng/mL), in some patients the saturation of the primary antibody of the immunoassay by massive amounts of analyte may lead to spuriously low prolactin concentrations, the so called "hook effect", which can be avoided by diluting the serum sample prior to the assay.

Conclusions

NFPAs are an heterogeneous group by all dimensions. Clinically they range from being completely asymptomatic, and therefore detected either at autopsy or as incidental findings on head MRI or computed tomography scans performed for other reasons, to causing significant hypothalamic/pituitary dysfunction and visual symptoms due to their large size. They comprise a significant proportion of sellar region tumors and it is important that they are properly characterized by radiological and endocrinological investigations. Correct diagnosis is crucial, in order to select the right therapeutic approach.

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