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Diagnostic Evaluation of the Lesions of the Sellar and Parasellar Region

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1. Introduction

The sellar and parasellar region is an anatomically complex area that represents a critical junction for important contiguous structures (Ruscalleda, 2005). While the sellar region has specific anatomical landmarks, the parasellar region is not clearly delineated. It includes, laterally, the dural walls of the cavernous sinus (Smith, 2005), and is in close relation with the basisphenoid and sphenoid sinus inferiorly, and superiorly with the suprasellar subarachnoid spaces (Ruscalleda, 2005). The nasopharynx and the temporal lobes are also closely related to the region (Smith, 2005). A wide range of neoplastic, inflammatory, infectious, developmental and vascular diseases may embroil vital structures in this region (Freda & Post, 1999). The most frequently involved are the brain parenchyma, meninges, the optic pathways and cranial oculomotor nerves (III, IV, VI) and the V1 and V2 branches of the trigeminal nerve, major blood vessels, hypothalamo-pituitary system, tuber cinereum, anterior third ventricle and bone compartments.

Data from cancer registries suggest that prevalence of primary central nervous system (CNS) tumors is 130–230 cases per 100,000 of the population (Davis et al., 2001). Lesions of the sellar and parasellar region are very common, accounting for 10–15% of intracranial masses based on surgical experience (Terada et al., 1995), and in 3–24% of unselected autopsies depending on the sections examined (Kovacs et al., 2001).

The malignant potential of these tumors may be defined according to the WHO classification of tumors of the CNS (Louis et al., 2007; Lloyd et al., 2004b):

- WHO grade I, i.e. tumors with low proliferative potential and possibility of cure following surgical resection;
- WHO grade II, i.e. infiltrative tumors with low mitotic activity that can recur and progress to higher grades of malignancy;
- WHO grade III, i.e. tumors with histological evidence of malignancy;
- WHO grade IV, i.e. mitotically active tumors with rapid evolution of disease.

A number of other non-neoplastic lesions, such as inflammatory, granulomatous, infectious and/or vascular pathologies can also involve the parasellar region. The different lesions are listed in table 1, according to an etiologic and anatomic classification, and systematically addressed in the following section. Classifications are created to accommodate a large spectrum of entities, from the typical and frequent to the unusual and exceptional, but they are never comprehensive enough to satisfactorily reflect the diversity of nature and the wide range and variety of human diseases (Kovacs et al., 2001).

Pituitary adenomas account for about 90% of lesions of the sellar and parasellar region according to different large surgical series: Freda & Post (Freda & Post, 1999) collected 1120 cases in 18 years in a single center, the German Registry of pituitary tumors (Saeger et al., 2007) collected 4122 cases in 10 years, Valassi et al. (Valassi et al., 2010) collected 1469 cases in 10 years in a single center. Thus in ~8-15% of cases, an etiology other than a pituitary adenoma is encountered: other tumors in 4.2-5.6%, malformative lesions in 2.9-5.2%, inflammatory lesions in 0.7-1.2% of cases (Freda & Post, 1999; Saeger et al., 2007; Valassi et al., 2010). In these series vascular lesions are of course underrepresented.

A recent radiological series, retrospectively evaluating 2598 MRIs performed over 11 years (Famini et al., 2011), showed that after exclusion of normal pituitaries (47%), non-adenomatous lesions accounted for 18% of observed lesions.

Sellar and parasellar masses occur with overlapping clinical and radiological features, ranging from asymptomatic incidental presentations to hormonal symptoms, or compressive local mass effects on nearby vital surrounding structures. The severity depends on the location, size and growth potential of the tumors (Famini et al., 2011; Glezer et al., 2008).

The most common symptom is represented by visual troubles (from minimal visual field defect to blindness) and headache that may be severely disabling. Several mechanisms have been proposed to explain headaches in patients harboring pituitary masses. Some are not related to the volume of the mass, such as distortion of the sellar diaphragm or irritation of the parasellar dura (Arafah et al., 2000; Levy et al., 2004).

Hypopituitarism and hyperprolactinemia (due to the lack of physiologic dopamine inhibition of PRL secretion) are common, whereas diabetes insipidus (DI) and cranial nerve palsies are atypical for adenomas but common for other lesions of the region (see below).

Hypothalamic localization may produce the diencephalic syndrome in children, manifesting as wasting, poor development and sexual immaturity, whereas disruption of appetite control can occur in adults, causing severe obesity or starvation.

A correct diagnosis of such lesions thus implicates a multidisciplinary approach, requiring detailed endocrine, neuroimaging, and ophthalmological studies. Correct diagnostic orientation is crucial in order to choose the proper treatment for each different case (Kaltsas et al., 2008). Histological confirmation is not necessary in formulating a management plan in most cases. It is indeed redundant (and may be even dangerous) when clinical, endocrine and/or radiological features are clear-cut. But what about the uncommon borderline situations? Samples for histological evaluation can be nowadays collected by mini-invasive image-guided techniques (Frighetto et al., 2003; Samandouras et al., 2005). The procedure should be reserved only to those cases when radiologic features are not clearcut, but risks and benefits of such procedures must be strongly considered.

Tumors deriving from adeno-hypophyseal cells	Pituitary adenoma Pituitary carcinoma	
Tumors deriving from neuro-hypophyseal cells	Pituitocytoma Granular cell tumor (choristoma)	
Parasellar tumors	Malignant	Glioma Germ cell tumor Primary lymphoma Pituitary metastases Supratentorial primitive neuroectodermal tumor Ependymoblastoma
	Potentially malignant (low-grade)	Chordoma Chondrosarcoma Chondroma Langerhans' cell histiocytosis Hemangiopericytoma Solitary fibrous tumors Plasmacytoma
	Usually benign	Craniopharyngioma Meningioma Paraganglioma Lipoma Neurinoma/Schwannoma Gangliocytoma
Malformative lesions	Rathke's cleft cyst Epidermoid Dermoid Hamartoma Empty sella Arachnoid cyst	
Granulomatous, infectious and inflammatory lesions	Hypophysitis Pituitary abscess Pseudotumor Tuberculosis Mycoses Sarcoidosis Wegener's granulomatosis Sphenoidal mucocele	
Vascular lesions	Aneurysm Carotid-cavernous fistula Cavernous sinus thrombosis	

Table 1. Classification of sellar and parasellar lesions

2. From theory to practice

Patient 1 is a 55 year-old woman, complaining of headache and visual troubles for a few months. She had two pregnancies and is post-menopause since two years. Previous medical history is unremarkable, except for hypertension, treated with ACE-inhibitor since 5 years. Physical examination is negative, except for peripheral visual loss at confrontation.

Patient 2 is a 34 year-old woman, complaining of amenorrhea since 8 months. She had one uneventful pregnancy and lactated 3 years ago. Previous medical history is unremarkable. On physical examination she is slightly overweight.

Patient 3 is an 8 year-old male whose parents perceived growth arrest and worsening of school performance. After his pediatrician's evaluation showing GH deficiency, he performed MRI and was referred to neurosurgeon for a mass in the sellar region. The neurosurgeon requires an endocrine evaluation prior to the planned mass resection.

Patient 4 is a 45 year-old male, referred to the endocrinologist after finding a 7-mm lesion in the pituitary on MRI performed after a road accident.

3. Systematic of sellar and parasellar lesions

3.1 Lesions deriving from adeno-hypophyseal cells

3.1.1 Pituitary hypertrophy/hyperplasia

First of all, it should be stressed that also physiological conditions can drive enlargement of the pituitary gland. Sex- and age-dependent variations in size and shape of the pituitary have been indeed reported (Chanson et al., 2001). Pituitary height in healthy subjects can be higher than 9 mm in 0.5%, simulating a pituitary lesion, mostly in adolescent girls (figure 1 a, b) but also in menopausal women (Tsunoda et al., 1997). Furthermore, reversible pituitary hyperplasia can be observed during pregnancy (Elster, 1991) as well as in pathological conditions such as long-term severe failure of target organs (hypothyroidism - Hutchins et al., 1990 -, hypoadrenalism - Clayton et al., 1977 -, hypogonadism - Kido et al., 1994) (figure 1 c, d) and CRH or GHRH hypersecretion (Asa et al., 1984; Sano et al. 1988). In such conditions the pituitary gland is homogeneously increased both on plain and contrast-enhanced images.

It is worth considering this diagnosis in the patients undergoing MRI for any reason, particularly in young females.

A biopsy is not necessary to diagnose such lesions. In the event tissue is examined in cases of GHRH or CRH hypersecretion, silver stains (Gomori, Gordon-Sweet, etc.) are needed in order to distinguish hyperplasia from adenoma. These techniques demonstrate the delicate reticulin fiber network, surrounding the acini. This acinar pattern is preserved in hyperplasia and disrupted in adenoma (Kovacs et al., 2001).

3.1.2 Pituitary adenomas

Classification and epidemiology

Pituitary adenomas are defined as benign lesions arising in the anterior pituitary. They can be classified according to size (microadenomas and macroadenomas being, respectively,

smaller and larger than a conventional 10-mm cut-off), extension (intrasellar and extrasellar, being, respectively, enclosed or not within sellar limits, irrespective of their size), and secretory status. Most adenomas are PRL-secreting, followed by clinically non-functioning (NFPA), GH-secreting, ACTH-secreting, and last by TSH-secreting ones.



Fig. 1. a and b: adolescent girl (courtesy of P. Doneda, MD). T1 MRI shows diffuse enlargement of the pituitary gland, with convex superior margin and posterior pituitary “bright spot” (a), homogeneously enhancing (b). c and d: 8 yo girl, with primary hypothyroidism. MRI at diagnosis (c) shows enlarged, homogeneously enhancing pituitary gland with suprasellar extension; after replacement treatment with L-thyroxine pituitary size is reduced and normal (d).

Adenomas can be eventually classified as typical or atypical. The atypical adenoma is defined as an invasive tumor with elevated mitotic index, Ki-67 (MIB-1) proliferation index of 3% or more, and an extensive nuclear immuno-staining for p53 (Jaffrain-Rea et al., 2002; Turner & Wass, 1999.). The poorer prognosis of this adenoma is due to a higher degree of

invasiveness, larger size, and accelerated growth that reduce the chances of radical removal. It accounts for less than 3% of pituitary tumors in the German Registry (Saeger et al., 2007) and differs from pituitary carcinoma (0.12% of cases in the German Registry) only in the lack of metastases (see below).

As for epidemiology, a pathological systematic review (Ezzat et al., 2004) combined the findings from seven autopsy series: among a total of 3375 autopsied pituitaries, the overall prevalence of adenomas was 14.4% and the most frequent were PRL-staining ones. Thereafter, in a single series of 3048 autopsy (Buurman & Saeger, 2006) a total of 334 adenomas in 316 pituitary glands were reported, only 22.7% being > 3 mm (3 macroadenomas).

The mean radiological prevalence of pituitary adenomas was 22.3%. In a combined analysis including both radiological and pathological data, the prevalence of unsuspected pituitary adenomas was 16.7% (Daly et al., 2009).

From the clinical point of view, it was recently indicated that prevalence of pituitary adenomas is 3–5 times higher than previously believed. In 2006 a cross-sectional study in a definite area of Belgium using an intensive case-finding approach involving all the general practitioners and relevant specialists, reported a mean prevalence of 94 cases per 100,000 (Daly et al., 2006). Once again the most frequent tumors were prolactinomas, accounting for 2/3 of cases. An international, multicenter study in Europe, South America and other sites with a total population of 862,000 found similar results (Daly et al., 2009).

Clinics

Macroadenomas can cause a common clinical picture, due to mass effect of expanding tumor impinging on neighbor structures: visual defects (from minimal visual field defect to typical hemianopsia to amaurosis), headache, and hypopituitarism. Giant adenomas can give rise to cavernous sinus syndrome with oculomotor nerve palsies or seizures (when expanding through cavernous sinus to temporal lobe), or DI. These latter manifestations are so rare that must prompt an accurate differential diagnosis with non-adenomatous lesions of the region.

Each secretory adenoma causes a typical hypersecretory syndrome:

- PRL-secreting adenomas produce amenorrhea and galactorrhea in women, loss of libido and hypogonadism in men, and secondary osteoporosis in both sexes (Colao, 2009);
- GH-secreting adenomas cause acromegaly (or gigantism before puberty) (Melmed, 2006);
- ACTH-secreting adenomas are the main cause of Cushing's disease (Bertagna et al., 2009);
- TSH-secreting adenomas cause central hyperthyroidism (Beck-Peccoz et al., 2009).

All these entities, mostly Cushing's disease and acromegaly, are associated to increased morbidity and mortality, when untreated.

Although commonly defined as benign tumors, invasion of surrounding tissues can occur in half of pituitary adenomas (Bonneville et al., 2005; Meij et al., 2002), depending on size and subtype (in increasing order from the lowest rate in Cushing's disease, to intermediate in acromegaly, PRLomas, null cell, and plurihormonal adenomas, to the highest in Nelson's syndrome, and TSHomas).

Imaging

MRI is nowadays the gold standard for imaging pituitary gland and hypothalamic disorders.

The normal anterior pituitary has signal intensity similar to the white matter on T1 and T2, whereas a spontaneous hyperintensity on T1 images, the so-called bright spot, appears in the posterior pituitary of most patients (figure 2). It is related to the phospholipid membrane of the ADH-containing neuro-secretory granules in the posterior pituitary. The lack of bright spot is closely correlated with a loss of function of the neuro-hypophysis but nonspecific because it occurs also in 10-20% of normal subjects. With the administration of paramagnetic contrast agent, the pituitary and its stalk enhance or become brighter in signal intensity (Freda & Post, 1999).

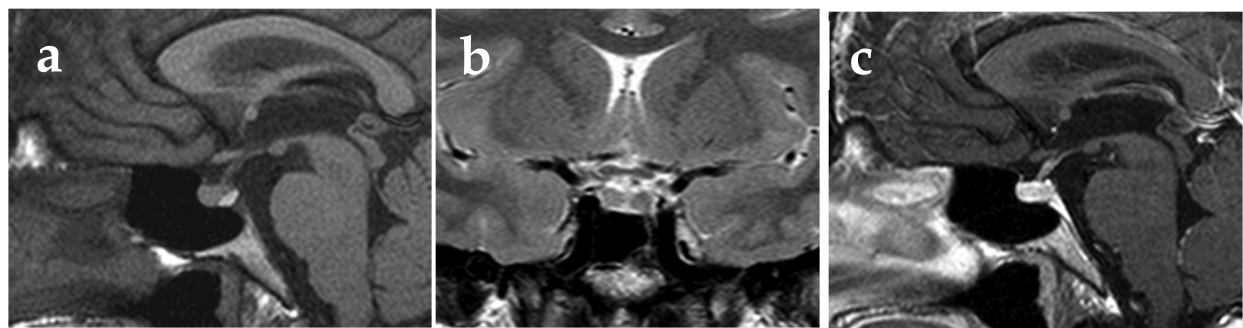


Fig. 2. Normal MRI of pituitary. Anterior pituitary has signal intensity similar to white matter on T1 (a) and T2 (b). The typical “bright spot” is shown in posterior pituitary gland. The pituitary and stalk enhance strongly (c).

Most microadenomas on precontrast T1-weighted images show abnormal low signal, whereas some may appear hyperintense due to internal bleeding (Rumboldt, 2005). On T2-weighted images microprolactinomas are usually hyperintense and GH-secreting adenomas are iso-hypointense (Bonneville et al., 2005)(figure 3). About 5% to 10% of microadenomas are detected exclusively on post-contrast images.

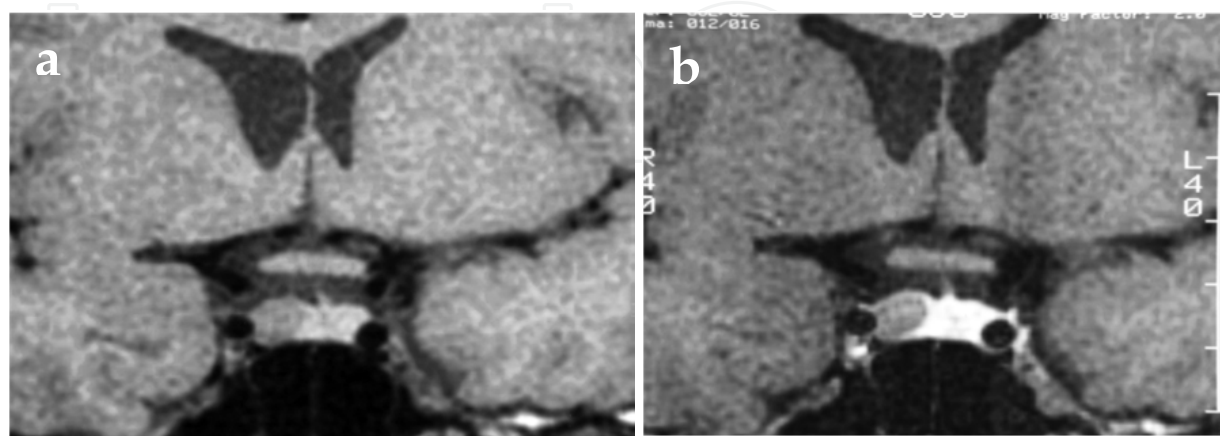


Fig. 3. Typical microadenoma: coronal MRI on T1 (a) shows a well-demarcated hypointense intrapituitary mass, < 10 mm in diameter, with contralateral stalk deviation. Contrast enhancement is slower into the microadenoma (b).

The peculiar vascularization of the adeno-hypophysis, supplied by a portal rather than an arterial circle, allows dynamic MR imaging. Using this technique, the normal gland enhances later than the pituitary stalk and cavernous sinuses. The tumors show delayed enhancement. Dynamic post-contrast imaging is thus a useful tool to increase the sensitivity of the exam (Bonneville et al., 1993). Indirect radiologic signs, like unilateral bulging of the superior pituitary margin and stalk deviation, may be helpful. Anyway, stalk deviation is a nonspecific sign, being observed even in normal subjects. Moreover, the deviation can be either contralateral or more rarely ipsilateral to the microadenoma (Ahmadi et al., 1990).

The finding of a focal pituitary lesion may be incidental (so-called incidentaloma, see below) and not related to any clinical picture (Teramoto et al., 1994).

Macroadenomas are occasionally heterogeneous on MRI. Cystic, necrotic, or hemorrhagic portions may appear as hyperintense areas (Rumboldt, 2005) (figure 4). Sometimes macroadenomas with suprasellar extension, due to constriction at the level of the diaphragm appear like a number 8 or a snowman. Further information provided by MRI is that bizarre and irregular shape usually points to PRLomas. Tumors that are isohypointense with the normal gland on T2-weighted sequences tend to be more fibrotic (Elster, 1993). Post-contrast images are acquired in order to visualize the normal pituitary tissue, strongly enhancing and displaced (laterally or posteriorly or superiorly) by the expanding mass, as well as the relationships with the optic pathways and cavernous sinus (Cottier et al., 2000; Knosp et al., 1993).

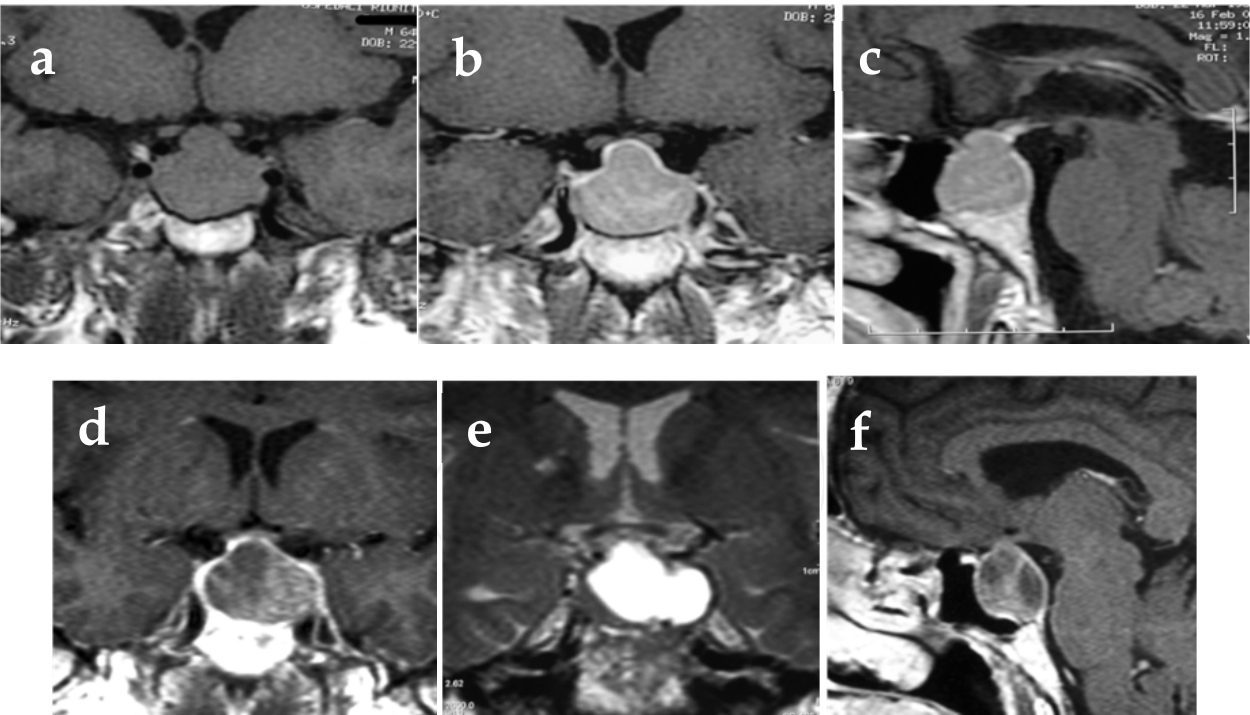


Fig. 4. a-c: Typical macroadenoma. Coronal (a and b, before and after contrast administration, respectively) and sagittal (c) MRIs show intra/suprasellar mass. The lesion looks like a “snowman” on morphology, is isointense with gray matter and enhances homogeneously. It compresses optic chiasm and left cavernous sinus without definite invasion. d-f: cystic macroadenoma in another patient. The lesion appears homogeneously hyperintense on T2 (e), moderately and heterogeneously enhancing (d and f).

Pituitary incidentaloma

Pituitary adenomas have been found at post-mortem examination in 10-15% of subjects without any clinical manifestation, regardless of age or gender. Very few were macroadenomas. It was thus hypothesized (Molitch, 2009) either that the growth from micro- to macroadenoma is an exceedingly uncommon event, or that a macroadenoma cannot miss clinical diagnosis, but more data are needed.

Due to the large availability of sophisticated imaging techniques an ever-growing amount of lesions in the pituitary region are incidentally found. MRI scans of subjects examined for reasons unrelated to pituitary disease (excluding thus scans performed for visual loss, or a clinical manifestation of hypopituitarism or hormone excess) have visualized silent pituitary tumors sized ≥ 3 mm in approximately 10% of them (Hall et al., 1994). Therefore there is an outbreak of so-called pituitary incidentalomas, in analogy to adrenal lesions. In this setting also macroadenomas can be encountered in 0.2-0.3% of normal subjects (Nammour et al., 1997; Vernooij et al., 2007; Yue et al., 1997).

What is the correct and cost-effective approach to this situation, both at diagnosis and during follow-up (Dekkers et al., 2008; King et al., 1997; Randall et al., 2010), considering that sensitivity and specificity of MRI were reported to be of 99% and 29%, respectively (Famini et al., 2011)?

To screen hypersecretory syndromes, even without a clear-cut clinical picture, is mandatory. The minimal panel to diagnose hypersecreting adenomas includes:

- PRL assay after thorough exclusion of physiological, i.e. pregnancy and stress, pharmacological (mostly anti-psychotic, anti-depressive, and gastroenteric drugs, acting as anti-dopaminergic) and pathological causes of secondary increase of plasma PRL levels (such as hypothyroidism, renal or liver failure, lung or kidney tumors) to rule out hyperprolactinemia;
- IGF-I levels to rule out acromegaly, when a reliable assay is available and main causes of spurious decrease, i.e. liver disease and malnutrition have been excluded;
- free thyroxine (FT₄) and TSH to rule out central hyperthyroidism;
- morning cortisol after overnight suppression test (or night salivary cortisol if available) to rule out Cushing's disease.

More formal evaluation can be required as a subsequent step, if first level assessment is uncertain.

- Whereas very high PRL levels (i.e. > 200 ng/mL) are diagnostic of PRLomas, lower levels may require further testing to distinguish between stalk compression (due to any mass in the region, inhibiting the physiologic dopamine inhibition of PRL secretion, with PRL levels seldom exceeding 100 ng/mL) and different clinical conditions. Serial PRL sampling will overcome stress, sample dilutions or PEG precipitation will rule out, respectively, hook effect (due to saturation of capture antibodies in presence of large amounts of antigen, as observed in very large PRL-secreting tumors) or macroprolactinemia (circulating macroaggregates of PRL without biological effect).
- GH assay during oral glucose load because the physiologic GH suppression is lost in GH-secreting tumors.

- One or more among the numerous available tests for diagnosing Cushing's disease.

To establish a diagnosis of hypopituitarism it is useful to perform assays of serum cortisol at 8 a.m., FT₄, and testosterone, to rule out hypoadrenalism, hypothyroidism, and male hypogonadism, respectively. To evaluate gonadal function in females, a history of regular menses in fertile age or FSH assay post-menopause is sufficient. Hypopituitarism can be partial or total and it generally occurs only in patients with macroadenoma (up to half of patients). Microadenomas usually do not cause disruption of normal pituitary function, even though it has been recently reported GH deficiency even in this setting (Yuen et al., 2008). Thus, all patients bearing a macroadenoma should be screened for hypopituitarism. It is commonly accepted that GH deficiency should be screened only in those patients candidate to ensuing GH substitutive treatment.

Obviously all hypersecreting tumors, whether clinically or incidentally diagnosed, should be appropriately treated with surgery or drugs, according to type of tumor and relative guidelines (Biller et al., 2008; Cozzi et al., 2009a; Melmed et al., 2011). This is not always the case for clinically non-functioning pituitary adenoma (NFPA). Whereas surgery is clearly indicated in macroadenomas impinging or near the optic pathways, unless absolute contraindications exist, the same is not true for the incidentally found microadenoma or macroadenoma. NFPAs are a very heterogeneous population from a biological and clinical point of view (Honegger et al., 2008), and some series with serial evaluation over many years clearly demonstrated that progressive growth is not the rule. It was observed only in 10% of microadenomas, while any change in size has been shown in the vast majority and even a reduction occurred in 6% (Dekkers et al., 2007; Karavitaki et al., 2007.).

In a meta-analysis, 8.2% of incidentalomas enlarged per year (1.7% of microincidentalomas) with a follow-up of 472 person-years (Fernandez-Balsells et al., 2011). Importantly, none of the patients with microincidentalomas developed new visual field defects requiring surgery. Watchful waiting can thus be considered a safe option (Freda et al., 2011). In microadenomas we suggest to perform the first MRI at 12 months, and the second after additional 18-24 months: if no growth is observed further monitoring can be safely withdrawn, unless new neuro-ophthalmological symptoms occur. In macroadenomas not undergoing surgery, we recommend visual assessment every 6 months; MRI should be performed at 6-month intervals for the first year, then yearly. Images must be always personally compared with the first one (and not only with the last): if no growth occurs and visual fields are intact, intervals between imaging can be progressively lengthened.

Unless clinical picture changes, it is useless to repeat screening of hypersecretions during follow-up. Yearly evaluation of basal serum cortisol, FT₄ and testosterone is warranted in macroadenomas, to timely start substitutive treatment(s) when necessary.

Pituitary apoplexy

An acute condition to be aware of is pituitary apoplexy. This may be a life-threatening clinical syndrome, characterized by sudden onset of headache, vomiting, visual impairment and decreased consciousness caused by the rapid expansion of sellar-suprasellar mass. It is usually the result of a hemorrhage or an infarction in a preexisting adenoma (most often a NFPA, but any type can be involved), and it has a rapid clinical progression (within hours or days) (Nawar et al., 2008).

Notably, in 60-80% of cases the adenoma was previously unknown. Pituitary tumor apoplexy occurs as the first manifestation of disease in a previously asymptomatic patient mainly in the fifth or sixth decade.

The apoplexy syndrome should be distinguished from two different situations: ischemic changes occurring in otherwise normal pituitary glands, after prolonged hypotensive episodes, generally in women after excessive postpartum bleeding (Sheehan's syndrome-Dash et al., 1993), and small hemorrhages frequently (up to 25% of cases) found in adenomas without any specific acute clinical picture. These are sometimes inappropriately defined as silent or subclinical pituitary tumor apoplexy. The term apoplexy is appropriate only when signs of compression of perisellar structures or meningeal irritation occur after hemorrhagic infarction of an adenoma (Arafah et al., 1997; Dubuisson et al., 2007; Nielsen et al., 2006; Onesti et al., 1990; Randeva et al., 1999; Sibal et al., 2004).

The reported incidence is near 2% (Bonicki et al., 1993; Nawar et al., 2008).

On a retrospective evaluation, a lot of events have been advocated as precipitating factors in at least 25-30% of patients (Biousse et al., 2001; Möller-Goede et al., 2011; Semple et al., 2007). Anticoagulant/antiaggregant therapy and coagulopathies, head trauma, hypotension or hypertension, previous irradiation, myocardial infarction, major surgery (in particular coronary artery bypass surgery), hemodialysis, angiography, spinal anesthesia, initiation or withdrawal of dopamine agonists, pregnancy and estrogen therapy, and dynamic testing of pituitary function have been reported. Gonadotrophin-releasing hormone, thyrotrophin-releasing hormone, corticotrophin-releasing hormone and insulin tolerance test have all been reportedly involved in apoplexy. Whenever the association with dynamic tests was described, it occurred within 2 hours in 83% and within 88 hours in all patients (Levy, 2003; Yoshino et al., 2007). This finding coupled to inefficiency in differential diagnosis and cost of testing prompted a drastic reduction in the overall use of such procedures in the last years and suggests that these procedures should be abandoned.

The earliest and most frequent symptom of pituitary tumor apoplexy is sudden and severe headache (75-100%), often accompanied by vegetative (nausea and vomiting) and neurological symptoms. Cranial nerve palsies, mainly diplopia, occur in 70% of patients; visual impairment, from visual field defects to decreased visual acuity up to blindness, occurs in nearly 75% of the cases.

Hypopituitarism is very common (near 80%) and may be life-threatening if unrecognized and untreated. In contrast to the common rule that ACTH-secreting cells are the most resistant to injuries of any kind, central hypoadrenalism is reported in up to 70% of the patients. DI is rare (8%) but may occur and be permanent. Low PRL levels indicate a poor prognosis for pituitary function recovery (Zayour et al., 2004). On the other hand, pituitary hypersecretion can be "cured" in patients surviving apoplexy (Glezer et al., 2008).

Blood in the tumor is characteristically appreciated on imaging according to time elapsed from bleeding. Within 3 hours from onset CT (performed without contrast administration) is superior to MR. A high-density or heterogeneous gland with or without evidence of subarachnoid hemorrhage can be visualized on the former, but no specific sign on the latter. With the progressive breakdown of oxyhemoglobin to deoxyhemoglobin after 3 hours from

bleeding and owing to the paramagnetic properties of intracellular or extracellular methemoglobin, apoplectic pituitary appears isointense on T1-weighted images and very hypointense on T2-weighted images (figure 5). Thereafter there is focal hyperintensity on T1-weighted images, and focal hyper- or hypointensity on T2-weighted images. Areas of old bleeding appear cystic on CT and often hypointense on T1-weighted MRI due to increased proton density (Piotin et al., 1999). Late follow up usually shows a decrease in tumor volume.



Fig. 5. Hemorrhagic pituitary apoplexy (MR performed 6 hours after the onset of clinical picture). Axial and sagittal T1 (a and d) show confluent hyperintensity in enlarged gland, with moderate, rim enhancement. On coronal T2 (b) the intra and suprasellar mass appears hypointense. Optic chiasm is strained (c and e).

According to recent British Guidelines (Rajasekaran et al., 2011), a high degree of clinical suspicion is needed to diagnose pituitary apoplexy. All patients presenting with acute severe headache with or without neuro-ophthalmic signs, should be submitted to urgent neuroradiological imaging. Patients should undertake visual fields assessment as soon as possible when clinically stable, and be administered iv steroids after baseline endocrine function tests (serum cortisol and FT₄) if hemodynamically unstable. Urgent referral to a neurosurgeon is mandatory when visual deterioration is present. Emergency surgery is usually indicated in these cases.

3.1.3 Pituitary carcinoma

Most pituitary tumors are noninvasive adenomas with local expansion along the lines of minor resistance. Near half can become locally invasive infiltrating surrounding tissues

(dura and bone) by radiologic or pathologic criteria (Meij et al., 2002), and some are defined “atypical”, according to a proliferative index higher than 3% in pathology sections. The proliferative index (Ki67/MIB-1) has no useful clinical relevance, in our experience, and no particular follow-up is needed in these cases.

Pituitary carcinoma is a rare entity (< 0.5% of pituitary adenomas) whose definition until now relies upon the presence of metastases (Kaltsas et al., 2005). It must be stressed that this definition is far from being satisfying from a clinical (and logical) point of view. Very aggressive tumors, requiring multiple resections by skilled operators and adjuvant radio and chemotherapy cannot be labeled carcinomas owing to the lack of metastases. Metastases are sometimes found in patients whose tumor has the same proliferative index, mitoses, hypercellularity, nuclear pleomorphism, necrosis, hemorrhage, etc. of “normal” adenomas (Kovacs et al., 2001).

Current working consensus to diagnose pituitary carcinoma requires fulfillment of all the following criteria (Lloyd et al., 2004a):

- histologic diagnosis of primary pituitary tumor;
- presence of metastases without any continuity with primary pituitary tumor;
- strict correspondence or at least similarity in cytohistologic features and biomolecular markers between metastases and primary pituitary tumor;
- exclusion of any possible alternative primary tumor.

The great majority of pituitary carcinomas are associated with excessive hormonal secretion (mostly ACTH or PRL, but any type was reported), with progressive loss of hypersecretion heralding dedifferentiation. A variable latency period (mean 7 years, Kaltsas et al., 2005) elapses between the clinical onset of what is initially diagnosed as an aggressive pituitary macroadenoma and the appearance of metastases. Thereafter the mean survival is less than 4 years, even though a wide variation is described.

Metastases can localize in the brain and spine (40%, through invasion into the subarachnoid space), can be systemic (47%, through hematogenous or lymphatic dissemination, common sites being liver and bone) or can be found at both locations (13%) (Kaltsas et al., 2005).

3.2 Lesions deriving from neuro-hypophyseal cells

3.2.1 Pituitocytoma

Pituicytes are specialized glial cells lodged in the stalk and posterior pituitary. They can transform in pituitocytoma, a rare low-grade neuro-hypophyseal glial tumor, also known as pituitary astrocytoma, histologically distinct from pilocytic astrocytomas (Brat et al., 2000; Huang & Castillo 2005; Katsuta et al., 2003).

Pituicytomas usually occur in young to middle-aged women; they are ubiquitous in the hypothalamic-pituitary axis and can be entirely intrasellar or suprasellar or involve both compartments. Clinical presentation is similar to that of other regional masses: headache and hypopituitarism are the most common trouble. Despite the neuro-hypophyseal origin, DI is not common.

Imaging does not enable differentiation from other neuro-hypophyseal tumors and the diagnosis is histologic. MRI shows a solid, demarcated, enhancing sellar or suprasellar mass,

usually isointense to gray matter on T1 and hyperintense on T2, occasionally displacing anteriorly the normally enhancing adeno-hypophysis (figure 6).

Although histologically benign, the location and high vascularization can make radical resection difficult (Glezer et al., 2008; Kowalski et al., 2004).

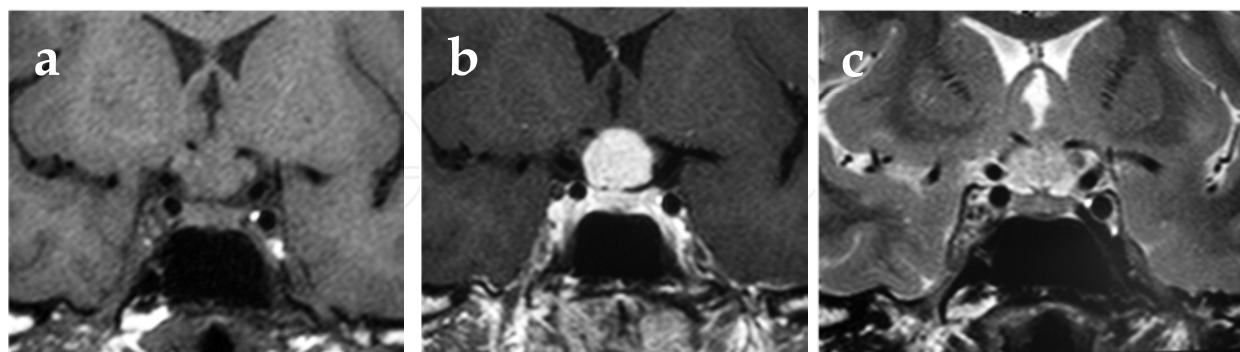


Fig. 6. Pituitocytoma in a young man complaining headache, decreased libido, and diabetes insipidus. MRI depicts a suprasellar, nodular mass, arising from pituitary stalk, isointense on T1 and T2 (a and c, respectively), strongly enhancing (b), like meningioma, compressing the optic chiasm.

3.2.2 Granular cell tumor

They are the most common (found in up to 17% of non selected adult autopsies) primary tumor originating from either the neuro-hypophysis or infundibulum, also referred to as choristomas, myoblastomas, and infundibulomas (Freda & Post, 1999; Huang & Castillo, 2005; Kaltsas et al., 2008).

Granular cell tumors are benign tumors, arising from granular cell-type pituicytes (Cohen-Gadol et al., 2003). They are usually asymptomatic, even though they can present, mainly in the fifth decade, with symptoms related to size and mass effect. Headache is common, 90% of symptomatic patients have visual complaints, and 50% have hypopituitarism or hyperprolactinemia. In spite of their origin from the infundibulum and/or posterior lobe, they are not typically associated with DI.

Most symptomatic patients have intra and suprasellar tumors, but in 11% tumor is purely intrasellar. The imaging appearance is nonspecific (Bubl et al., 2001; Iglesias et al., 2000). They appear isointense to gray matter on both T1- and T2-weighted sequences, with intense enhancement reflecting high vascularity. Calcifications may be present, as well as the loss of the so-called bright spot.

Surgical treatment for symptomatic granular cell tumors is indicated.

3.3 Malignant parasellar tumors

3.3.1 Glioma

Gliomas may arise in the hypothalamus and optic pathways.

Optic nerve gliomas are rare tumors accounting for 3.5% of intracranial tumors in children and 1% of intracranial tumors in adults, in whom they have a malignant behavior (Black & Pikul 1999; Freda & Post, 1999; Guillamo et al., 2001; Kaltsas et al., 2008; Kitange et al., 2003).

The **childhood variety**, occurring within the first decade of life, is typically pilocytic astrocytoma (WHO grade I), a benign and slow-growing lesion. The tumor usually grows infiltrating the chiasm and optic nerves. About 30% of patients with optic pathway gliomas have neurofibromatosis type 1 (NF-1), while about one third of patients with NF-1 will develop multicentric optic pathway gliomas, low-grade brain stem gliomas and basal ganglia non-neoplastic hamartomas (Kornreich et al., 2001). The most frequent presenting symptoms in children are loss of vision, headaches, and proptosis. Often, the visual loss remains unrecognized until the tumor is advanced. Imaging shows a hypointense lesion on T1 sequences with contrast enhancement, in the chiasm or optic nerve. The best therapy for optic gliomas confined in one optic nerve is surgery. Surgery plus radio and chemotherapy are an option in all the other cases, but a rule does not exist at the moment.

The **young adult type** of gliomas can develop in the brainstem and extend into the parasellar region. Diffuse intrinsic low-grade glioma (WHO grade II) is the most prominent type, whereas purely malignant brainstem glioma (WHO grades III-IV) occurs in 31% of cases. The initial presentation is often monocular blurring of vision and retrobulbar pain, which may progress rapidly to blindness (Glezer et al., 2008). The pattern of field defects is extremely variable and nonspecific. Presentation of an optic nerve glioma as an intrasellar cystic mass is exceedingly rare. On MR imaging, these lesions can usually be localized into the optic chiasm. The sella is normal in most patients. Typically, they are isointense to hypointense on T1-weighted images and hyperintense on T2-weighted images, with infiltration along the optic nerves and optic tracts, homogeneously enhancing. Radiotherapy is probably the best palliative therapy.

Hypothalamic gliomas present almost always in early life, with disruption of hypothalamic function, failure to gain weight, DI, and visual loss with optic atrophy. On MR imaging, these tumors do not spread along the optic nerves but rather are large masses in the suprasellar region, more invasive into the hypothalamus, infiltrating the brain and the third ventricle. Hypothalamic gliomas are hypo to isointense on T1-weighted images and isointense to hyperintense on T2-weighted images, homogeneously enhancing (figure 7). The tumor may extend into the suprasellar cistern or the surrounding brain parenchyma, usually without necrosis, hemorrhage or calcification. They may encase the vessels of the circle of Willis, and hydrocephalus is common (Smith, 2005).

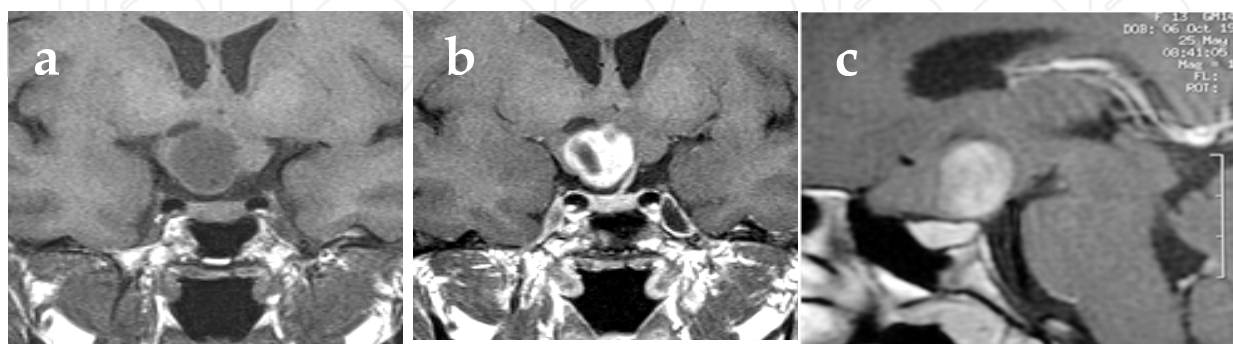


Fig. 7. Hypothalamic glioma in a 10 yo girl with NF1, complaining sight loss, without endocrine disturbances. Coronal and sagittal MRIs reveal an infiltrating hypothalamic mass involving the optic chiasm, isointense to the brain, with nodular and cystic components. The nodular portion enhances brightly and dislocates the pituitary stalk to the left.

Diagnosis can be accomplished by stereotactic or open biopsy.

Optic pathway gliomas are generally very slow growing tumors, while tumors around the chiasm/hypothalamus can be more aggressive (5-year survival 50%).

The best therapeutic approach is uncertain: watchful waiting, surgery, glucocorticoids and irradiation, and chemotherapy with temozolomide and/or other agents have been proposed with variable degree of success.

3.3.2 Germ cell tumors

Intracranial germ cell tumors are rare malignant tumors, representing 0.1-2% of all primary brain neoplasms. They are tumors of the suprasellar region arising from totipotent germ cells that fail to migrate to the genital crest during embryonic life. They are subdivided into germinomas (two thirds of the intracranial ones), teratomas, embryonal cell carcinoma, choriocarcinoma, endodermal sinus (yolk sac) tumors, and mixed germ cell tumors (Huang & Castillo 2005).

Their usual localization is in the midline, most frequently at the pineal gland region (80%). Three patterns are described: germinomas of the ventral hypothalamus associated with germinoma in the pineal region; germinomas in the anterior third ventricle that can involve the pituitary fossa as an extension; and intrasellar germinoma mimicking an intrasellar adenoma (Packer et al., 2000). All these can spread to involve the chiasm and optic nerves and may disrupt pituitary function.

Germinomas have a peak incidence in children and adolescents. Pineal localization is more frequent in males and supra and intrasellar one is more frequent in females.

Patients most commonly present with endocrine abnormalities: DI is the most common symptom (80%). It is worth noting that DI may persist for years before a diagnosis is made. Other manifestations include hypopituitarism in children and adolescents and hypogonadism in adults. Hyperprolactinemia and precocious puberty have been observed. Large tumors and primarily suprasellar tumors may present with visual field defects or optic atrophy, oculomotor palsies or hydrocephalus, and signs of increased intracranial pressure (Freda & Post, 1999; Glezer et al., 2008; Janmohamed et al., 2002; Kaltsas et al., 2008).

Diagnosis is established by histology but a subgroup can be diagnosed on the basis of elevation of specific tumor markers (Calaminus et al., 2005), or typical radiological features. Alpha-fetoprotein and chorionic gonadotrophin can be detected in the serum and/or cerebro-spinal fluid (CSF), and they are a pathognomonic sign of yolk sac tumors and choriocarcinomas, respectively (Calaminus et al., 2005; Matsutani et al., 1997).

CT scanning depicts isodense or hyperdense masses, sometimes multicentric, which enhance markedly. The concomitant presence of similar lesions in the suprasellar and pineal region is diagnostic (Freda & Post, 1999; Glezer et al., 2008; Kaltsas et al., 2008; Smith, 2005).

On MRI the lack of the posterior bright spot is an early but unspecific sign. It can be followed by swelling of the stalk and subsequent mass formation, which may displace anteriorly the enhancing pituitary gland (figure 8). At last a germinoma can appear as an enhancing solid homogenous mass with well defined margins, that appears isointense to

gray matter on T1-weighted images and isointense-slightly hyperintense on T2-weighted images, displacing anteriorly the adeno-hypophysis with or without suprasellar extension (Rennert & Doerfler, 2007). Cystic changes, hemorrhage, or calcification are rarely observed (Freda & Post, 1999; Glezer et al., 2008; Kaltsas et al., 2008; Rennert & Doerfler, 2007; Smith, 2005; Sumida et al., 1995).

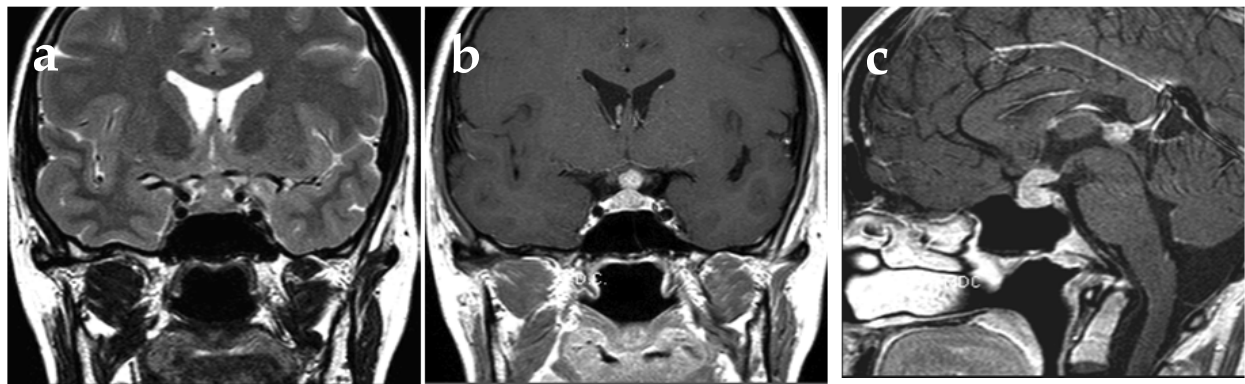


Fig. 8. Germinoma in a young boy with diabetes insipidus at presentation. Coronal MR shows a sellar and suprasellar lesion, isointense on T2 and homogeneously enhancing. Sagittal MRI (c) depicts a synchronous lesion in the pineal region, that “engulfs” the pineal gland.

Teratoma appears in imaging as a well-delineated mixed cyst with fat and calcification. This tumor can undergo ossification, teeth formation, or malignant transformation (Glezer et al., 2008).

Histological confirmation on a sample obtained using stereotactic or neuroendoscopic biopsy is the ‘gold standard’ diagnostic method. It will show a granulomatous infiltrate around germ cells. Biopsy can be avoided if clear-cut results have been obtained by imaging and biochemical markers (Calaminus et al., 2005).

Direct surgery is rarely indicated and ventricular shunting may be the only surgical procedure required (Janmohamed et al., 2002). Germinomas usually respond well to chemotherapy and radiotherapy.

3.3.3 Primary parasellar lymphoma

Primary CNS lymphoma is defined as a lymphoma limited to the cranio-spinal axis without systemic disease. Most originate from B-cell. They are distinct from systemic lymphomas that secondarily metastasize to the CNS (an event reported in about 30% of patients), and account for 1-2% of non-Hodgkin lymphomas and for about 3% of all intracranial neoplasms (Giustina et al., 2001). Primary localization at the pituitary is extremely rare (less than 1% in patients undergoing trans-sphenoidal surgery – TSS - for a sellar mass) (Freda & Post 1999, Moshkin et al., 2009). They were initially described in immunocompromised patients, but recently they have been documented even in immunocompetent patients (Giustina et al., 2001).

Peak incidence is between the 6th and 7th decade in non immune-depressed subjects and earlier in the immune-depressed ones, with a male preponderance (Pels et al., 2000).

Systemic symptoms, such as fever of unknown origin, are uncommon at presentation (22%), whereas local compressive symptoms are more frequent (headache, diplopia, and visual field defects in 56%, 39%, and 28%, respectively), as well as hypopituitarism (72%) and DI (39%) (Liu et al., 2007).

Lymphomas usually appear iso- or hyperdense on CT scanning, whereas appearance may be different on MRI based on whether patients have normal or suppressed immunity (Erdag et al., 2001; Huang & Castillo 2005; Johnson et al., 1997). Imaging of a sellar localization is largely nonspecific with diffuse enlargement of the pituitary (94%), suprasellar extension (44%), cavernous sinus extension (39%) and stalk thickening (22%). Most cases appear isointense on T1-weighted sequences, homogeneously or heterogeneously enhancing, usually without calcifications and hemorrhages, but isointense to hypointense relative to gray matter on T2-weighted imaging (Buhring et al., 2001).

The diagnosis of primary lymphoma is established histologically by stereotactic biopsy, but noninvasive tests can now be used with confidence, such as SPECT or PET or rather identification of EBV DNA in the CSF that is sensitive and usually unique for this disease (Castagna et al., 1997).

Treatment options include surgery, chemotherapy and radiotherapy (Glezer et al. 2008).

3.3.4 Metastases to the sellar and parasellar region

Metastases to this region are rare, less than 1% of patients undergoing TSS for sellar/parasellar lesions (Komninos et al., 2004). Autoptic series reported involvement of the region in up to one quarter of patients with intracranial dissemination. Furthermore, metastases have been diagnosed more and more frequently in recent years, owing to amelioration of imaging techniques, as well as improved survival in oncologic patients.

Even though metastases are usually part of a generalized spread in elderly patients without sex predominance, they can occur in young patients too, and occasionally are the first manifestation of an occult cancer or the only site of metastasis.

The most common primary tumors are breast and lung cancer, in females and males, respectively, accounting for two-third of reported cases, but any neoplasm can spread to the pituitary region and the primary tumor remains undetected in approximately 3% of cases despite intensive investigation.

Metastatic cells can spread to the sellar region via different ways: through the portal vessels, through the suprasellar cistern, by extension from the skull base, and directly through arterial blood circulation.

DI is the most frequent symptom at presentation, reported in 28% to 70% of patients (up to 100% in some series). It may be the initial manifestation of the malignancy. Anatomical reasons account for this pattern: the posterior lobe is directly supplied by arterial vessels and has a larger area of contact with the adjacent dura, in contrast with the anterior lobe supplied by the portal system. DI may occasionally be transient or intermittent, because regeneration of neuro-hypophyseal fibers may occur. In addition it can be masked by concomitant central hypoadrenalism until corticosteroid treatment is started (Freda & Post, 1999; Kaltsas et al., 2008).

Hypopituitarism is less frequent, both for the above described anatomical reasons and because it can be clinically masked by nonspecific symptoms (weakness, vomiting, weight loss) attributed to neoplasm. Cranial nerve palsies (mostly of the 6th nerve) may be found in 12-43% of patients.

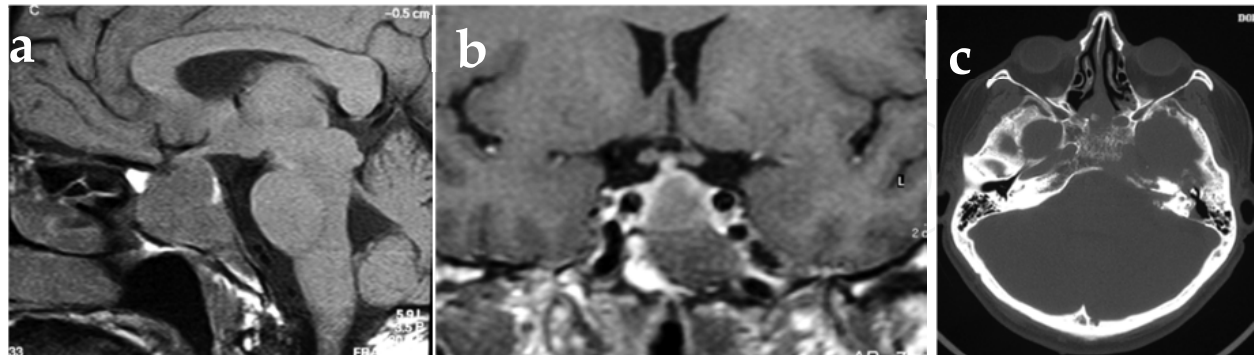


Fig. 9. Metastases in a 56 yo woman with breast cancer. Sagittal and coronal MRI reveals an intra and suprasellar solid mass, infiltrating the clivus and sphenoid sinus. The lesion is moderately hypointense on T1 and heterogeneously enhancing. Axial CT-bone (c) demonstrates a large erosion of the central skull base.

It is worth noting that the majority of metastases to the pituitary are clinically silent and even when symptomatic, cannot be reliably distinguished from primary sellar tumors on the basis of clinical and radiographic presentation. They often may mimic a pituitary adenoma or a variety of sellar area lesions, benign or malignant, especially when clinical evidence of primary malignancy is absent. Besides, even in patients with known malignancy, a sellar lesion is not always a metastasis; a benign lesion, like a pituitary adenoma, can be present and trigger clinical troubles in 1.8-16% of patients with known malignancy. It is thus essential a correct diagnosis, to appropriately plan the following therapeutic steps.

CT usually shows a hyperdense or isodense mass, homogeneously or inhomogeneously enhancing (if cystic degeneration, hemorrhage, or necrosis exists).

On MRI, pituitary metastatic lesions appear as enhancing isointense or hypointense sellar/suprasellar mass on T1, and usually hyperintense on T2. The mass may sometimes overrun the sellar diaphragm (so-called dumbbell-shape best seen on sagittal images), in contrast to adenomas, which usually upward displace the diaphragm (figure 9). Bone erosions, as well as the loss of posterior pituitary bright spot and stalk thickening, are nonspecific findings (Freda & Post, 1999; Kaltsas et al., 2008).

Lumbar puncture may be essential, pointing to malignancy in cases in which a meningeal spread is present.

Most of the times in absence of a primary and/or other metastatic lesions, diagnosis relies on histology. Immunohistochemical analysis is mandatory because local infiltration and cytological features such as nuclear pleomorphism, multinucleate cells and mitotic figures cannot reliably distinguish between malignancy and adenomas.

As a trans-sphenoidal approach is needed to gain a histological diagnosis in all sellar-suprasellar masses, resection, as radical as possible, should be undertaken. An extended

approach is needed in almost every case. Adjuvant treatments by radiation and chemotherapy should be individually tailored, with adequate hormonal substitution.

The overall prognosis is poor, owing to the aggressiveness of the primary neoplasm, with a median survival of less than 2 years (Laigle-Donadey et al., 2005).

3.4 Potentially malignant parasellar tumors (low-grade malignant tumors)

3.4.1 Tumors of cartilaginous origin

Approximately 10% of non-pituitary parasellar lesions are cartilaginous (chordomas, chondromas and chondrosarcomas) originating from the primitive notochord in the skull base (Kaltsas et al., 2008). They are located within the clivus in nearly 40% of cases or elsewhere within the sellar or parasellar region.

Chordomas are rare (1% of all malignant bone tumors and 0.1-0.2% of all intracranial neoplasms), locally invasive slow-growing tumors of the midline, most commonly arising around the ends of the notochord, within the sacrum and clivus. In 35% of cases they arise in skull base around the spheno-occipital synchondrosis, and rarely within the sella, in which case they are difficult to distinguish from pituitary macroadenomas (Thodou et al., 2000). They can occur in adults of all ages, mostly between 30 and 50 years.

Symptoms depend on the direction of tumor growth, usually posterior with extension into the prepontine cistern (Rennert & Doerfler, 2007). The most common presenting symptoms are headache (occurring early in a third of patients) and visual complaints, mainly diplopia due to typically asymmetric involvement of the sixth, third, or fourth cranial nerve. Field defects, when present, are similar to those seen with pituitary adenoma. Chordomas can reach considerable size at the time of diagnosis and patients may develop neck pain and nasopharyngeal obstruction (Rennert & Doerfler, 2007). Endocrine dysfunction is unusual, but hypopituitarism or mild hyperprolactinemia may occur. Less common presentations include dizziness, tinnitus, facial sensory deficits, ataxia, and hemiparesis.

Chordomas can be quite aggressive, causing local infiltration and extensive bone destruction in the skull base; in addition, they relapse and may progress to malignant transformation (Erdem et al., 2003; Gehanne et al., 2005).

CT scan of patients with clival chordoma shows a bone destroying mass, with frequent intra-tumoral calcifications (50%). MRI shows a destructive invasive lesion in the clivus, isointense to gray matter on T1, heterogeneously hyperintense on T2, heterogeneously enhancing with honeycomb-like internal septations, with involvement of the neural and vascular structures (Korten et al., 1998)(figure 10). Occasionally, cyst-like hypodense centers secondary to necrosis can be found (Erdem et al., 2003; Gehanne et al., 2005; Rennert & Doerfler 2007). In some cases, the normal pituitary gland can be distinguished from the tumor, a helpful finding to differentiate chordomas from invasive pituitary adenomas, which can likewise produce extensive bone destruction, even though usually causing sellar ballooning rather than destruction (Glezer et al., 2008).

Chondroma is another bone destructing, nodular/lobular tumor, arising from cartilaginous remnants in the area of the foramen lacerum, that undergo mucinous, cystic regression and calcification. Imaging findings are similar to those in chordoma (Rennert & Doerfler, 2007).

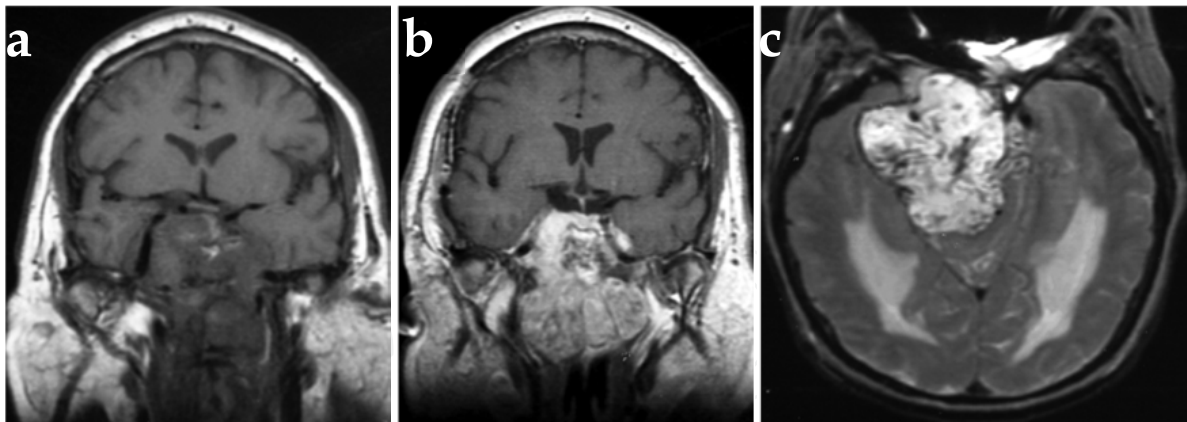


Fig. 10. Clival chordoma. Coronal T1 MR (a) reveals an invasive central skull base mass, infiltrating clivus and basisphenoid, sella, right cavernous sinus, and nasopharynx. The lesion is strongly and heterogeneously enhancing (b). On axial T2 (c) the signal is characteristically heterogeneously hyperintense.

Chondrosarcoma (Korten et al., 1998; Meyers et al., 1992) is a malignant tumor (WHO grades II–III), arising off the midline, at the petro-clival junction also associated with extensive bone destruction and compression on adjacent structures.

Chondromas and chondrosarcomas are centered along the lateral margin of clivus in petro-occipital fissure and display chondroid calcifications in more than half of cases.

An immunohistochemical distinction can be made as all these tumors are positive for S-100 protein but chondrosarcomas are negative for cytokeratin markers and epithelial membrane antigens (Kaltsas et al., 2008).

Surgery is the treatment of choice for all these tumors, but radical resection is usually not possible due to bone invasiveness (Glezer et al., 2008). RT adjuvant therapy is mandatory. Proton Beam therapy has shown the best results in chordomas, but in general the prognosis of these tumors remains poor on the long term.

3.4.2 Langerhans' cell histiocytosis

Langerhans' cell histiocytosis (LCH) or class I histiocytosis is a rare multisystem disorder. In the traditional classifications of parasellar tumors it is frequently described among the granulomatous disorders. Since it was discovered to be stemmed from the clonal proliferation of specific dendritic cells belonging to the monocyte-macrophage system, called Langerhans' cells, it is to be regarded as a genuine neoplastic disease.

Proliferation of histiocytes forms granulomas that infiltrate and destroy many sites, such as bone, lung, skin, hypothalamic-pituitary axis, and, less frequently, liver, spleen, lymph nodes, and bone marrow (Kaltsas et al., 2000).

The incidence is 3–4 cases per million per year in children younger than 15 years (only 1/3 of the cases are reported in adults), with males being 2 times more frequently affected than females (Glezer et al., 2008).

The disease has a particular tropism for the hypothalamo-pituitary system. DI affects half of the patients. Often it is the presenting sign and may even remain the unique feature of the

disease. In childhood, LCH is the second most common cause of DI; consequently, this diagnosis should be actively pursued in childhood-onset DI (Prosch et al., 2006). Hypothalamic or stalk involvement can result in growth failure, frequent in children, or visual impairment. Bones may commonly appear as punched out, in particular skull, mandible, or long bones (Grois et al., 2004; Horn et al., 2006; Kaltsas et al., 2000; Makras et al., 2007).

On MRI there is no specific sign but in all patients with DI the 'bright spot' of the posterior pituitary is lost. In addition a suprasellar mass, hypothalamic lesions, and a thickened stalk (> 3.5 mm) are common findings (Kaltsas et al., 2000). They appear hypointense or isointense on T1 and hyperintense on T2, and enhance brightly with contrast (Lury et al., 2005)(figure 11).

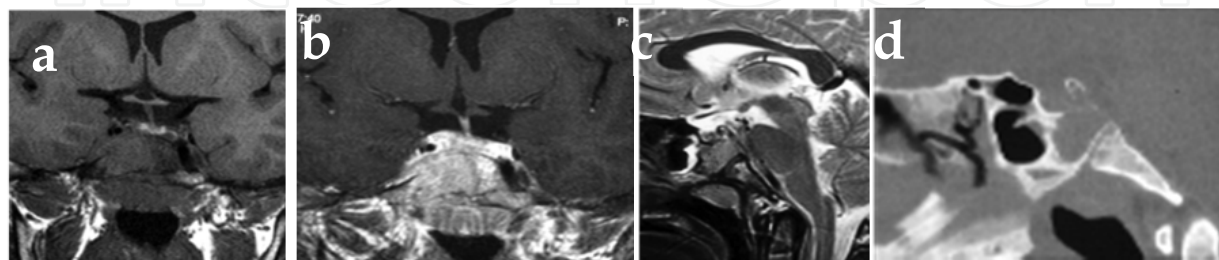


Fig. 11. Young female with known Langerhans' cell histiocytosis. MR shows a lesion in the basisphenoid, infiltrating the sella and nasopharynx, isointense on T1 (a) and slightly hiperintense on T2 (c). Sagittal CT-bone (d) demonstrates clivus and sellar erosion.

To achieve an early and accurate diagnosis is important due to the high mortality rate (20%) and permanent consequences (50%) associated to multisystem disease (Makras et al., 2007). The diagnosis may be established on the basis of symptoms, imaging, and biopsy of involved sites (Glezer et al., 2008; Kaltsas et al., 2000.), with immunohistochemical characterization of Langerhans' cells (S-100 protein, a CD1a antigen). Pituitary stalk biopsy is not routinely recommended in small lesions (< 7 mm).

Due to the systemic nature of the disease, chemotherapy is indicated, with possible radiotherapy on the parasellar region (Makras et al., 2007).

3.4.3 Other tumors

Case reports described a lot of other tumors arising in the parasellar region: hemangioblastomas (Rumboldt et al., 2003), hemangiopericytomas (Jalali et al., 2008), fibrosarcomas (Lopes et al., 1998), rhabdomyosarcomas of the sphenoid sinus (Jalalah et al., 1987), solitary fibrous tumors (Furlanetto et al., 2009), esthesioneuroblastomas (Sajko et al., 2005), pituitary blastomas (Scheithauer et al., 2008), supratentorial primitive neuroectodermal tumors (Ohba et al., 2008), ependymomas (Mukhida et al., 2006), plasmacytomas (Sinnott et al., 2006), melanocytic tumors (Rousseau et al., 2005), and epidermoid carcinomas (personal observation).

3.5 Benign parasellar tumors

3.5.1 Craniopharyngioma (Karavitaki et al., 2006, 2009)

Craniopharyngiomas are uncommon tumors (incidence is 0.13 per 100,000 person-years). They account for 2–5% of all primary intracranial neoplasms. There is no gender difference.

A bimodal age distribution is known, with peaks in children (5–14 years, 5.6–15% of intracranial tumors in children, 10–20 times more common than adenomas) and in older adults (50–74 years) (Karavitaki et al., 2005), but they may be detected at any age (Bailey et al., 1990). Nearly two thirds occur before the age of 20 years.

Craniopharyngiomas are grade I tumors, according to the WHO classification, but in spite of a benign histological appearance, their aggressive behavior with infiltrative tendency into critical parasellar structures heralds a significant surgical morbidity and mortality (Karavitaki et al., 2006). Malignant transformation, even if exceedingly rare (possibly triggered by previous irradiation) has been reported (Kristopaitis et al., 2000; Nelson et al., 1988). Craniopharyngiomas are derived from squamous cell rests in the remnant of Rathke's pouch between the adeno-hypophysis and neuro-hypophysis and can develop anywhere along the path of the craniopharyngeal duct, from the nasopharynx to the third ventricle. The majority (95%) is located in the sellar/parasellar region with a suprasellar component (purely suprasellar in 20–41%, both supra- and intrasellar in 53–75%), but also entirely intrasellar tumors can occur (Karavitaki et al., 2005; Van Effenterre & Boch, 2002).

Craniopharyngiomas are typically described as tumors with a lobular shape (Fahlbusch et al., 1999). Their consistency is purely or predominantly cystic in 46–64%, purely or predominantly solid in 18–39% and mixed in 8–36%. Calcifications are present in 45–57% (in 78–100% of children) with a pattern varying from solid lumps to popcorn-like foci or less commonly, to an eggshell pattern lining the cyst wall. Two pathological varieties are classically described – the adamantinomatous and the papillary – with occasional mixed forms (Zhang et al., 2002).

The adamantinomatous type is the most common, mainly affecting children and adolescents, even though it may occur at any age. There are solid and cystic components, necrotic debris, fibrous tissue, and calcifications. The cysts may be multiloculated, with a typical macroscopic appearance of machinery oil. Tumor margins are irregular, often intermingled with the surrounding brain tissue and the vascular structures. Three layers of cells are histologically visualized: a basal layer of palisading cells resembling the basal cells of the epidermis, an intermediate layer constituted by loose aggregates of stellate cells, and a top layer lining the cyst lumen with flattened and keratinized squamous cells, desquamating to form nodules of 'wet' keratin. These are heavily calcified and appear grossly as white speckles, capable of eliciting an inflammatory and foreign-body giant cell reaction.

The papillary type is typical of adults. It is usually better defined with respect to brain tissue, calcifications are rare and the cyst content is viscous. The histological examination shows rare mature squamous epithelial cells forming pseudopapillae and an anastomosing fibrovascular stroma.

Investigators have argued that papillary and adamantinomatous subtypes may represent two distinct entities located at the opposite ends of a pathological continuum (Zada et al., 2010).

The most common clinical presentations are, as usual for lesions in this area, DI, headache, nausea/vomiting, cranial nerve palsies, visual troubles and endocrine manifestations. Growth failure or delayed sexual development are described in 93% and 20% of children respectively, GH deficiency in 35–95% of the evaluated patients, FSH/LH deficiency in 38–82%, ACTH deficiency in 21–62%, TSH deficiency in 21–42%, and DI in 6–38%. The visual

and endocrine abnormalities are frequently unrecognized initially (time elapsed between the onset of symptoms and diagnosis reportedly ranges between 1 week and 31 years), mostly in children that do not realize visual deficiency and increased thirst. As a result, these tumors can become large and cause liquoral obstruction and signs of increased intracranial pressure before the diagnosis is made. Hydrocephalus is observed indeed in up to 38% of cases and it is a more common finding in children (Karavitaki et al., 2005). Many patients suffer from chronic obesity even before surgery, secondary to hypothalamic dysfunction (Honegger et al., 1999; Karavitaki et al., 2006).

On CT, the cystic lesions are non-enhancing areas of low attenuation. The contrast medium enhances any solid portion, as well as the cyst capsule. Calcification is evident in 60% of tumors and it's more common in pediatric cases and in the adamantinomatous subtypes (Karavitaki et al., 2006. Sartoretti-Schefer et al., 1997).

The MR appearance of craniopharyngiomas depends on the proportion of the solid and cystic components, the content of the cyst(s), and the amount of calcification (Huang & Castillo 2005)(figure 12). The solid portions of the tumor appear as iso- or hypointense relative to the brain on pre-contrast T1-weighted images, but can also have a mottled appearance owing to calcific regions; they are usually of mixed hypo- or hyperintensity on T2-weighted sequences, and heterogeneously enhance following Gd administration (Choi et al., 2007; Hald et al., 1994). Large calcifications may be visualized as nodular or curvilinear areas of low signal on both T1- and T2 (Curran & O'Connor, 2005; Smith, 2005), and are more evident on CT. The cystic components are hyperintense on T1 with a thin peripheral contrast-enhancing rim, and have high or mixed intensity on T2 images (Sartoretti-Schefer et al., 1997). Fluid debris levels can be seen within the cysts. Protein, cholesterol and methemoglobin may cause high signal on T1, while very concentrated protein and various blood products may be associated with low T2-weighted signal (Sartoretti-Schefer et al., 1997). Whenever a craniopharyngioma is suspected, CT and MRI should both be acquired because the combination of these two exams is able to establish a firm diagnosis in almost every case.

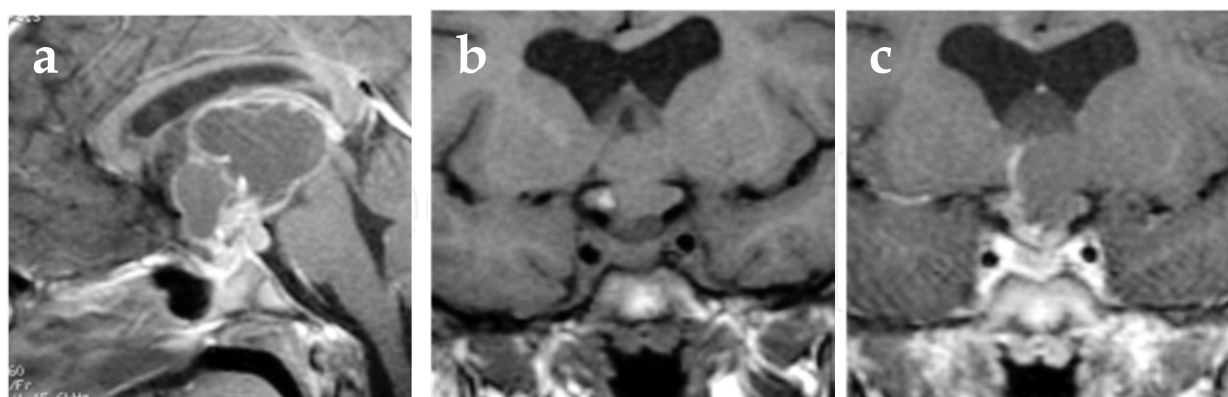


Fig. 12. Craniopharyngioma in a 10 yo girl. MRI on T1 shows a suprasellar, heterogeneous mass, with a small intrasellar component; solid portions and cystic walls enhance heterogeneously, with nodular and rim components (c).

Craniopharyngioma increases mortality (10-year survival rate is 83-92.7% overall and 29-70% in childhood), due to direct tumor effect on critical intracranial structures, surgery associated effects (among the others severe dehydration due to adipsic syndrome with likely

complications), hypopituitarism, and increased cardio-cerebrovascular and respiratory mortality (Bülow et al., 1998; Müller, 2011).

It is often associated to severely impaired quality of life (Dekkers, 2006).

Up to now surgery is the only valid therapeutic option, with the goal of total removal at first operation, thus preventing recurrences, which are very difficult to remove completely at repeated surgery. In recent years the application of a trans-nasosphenoidal extended endoscopic approach in these cases has shown to be more effective and less harmful for the surrounding nervous structures than traditional craniotomic approaches. It is a matter of debate if surgery has to be necessarily performed in patients without neuro-ophthalmologic signs or symptoms. Radiosurgery can be a valuable option in case of residual tumor after an operation (Suh & Gupta, 2006). If large cystic portions cannot be resected, it has been reported that instillation of radioisotopes or bleomycin may provide benefits (Karavitaki et al., 2006). Systemic chemotherapy and interferon have been proposed in recurrent tumors and those that have undergone malignant transformation (Karavitaki et al., 2006). Recurrences usually develop within 4 years, occasionally with aggressive growth, even though longer delays have been described (up to 26 years).

3.5.2 Meningioma

Meningiomas are benign, slow-growing tumors arising from arachnoid cells. They can be localized in the sellar/suprasellar region and can reach considerable size at the time of diagnosis.

They are the most common non-glial primary brain tumor, accounting for 20% of all intracranial neoplasms, with an annual incidence of 6 per 100,000. Peak incidence is around 60-70 years and they are 2 times more common in females (Bondy & Ligon, 1996).

There is a strong association between meningiomas, neurofibromatosis (multiple tumors) and previous exposure to ionizing radiation (Hartmann et al., 2006).

According to the current WHO classification, around 90% are grade I tumors, 5-7% are atypical meningiomas (grade II) and 1-3% are anaplastic variants (grade III) (Hartmann et al., 2006; Whittle et al., 2004). Any type of meningioma, however, is able to assume a malignant behavior, although very rarely (Ko et al., 2007).

Meningiomas can arise from any part of the dura, most commonly at sites of dural reflections, at the skull vault, and from the skull base (Smith, 2005; Whittle et al., 2004). In 15-30% of cases, meningiomas may arise from the parasellar region (tuberculum sella, cavernous sinus, planum sphenoidale, diaphragma sellae, clinoid process). They represent the most common tumor of the region after pituitary adenomas; rarely, they grow entirely within the sella, arising from the undersurface of the diaphragma sella or from the dorsum sellae, but even from the floor or walls of the sella (Huang & Castillo, 2005).

Intra-suprasellar meningiomas may mimic NFPA's, with headache (both frontal and orbital), visual troubles, and endocrine abnormalities (hypopituitarism or hyperprolactinemia). Visual loss is the most common symptom, even without endocrine dysfunction, but intrasellar meningioma mimicking pituitary apoplexy was reported (Orakdogeny et al., 2004). The visual loss may begin with monocular blurring and then progresses to bilateral

loss of vision. Different visual field defects have been reportedly associated to meningiomas: from deficits of either central or peripheral visual fields up to an asymmetric variant of bitemporal hemianopsia. Visual loss is gradual rather than abrupt. Optic atrophy is often observed but without pain on eye movement, in contrast to retrobulbar neuritis. Extraocular muscle palsies may occur. Meningiomas have been reported to increase in size during pregnancy and to become symptomatic (Freda & Post, 1999).

Imaging features of meningiomas are frequently characteristic and permit to distinguish them from other parasellar tumors (Smith, 2005). On CT meningiomas appear as a hyperdense lesion with well-defined margins, uniformly enhancing, arising from the dura with an extensive attachment. They can fill and expand the cavernous sinus; hyperostosis (thickening and sclerosis) of the contiguous bone can be present (Smith, 2005). Dense calcification is suggestive of meningiomas, in particular at the tuberculum sellae (Glezer et al., 2008).

On MR meningiomas are typically isointense on T1 and T2, enhancing homogeneously and brightly, with occasional areas of diffuse calcification. Forty per cent are hyperintense on T2 (Karavitaki et al., 2009). Less commonly, they may have cystic or fat areas (Smith, 2005). The dural tail, a linear enhancing thickening of the dura in continuity with convexity extending away from the lesion, is not specific to meningioma (Guermazi et al., 2005). The sella is usually normal in size and the pituitary gland can be distinctly visualized. When a meningioma invades the cavernous sinus, the carotid artery lumen can be reduced more than with other tumors (Young et al., 1988) (figure 13).

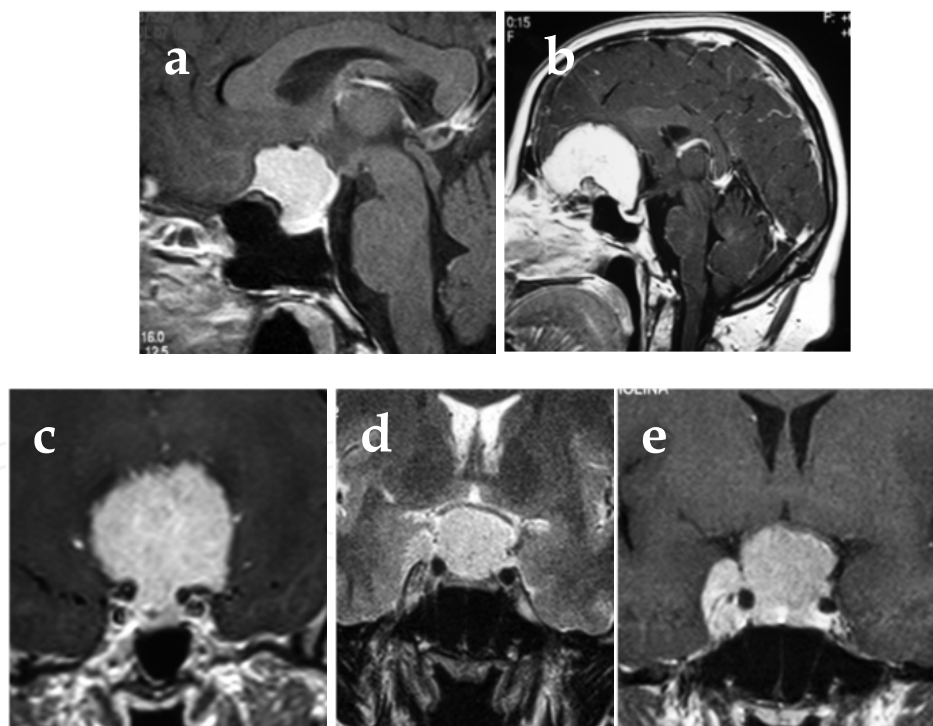


Fig. 13. Meningiomas. Coronal and sagittal contrast-enhanced MRIs show dural-based, mostly homogeneously enhancing mass. Planum sphenoidal meningiomas can completely (a) or partially (b) invade sella, compressing pituitary gland. Note typical hyperostosis and dural “tail”. Diaphragma sellae meningiomas (c) can invade suprasellar cistern, compressing optic chiasm and lightly down-pushing normal pituitary gland (best seen on coronal T2, d), or they can overrun sella and cavernous sinus (e).

These lesions can remain stable for a long time and therefore can be safely followed-up only by serial imaging, but in the presence of symptomatic or growing lesions surgery is the treatment of choice. Most of these tumors are approached by a trans-cranial approach; in recent years, however, trans-sphenoidal extended endoscopic approaches have gained momentum (Cappabianca et al., 1999). A strong debate is underway among neurosurgeons about the approach to be preferred. Although benign, meningiomas can be locally aggressive, even with encasement and, ultimately, occlusion of an internal carotid artery. Furthermore they can recur after incomplete resection: in 7–20% of grade I tumors, in 39–40% and 50–78% of atypical and anaplastic tumors, respectively (Ko et al., 2007). Malignant histology is associated with a poor prognosis (survival less than 2 years) (Hartmann et al., 2006).

Also radiosurgery is used either as primary treatment of small (up to 3 cm diameter) tumors or for the treatment of residual disease or initial recurrence after surgery (Freda & Post, 1999). Nowadays it can be considered the choice treatment to prevent growing of small asymptomatic tumors. After the advent of the MRI, asymptomatic tumors are very frequently detected, thus posing a problem of treatment.

Due the presence of specific receptors in the tumor (Arena et al.), radiometabolic treatment with somatostatin analogs is under evaluation (Bartolomei et al., 2009).

Replacement treatment with estroprogestinic drugs in young females presenting with iatrogenic amenorrhea after radiosurgery is also a matter of debate due to the presence of estrogen and progesterone receptors on tumoral cells (Pravdenkova et al., 2006).

3.5.3 Paranglioma (Naggara et al., 2005)

Parangliomas (or glomangiomas) are rare benign encapsulated neoplasms (WHO grade I), arising in specialized neural crest cells associated with autonomic ganglia, and demonstrated in the pituitary also (Boari et al., 2006). Five percent of CNS parangliomas produce metastasis (Boari et al., 2006). The presenting symptoms are nonspecific (mass effects and hypopituitarism).

MR images reveal a highly vascularized lesion, with characteristic “salt and pepper” appearance on T1. Salt corresponds to high signal areas in the tumor parenchyma secondary to subacute hemorrhage, whereas pepper zones are low signal foci from high-velocity flow voids. Bone-only CT can depict a wormhole pattern of sellar walls. CT, MRI and angiography (in order to search for other possible localizations of a multicentric tumor) are all required before surgical resection of this highly vascularized tumor.

3.5.4 Lipoma

Lipomas are benign fatty tumors (Smith, 2005) that may occur even in the sellar region, as lesions adherent to the surface of the infundibulum, floor of the third ventricle or adjacent cranial nerves. They are usually discovered incidentally but rarely may enlarge. On CT and MRI they appear as well delimited, homogeneous not enhancing lesions, with possible rim calcification, that disappear on fat-suppressed sequences (Kurt et al., 2002; Smith, 2005)(figure 14). There is no indication to a treatment whatsoever.

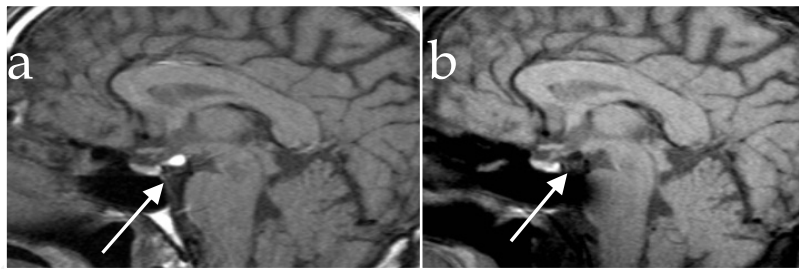


Fig. 14. Lipoma at the tuber cinereum, appearing as an ovoid hyperintense lesion on T1 (a) and disappearing on T1 fat-saturating sequence (b).

3.5.5 Schwannoma/neurinoma

These slow-growing tumors (WHO grade I) develop from the Schwann cells of sensory nerve sheaths. They are very rare in the parasellar region, usually arising from the first or second trigeminal branch or from oculomotor nerves (Rennert & Doerfler, 2007; Sarma et al., 2002). Schwannomas (associated in 60% with neurofibromatosis 2) can cause bone remodeling of the lateral portion of the sella or the apex of the petrous bone (Rennert & Doerfler, 2007). Symptoms depend on trigeminal involvement. They can rarely undergo malignant change. On CT and MRI, they appear as a parasellar mass that is isodense on CT, hypointense on T1 and usually hyperintense on T2 with intense homogenous contrast enhancement (Freda & Post, 1999; Rennert & Doerfler, 2007). Surgery and or radiosurgery are generally indicated.

3.5.6 Gangliocytoma

Ganglion cell tumors or gangliocytomas are rare benign tumors that may originate in the pituitary or elsewhere in the sellar and suprasellar regions. They may consist of purely neuronal or more frequently mixed adenomatous and neuronal tissue (Geddes et al., 2000). These tumors occur in adults and are more common in females. Approximately 75% of patients with pituitary gangliocytomas demonstrate pituitary hormone hypersecretion due to overproduction of hypothalamic releasing-hormones, either GHRH with consequent hypersecretion of GH and acromegaly or, more rarely, CRH causing Cushing's disease. Local mass effect can also occur. On MR imaging, these lesions may not be distinguishable from pituitary macroadenomas and appear as an enhancing sellar and suprasellar mass (Freda & Post, 1999).

3.6 Malformative lesions

3.6.1 Rathke's cleft cyst

Rathke's cleft cysts (RCCs) are non neoplastic cysts arising along the craniopharyngeal duct from remnants of squamous epithelium of Rathke's pouch, when there is incomplete obliteration of the central embryonic cleft separating the anterior lobe of the pituitary from the pars intermedia (Byun et al., 2000).

RCCs consist of a single layer of cuboidal or columnar epithelial cells with mucoid, cellular or serous components in the cyst fluid (Spampinato & Castillo, 2005).

They are often discovered incidentally and have been identified in up to 22% of the population according to routine examination of autopsy specimens. The peak age at the time of clinical presentation is generally 40–50 years, and they have a female to male ratio of 2:1 (Freda & Post, 1999).

RCCs can remain small, intrasellar, between the anterior and posterior pituitary lobes or anterior to the pituitary stalk, but 60% have some suprasellar extension, whereas the entirely suprasellar cases are rare (Billeci et al., 2005; Freda & Post, 1999; Mukherjee et al., 1997). Rarely, they may be associated with pituitary adenomas. RCCs range in size from a few millimeters to very large, in excess of 4.5 cm.

RCCs may become symptomatic in a minority (only 5–9% of all surgically resected sellar lesions, Aho et al., 2005; Kim et al., 2004), owing to slow cyst growth (due to an imbalance between secretion and reabsorption of cyst content) and/or more rarely intracystic bleeding or infection, leading to symptoms similar to those associated with adenomas (Isono et al., 2001; Billeci et al., 2005; Kim et al., 2004; Spampinato & Castillo, 2005). Less frequently, RCCs can present with aseptic meningitis, abscess, lymphocytic hypophysitis, or intracystic hemorrhage and apoplexy (Kim et al., 2004). RCCs can also cause symptoms in children, potentially resulting in somatic and/or sexual retardation (Zada et al., 2010).

On CT scanning, the cyst density ranges from hypodense, to isodense or to mixed (Billeci et al., 2005), without enhancement. Wall calcification is uncommon (Huang & Castillo, 2005). The lack of calcification is important to differentiate RCCs from craniopharyngiomas (Glezer et al., 2008).

On MRI, RCCs often appear as well circumscribed, centrally located spherical or ovoid, non-calcified cyst lesions of the sellar region (figure 15). The majority of these smooth contoured cysts are unilobar with a diameter ranging between 5–40 mm (Kim et al., 2004; Nishioka et al., 2006; Shin et al., 1999). The center of the lesion is often located in the region of the pars intermedia between the anterior and posterior pituitary gland. The normal pituitary gland may be displaced in any direction by a RCC, including circumferentially if the cyst arises in and remains encased within the gland. After the administration of Gd a thin peripheral rim of enhancement may be seen in a small number of cases and has been attributed to squamous metaplasia, inflammation or deposition of hemosiderin or cholesterol crystals in the cyst wall (Kim et al., 2004). Rim enhancement may be also present when a circumscribed area of pituitary tissue is present peripheral to the cyst.

MR signal intensity of cyst fluid never enhances after contrast administration (Byun et al., 2000), but basal signal demonstrates high variability on T1- and T2-weighted sequences: on T1 images, approximately half are hyperintense and half hypointense, whereas on T2 images, 70% are hyperintense and 30% iso- or hypointense (Billeci et al., 2005). Signal intensity correlates with the heterogeneous nature of the cystic content, which ranges from serous to mucinous (Tominaga et al., 2003). Although most RCCs display a homogeneous signal intensity, up to 40% contain a waxy intracystic nodule, presenting with lower T2 and higher T1 signal intensity than the rest of the cyst, composed of protein and cellular debris that typically fails to enhance following contrast administration and is virtually pathognomonic for the RCC (Byun et al., 2000). Sometimes differentiation from acute hemorrhage can be difficult.

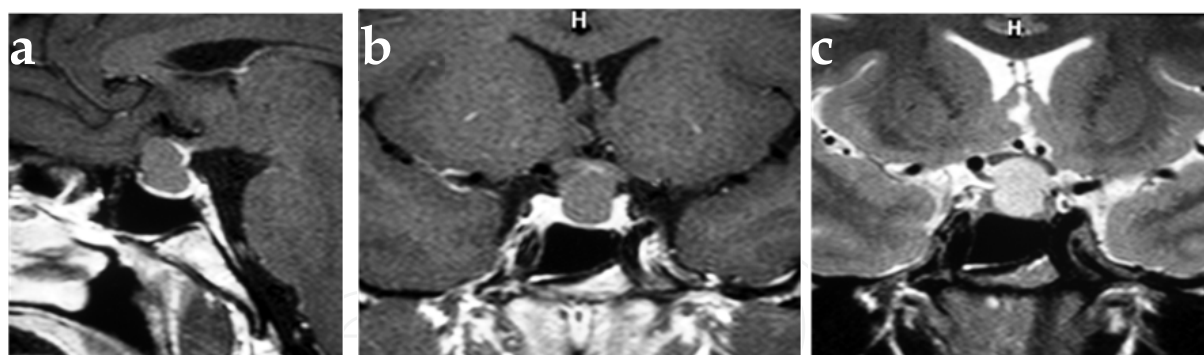


Fig. 15. Rathke's cleft cyst. MRI shows a well-delineated, lobulated, non-enhancing intra and suprasellar cyst, compressing normal pituitary gland and optic chiasm. The lesion is fairly isointense to CSF.

The symptomatic cases are managed by surgery (mostly TSS). A preoperative correct diagnosis is very important for surgical planning because the treatment of symptomatic RCCs differs from that of other sellar masses and usually consists of drainage of the cyst with or without resection of the cystic wall (Freda & Post, 1999; Mukherjee et al. 1997). The endocrine outcome following surgery remains poor, as the reversal of pituitary deficits is not common (Billeci et al., 2005).

3.6.2 Epidermoid and dermoid

These are benign tumors (WHO grade I), accounting for less than 2% of all intracranial tumors. They arise as a result of incomplete separation of the neuroectoderm from cutaneous ectoderm, with inclusion of epithelial elements during neural tube closure. They occur in the cerebellopontine angle, pineal region, middle cranial fossa, as well as in the suprasellar region (Kaltsas et al., 2008).

The clinical presentation may be due to local mass effect, but irritative symptoms are more frequent (Freda & Post, 1999).

Epidermoid tumors can occur anywhere in the intracranial cavity, but often arise away from the midline in the sellar and parasellar region (Tatagiba et al., 2000). The cyst contains a white cheesy material (keratin) within a thin capsule, lined with squamous epithelium, kerato-hyaline granule layers, and stratifications of "dry" keratin, but without hair follicles or sweat glands. Epidermoids usually present clinically in the 4th and 5th decades, when the cyst has grown by the accumulation of desquamated epithelial cells and exerts mass effect on adjacent structures (Gelabert-Gonzalez, 1998; Harrison et al., 1994). Some reports have also described an uncommon clinical presentation mimicking that of pituitary apoplexy. The cyst content can be caustic to the surrounding tissue, often resulting in hypophysitis, meningitis, or neurological deficits (Zada et al., 2010). The desquamated debris, which contains dead cells, keratin, and cholesterol crystals, appears almost identical to CSF on CT scans, and on T1- and T2-weighted MR images with no enhancement after contrast (Spampinato & Castillo, 2005).

Intracranial **dermoids** present earlier than epidermoids, in the 20-30-year age range, with a male predominance (Gelabert-Gonzalez, 1998; Harrison et al., 1994). They are also lined with squamous epithelium, but beyond desquamated epithelium the cysts contain

sebaceous material, and, sometimes, dermal appendages, including hair follicles, teeth, and sweat and sebaceous glands. Unlike epidermoids, dermoids most commonly arise in the midline, usually in the posterior fossa or suprasellar area. Dermoids may break with leakage of tumor contents along the subarachnoid spaces, resulting in recurrent aseptic meningitis that may be a clue to the diagnosis (Smith, 2005). On imaging studies, dermoids are typically not enhancing midline well-circumscribed heterogeneous lesions, that appear hypodense on CT scanning, and heterogeneous and bright on T1-weighted images, owing to fat signal within the tumor, and heterogeneously hyperintense in T2-weighted images (Civit et al., 1999; Freda & Post, 1999; Rennert & Doerfler, 2007; Smith, 2005; Spampinato & Castillo, 2005.). Resection is the choice treatment.

Standard MR imaging cannot be reliably used in all cases to definitively establish a diagnosis of epidermoid or dermoid tumors, on account of their nonspecific features. Diffusion-weighted images can be helpful, typically showing a markedly restricted water diffusion in both (Rennert & Doerfler, 2007). Excision remains the most effective modality of treatment. Radical resection, however, is possible in less than half of cases, due to tight adhesion between the capsule of the lesion and key vascular and nervous structures. Symptomatic regrowth is reported in a quarter of patients.

3.6.3 Hamartoma

Hypothalamic hamartoma is a congenital malformation of neuronal origin characterized by disorganized, ectopic foci of gray matter, most frequently arising near the mammillary bodies or tuber cinereum. It is not a true neoplasm, but may increase in size slowly over time (Rennert & Doerfler, 2007). Hypothalamic hamartomas can be classified as parahypothalamic, arising from the floor of the third ventricle, sometimes pedunculated, with minimal or no displacement of the third ventricle, and intrahypothalamic, involving the hypothalamus or surrounded by hypothalamic tissue, with distortion of the third ventricle (Spampinato & Castillo, 2005).

Hamartomas mostly affect children and owing to their small size (usually < 1-2 cm) they produce few symptoms of mass effect (Freeman et al., 2004). Hamartomas usually present with partial and later generalized seizures and mental retardation with speech and behavioral abnormalities. Seizures originate from mechanical compression of the mammillary body and/or abnormal neuronal connections between the hypothalamus and the limbic system (Spampinato & Castillo, 2005). Rarely, but characteristically, the seizures may take the form of spasmodic laughter, so called gelastic seizures (Striano et al., 2005). The parahypothalamic type is typically associated with isosexual precocious puberty, present also in half of the intrahypothalamic type (Debeneix et al., 2001). Precocious puberty may be due to an abnormal secretion of LHRH by the hamartomas (GNRH1 neurons have been demonstrated in the tumor) or to aberrant stimulation by the hamartomas of LHRH-producing hypothalamic neurons (Judge et al., 1977). Occasional asymptomatic cases have been described.

On MRI, the characteristic appearance of hamartoma is a pedunculated, round, non-enhancing mass arising between the pituitary stalk and the mammillary bodies, best seen in coronal and sagittal images, isointense to gray matter on T1-weighted images and isointense or slightly hyperintense on T2-weighted images or FLAIR (Rennert & Doerfler, 2007; Smith, 2005; Spampinato & Castillo, 2005) (figure 16).

There is usually no indication to surgical resection. The only treatment is aimed to control precocious puberty or seizures.

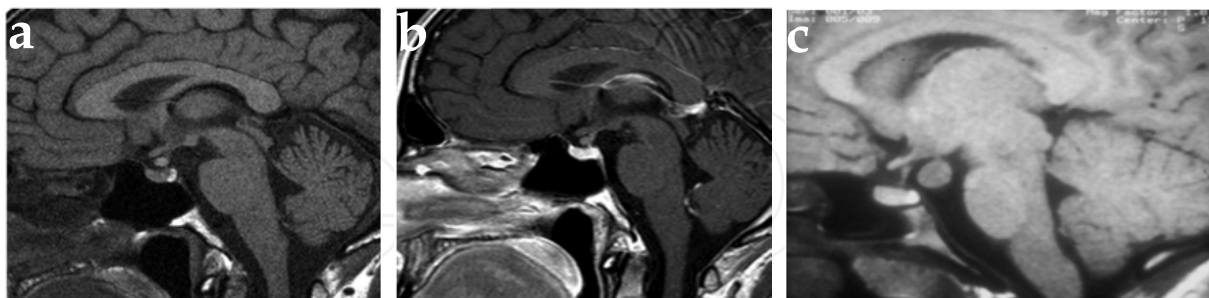


Fig. 16. Hamartomas. MRI on T1 shows a well delineated, nodular, not enhancing mass, isointense to the gray matter lesions, close to the pituitary stalk (a and b) or to the tuber cinereum (c). The pituitary gland appears normal and the "bright spot" in posterior pituitary gland is present.

3.6.4 Arachnoid cyst

Arachnoid cysts, arising from herniation of an arachnoid diverticulum through an incomplete diaphragma sellae, may be suprasellar or intrasellar. While the formers usually present in children with symptoms due to local mass effect, the latter are regarded as acquired and may become symptomatic later in life (Rennert & Doerfler, 2007).

Clinical symptoms may include increased intracranial pressure up to hydrocephalus, hormone deficiency, gait disturbance and visual impairment.

On MRI, arachnoid cysts appear as smooth, contoured, well-margined lesions that are isointense to CSF on all sequences. Calcifications are absent, and these cysts do not exhibit central or rim enhancement with contrast. Although usually indistinguishable from RCCs, they typically displace anteriorly the adeno-hypophysis and posteriorly the infundibulum (Freda & Post, 1999; Nomura et al., 1996.). If needed, surgical treatment (either fenestration or derivation of the cyst) is the only therapeutic option.

3.6.5 Pars intermedia cyst

The pars intermedia is rudimentary in humans after fetal life. One or more small cysts (usually < 3 mm), regarded as embryological remnants of the Rathke's cleft, can be seen microscopically in pituitary specimens, coated by a single layer of cuboidal or columnar epithelium and filled with proteinaceous fluid or cellular debris. Occasionally, they can enlarge and become detectable on imaging within the pituitary gland (Spampinato & Castillo, 2005). No treatment is usually necessary.

3.6.6 Empty sella syndrome

Empty sella (ES) is defined as a herniation of the subarachnoid space into the sella turcica, associated with stretching of the pituitary stalk and flattening of the pituitary gland against the sellar floor (Giustina et al., 2010).

ES has been classified as either primary (attributed to congenital incomplete formation of the sellar diaphragm and/or increase in intracranial pressure, either unremitting or intermittent) or secondary to any cause, mainly necrosis of pituitary adenoma.

ES is a frequent finding, observed in up one third of subjects either at post-mortem examination or on in vivo imaging, mainly in obese females (De Marinis et al., 2005).

Primary ES may be an incidental radiologic finding. It has been variably associated to different clinical conditions (headache, obesity, hypertension, menstrual disturbances, and endocrine dysfunctions), even though a selection bias cannot be ruled out and a causal relation is far from being demonstrated. Compression of the pituitary gland and stretching of the pituitary stalk may sometimes trigger mild hyperprolactinemia (10-12%) and/or various degrees of hypopituitarism (mostly GH deficiency). DI and panhypopituitarism are very rare (Del Monte et al., 2006). On the other hand ES has been reportedly associated with active Cushing's disease (16%) or acromegaly (5%). Hypopituitarism and visual abnormalities are more frequent in children (where ES is less frequent) than in adults, regardless of the size of residual pituitary gland (Yamada et al., 2005). In this setting it was reported a strong association with defects in specific genes controlling the hypothalamo-pituitary development during fetal life (Naing & Frohman, 2007). CSF rhinorrhea is very uncommon.

On imaging (figure 17) ES can be conventionally classified as complete or partial, when less than half of the sellar cavity is occupied by CSF and pituitary thickness is still > 2 mm (De Marinis et al., 2005). Sellar size in primary ES may be normal or enlarged with symmetrical ballooning, usually without lateral displacing of the pituitary stalk, features allowing the differential diagnosis with secondary ES in which the dorsum sellae is usually posteriorly displaced. The radiological and clinical findings of primary ES generally remain constant over time (De Marinis et al., 2005). Surgical treatment is generally not necessary except when clear-cut campimetric or visual defects are present.

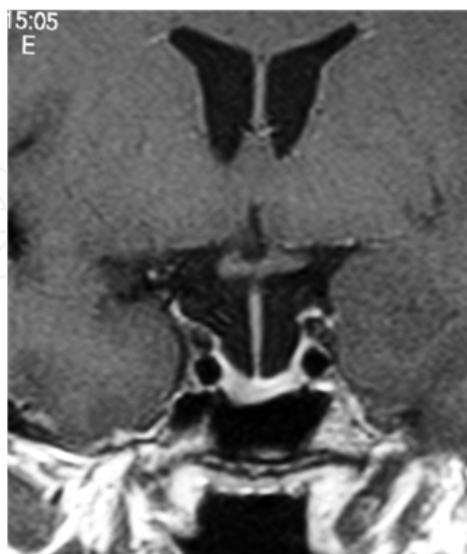


Fig. 17. Empty sella. Contrast-enhanced T1 MRI demonstrates CSF-arachnoid spaces protruding inferiorly through diaphragma sellae, compressing pituitary gland, enlarging sella without eroding sellar floor. The stalk is thin and centrally located.

3.7 Granulomatous, infectious and inflammatory lesions

3.7.1 Hypophysitis

Primary hypophysitis is isolated to the gland, whereas secondary hypophysitis is usually associated with an underlying systemic disorder (Lury et al., 2005)(table 2).

Primary	Lymphocytic autoimmune Granulomatous Xanthomatous	
Secondary	Infectious	Tubercular Bacterial Fungal Viral
	Non infectious	Wegener's Sarcoidosis Crohn's Takayasu's Ruptured cyst

Table 2. Classification of hypophysitis (modified from Lury et al., 2005)

Lymphocytic hypophysitis is an autoimmune disorder frequently (20-25%) associated with other autoimmune diseases, most commonly autoimmune thyroiditis (about 75%), but also adrenalitis, ovarian failure, atrophic gastritis, pernicious anemia, or systemic lupus erythematosus.

It occurs mostly in women, and in 60% to 70% of cases it presents in the last two trimesters of pregnancy or until 6 months after delivery (Caturegli et al., 2005).

Headache and visual disturbances due to compression of adjacent structures are the most common (56-70%), and usually the initial, complaints. Other common symptoms are due to partial or complete deficiency of anterior pituitary hormones (66-97%). Secretion of ACTH is the most frequently affected, reported in 60-65% of cases (Rivera, 2006). In order of frequency, secretion of TSH (47%), gonadotropins (42.2%), and GH (36.7%) are then impaired. PRL may be increased (38%) or decreased (33.7%), with inability to lactate. It is worth underlining that hypopituitarism often appears disproportionate to the extent of changes on pituitary MRI, especially when compared with what usually happens in pituitary adenomas. DI (50%) corresponds well to pituitary stalk thickening on MRI and can be attributed either to direct immune destruction or to compression of the posterior lobe and infundibular stem (PRL levels are increased in the latter case) (Gutenberg et al., 2006). Occasionally presentation can resemble apoplexy (Dan et al., 2002).

The typical (95% of cases) MRI findings of lymphocytic hypophysitis include a symmetric enlargement of a homogeneous pituitary gland, a thickened stalk (rarely displaced, with a greater diameter > 3.5 mm at the level of the median eminence, and loss of the normal smooth tapering), a non specific loss of bright spot, and an usually intact sellar floor (Gutenberg et al., 2006, Lury et al., 2005)(figure 18). The lesion is contrast enhancing (70%)(Heinze & Bercu, 1997), often with suprasellar extension (62-75%) in some cases into the hypothalamus (Freda & Post, 1999). A triangular enhancement of the anterior pituitary

(reflecting extension of the process towards the pituitary stalk) along with enhancement of the diaphragma sellae (possibly reflecting inflammation by contiguity), although described in a few cases only, and a tongue-like extension towards the hypothalamus (Honegger et al., 1997) seem to be particularly specific of lymphocytic hypophysitis. A ring-like enhancement is consistent with central necrosis (Rivera, 2006), a feature that may account for some cases of sterile pituitary abscesses (see below) in which no species are cultured and only inflammation is seen (Perez-Nunez et al., 2005). Dynamic MRI documented a hypothalamic-pituitary vasculopathy in some cases (Sato et al., 1998), showing delayed enhancement of the whole pituitary and doubling of peak time of posterior pituitary enhancement.

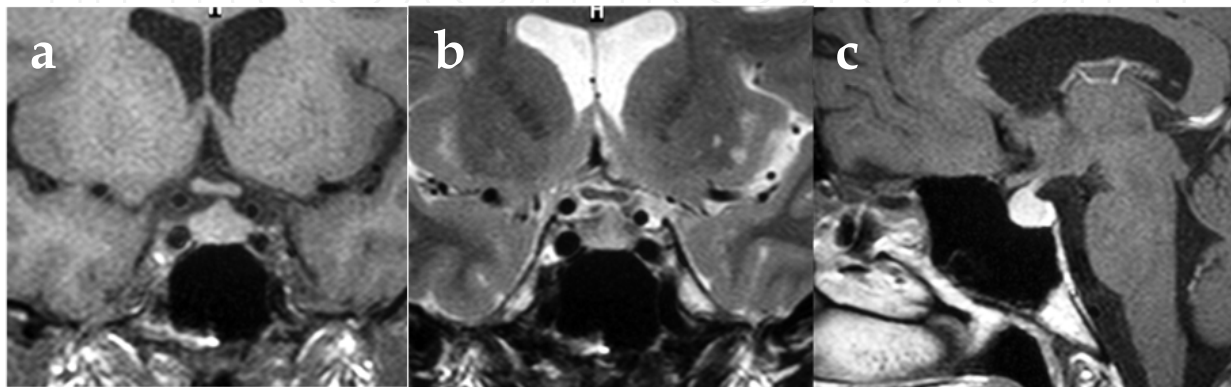


Fig. 18. Lymphocytic hypophysitis in a young female a few weeks after delivery. MRI on coronal (a) and sagittal (c) T1 shows an enlarged, uniformly enhancing pituitary gland and infundibulum. On coronal T2 (b) the characteristic central, triangular signal hyperintensity is shown.

Although the autoimmune nature of lymphocytic hypophysitis is well established, the pathogenic autoantigens targeted in this disease remain to be identified (Caturegli et al., 2005). PRL cell autoantibodies were the first to be detected, followed by antibodies to other pituitary hormone-producing cells (often, however, with low sensitivity and specificity) (Carpinteri et al., 2009). The role of anti-pituitary antibodies in this disease has yet to be clarified (Bellastella et al., 2003). Currently, a reliable serologic test based on implicated autoantibodies is not yet available for routine diagnostic purposes (Caturegli, 2007). Consequently, a diagnosis of lymphocytic hypophysitis can only be achieved with certainty by histological examination of the pituitary gland. Anyway, at present, approximately 40% of patients undergo surgery for a presumptive diagnosis of pituitary adenoma (Gutenberg et al., 2009). A diffuse polyclonal lymphocytic infiltration with predominance of T cells, particularly CD4 cells, is characteristic. Scattered plasma cells, a few eosinophils, edema, and fibrosis replacing pituitary acini are also commonly present. Electron microscopy has shown interdigitation of inflammatory cells with pituicytes and the presence of lysosomal bodies and oncocyctic changes in some pituitary cells (Rivera, 2006).

The natural history of lymphocytic hypophysitis is thought to progress from inflammation (with enlargement of the gland corresponding to the period of mass-effect symptoms and often, subclinical hormone deficits) to fibrosis and subsequent tissue destruction and atrophy associated with permanent hypopituitarism, which can later present as an ES in imaging studies (Bellastella et al., 2003). In some cases the course of the disease can be rather insidious, and relapsing remitting cases have been reported (Matta et al., 2002). The

inflammatory process can also be self-limited, spontaneously or with conservative corticosteroid and hormone replacement therapy, and radiological follow-up can show regression of the sellar mass in about 2 years. However, complete or partial DI may be permanent, probably because of neuronal destruction (Caturegli et al., 2005; Rivera, 2006).

Idiopathic **granulomatous hypophysitis**, a rare chronic inflammatory condition, is distinct from secondary granulomatous hypophysitis associated with systemic disorders (Caturegli et al., 2005). It is not yet definitely established whether lymphocytic and idiopathic granulomatous hypophysitis are different diseases or opposite ends of the spectrum of the same disease, with fibrosis representing the end stage of the inflammatory process (Flanagan et al., 2002). Granulomatous hypophysitis however lacks the key epidemiological features that are present in lymphocytic hypophysitis, such as the female preponderance, the occasional spontaneous resolution, the association with pregnancy and other autoimmune diseases (Caturegli et al., 2005; Cheung et al., 2001).

Granulomatous hypophysitis usually occurs in older patients and is characterized histologically by multinucleated giant cells, epithelioid histiocytes and true granulomas (Rivera, 2006).

Clinical presentation consists of headache, visual disturbances, nausea, vomiting, DI, and hyperprolactinemia, and pituitary function is severely impaired (Caturegli et al., 2005; Cheung et al., 2001).

The striking CT features are an intrasellar mass with cystic areas and ring enhancement. On MRI, the diffusely enlarged gland is usually isointense to gray matter on T1-weighted images (but also hyperintense due to hemorrhage) and heterogeneous on T2 sequences, with abnormal thickening of the infundibulum. Contrast enhancement is frequently homogeneous, occasionally extending to the optic chiasm, but cystic areas with ring enhancement may be seen. Findings suggesting inflammation, such as linear enhancement of the dura, sphenoid mucosal thickening, and adjacent bone marrow abnormality, may be also observed. These findings are nonspecific and indistinguishable from those caused by other neoplastic or inflammatory pituitary processes (Lury et al., 2005).

Xanthomatous hypophysitis is rare and can be considered an inflammatory response to ruptured cysts components (Glezer et al., 2008; Roncaroli et al., 2004). Cystic-like areas of liquefaction, infiltrated by lipid-rich foamy histiocytes and lymphocytes, are present in the pituitary gland (Caturegli et al., 2005).

Immunosuppression with high-dose glucocorticoids or other drugs, such as azathioprine, methotrexate and cyclosporin, have been reported effective in reducing pituitary mass, and improving pituitary function and DI (Rivera, 2006).

3.7.2 Tuberculosis

Pituitary tuberculosis is rare. It may present with meningitis, a dense plaque-like exudate mostly at the base of the brain, involving the sellar and parasellar region, or as a tuberculoma (suprasellar or intrasellar). Signs of mass lesion, and possible impairment of hypothalamic or pituitary function and involvement of the optic chiasm may be present (Domingues et al., 2002; Freda & Post, 1999).

Although most patients with hypothalamic-pituitary tuberculosis have signs of active tuberculosis elsewhere, this is not invariably true. As a result, the diagnosis of a tuberculoma in the region may, in some cases, be made only histologically after TSS (Freda & Post, 1999).

Imaging studies show involvement of pituitary fossa, along with thickening of the pituitary stalk. Simultaneous involvement of the clivus may be an additional unspecific feature. MRI shows a hypointense pituitary mass on T2, with or without an absent posterior pituitary bright signal. Tubercular pituitary abscesses appear isointense to hypointense on T1 (occasionally hyperintense owing to high protein/lipid content) and hyperintense on T2. Tuberculomas show strong enhancement with contrast and are often accompanied by thickening and enhancement of the stalk and dura. These signal characteristics are nonspecific and overlap those of pituitary adenomas. Tubercular abscesses may show peripheral contrast enhancement and adjacent meningeal enhancement on contrast-enhanced MR (Lury et al., 2005).

3.7.3 Other infections

Fungal (*Histoplasma*, *Coccidioides*, *Cryptococcus*, *Candida*, and *Aspergillus*), parasitic (*Cysticercus*) and opportunistic (*Toxoplasma*, *Pneumocystis Carinii*, *Mucor*) infections may rarely develop in the sellar region, particularly in immunocompromised patients, and may simulate a pituitary adenoma (Freda & Post, 1999).

Aspergillosis is a mycotic disease of paranasal sinuses, frequently extending into the orbital region, or invading the skull base. The organism has a typical tropism for vascular intima-media layer, thus enabling hematogenous spreading to basal nuclei, occasionally until hemorrhagic vasculitis. The invasive forms are usually observed in immunocompromised patients (Pinzer et al., 2006). Aspergillosis of the sphenoid sinus extending into the sellar region and simulating a pituitary tumor is extremely rare, but it was reported even in immunocompetent patients. Imaging studies show lesions moderately hyperintense on T1, hypointense on T2 and brightly enhancing. The diagnosis can be achieved only as a result of surgical exploration of the invaded areas (Carpinteri et al., 2009).

Another rare fungal infection to be considered when evaluating patients with a pituitary mass and ophthalmoplegia is **coccidioidomycosis**, where unilateral ophthalmoplegia may acutely appear and radiological studies show a mass lesion involving the pituitary gland and cavernous sinus (Scanarini et al., 1991).

3.7.4 Sarcoidosis

Sarcoidosis involves the CNS in 5-15% of patients with this disease. Neurosarcoidosis is usually associated with systemic sarcoidosis: only 5% of cases have no disease elsewhere. In rare cases neurosarcoidosis is the initial or only sign of the disease (Freda & Post, 1999).

Neurosarcoidosis has a predilection for the hypothalamic-pituitary region and therefore DI and headache are common, hyperprolactinemia and cranial neuropathy may be present.

On MR imaging, the intraparenchymal, meningeal, or sellar lesions of sarcoidosis appear isointense on T1 and variable on T2, and are contrast-enhancing. The stalk may be thickened and also enhancing. Very rarely a cystic appearance has been reported. Leptomeningeal

involvement in the region of the hypothalamus and pituitary infundibulum may be seen as an isolated finding or associated with involvement of the basilar leptomeninges (Lury et al., 2004).

When neurosarcoidosis is suspected, CSF examination is indicated, evaluating angiotensin-converting enzyme, and cytology. In some patients, the diagnosis is made only by biopsy of the granulomatous lesion (Glezer et al., 2008).

Corticosteroids are the therapy of choice, but various adjuvant immunosuppressant drugs have been reportedly employed (Glezer et al., 2008).

3.7.5 Other systemic diseases

Pituitary granulomatous involvement has been described in isolated case reports with other systemic diseases (Carpinteri et al., 2009):

- Wegener's granulomatosis, with central DI usually occurring after pulmonary or kidney lesions in less than 1% of affected subjects (Goyal et al., 2000);
- Erdheim-Chester disease, with DI, hypopituitarism and hyperprolactinemia, cerebellar syndromes, orbital lesions, and extra-axial masses involving the dura (Kovacs et al., 2004);
- Crohn's disease, with hypopituitarism, progressive bitemporal haemianopsia and intrasellar mass (de Bruin et al., 1991);
- Takayasu's disease, with pituitary mass, hypopituitarism and DI (Toth et al., 1996);
- Cogan's syndrome, with pituitary enlargement, DI and secondary hypothyroidism (Kanatani et al., 1991).

3.7.6 Pituitary abscess

Pituitary abscess is a rare potentially life-threatening disease, occurring in all age groups, estimated to account for less than 1% of clinically apparent pituitary disease and 0.27% of pituitary surgeries (Famini et al., 2011; Vates et al., 2001).

In most cases, it develops from direct extension of an adjacent infection (sphenoid sinus meningitis, contaminated CSF fistula or very rarely cavernous sinus thrombophlebitis) or is caused by hematogenous seeding. The infection source cannot occasionally be identified (Glezer et al., 2008).

Abscess can be primary (in two thirds of the cases), occurring in a previously normal pituitary, or secondary, arising in glands that harbor a pre-existing lesion (adenoma, craniopharyngioma or RCC). Other risk factors include an underlying immunocompromised condition, previous pituitary surgery, CSF rhinorrhea with recurrent meningitis and irradiation of the pituitary gland (Freda & Post, 1999; Liu et al., 2011).

Isolated organisms are typically gram-positive cocci; fungi, such as *Aspergillus*, *Cryptococcus* or *Candida Albicans*, and other organisms (*Mycobacterium Tuberculosis*, *Toxoplasma*, *Clostridium Difficile*, *Staphylococcus* or *Pseudomonas*) have been reported as well (Famini et al., 2011; Freda & Post, 1999; Glezer et al., 2008; Liu et al., 2011). In at least half of cases pituitary abscesses are reported to be sterile.

Fever, meningism and leukocytosis have been reported in one third of cases only, in spite of the presence of meningitis along with the abscess in approximately 60% of patients. Most

patients present with a chronic and indolent course with few infective manifestations, thus mimicking a pituitary tumor (Glezer et al., 2008). DI and headache are the most common presenting complaint (70%) (Fuyi et al., 2010), and over half of the patients complain of visual disturbances. Most patients (85%) have partial or total hypopituitarism (including PRL deficiency). In a recently reported series (Fuyi et al., 2010) the median time between the onset of symptoms and diagnosis was 6 months. Mortality can reach 30% to 50% of cases when it is complicated by meningitis (Glezer et al., 2008).

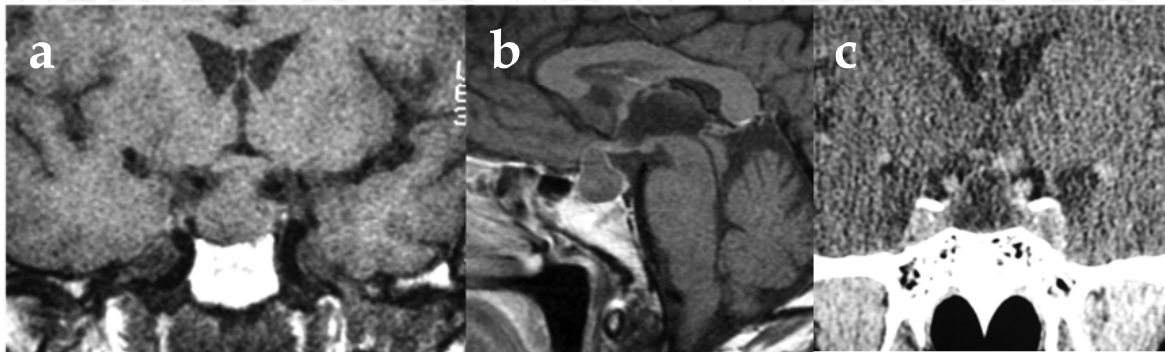


Fig. 19. Pituitary abscess in a patient with staphylococcal sepsis. Coronal T1 (a) and sagittal T1 enhanced (b) MRI shows an intra/suprasellar cystic lesion, isointense to the brain, with thin regular rim enhancement. Coronal CT after contrast (c) depicts a homogeneously hypodense lesion, with rim enhancement, sparing cavernous sinus. Note non pneumatized sphenoidal sinus.

The typical MR features of an abscess are the presence of a round cystic or partially cystic sellar mass that appears as hypo- or isointense on T1 and hyper- or isointense on T2, with an enhanced rim after Gd injection and a central cavity that is isointense to the brain (Freda & Post, 1999; Glezer et al., 2008; Rennert & Doerfler, 2007)(figure 19). The sella may be enlarged and, occasionally, extensively eroded.

Surgical resection and appropriate long-term antibiotic coverage is the choice treatment. Abscesses may recur requiring further surgery.

3.7.7 Sphenoid sinus mucocoele

Primary mucocoele is a congenital mucous retention cyst expansion, whereas the commoner secondary mucocoele results from a chronic obstruction of the sinus that leads to accumulation and dehydration of secretions. Predisposing factors are inflammatory conditions, tumors, trauma, and previous surgery in the sphenoid sinus.

There is no specific age preponderance.

Mucocoele can rarely extend to the pituitary fossa, parasellar and suprasellar regions, nasopharynx, orbits, clivus, or ethmoid air cells. A cystic accumulation of secretions expands and erodes the sinus walls, eventually compressing surrounding structures such as the cavernous sinus, the pituitary gland, the cranial nerves I through VI, and the carotid arteries. Sphenoid mucocoeles usually evolve over a long period, often years, with nonspecific, usually severe, headaches and atypical facial pain with paresthesias secondary to trigeminal nerve irritation. Visual loss owing to direct nerve compression by the mass or

from scarring caused by an inflammatory reaction is usually slowly progressive but may be suddenly worsened by vascular compromise of the optic nerve. Optic neuropathy is most often unilateral, and visual field deficits are typically absent. Exophthalmos is present in about half of patients. Diplopia due to dysfunction of the third and, less often, the fourth cranial nerves is common (Freda & Post, 1999). Hypopituitarism is less common.

On CT, a non-destructive mass causing a thinning and bulging of the bone sinus walls may be seen, and the sellar contents can mimic a para- or suprasellar mass.

MRI appearance is variable. Expansion of the sphenoid sinus, usually with intact but occasionally eroded walls, and prominent opacification of its content is present in most patients, most often with a high signal on T2 images and, because of its high protein content, a homogeneously hyperintense T1 signal. After contrast administration it appears a thin regular rim of enhancement (Akan et al., 2004; Glezer et al., 2008; Rennert & Doerfler, 2007) (figure 20).

Surgical drainage is indicated only when the lesion is highly symptomatic or erosive of bone.

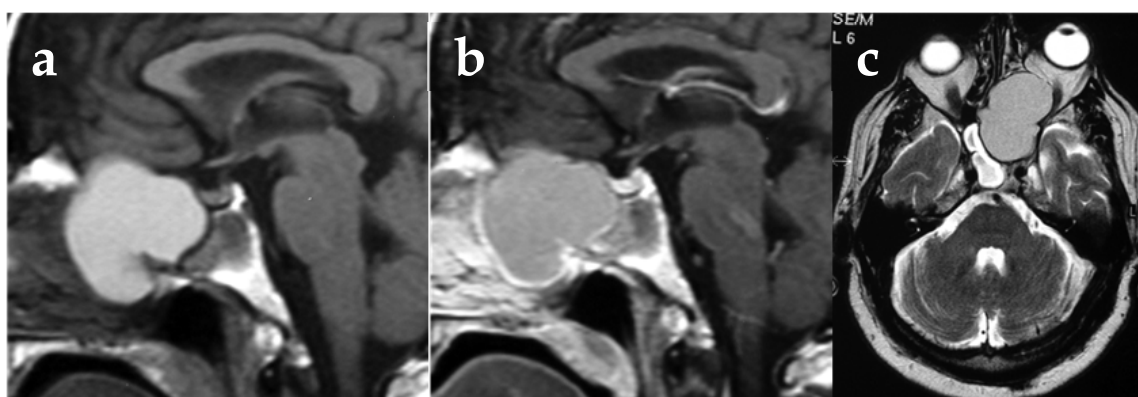


Fig. 20. Mucocele. Sagittal T1 (a) and axial T2 (c) MR show a cystic mass, filling and enlarging the left sphenoid sinus recess. The lesion appears homogeneously hyperintense on T1 (a) with rim enhancement (b). Chronic sinusitis is evident in the right sphenoidal recess.

3.8 Vascular lesions

3.8.1 Aneurysm

Aneurysms of the sellar region account for approximately 10% of all cerebral aneurysms. They usually originate from the cavernous, infraclinoid, or supraclinoid internal carotid arteries, but also from the anterior or posterior communicating arteries, or the ophthalmic arteries. Aneurysms in the parasellar and suprasellar region may sometimes reach great dimensions and compress the optic nerve, chiasm, or both and produce signs of visual loss. They may also extend into the sella, causing direct pituitary compression and thus modest hyperprolactinemia and hypopituitarism (Freda & Post, 1999).

Intrasellar aneurysm can mimic other parenchymal masses and imaging is essential to distinguish among the different disorders before surgery. If within the sella, aneurysms are usually eccentrically located. Their appearance is mostly affected by the amount of

calcification and thrombosis present within the aneurysm. Asymmetric enlargement and destruction of the sella turcica may occur in association with a giant aneurysm. CT cannot reliably distinguish an aneurysm from other pituitary lesion, but very intense, homogeneous blush with contrast may suggest an aneurysm (Rennert & Doerfler, 2007). On conventional spin-echo MRI, the aneurysm is contiguous to vessels, has well-defined margins, and appears heterogeneous (Glezer et al., 2008). Aneurysmatic sack may appear as a flow void or alternatively as a brightly enhancing spot corresponding to residual true lumen, according to vascular flow velocity. There may be variable amount of thrombosed lumen, which may contain crescent or ring shaped layers of different aged blood products or fibrosis, appearing heterogeneous on T1 and mostly hypointense on T2. There may be rings or arcs of calcification, especially at the periphery. A rim of calcification in the wall is characteristic but may resemble a craniopharyngioma.

There have been many case reports of aneurysms associated with pituitary adenomas (Smith, 2005). In any case, if an aneurism is suspected, angiography should be immediately performed. Angio-CT, angio-MRI or digital subtraction angiography are all suitable. The last is the gold standard because it allows concomitant treatment by embolization if needed.

3.8.2 Cavernous sinus thrombosis

Thrombosis of the cavernous sinus is a very rare condition, often secondary to iatrogenic or septic etiologies. On MRI and CT, enlargement of the cavernous sinus with internal filling defects and incomplete enhancement of the sinus may be noted. MRI shows high signal thrombus within the cavernous sinus. Additionally, periorbital edema, exophthalmos or dilatation of the superior ophthalmic vein can occur (Rennert & Doerfler, 2007).

3.9 Collision lesions

Collision tumors represent two morphologically different tumors attached to each other. Extending this definition, collision lesions refer to histologically different pathological conditions found in combination and may include neoplastic, vascular, congenital, or infectious/inflammatory lesions. The presence of a collision sellar lesion represents a very uncommon event. Most include a pituitary adenoma coexisting with a second lesion like a craniopharyngioma, arachnoid cyst, epidermoid cyst, lymphocytic or granulomatous hypophysitis, as well as sarcoidosis within a pituitary adenoma and metastatic carcinoma to a pituitary adenoma (Koutoroisui et al., 2010)(figure 21).

Multiple pituitary adenomas are rarely encountered in patients undergoing pituitary surgery. In a large surgical cohort of more than 3,000 resected pituitary adenomas the percentage of double adenomas was 0.37% (Kontogeorgos et al., 1992). The same authors in the largest ever-reported autopsy study of more than 9,300 pituitary glands, identified 20 cases of multiple adenomas (Kontogeorgos et al., 1991).

Double pituitary adenomas can be divided into contiguous and clearly separated double tumors. Most contiguous tumors are surgically removed as one tumor and the co-existence of different adenoma types is established by immunohistochemical and electron microscopic examination of the surgical specimen (Kim et al., 2004). The most common hormone-active adenoma identified in surgical series of double adenomas is GH-secreting, but also ACTHomas are reported.

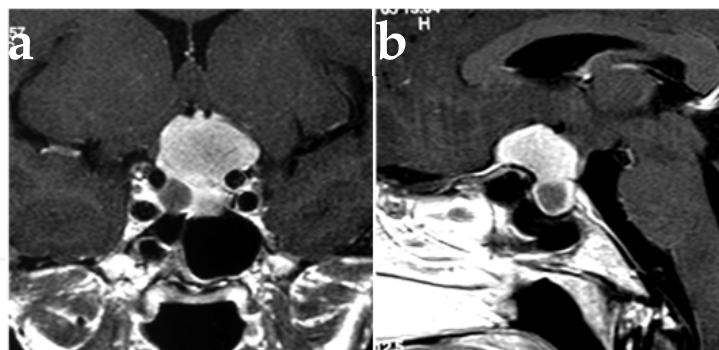


Fig. 21. T1 enhanced MR shows an intrasellar nodular, relatively hypointense, right lesion, characteristic for a pituitary microadenoma, close to a suprasellar mass, with features of diaphragma sellae meningioma.

4. Differential diagnosis

The differential diagnosis among the various neoplastic and non-neoplastic processes potentially involving the parasellar region is critical in the work-up of patients. It should always be performed jointly by the neurosurgeon, the endocrinologist and the neuroradiologist. The neuroradiological finding of a sellar mass may not always mean the presence of a pituitary adenoma, even though these are the great majority, and the correct screening among alternative diagnoses is crucial for an appropriate therapeutic planning. Some neoplasms should indeed not undergo surgery, unless requiring urgent decompression. A correct preoperative diagnosis allows to select the necessary treatment and eventually the correct surgical approach (trans-cranial vs. trans-sphenoidal) and strategy. Combining epidemiological, clinical and imaging data will allow progressively focusing of diagnosis.

4.1 Clinical data

Headache and hormone dysfunction are not always helpful in the differential diagnosis of a sellar suprasellar lesion (Valassi et al., 2010), unless hypersecretory syndrome occurs. The neuro-ophthalmological examination is the basic investigation that allows to raise suspicion of a lesion, but it is of no practical value to establish a diagnosis of nature of a para-suprasellar lesion.

Some classical campimetric defects are related to the location of a given lesion and its relationships with the visual apparatus (Freda & Post, 1999):

- Lesions extending over the sella, such as adenomas and RCCs, produce the typical bitemporal hemianopsia due to chiasmal compression from below;
- Lesions arising in the suprasellar area, such as meningiomas, can present with bitemporal field cuts of the classic superior chiasmal compression variety;
- Lesions anterior to the chiasm, such as meningiomas of the optic nerve sheath, can produce unilateral visual loss;
- Lesions compressing the visual system more posteriorly along the optic tract, such as meningiomas or aneurysms, provoke homonymous hemianopsia.

DI at presentation is highly atypical for pituitary adenomas, occurring in 0.01-3% vs. 11% of non-adenomatous lesions according to a recent overview (Famini et al., 2011). In our

personal experience DI is associated to pituitary adenomas mainly when apoplexy occurs. DI should always lead to consider alternative diagnoses. Craniopharyngioma, metastases, and sarcoidosis are the most frequent. Vasopressin deficiency may be partial or transient because of spontaneous regeneration (Freda & Post, 1999). DI may apparently improve in some patients when hypoadrenalism develops.

The acute onset of cranial neuropathy often accompanies pituitary apoplexy, but the presence of ophtalmoplegia at presentation of a sellar/parasellar mass is suggestive of alternative etiologies (Freda & Post, 1999).

Hypothalamic dysfunctions may be observed in large tumors (exceptionally rare in adenomas) leading to poor development and sexual immaturity in children and disruption of the control of appetite in adults (Freda & Post, 1999).

4.2 Imaging data

Intratumoral calcifications are observed mainly in craniopharyngiomas, but also in meningiomas, teratomas, gliomas, cartilaginous tumors, and even in aneurysms and pituitary adenomas (Freda & Post, 1999).

Cartilaginous tumors and metastases typically destroy the bone of the skull base.

An enlarged pituitary stalk can be found in different diseases (hypophysitis, germinoma, lymphoma, tuberculosis, sarcoidosis, or LCH) (Gutenberg et al., 2009).

Neoplasms in the clival region include chordoma, chondrosarcoma, hemangiopericytoma, meningioma, lymphoma, plasmocytoma, paraganglioma, and metastasis (Rennert & Doerfler, 2007).

Location (midline vs. not midline) and consistence (mostly solid vs. cystic) of the lesion are among the key imaging data to consider (table 3).

	Midline	Away from midline
Solid	Adenoma Hypophysitis Germinoma Lymphoma Chordoma Metastases	Meningioma Chondroma Schwannoma Glioma LCH (Metastases)
Cystic	Craniopharyngioma RCC Arachnoid cyst Abscess	(Abscess) Mycoses

Table 3. Classification of lesions according to consistence and location

Tables 4 and 5 show synoptically key features of the different parasellar lesions (data are derived from the following references: Carpinteri et al., 2009; Famini et al., 2011; Freda & Post, 1999; Glezer et al., 2008; Huang & Castillo, 2005; Kaltsas et al., 2008; Karavitaki et al., 2006; Lury, 2005; Rennert & Doerfler, 2007; Ruscalleda, 2005; Smith, 2005; Spampinato & Castillo 2005).

Lesion	Midline	Location	Age	Sex	DI*	Hypopit°	HypoPRL§	CN palsies#
NFPA	yes	centered on sella	most > 40 yrs		very rare	possible	no	rare
Pituitary apoplexy	yes	centered on sella	30-50 yrs		rare	frequent	yes	frequent
Pituitary carcinoma	yes		not different from adenoma except for metastases					
Pituitocytoma	yes	intrasellar and/or suprasellar or stalk	young & middle aged	F	rare	frequent		
Choristoma	yes	intrasellar and suprasellar	40-50 yrs		rare	common		
Germ cell tumor	yes	suprasellar (+ pineal) or intrasellar	children and adolescents		frequent			common
Lymphoma	yes	intrasellar or suprasellar, cavernous sinus	50-70 yrs	M	common	frequent		
Chordoma	yes	clivus	30-50 yrs			uncommon		frequent
Gangliocytoma	yes	intrasellar and suprasellar	adult	F		no (hyper*)		
Metastases	yes/not	intrasellar and/or suprasellar or stalk	usually elderly		frequent	common		common
Hypophysitis	yes	intrasellar and stalk	near pregnancy if lymphocytic, elderly if granulomatous		common	frequent	possible	rare
Hamartoma	yes	parasellar or intrahypothalamic, tuber cinereum	childhood					
Craniopharyngioma	yes	suprasellar and/or intrasellar	5-14 yrs and 50-74 yrs		frequent	common		possible
Rathke's cleft cyst	yes	intrasellar (and suprasellar)	40-50 yrs	F	rare	possible		
Dermoid	yes	suprasellar (posterior fossa)	20-30 yrs					
Abscess	yes	intrasellar			frequent	frequent	yes	
Arachnoid cyst	yes	suprasellar	childhood			common		
Mucocoele	yes	sphenoid sinus extending in parasellar and suprasellar, nasopharynx, orbits, clivus, or ethmoid				uncommon		common
Glioma	no	optic nerve/hypothalamus	childhood or young adult/ hypothalamic in early life					
Langerhans' cell hystiocytosis	no	hypothalamus	< 15 yrs in 2/3	M	frequent	common		
Meningioma	no	dura at any site	50-70 yrs	F		common		infrequent
Tuberculoma	no	intrasellar or suprasellar (paranasal sinuses, clivus)						
Chondrosarcoma	no	petro-occipital fissure						
Schwannoma	no	cavernous sinus						
Epidermoid	no	intrasellar and parasellar	30-50 yrs					
Aneurysm	no	cavernous sinus				possible		
Lipoma	yes	surface of the infundibulum, floor of the 3 rd ventricle or adjacent cranial nerves						
Sarcoidosis	yes	suprasellar			common			possible

* Diabetes insipidus; ° Hypopituitarism; § PRL deficiency; # Cranial nerve palsies; + Hypersecretions

Table 4. Clinical aspects of the different parasellar lesions

Lesion	Consistency	CT	CT contrast enhancement	Calcification	T1-weighted	T2-weighted	MR contrast enhancement	Notes
NFPA	solid (cystic)	isodense	moderate	rare	isointense (hyperintense with level if hemorrhagic)	isointense (hypointense if fibrotic)	heterogeneous, normal pituitary usually displaced laterally or upwards	nodular expansion towards suprasellar cisterns
Pituitary apoplexy	solid (mixed)	possible SAH, hyperdense	minimal or no	no	acute: hypointense (ischemic); isointense then hyperintense (hemorrhagic)	acute: hyperintense (ischemic); iso- hypointense (hemorrhagic)	rim	DWI: restricted diffusion
Pituitary carcinoma				not different from adenoma except for metastases				
Pituitocytoma	solid	hyperdense	strong	rare	isointense to hypointense	hypointense to isointense	strong, homogeneous	
Choristoma	solid	hyperdense	strong	possible	isointense	isointense	yes	
Germ cell tumor	solid (teratoma mixed)	isodense or hyperdense	strong	frequent in teratoma	Isointense or hyperintense	isointense/ hypointense	strong	precocious puberty (alphaFP, hCG) DWI: restricted diffusion
Lymphoma	solid	isodense or hyperdense	strong	no	isointense or slightly hypointense	isointense or slightly hypointense	yes	DWI: restricted diffusion
Chordoma	solid	bone destruction; iso to hyperdense	heterogeneous	common, diffuse	isointense to hypointense with septations and necrosis as macroadenomas	hyperintense	heterogeneous	
Gangliocytoma	solid	isodense	moderate	rare	as macroadenomas	as macroadenoma	yes	acromegaly, Cushing's
Metastases	solid	hyperdense or isodense or hypodense	yes	rare	hypointense to hyperintense	hyperintense	yes	dumbbell
Lymphocytic hypophysitis	solid	hypodense	yes	no	hypointense	hyperintense	yes	symmetric enlargement, thickened stalk
Granulomatous hypophysitis	solid and cystic	hypodense to isodense	ring	no	isointense (hyperintense if blood)	heterogeneous	homogeneous, ring in cystic areas	thickened stalk
Hamartoma	solid	isodense	no	no	pedunculated isointense	isointense or slightly hyperintense	no	precocious puberty, seizures
Cranio-pharyngtoma	cystic (solid)	heterogeneous	yes (solid portions)	frequent, nodular or curvilinear	solid: isointense or hypointense or mottled; cystic: hyperintense without levels	solid: hypointense or hyperintense; cystic: hyperintense or hypointense	strong in cyst walls, heterogeneous in nodular portions	normal pituitary usually displaced downwards, rare expansion in cavernous sinus
Rathke's cleft cyst	cystic	hypodense, isodense, mixed	no	uncommon	hypointense rarely isohyperintense	hyperintense (isointense), with small hypointense nodules	rim only if inflammatory, normal pituitary usually displaced downwards	meningitis
Dermoid	cystic	hypo-isodense	no	focal	hyperintense, heterogeneous	hyperintense	no	meningitis

Lesion	Consistency	CT	CT contrast enhancement	Calcification	T1-weighted	T2-weighted	MR contrast enhancement	Notes
Abscess	cystic	hypodense, sellar enlargement and erosion	rim	no	hypointense or isointense	hyperintense or isointense	rim (thick wall)	
Arachnoid cyst Mucocoele	cystic	hypodense	no	no	isointense to CSF	isointense to CSF	no	facial pain and paresthesias
	cystic	hypodense to isodense, thinning and bulging of the bone sinus walls	rim	no	hyperintense	hyperintense	rim	
Glioma	solid	hypodense-isodense	variable	rare	hypointense; young adult isointense or hypointense; hypothalamic hypointense-isointense	hyperintense; hypothalamic isohyperintense	variable	proptosis, NF
Langerhans' cell histiocytosis	solid	isodense	yes	no	isointense	hyperintense	bright, homogeneous of stalk	thickened stalk
Meningioma	solid	isodense or slightly hyperdense, hyperostosis	homogeneous, strong	common	isointense, very homogeneous	isointense (hyperintense or hypointense)	strong	carotid narrowing, normal pituitary usually displaced downwards, NF, ionizing radiation, increase during pregnancy
Tuberculoma Chondro-sarcoma	solid	isodense	yes	rare	isointense	hypointense	yes	thickened stalk
	solid	isodense to hyperdense, bone destruction	variable	yes	isointense to hypointense	hyperintense	heterogeneous	
Schwannoma	solid	isodense	yes	no	hypointense	hyperintense	intense, homogeneous	
Epidermoid	cystic	as CSF	no	no	as CSF	as CSF	no	DWI: restricted diffusion
Aneurysm	mixed	isodense to hyperdense	intense homogeneous blush	rim	mixed, hypointense	mixed, hypointense	bright, homogeneous	flow void
Lipoma	solid	hypodense	no	rim	hyperintense	hypointense	no	disappear with fat suppression
Sarcoidosis	solid	isodense to hyperdense	yes	no	isointense	isointense to hypointense	yes	thickened stalk

SAH = subarachnoid hemorrhage; DWI: diffusion weighed images; NF = neurofibromatosis

Table 5. Imaging of the different parasellar lesions: for each lesion the most common picture is reported

4.2.1 Solid lesions

Sellar enlargement is typical but not exclusive of macroadenomas because it can occur in half of non-adenomatous masses of the region, such as meningiomas, craniopharyngiomas, empty sella, and RCCs. Therefore, only the lack of sellar enlargement is helpful in diagnosis, pointing to a non-pituitary lesion (Freda & Post, 1999).

Bone erosion or invasion is not particularly helpful in the differential diagnosis because it can be seen with adenomas, chordomas, intracavernous aneurysms, meningiomas of the middle fossa, RCCs, arachnoid diverticula, and elevated intracranial pressure from any source (Freda & Post, 1999).

The sudden onset of severe headache and ophthalmoplegia should always raise the suspicion of pituitary apoplexy. Since the presence of a pre-existing pituitary tumor is mostly unknown, diagnostic difficulties and delays can result in significant morbidity and rarely mortality. The diagnosis can often be difficult because patients may present in different clinical facilities, without immediate access to a skilled neuroradiologist. Clinical characteristics are not of help most of the times. On imaging CT and MRI will demonstrate an intrasellar mass and signs of bleeding or ischemia. Attention must be paid to the reported concomitant occurrence of pituitary adenomas and cerebral aneurysms (in 7%), requiring angiography. It must be pointed out that neuroradiology (CT scan and then MRI) is nowadays mandatory in every emergency case. Clinical data are of very little relevance in this setting.

NFPA vs. hypophysitis

On MRI lymphocytic hypophysitis appears as a symmetric enlargement of a homogeneous pituitary gland, with thickened but rarely displaced stalk and an intact sellar floor (Gutenberg et al., 2006; Lury, 2005), whereas macroadenomas are heterogeneous, frequently asymmetric lesions growing toward the suprasellar cistern and cavernous sinus, often displacing an intact stalk, depressing or eroding the sellar floor (Gutenberg et al., 2009; Lury, 2005). Intense and homogenous enhancement of the anterior pituitary, similar to that of the cavernous sinuses, is suggestive of hypophysitis.

It was suggested that hypophysitis should be suspected in a patient with pituitary dysfunction whenever there is the coexistence of 3 or more of the 9 following items (Rivera, 2006):

- young age;
- women presenting during the peripartum period;
- acute onset of headache with ophthalmoplegia, visual field defects, nausea or vomiting (present also in pituitary apoplexy where presentation is more catastrophic and imaging shows bleeding or ischemia);
- acute onset of DI with headache and mass-effect symptoms (present also in sarcoidosis and LCH, with a more insidious presentation);
- characteristic MRI findings;
- isolated, early or disproportionate impairment of ACTH secretion (usually the last hormone to be affected in patients with pituitary adenomas) and in general, disproportionate involvement of pituitary function for the magnitude of the changes on MRI;

- presence of other autoimmune conditions and/or autoantibodies;
- lymphomonocytic pleocytosis in the CSF, without clinical meningitis and antiviral antibodies;
- presence of circulating antipituitary antibodies, where available.

Recently a case-control study was performed on 402 lesions (histological diagnosis was NFPA and autoimmune hypophysitis in 304 and 98, respectively) evaluating the predictive value of different features before surgery (Gutenberg et al., 2009). Authors concluded that no single radiologic sign had sufficient accuracy to distinguish with certainty hypophysitis from pituitary adenomas. In a multiple logistic regression model, however, some features contributed significantly to the correct classification of lesions: relation to pregnancy, pituitary symmetry, stalk size, signal intensity and homogeneity after contrast supported the diagnosis of hypophysitis, whereas greater pituitary mass volume and mucosal swelling in the sphenoid sinus supported the diagnosis of adenoma.

NFPA vs. meningioma

Meningiomas grow typically in the suprasellar space, with obtuse margins at the edge. In the vast majority of cases pituitary function is normal, the sella is not invaded and a normal pituitary is easily recognizable even in the rare instance of sellar invasion.

If cavernous sinus is invaded, meningiomas tend to narrow the carotid artery lumen more than any other tumors (Young et al., 1988).

The so-called dural tail, previously regarded as pathognomonic of a meningioma, is now considered nonspecific, because it can be seen in association with adenoma, metastases, lymphoma, and lymphocytic hypophysitis (even though DI is frequent in these last 3 cases and not in meningiomas). This asymmetric tentorial enhancement is thought to be caused by venous congestion due to compression or invasion of the ipsilateral cavernous sinus rather than to meningeal inflammation or tumor invasion (Guerhazi et al., 2005; Nakasu et al., 2001; Rumboldt, 2005)(figure 22).

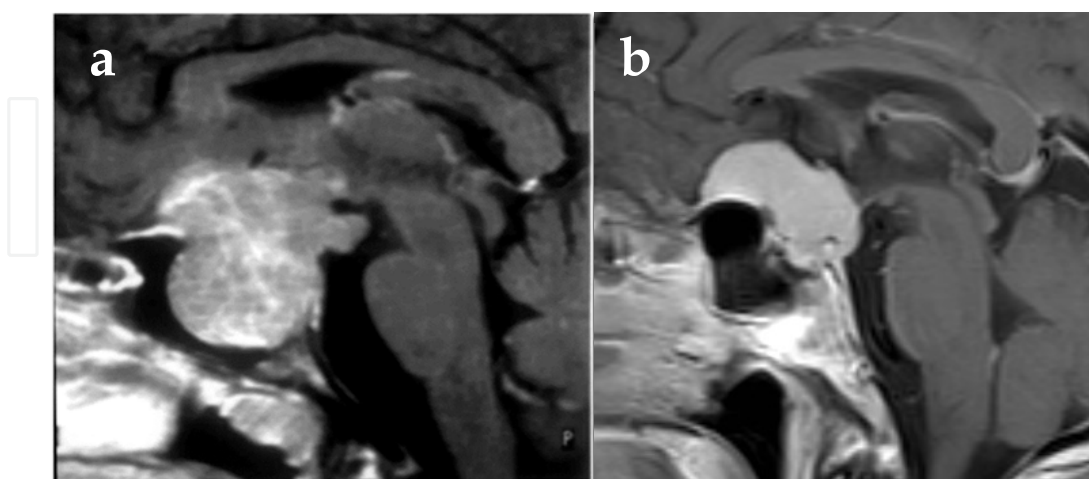


Fig. 22. Macroadenoma vs. meningioma (a vs. b): the former causes sellar enlargement and erodes sellar floor, the latter arising from planum sphenoidale, invades the sella that appears normal in size, and enhances strongly and homogeneously. In both cases dural tail is apparent.

Purely intrasellar meningiomas are extremely rare. They can be extremely difficult to distinguish from adenomas (Cappabianca et al., 1999). MRI is not different either on basal T1 or T2. However, post-contrast enhancement is marked, rapid and homogeneous in more than 90% of meningiomas, whereas adenomas generally enhance less intensely and more heterogeneously, with a longer time-to-peak enhancement on dynamic imaging (Huang & Castillo, 2005). Other features pointing to a meningioma (when present) are liquor cleft between the tumor and the gland, hyperostosis of the floor of the sella or adjacent bone structures, flow voids and prominent vessels, and calcifications (Huang & Castillo, 2005).

NFPA vs. metastasis

No radiological sign can accurately discriminate between the two conditions, even though bone lytic reactions usually accompany the latter (Komninos et al., 2004).

NFPA vs. chordoma

Posterior location, bone destruction with honeycomb aspect, and calcification as well as MR signal characteristics usually point to chordoma (Glezer et al., 2008).

NFPA vs. solid craniopharyngioma

Calcifications at CT are usually present in craniopharyngiomas. The apparent diffusion coefficient of craniopharyngiomas is higher than that of adenomas on average (Yamasaki et al., 2005; Zada et al., 2010).

Meningioma vs. solid craniopharyngioma

On T2-weighted images meningiomas typically appear isointense, whereas craniopharyngiomas (and RCCs) typically look hyperintense (Freda & Post, 1999).

Meningioma vs. neurinoma

Patients with neurinoma usually complain of 5th nerve pain or numbness and deficit is usually present at the neurological examination. Schwannomas follow the expected course of a cranial nerve or its branches, occasionally enlarging the cranial nerve outlet foramen in the skull base, such as the foramen ovale or rotundum (Smith, 2005). Furthermore, on dynamic contrast enhancing MRI sequences meningiomas usually show early enhancement, while neurinomas present gradual but brighter enhancement (Rennert et al., 2007).

Lipoma vs. other tumors

Lipomas can be distinguished from other lesions, similarly bright on precontrast T1-weighted images (such as hemorrhagic or proteinaceous lesions), by using suppressing fat sequences, which obtain their disappearance (Smith, 2005).

Fat containing dermoids and teratomas are less homogenous than lipomas.

Hamartoma vs. other tumors

Tuber cinereum hamartoma can be differentiated from other pathologies in this region (gliomas, LCH, and germ cell tumors) by clinical presentation, absence of contrast enhancement, and unchanging appearance on follow-up without growth or invasion (Spampinato & Castillo, 2005).

4.2.2 Cystic lesions

The spectrum of cystic pathologies occurring in the sellar region includes craniopharyngiomas, RCCs, arachnoid cysts, cystic pituitary adenomas, epidermoid cysts, dermoid cysts, and several others (Laws, 2008). A firm diagnosis is easily reached in most cases, while in others a diagnosis can be established only at surgery, when it is clinically indicated (Harrison et al., 1994; Zada et al., 2010).

Cysts vs. ES

Arachnoid cysts or RCCs may simulate ES, but in the latter the pituitary stalk remains usually in the median position and can be visualized down to the sellar floor (Giustina et al., 2010).

Cystic NFPA vs. RCC

Both intrasellar and suprasellar cysts can produce signs and symptoms similar to those of adenomas, such as visual impairment or hypopituitarism (Freda & Post, 1999).

Presence of a fluid-fluid level on sagittal or axial images is highly indicative of adenomas, representing intratumoral degeneration and hemorrhage, which almost never occur in cysts (Rumboldt, 2005).

RCCs are located in the center of the gland, have complete absence of contrast enhancement, and may contain characteristic nodules of low T2 signal or be completely hypointense on T2-weighted images (Byun et al., 2000).

Cystic NFPA vs. craniopharyngioma

Cystic pituitary adenomas are located within the anterior pituitary lobe, are surrounded by normal pituitary tissue, and the cyst wall consists of enhancing tumor tissue. Cystic craniopharyngiomas are more commonly suprasellar and located superior to the pituitary gland and show enhancing solid components and calcifications (Spampinato & Castillo, 2005).

Cystic NFPA vs. abscess

In contrast to adenomas, abscesses typically show ring enhancement and high signal intensities on diffusion weighted (DW) images together with a reduction in the apparent diffusion coefficient (ADC), whereas necrotic tumors display a hypointensity on DW images and higher ADC values (Takao et al., 2006). Furthermore, meningeal enhancement due to concurrent meningitis may be observed in pituitary abscess (Vates et al., 2001).

RCC vs. cystic craniopharyngioma

Presenting clinical features are not reliable in this differentiation.

The two lesions can be classically distinguished on MRI: craniopharyngiomas typically show prominent cystic components and calcifications, may be multilobulated or with an irregular shape or rim enhancement, with heterogeneous T1 signal demonstrating heterogeneous or strong homogeneous enhancement as well as solid enhancing nodules in the cyst; RCCs are typically small, round, purely cystic lesions lacking calcification with homogenous hypointense T1 signal intensity and midline anterior infundibular displacement (Famini et al., 2011). RCC may however have a variable imaging appearance

depending on the nature of the cyst contents, making the differential diagnosis challenging in some cases.

Imaging parameters that can be used to support a diagnosis of craniopharyngioma over RCC include: presence of calcification, greater tumor diameter (> 2 cm), suprasellar location with superior tumor lobulation, and compression of the third ventricle (Choi et al., 2007). Radiological parameters supporting a diagnosis of RCC are an ovoid shape, small cyst volume, and thin or no cyst wall enhancement.

Suprasellar calcification in a child is highly suggestive of the diagnosis of craniopharyngioma. Although the presence of calcifications may be helpful in the differential diagnosis, it is not specific. On CT scanning 42–87% of craniopharyngiomas exhibited calcification, compared with only 0–13% of RCCs. It is important to note, however, that several cases of RCCs have been reported to occur with ossification and no evidence of neoplastic features, and that the presence of calcium is not necessarily pathognomonic for craniopharyngiomas (Zada et al., 2010).

RCC vs. arachnoid cyst

Arachnoid cyst typically contains CSF, while the content of RCC (and its imaging characteristics) is variable. RCC exhibits some degree of rim enhancement, as opposed to minimal or no enhancement in arachnoid cyst (Valassi et al., 2010).

Epidermoid cyst vs. arachnoid cyst

Neither epidermoids nor arachnoid cysts enhance but epidermoids are usually bright on FLAIR and DW images, while the arachnoid cyst is dark on both sequences. Furthermore, epidermoids tend to insinuate between vessels and other adjacent structures, while arachnoid cysts displace them (Spampinato & Castillo, 2005).

5. Back to clinics

5.1 Patient 1

The 55 yo woman with headache and visual troubles needs a careful ophthalmologic, neuroradiological and endocrine evaluation. Initially, visual troubles must be better defined by performing a complete examination, including formal visual field testing. Bitemporal hemianopsia is shown together with previously unknown decreased left visual acuity. MRI shows a solid mass isointense on T1, hyperintense on T2, heterogeneously enhancing after Gd administration. The lesion enlarges the sella, extends in the suprasellar region impinging on the optic chiasm, while apparently sparing the cavernous sinuses. The patient denies polydipsia and polyuria. No clinical sign of hypersecretion is present. Screening of hypersecretions is negative: PRL is 88 ng/mL (no change after serum dilution 1:10 to rule out hook effect), IGF-I is 120 ng/mL (that is normal for her age range), and morning cortisol is normally suppressed after overnight dexamethasone suppression test (0.5 µg/dL). Screening of hypopituitarism is negative as well: morning cortisol, FT₄, and FSH are 10 µg/dL, 1 ng/dL, and 45 U/L, respectively. All data (epidemiologic, clinical, endocrine and imaging) thus point to a diagnosis of NFPA. The patient is operated on by a trans-sphenoidal endoscopic approach, without perioperative steroid coverage (Cozzi et al., 2009b). Headache disappears and visual field normalizes. Histological evaluation confirms

pituitary adenoma. Immunohistochemistry is negative for pituitary hormones, and Ki67 is 0.5%. Post-operative course is uneventful. At 4 months, a radical resection is shown on MRI, as well as normalization of visual acuity and visual fields; morning cortisol and FT₄ are 12 µg/dL and 1.1 ng/dL, respectively. Follow-up is scheduled with yearly evaluation of MRI for 3 years, thereafter progressively lengthening intervals.

5.2 Patient 2

In the 34 yo woman with amenorrhea since 8 months work-up must start from endocrine evaluation. PRL is 850 ng/mL. This value is diagnostic of prolactinoma, because no other disease is associated to such high values. It is useful to evaluate IGF-I levels, to rule out a concomitant GH hypersecretion (210 ng/mL, that is normal for her age range), and pituitary function to screen for hypopituitarism. Morning cortisol and FT₄ are within normal limits (13 µg/dL and 1.2 ng/dL, respectively), whereas estradiol, LH and FSH are low as expected (40 pg/mL, 0.7 U/L, and 3.5 U/L, respectively). Visual field examination shows superolateral bilateral quadrantopsia and MRI demonstrates a large mass, hypointense on T1, hyperintense on T2, heterogeneously enhancing after Gd administration due to multiple cysts, with irregular extrasellar extension up to optic chiasm, and in the sphenoid and cavernous sinuses. Macroprolactinoma is the only clinical situation where neurosurgery is not the first line therapeutic option in spite of visual pathways compression. Cabergoline, a selective dopamine agonist drug, is started at 0.25 mg/week at bedtime, obtaining visual field normalization within one week. Follow-up is scheduled with clinical and PRL evaluation monthly for the first 3 months, at 3-month intervals in the first year, and at 6-month intervals in the following two years. PRL levels progressively decrease until normalization in 6 months, with menses restoration. After the first control at 3 months, MRI should be repeated at 6 and 12 months. If there is progressive shrinkage (in this patient it is substantial), successive controls can be performed yearly or even at more prolonged intervals, provided that PRL levels are still suppressed.

5.3 Patient 3

The 8 yo boy with growth arrest and mass in the sellar region needs a thorough evaluation. On physical examination height is at the 25th centile (genetic target over 50th), weight at the 75th centile, puberty at Tanner stage I. Adenoma is not the most frequent diagnosis in this age group, nonetheless the screening for prolactinoma and Cushing's disease (even though macroadenoma would be exceptionally rare) is warranted. PRL is 60 ng/mL and morning cortisol is normally suppressed after overnight dexamethasone suppression test (basal 9 µg/dL, after dexamethasone 0.8 µg/dL). Beyond growth arrest and worsening of school results, weight increase and excessive thirst are reported. Serum sodium is 148 mEq/L and glucose 65 mg/dL. Thyroid function is slightly impaired (FT₄ 0.7 ng/dL, with normal values 0.8-2.2). On the basis of history and sodium values, partial central DI is diagnosed and desmopressin is started. On MRI a heterogeneous intra and suprasellar mass is observed, with mottled appearance on T1, heterogeneously hyperintense on T2. Multicystic appearance is evident after Gd administration, with rim enhancement. CT scan shows multiple calcifications. Epidemiologic, clinical and radiological data point to craniopharyngioma. The patient undergoes neurosurgery by trans-sphenoidal approach. Post-operatively, DI worsens and panhypopituitarism develops, requiring full substitutive

treatment with desmopressin, hydrocortisone and thyroxine. Follow-up is scheduled with MRI, to evaluate the radicality of resection. Metabolic and weight control is of particular concern. GH treatment is started. Puberty induction will be postponed until attainment of satisfactory height for the genetic target.

5.4 Patient 4

In the 45 yo male with the incidental finding of microlesion in the pituitary, the first task is screening of hypersecretory syndromes. PRL is 13 ng/mL, IGF-I 150 ng/mL, FT₄ 1 ng/dL, TSH 1 mU/L, and morning cortisol after overnight dexamethasone suppression test 1 µg/dL (all within normal limits). The 7-mm lesion is located in the left inferior portion of the gland, is hypointense on T1, hyperintense on T2, and moderately enhancing. All data point to a non-functioning microadenoma. On the basis of clinics (non functioning), size (micro) and location (far from critical structure), watchful waiting is an appropriate choice. MRI control is scheduled at 12 and 24 months, without any hormonal control. Size is unchanged and the patient is reassured about the lack of evolutivity of the lesion. There is disagreement between the neurosurgeon and the endocrinologist about further follow-up: it is to be prolonged life-long for the former (with MRI at 2-year intervals), and it is redundant for the latter.

6. Expert suggestions and conclusions

A few key-points are to be kept in mind.

- Most lesions are pituitary adenomas but alternative diagnoses must always be considered.
- A screening of hypersecretory syndromes and hormonal deficiencies is mandatory. This can be accomplished by a few focused hormonal assays.
- In diagnostic reasoning, consider epidemiological factors.
- Take always into account comorbidities: a hypothalamic-pituitary lesion can be a local manifestation of a systemic disease.
- Imaging must be critically reviewed together with the radiologist.
- Don't miss red flags even though virtually nothing is pathognomonic.

The flow-chart in figure 23 is a simple but not exhaustive guide to diagnostic reasoning.

A plausible diagnosis is possible in many cases of parasellar lesions on the basis of epidemiological, clinical and neuradiological data. This involves a multidisciplinary collaborative effort among the endocrinologist, the neuroradiologist, and the neurosurgeon. Skilled individuals in an organized team, the pituitary unit, better perform this task. In cases of doubt, a histological diagnosis may still be required for a correct diagnosis and to allow appropriate treatment planning. Although most parasellar tumors are slow growing and benign, it is important to identify on the basis of clinical context, laboratory data, and serial imaging those which exert a strong malignant potential or are malignant. Treatment as well involves a joint effort requiring the collaboration of different specialists: the neurosurgeon, the endocrinologist, and the radiotherapist, with the neuro-oncologist and the nuclear physician entering as a second-line in a few cases.

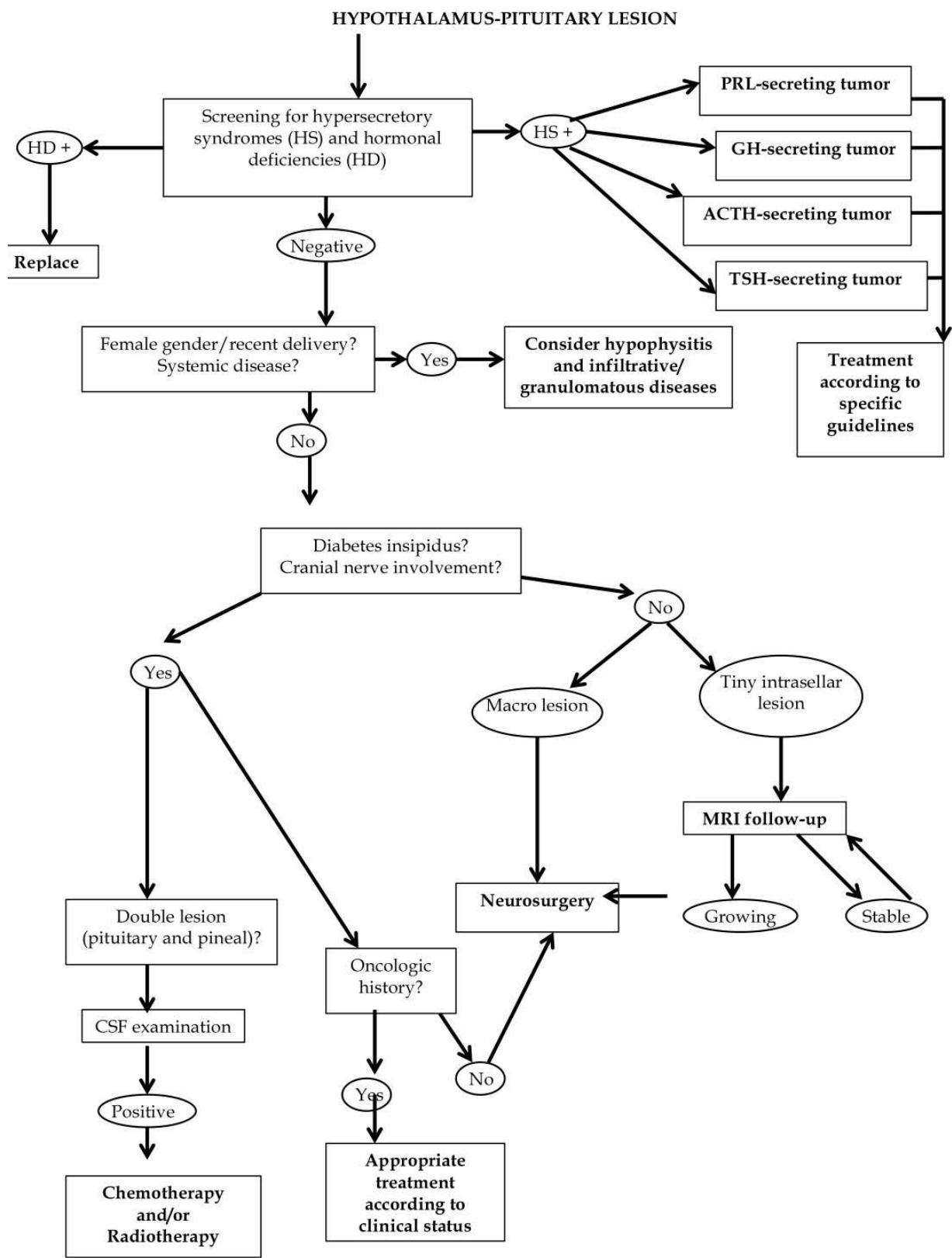


Fig. 23. Flow-chart for diagnosis

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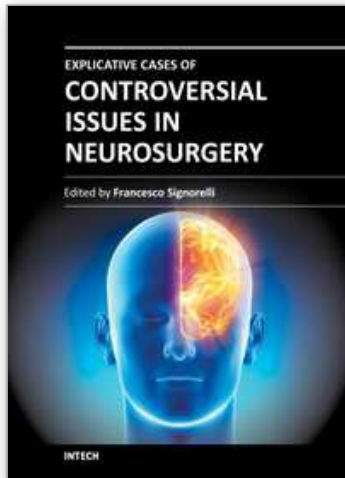
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