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REVIEW ARTICLE

Pituitary tumors: epidemiology and clinical presentation spectrum

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Abstract

Pituitary tumors (PTs) are a heterogeneous group of lesions of the central nervous system that are usually benign. Most of them occur sporadically, but 5% can do so within family syndromes, usually at a young age. There are differences by sex, age, race, and genetic factors in the prevalence of different tumor cell types and clinical presentation. Functioning-PTs (FPTs) are usually diagnosed earlier than non-functioning PTs (NFPTs). However, this depends on the PT type. Headaches and visual disturbances are the most frequent mass-effect symptoms, but seizures or hydrocephalus may also occur. Pituitary apoplexy is another possible mode of presentation, and it requires special attention because of its potential severity. PTs in pregnancy, childhood, and old age present a series of clinical peculiarities that must be taken into account when evaluating these patients. Ectopic PTs (EPTs) are uncommon and share the same clinical-epidemiological data as eutopic PTs, but, depending on their location, other types of clinical manifestations may appear. Silent PTs are often detected as an incidentaloma or due to neurologic symptoms related to mass-effect. Aggressive PTs and pituitary carcinomas (PCs), which are very rare, are characterized by multiple local recurrences and metastases, respectively. This review addresses the epidemiology and clinical presentation of PTs, from the classical hormonal and mass-effect symptoms to the different rare presentations, such as pituitary apoplexy, hydrocephalus, or diabetes insipidus. Moreover, special situations of the presentation of PTs are discussed, namely, PTs in pregnancy, childhood, and the elderly, EPTs, silent and aggressive PTs, and PCs.

Keywords Pituitary tumors · Non-functioning pituitary tumors · Mass-effect symptoms · Hormonal symptoms · Pituitary apoplexy

Introduction

Recently, the European Pituitary Pathology Group (EPPG) proposed the replacement of adenoma with the term pituitary neuroendocrine tumor (PitNET) to better reflect the similarities between adenohypophyseal and neuroendocrine tumors of other organs [1]. They contend that pituitary endocrine neoplasms exhibit a spectrum of behaviors that are not entirely benign and can cause significant morbidity, even when they are not metastatic. For safe and accurate diagnosis of PitNETs, the EPPG recommends a multi-step approach, including clinical and neuroimaging features, immunohistochemistry for hormones and pituitary transcription factors, assessment of proliferation, and, when indicated, the use of markers predictive of treatment response [1]. Taking into account the EPPG proposal and the fact that a small subgroup of high-risk pituitary adenomas are not entirely benign, while the majority do not behave like neuroendocrine tumors, the Pituitary Society has recently addressed this issue through a position statement. They suggest that the proposed PitNET nomenclature does not advance patient care, plays only a small role in guiding decision-making, and will likely lead to unnecessary patient concerns. They conclude that there is not yet a compelling case to call pituitary adenomas/tumors other than what they are [2].

PTs are a heterogeneous group of lesions of the central nervous system (CNS) that are usually benign [3]. They are relatively common, the overall estimated prevalence of PTs in the general population being estimated to being 16.7% [4]. Their frequency varies greatly according to age and sex, although they are slightly more frequent in females and between the ages of 40 and 60 years [5]. Even though most of them (95%) arise sporadically, up to 5% of PTs could be related to

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familial pituitary tumor syndromes, the most frequent of them being multiple endocrine neoplasia type 1 (MEN1) syndrome [6–11].

PTs can develop a wide clinical spectrum (Fig. 2). Some PTs cause prominent symptoms, while others may result in slowly developing, insidious, non-specific complaints, thus delaying accurate diagnosis. Many PTs remain symptomless and are detected only incidentally (pituitary incidentalomas) [3]. Functional PTs (FPTs) present mainly as Cushing's syndrome, acromegaly/gigantism, hyperthyroidism, or hypogonadism due to hyperprolactinemia [12].

The diagnosis of PTs during pregnancy, old age, or childhood and adolescence can be a great diagnostic challenge due to the presence of atypical clinical data that can be confused with those of other clinical or even physiological conditions in some of these age groups [13–15]. Ectopic PTs (EPTs) also present clinical peculiarities related to their localization [16]. Silent PTs (SPTs) can be clinically silent or totally silent depending on whether or not, respectively, they secrete hormonal products in excess that can be detected by biochemical testing [17]. Aggressive PTs (APTs) present as radiologically invasive tumors and an unusually rapid tumor growth rate, or clinically relevant tumor growth despite optimal standard therapies [18]. Pituitary carcinomas (PCs) are defined as adenohypophyseal tumors with metastatic activity within and outside the boundaries of the CNS [19].

This review focuses on the epidemiology and clinical presentation of PTs, from their classical hormonal and mass-effect-symptoms to their different rare clinical presentations. Moreover, special situations of the presentation of PTs are discussed, namely, PTs in pregnancy, childhood and old age, EPTs, SPTs, APTs, and PCs.

Epidemiology

PTs were considered rare, but recent studies have shown that the prevalence is higher than previously thought, this being due to the increase in and improvement of diagnostic tests [3, 20]. Data from cancer registries report a prevalence of approximately 130–230 cases per 100,000 population, while population studies estimate a prevalence of 190–280 cases per million [21]. They are the second most frequent intracranial neoplasm behind meningiomas. Radiological series report PTs in up to 40% of the studies and autopsies in up to 35% [4]; macroincidentalomas were found in 0.2% of patients who underwent CT scans for CNS symptoms [22], and by MRI, in 0.16% of a population study cohort [23].

The highest incidence of PTs is in the 40–60-year age group [3]. The incidence of PTs depends on tumor type, sex, and race. For instance, prolactinomas tend to manifest earlier than NFPTs [24], while the incidence of prolactinomas tends to decrease with aging [24]. The most common PTs in early childhood are ACTH-secreting PTs; between the ages of 20 and 40 years, prolactinomas, followed by NFPTs, are the most frequent [5].

Tumor distribution varies in the different population-based studies. Agustsson [25] et al. in their series of 471 patients identified NFPTs (43.0%) as the most prevalent PT, followed by prolactinoma (39.9%); Fernández et al. [26] in their population study, in the 63 patients with PTs described, found prolactinomas in 57%, NFPTs in 28%, followed by other PTs less frequently; in Clayton's study [27], 31.6–35.7% had prolactinomas and 32.1–36.8% had NFPTs, while Daly [28] reported prolactinomas in 66% of patients, and secondly NFPTs (14.7%).

Pituitary tumors in hereditary syndromes

Although most PTs are considered sporadic tumors, in younger patients or in the presence of other endocrinopathies, a hereditary origin should be suspected. Approximately 5% of all cases [7] occurs in the context of hereditary syndromes, such as MEN1 syndrome (MEN1 mutations), Carney complex (PRKAR1A mutations), and familial isolated pituitary adenomas (AIP mutations). Moreover, PTs can be seen in McCune-Albright syndrome (postzygotic mosaic mutations of the GNAS gene), MEN4 syndrome (CDKN1B mutations), isolated familial somatotropinoma (AIP mutations), patients presenting succinate dehydrogenase mutations, and DICER1 syndrome, among others [7, 8] (Table 1).

Regarding sex distribution, there is a female preponderance in prolactinomas, ACTH-secreting PTs, and TSH-secreting PTs; NFPTs and GH-releasing PTs occur mostly in males [25–28]. In older age groups, all PT types, except for NFPTs, tend to assume a more balanced gender distribution [5].

In addition, racial differences have been reported. Black women have a three times higher incidence of PTs than white women, while incidence rates for black men were four times higher than for white men [29]. The epidemiological study of Gittleman et al. also found a higher risk of PTs in blacks, while the average incidence for whites and blacks was 2.6 and 4.8, respectively [30].

Clinical presentation of pituitary tumors

Hormonal manifestations

Functional PTs account for approximately 48–78% of PTs [26, 31]. They present mainly as Cushing syndrome (CS), acromegaly/gigantism, or hyperthyroidism (Table 2). Drange et al. reported a mean time delay from onset to diagnosis of

Table 1 Familial syndromes associated with pituitary tumors [8–11]

Syndrome	Gene (Chromosome)	Clinical features
MEN1	90%: MEN1 (11q13.2) 10%: other genes	Pancreatic, and pituitary and parathyroid gland tumors. PTs occur in 40% of cases and can be the first presentation in 14%.
MEN4	CDKN1B (12p13.1)	MEN1-related phenotype
FIPA	AIP (11q13.2)	≥ 2 PTs in a family in the absence of other associated tumors
Isolated familial somatotropinoma	50%: AIP (11q13.2)	≥ 2 cases of acromegaly or gigantism in a family in the absence of MEN1 or CNC
X-linked acrogigantism syndrome[a]	GPR101 (Xq26.3)	Very young-onset gigantism and PTs or hyperplasia. Overgrowth is always detected before the age of 5 years.
Carney complex (CNC)	60%: PRKAR1A (17q24.2)	Myxomas, and testis and adrenal tumors as well as somatotroph hyperplasia or PT. PTs in 75%
NF1	NF1 (17q11.2)	Pigmentary lesions (café-au-lait macules, skinfold freckling, and Lisch nodules) and dermal neurofibromas. PTs in < 5%
McCune-Albright syndrome[a]	GNAS (somatic)	Peripheral precocious puberty, irregular café-au-lait skin pigmentation, and fibrous dysplasia of bone. PTs in 20%
SDH-related familial PitNET	SDHA (5p15.33) SDHB (1p36.13) SDHC (1q23.3) SDHD (11q23.1)	Pheochromocytomas/paragangliomas and PTs. PTs in < 1%
DICER1 syndrome	DICER1 (14q32)	Pleuropulmonary blastoma; cystic nephroma; Sertoli-Leydig cell tumors; goiter; and, more rarely, sarcomas, dysplasias, and pituitary blastoma (ACTH-secreting)

MEN1, multiple endocrine neoplasia type 1; *PTs*, pituitary tumors; *MEN4*, multiple endocrine neoplasia type 4; *FIPA*, familial isolated pituitary adenomas; *NF1*, neurofibromatosis type 1

[a] No autosomal dominant inheritance

3.0 ± 3.9 years for prolactinomas and 7.2 ± 7.7 years for GH-secreting PTs [12].

Mass-effect manifestations

The most frequent mass-effect-related symptom is visual impairment, which may appear in 13–60.8% of patients with NFPTs [37]. In MEN1 patients, PTs are two times more likely to be macroadenomas than in cases of sporadic PTs patients (85% vs. 42%, respectively); hence, tumor signs caused by local compression are more common in these cases [9] (Fig. 2(4)).

Classic visual impairment manifests as visual hemianopia, but it should be taken into account that PTs can grow asymmetrically and cause different types of campimetric involvement, or even loss of visual acuity or color vision (mainly green and red) secondary to optic nerve compression [38, 39]. Visual field defects and decreased vision occur in 9–32% and 4–16% of patients with PTs, respectively [40]. Less frequently (< 5%), diplopia may occur due to involvement of oculomotor nerves in the cavernous sinus, usually associated with large or fast-growing PTs or PA [37](Fig. 2(2)). Visual disturbances tend to correlate with tumor size; microadenomas do not impact vision and macroadenomas measuring < 2 cm are unlikely to cause significant visual impairment [38], but if the macroadenoma extends suprasellarly, it may compress the optic chiasm and cause visual impairment.

Headache is one of the most common initial compressive symptoms (37–70%) and, as, with other intracranial neoplasms, the presentation of headaches in PTs often resembles primary headaches, such as migraine or tension-type headache [41]. However, it is often difficult to determine the true relationship between pituitary injury and headache [41]. Headaches are believed to result from stretching of the dural sheath but do not necessarily correlate with tumor size [42]. Among FPTs, growth hormone (GH)–secreting PTs and prolactinomas have been specifically associated with headache, possibly mediated by the change in endocrine status rather than the pituitary mass per se [43].

Other symptoms arising from mass-effect are those related to hypopituitarism (or, in the case of hyperprolactinemia, due to inhibition of the pulsatile secretion of LH, leading to inadequate gonadal stimulation), which are present in 71% of prolactinomas and 44% of NFPTs [12]. Gonadotropic function (libido and sexual function) is usually the first affected, followed by somatotropic, thyrotropic, and corticotropic functions.

Rarely, the first clinical manifestation of a PT is diabetes insipidus (DI), as a result of neurohypophysis and/or pituitary stalk compression [14, 44] (Fig. 2(1)). However, an acute onset of isolated DI is almost never seen in PTs and should always orient the diagnosis toward a lesion involving the

Table 2 Clinical presentation and hormonal evaluation [32–36]

Pituitary axis	Clinical syndrome	Hormonal evaluation
Lactotroph	Hyperproduction: hyperprolactinemia -Men: decreased libido, gynecomastia, impotence, galactorrhea -Premenopausal women: oligomenorrhea or amenorrhea, galactorrhea, decreased libido Hypoproduction: hypoprolactinemia -Men and non-pregnant women: no clinical syndrome -Pregnant women: inability to breastfeed	Hyperproduction: basal serum prolactin: > 250 μg/L: prolactinoma, excluded drugs (risperidone, sulpiride, haloperidol, metoclopramide, etc.) > 500 μg/L: macroprolactinoma < 100 and macroadenoma (hook effect): 1:100 serum sample dilution Polyethylene glycol precipitation (macroprolactin): in asymptomatic hyperprolactinemia Hypoproduction: basal serum prolactin: low
Corticotroph	Hyperproduction: Cushing syndrome -Specific data: proximal muscle weakness, thin skin, easy bruising -Frequent data: weight gain, depression, hirsutism, decreased libido, menstrual irregularity, etc. Hypoproduction (secondary adrenal insufficiency (SAI)) -Frequent data: fatigue, weakness, weight loss, nausea, vomiting, and diarrhea	Hyperproduction Screening tests*: UFC (at least 2 measurements), late-night salivary cortisol (2 measurements), overnight DST (1 mg), 2-day low-dose DST (2 mg/day for 48 h) Confirmatory tests: 2 mg-DST, night serum cortisol, CRH test, DEX-CRH test, DDAVP test, BPSS, other studies Hypoproduction: basal serum ACTH: low or normal 8.00 am serum cortisol: > 18 μg/dL: SAI is ruled out** < 5 μg/dL: SAI is confirmed 5–18 μg/dL: functional test is recommended (ITT, 250 or 1-μg Synacthen): > 18 μg/dL: SAI is ruled out**, < 5 μg/dL: SAI is confirmed. *Screening should be performed only if clinical data suspicious of hypercortisolism exists. **If increased CBG levels are not suspected
Somatotroph	Hyperproduction: Acromegaly, gigantism (before closure of growth plate) Increase in hand and foot size, change in facial features, carpal tunnel symptoms, hyperhidrosis, fatigue, proximal muscle weakness, decreased libido, menstrual irregularity, hypertension, left ventricular hypertrophy, etc. Hypoproduction: GH deficiency -Adults (AGHD): increased fat mass, decreased lean body mass, osteopenia, dyslipidemia, insulin resistance, and/or glucose intolerance -Infancy: abnormally slow growth and short stature, hypoglycemia, micropenis, etc.	Hyperproduction: Serum IGF-1: Normal levels: exclude acromegaly/gigantism Elevated levels (for sex and age (see Table 2): 75-g OGTT for GH should be performed. If lack of GH suppression to < 1 ng/mL or < 0.4 ng/mL with ultrasensitive assays, the diagnosis is confirmed. Hypoproduction -Adults: Serum IGF-1: In patients with more than three pituitary hormone deficiencies, low IGF-1 is diagnostic of AGHD. If < 3 pituitary hormone deficiencies and low IGF-1, stimulating test should be performed (≥ 2 abnormal tests confirm the diagnosis). -Newborn: Baseline GH < 20 ng/mL + compatible clinical data confirm the diagnosis -Infancy: Low IGF-1 + compatible clinical data + ≥ 2 abnormal GH stimulating tests confirm the diagnosis
Gonadotroph	Hyperproduction -Premenopausal women: menstrual irregularity, infertility, galactorrhea, ovarian hyperstimulation syndrome -Postmenopausal women: no clinical syndrome -Men: testicular enlargement, hypogonadism Hypoproduction: Hypogonadism -Men: gynecomastia, impotence, decreased libido -Women: amenorrhea/oligomenorrhea, decreased libido	Hyperproduction: Serum FSH and LH: FSH within the reference range or mildly elevated; LH suppressed or within the reference range; serum α-subunit and inhibin normal or elevated Serum estradiol: elevated in premenopausal women Free and total serum testosterone: slightly below the reference range, normal, or elevated Hypoproduction. Serum FSH and LH: low or within the reference range Estradiol: low in premenopausal women (in postmenopausal women routine measurement is not recommended) Free and total testosterone: low
Thyrotroph	Hyperproduction: secondary hyperthyroidism, weight loss, heat intolerance, palpitations, anxiety, etc. Hypoproduction: secondary hypothyroidism, fatigue, weakness, weight gain, increased sensitivity to cold, constipation, dry skin, etc.	Hyperproduction Serum TSH: high or within the reference range. Serum FT4 and FT3: high α-GSU/TSH molar ratio: elevated

Table 2 (continued)

Pituitary axis	Clinical syndrome	Hormonal evaluation
		Dynamic test for the confirmatory diagnosis: no response to the T3 suppression test and TRH test Hypoproduction Serum TSH: low or normal Serum FT4: low

UFC, urinary free cortisol; *DST*, dexamethasone suppression test; *DEX-CRH test*, dexamethasone-CRH test; *DDAVP test*, desmopressin test; *BPSS*, bilateral petrosal sinus sampling; *ITT*, insulin tolerance test; *AGHD*, adult GH deficiency; *75-g OGTT*; 75-g oral glucose tolerance test; *FT4 and FT3*, free T4 and T3; *α-GSU*; alpha subunit of glycoprotein hormones

hypothalamic-hypophyseal axis, with other possibilities including craniopharyngiomas, Rathke cleft cysts, metastasis, and germ-cell tumors.

Large tumors with posterosuperior expansion toward the third ventricle may induce obstructive hydrocephalus. As a consequence, intracranial pressure is increased, and several symptoms, such as headache, nausea, papilledema, loss of bladder control, memory loss, poor coordination or balance, irritability, change in personality, problems with attention, sleepiness, or coma, may develop [45] (Fig. 2(6)). On the other hand, in the context of giant PTs, frontal lobe invasion may be associated with the following: generalized seizures [46] or even dementia [47]; anterior extension with nasal obstruction, headaches, recurrent nose bleeds, and/or rhinorrhea; inferior extension with craniocervical joint instability; and posterior extension with brainstem compression and cerebellar syndrome [45].

Pituitary incidentaloma

Pituitary incidentalomas are detected either at autopsy or as incidental findings on magnetic resonance imaging (MRI) of the head, or computed tomography (CT) scans performed for other reasons not related to pituitary symptoms [48, 49]. In other words, the imaging studies are not conducted for a symptom specifically related to the lesion, such as visual loss, or a clinical manifestation of hormone excess, but rather for the evaluation of symptoms such as headache, or other neurological or CNS complaints, or head trauma [48].

Pituitary incidentalomas have been found in 14.4% of postmortem studies and 22.5% of radiography studies [4], although their prevalence depends on the definition used in the different studies. They are distributed equally throughout the age groups (range, 16–86 years) and between the sexes [49]. Although most are either gonadotroph PTs or NFPTs, some may be silent lactotroph, somatotroph, or corticotroph PTs. Generally, they are smaller than 1 cm and remain stable throughout the follow-up. However, 10.6% of microadenomas and 24% of macroadenomas may grow; therefore, periodic surveillance by MRI is recommended for up to 20 years [49].

Pituitary apoplexy

A rare form of presentation requiring special attention is pituitary apoplexy (PA), characterized by a sudden onset of headache, loss of vision, or hypopituitarism due to intratumoral hemorrhage or pituitary infarction [50]. It occurs in 2–12% of patients with PTs. In a patient harboring a PT, it most often occurs in the context of a clinically non-functioning macroadenoma [51, 52]. It can occur at all ages, but is more frequent between the fifth and sixth decade and slightly more common in males.

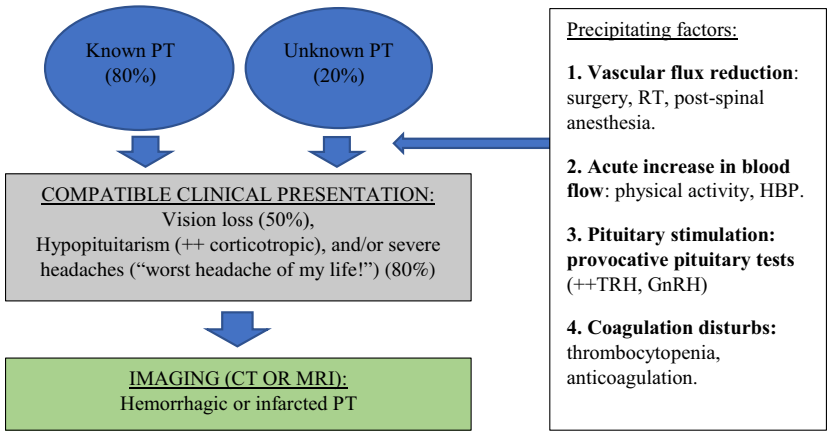
In 20–40% of the patients, precipitating factors are identified, such as anticoagulation, provocative pituitary tests, or surgery (Fig. 1). The most common presenting symptoms include headache (80%), nausea, diminished visual acuity or visual field (50%), ophthalmoplegia/paresis, and impaired mental status. At least one anterior pituitary deficiency is always present at PA onset. Corticotropic deficiency is the most common and important deficit in patients with PA, affecting 60 to 80% of patients [51] (Fig. 2(3 and 5)).

The diagnosis of PA is clinical, requiring both acute onset of symptoms, including vision loss, hypopituitarism, and/or severe headaches, as well as a hemorrhagic or infarcted pituitary lesion (Fig. 1) [53]. The evolution of PA is difficult to predict: the patient can deteriorate dramatically (subarachnoid hemorrhage from an apoplectic adenoma or cerebral ischemia secondary to cerebral vasospasm have been reported) or improve spontaneously, with or without any sequelae. PA can destroy the PT, although regrowth from a tumor remnant is possible [54].

Special situations

Pituitary tumors in pregnancy

Prolactinomas are the most common PTs diagnosed during pregnancy, followed by GH-producing PTs. During pregnancy, 2.7% of microprolactinomas, 22.9% of untreated macroprolactinomas, and 4.8% of previously treated macroprolactinomas may grow and produce mass-effect



PT= pituitary tumor; RT= radiotherapy; HBP= high blood pressure

Fig. 1 Pituitary apoplexy [42]. PT, pituitary tumor; RT, radiotherapy; HBP, high blood pressure

symptoms or hypopituitarism [13] (Fig. 2(3)). In acromegalic patients, biochemical control tends to improve despite the withdrawal of somatostatin analog therapy during pregnancy [55]. The occurrence of pregnancy in women with Cushing's

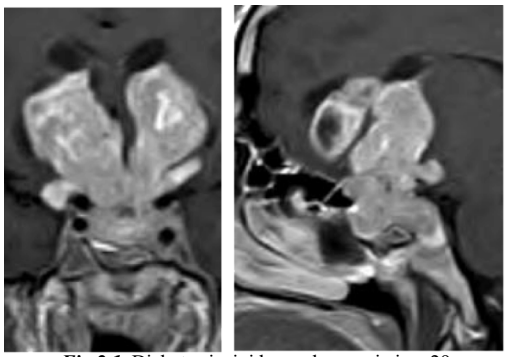


Fig 2.1. Diabetes insipidus and amnesia in a 29-year-old male with a NFPT.

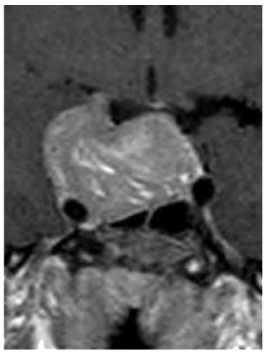


Fig 2.2. Diplopia in a 14-year-old male with a prolactinoma.

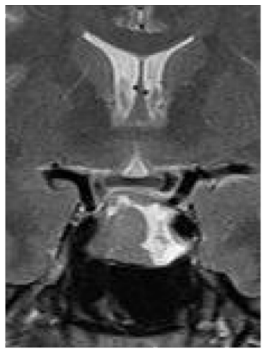


Fig 2.3. Headache in a pregnant with a hemorrhagic prolactinoma

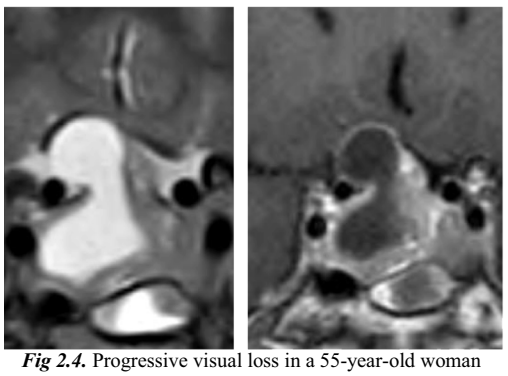


Fig 2.4. Progressive visual loss in a 55-year-old woman with a cystic NFPT

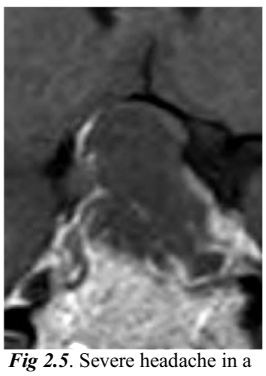


Fig 2.5. Severe headache in a 56-year-old woman with PA

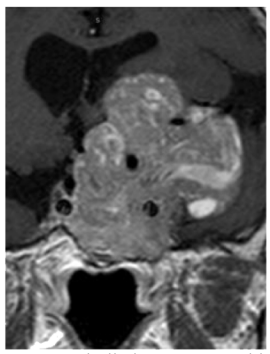


Fig 2.6. Abulia in a 70-year-old man with a corticotropinoma

Fig. 2 Pituitary tumors: spectrum of radiological and clinical presentation. (1) A 29-year-old male with central diabetes insipidus, behavioral changes, episodes of transient global amnesia, and decreased visual acuity at diagnosis. Diagnosis: giant non-functioning pituitary tumor (NFPT) with invasion of both frontal lobes and affectation of the anterior cerebral arteries. (2) A 14-year-old male with a history of 2 months of evolution of right ptosis, diplopia, and growth retardation. Diagnosis: giant prolactinoma with invasion of the right cavernous sinus and compressive involvement of the III right pair. (3) A 32-year-old pregnant woman (first trimester) who presented daily frontal headaches after onset of pregnancy. Diagnosis: prolactinoma with bleeding data. (4) A 55-year-old woman with MEN-1, who presented progressive deterioration of visual acuity mainly in the right eye. Diagnosis: NFPT with cystic degeneration and compression of the optic chiasma and right optic nerve. (5) A 56-year-old woman with severe headache of 24 h of evolution and sharp deterioration of visual acuity and adrenal insufficiency. Diagnosis: giant pituitary prolactinoma with chiasmatic affectation and radiological findings compatible with ischemic pituitary apoplexy (PA). (6) A 70-year-old male with progressive neurological deterioration, urinary incontinence, temporo-spatial disorientation, abulia, anterograde amnesia, and right amaurosis of 2 years of evolution. Diagnosis: giant silent corticotropinoma with invasion of the left cavernous sinus and intracranial extension with involvement of the anterior and middle left cerebral arteries

Table 3 Pituitary tumors in special situations

	PTs in general	PTs in pregnancy	PTs in childhood	PTs in the elderly	Ectopic PTs	Silent PTs	Aggressive PTs and PCs
Prevalence	16.7% of GP	10% of PTs	5% of PTs	10% of PTs	< 1% of PTs	37% of PTs	15 and 0.1% of PTs
Most frequent cell type	Prolactinoma	Prolactinoma	Prolactinoma	NFPT	ACTH-secreting PT	Gonadotroph PT	Corticotroph PT
Second in frequency	NFPT	GH-secreting PT	ACTH-secreting PT	GH-secreting PT	Prolactinoma	Null-cell PT	Crooke's cell PT and prolactin PC
Ratio: female, male	2:1	1:0	2:1	0.8:1	1.5:1	2:1	1:1
Special considerations	5% are associated with familial syndromes	Macroprolactinomas can increase in size	Genetic endocrine syndromes should be considered	PT-related clinical data could be misunderstood as age-related disturbances	Specific symptoms depending on the location	Higher aggressiveness and recurrence rate than NFPT	Rapid growth and site-specific clinical symptoms related with metastases

GP, general population; *PTs*, pituitary tumors; *NFPT*, non-functioning PT

disease (CD) is very unusual (there are fewer than 100 cases of CD during pregnancy reported in the literature), due to the deleterious effects of the disease on fertility [56]. Clinical diagnosis is more difficult than in non-pregnant women: indeed, some of the clinical signs of hypercortisolism overlap with classical signs observed during pregnancy, such as fatigue, weight gain, hirsutism, acne, and emotional instability. The combination of these three's CS signs (hypertension, ecchymosis, and muscle weakness) during pregnancy increases the suspicion of CD [56]. TSH-secreting PTs and NFPTs are very rare during pregnancy; they usually present as hyperthyroidism and mass-effect symptoms, respectively (Table 3). In general, the risk of hypopituitarism and relevant symptomatic growth during pregnancy is low in previously treated adenomas [13].

Pituitary tumors in childhood and adolescence

PTs in children and adolescents are rare tumors (5% of PTs) that often result from a tumor predisposition syndrome [14] (Table 1). They are more commonly diagnosed in females (2:1). PTs are typically benign, with prolactinomas as the most frequently encountered tumors (mostly teenagers), followed by corticotropinomas and somatotropinomas [57]. NFPTs represent only 5–10.5% of PTs in this age group.

Prolactinomas occur mainly in females (5:1) and present with primary or secondary amenorrhea; mass-effect symptoms are more frequent in men [58] (Fig. 2(2)). CD has a peak of incidence at the onset of puberty, and a female predominance, with a ratio of 3:1. In most children, the onset of CS is insidious and the most common presenting symptom is weight gain; in childhood, the lack of height gain with concomitant weight gain is the most common presentation of CS [59, 60]. Compared with CS in adults, sleep disruption, muscular weakness, myopathy, and problems with memory are less commonly seen in children. Moreover, skin striae are very rarely present before the age of 5–7 years of age [59]. GH-secreting PTs are uncommon; they often present in prepubertal children and infants, with a slight preponderance in males (2:1). If the clinical syndrome develops before the fusion of long bone growth plates, it is referred to as gigantism, and, if it presents after that stage, acromegaly [61]. TSH-secreting PTs are very rare in children. They present with the general signs of hyperthyroidism and usually manifest as macroadenomas with symptoms of mass-effect. NFPTs are usually discovered incidentally, in contrast to the case of adults, where they usually present with compressive symptoms. For example, in children, visual dysfunction occurs in fewer than 10% of cases [62].

Pituitary tumors in the elderly

PTs are one of the CNS tumors whose incidence increases with age [24]. Moreover, the increased life expectancy in

the general population is causing a rapid growth in the number of elderly patients with associated diseases. PTs in the elderly (above 65 years) represent less than 10% of all PTs. NFPTs are the most common type of PTs in this age group [15]. However, their incidence is probably underestimated, since the clinical presentation of PTs in the elderly differs from that in younger patients. Some endocrinological and neurological manifestations related to PTs could be misunderstood as age-related disturbances [15]. For example, hypopituitarism symptoms are difficult to identify because they can mimic those of aging. Hypogonadism symptoms are often overlooked, and the tumors are usually diagnosed as very large macroadenomas with mass-effect symptoms, such as visual deficits (Fig. 2(6)). In the same way, visual impairment due to chiasm compression can be easily confused with other age-related ophthalmological pathologies, such as cataract, macular degeneration, and vascular ocular diseases. Symptoms of acromegaly and CS in elderly patients are usually mild, while other findings, such as hypertension, diabetes mellitus, asthenia, and mood depression, may not be correctly interpreted because of the high prevalence of these symptoms in elderly subjects [15]. The primary presenting symptoms in the majority of these patients are a reduction in visual acuity or a field defect [63].

Ectopic pituitary tumors

EPTs are rare tumors described predominantly through case reports. Approximately 60% of them are seen in the sphenoid sinus and suprasellar region, and 30% are found in other locations, such as the clivus, nasal cavity, cavernous sinus, parasellar region, and sphenoid wing [16]. Patients with EPTs share a similar endocrine, age, and sex profile with those who have typical PTs. Sphenoid sinus EPTs present more frequently in the fourth to seventh decades of life, and women are affected more commonly than men [64]. Seventy-five percent of them are functioning EPTs (mostly ACTH and prolactin-secreting PTs) [65].

The symptomatology depends on the involvement of adjacent structures and hormonal activity [64]. Visual disturbances and facial paresthesia may occur due to compression of the cranial nerves by the tumor extending into the cavernous sinus or clivus. Sphenoid sinus EPTs can present with nasal obstruction, headache, and cerebrospinal fluid leak [66]. The common hormonal manifestations include hyperprolactinemia, CS, and acromegaly. Around 25% of EPTs are hormonally inactive [66].

Silent pituitary tumors

SPTs represent 37% of all PTs [67]. The mean age of patients and the female/male ratio is similar to those reported for PTs in general [68]. PTs can either lack secretion of a sufficient level of hormonal product to increase the serum concentration (totally silent) or can secrete hormonal products that do not cause clinical symptoms or signs that are usual for that hormone (clinically silent) [17]. The most frequent types are gonadotroph PTs (43%) [69] and null-cell PTs (33.7%). Clinically silent somatotroph PTs and clinically silent corticotroph PTs follow in frequency [17].

As the majority of SPTs are macroadenoma at diagnosis, two of the most common presenting symptoms are headache and visual field deficits [17]. Pituitary hormone deficiencies occur in up to 67% of patients [70]. Although rare, some cases may progress to a clinically apparent PT, especially in silent corticotroph PTs [71]. Patients with silent corticotroph PTs should be followed up carefully, as these tumors are associated with increased aggressiveness and higher recurrence rate compared with NFPTs [72]. Furthermore, since almost two-thirds of silent somatotroph PTs are mixed GH-prolactin PTs and sparsely granulated monohormonal GH PTs, recurrence and need for radiation is higher than for other NFPTs; thus, close follow-up is also warranted in these cases [73].

Aggressive pituitary tumors and pituitary carcinomas

APTs and PCs do not respond to standard medical treatment. APTs, which represent 15% of all PTs, are PTs exhibiting rapid growth, resistance to conventional treatments, and/or early/multiple recurrences. PCs represent 0.1–0.2% of all PTs and are defined by non-contiguous craniospinal or distant metastasis [18]. APTs are more frequently seen in younger rather than older adults [74]. Their development is more likely in certain tumor subtypes, such as silent corticotroph PTs, Crooke's cell PTs, and plurihormonal PIT-1 positive PTs. PCs typically present in the fourth to sixth decades of life, and the commonest PC subtypes are corticotroph and lactotroph neoplasms [75]. Some studies have found no gender predilection in APTs and PCs [75], while others have reported a slightly male [76] or female [77] predilection.

Regarding clinical presentation, there are some symptoms, such as headache and visual field loss, that overlap between APTs/PCs and PTs, in general, while cranial nerve palsies and obstructive hydrocephalus are more suspicious for APTs/PCs [77]. PCs are diagnosed with a delay of 6.5–9 years, but this is variable, depending on the type of endocrine function of the tumor (9.5 in corticotroph PCs and 4.7 years in prolactin PCs) [78]. In these patients, metastases may lead to other site-specific clinical symptoms, such as hearing loss, ataxia, motor weakness, and liver function derangement [79].

Conclusions

Pituitary tumors usually occur sporadically at the age of 40–50 years, but 5% may do so within family syndromes, usually

at an early age. There are differences by sex, age, race, and genetic factors in the prevalence of different tumor cell types and the form of clinical presentation.

Patients with FPTs are usually diagnosed before NFPT patients due to early symptomatology. However, this depends on the tumor type. Mass-effect symptoms are most frequent in NFPTs, headaches and visual disturbances, although other manifestations, such as seizures or hydrocephalus, may occur. Another possible form of presentation, which requires special attention because of its potential life-threatening risk if it is not diagnosed, is pituitary apoplexy.

Some biological situations may further complicate clinical recognition of PTs, such as in pregnancy or in elderly patients. PTs in adolescence and childhood and those of ectopic location also present a series of peculiarities that must be taken into account. Silent PTs usually present as macroadenomas, and aggressive PTs and PCs are associated with a higher recurrence rate.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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