Chapter 21
Craniopharyngioma and Other Sellar Tumors

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21.1 Pituitary Gland: Development, Anatomy and Function

Embriological basis of pituitary gland development may help in pituitary tumours understanding. Pituitary gland is a master neuroendocrine organ located at midline within the sella turcica recess of the sphenoid bone [1, 2]. It has an essential role in maintenance of homeostasis and reproductive function [3], regulating production and secretion of peptid hormones to develope and functioning of many organs, including thyroid, adrenal glands, gonads, mammary gland and liver [2].

The pituitary gland forms around the middle of the fourth embryonic week from an invagination of the oral ectoderm (stomodeum) to the rudimentary primordium (Rathke's pouch) [3]. Neurulation, neural plate development from ectoderm, occur at 3 weeks of gestation [4]. The anterior part of neural plate will grow to develope the forebrain, optic nerves, hypothalamus, anterior and posterior pituitary lobe [1]. To understand pituitary gland development the murine model has been used because is similar to other vertebrates and humans [5–7]. In the murine model pituitary organogenesis begins around E8.5 (embrionic day 8.5) with the appearance of Rathke's pouch, an invagination of the anterior pituitary placode from oral ectoderm. The dorsal portion of the pouch contacts the midline of the ventral diencephalon, evagination of which (around E10) acts as the main organizer for its patterning and differentiation of its cells [8]. So the hypothalamus (part of diencephalon derived from neural ectoderm) influences and regulate hypophysis gland development (derived from ectoderm) [7]. After 24 h of primordium Rathke's pouch development infundibulum (ventral diencephalon) invaginate to contact Rathke's pouch at the time that it severed from oral ectoderm achieving a fully developed definitive pouch [1].

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The final pituitary gland is composed of three lobes: the endocrine hormone-producing anterior and intermediate lobes originated from the oral ectoderm (Rathke's Pouch) and the posterior lobe (neurohypophysis) developed from the overlying neural ectoderm as does pituitary stalk [1].

The adenohypophysis (pituitary anterior lobe) produces six different hormones: corticotropin or adrenocorticotropic hormone (ACTH) by corticotrophs cells, growth hormone (GH) by somatotrophs cells, thyroid-stimulating hormone or thyrotropin (TSH) by thyrotrophs cells, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by gonadotrophs and prolactin (PRL) by lactotrophs cells [1, 2]. The production and secretion of all six hormones is controlled by factors synthesized and released from the axonal terminals of hypothalamic neurons to the hypophyseal portal system [9, 10] so the hypothalamus regulates posterior lobe but also anterior. Hypothalamus secretes: corticotropin-releasing hormone (CRH) that controls ACTH, GHRH that regulate GH secretion, thyrotropin-RH (TRH) for TSH, and gonadotropin-RH (GnRH) for LH and FSH; dopamine inhibits PRL secretion. All of them are trophic factors, releasing hormones (RH), that regulate the function of the anterior pituitary through modulation of cell proliferation, hormone synthesis, and secretion [9].

The neurohypophysis (pituitary posterior lobe) contains axonal terminals from hypothalamic and secretes oxytocin and vasopressin. These hormones are synthesized by neurons from hypothalamus and transported to the axonal terminis. Neurons from posterior lobe are surrounded by pituitocytes (astroglia) [9].

21.2 Pituitary and Sellar Tumours

As described previously, pituitary tumours are rare neoplasms in children. Incidence and prevalence of all CNS tumours in children in the United States showed 4.9 new cases per 100.000/year and 35.4 cases per 100.000, respectively [11]. Some series in literature estimate that up to 15% of all intracranial tumours in children are craniopharyngiomas [9] but, in general, it seems to be much less frequent neoplasm accounting for 1.2–4% of all intracranial tumours in children [12], so we can estimate an incidence around 0.06–0.2 cases per 100.000 patient/year and prevalence of 0.4 to 1.4 cases per 100.000 children. Pituitary adenomas are the second most common tumours in pituitary fossa although less frequent than craniopharyngioma.

21.2.1 Craniopharyngiomas

The first description of a craniopharyngioma was in 1857 by Zenker but the term craniopharyngioma was introduced in 1932 by Cushing [13]. They are the most frequent of all pituitary fossa tumours in children comprising 80–90% [9].

Incidence of craniopharyngiomas has bimodal distribution. First peak is between 5 and 14 years old and the second in the fift decade of life [14, 15].

Craniopharyngiomas are benign tumours that are probably the result of metaplastic changes in vestigial epithelial cell rests along the tract of the involuted hypophyseal–pharyngeal duct or Rathke's pouch that forms the adenohypophysis and glandular portion of the pituitary stalk (derived from an stomodeum diverticulum) [16].

There are two distinct histological patterns: adamantinomatous (children and adults) and squamous papilar (almost in adults). There are two theories to explain craniopharyngiomas development related to embriology of pituitary gland as described before. The embryogenetic theory: adamantinomatous craniopharyngiomas arise from epithelial remnants of the craniopharyngeal duct or Rathke's pouch (derived from parts of the stomadeum that form tooth primordial). The metaplastic theory: squamous papillary tumors arise from metaplasia of squamous epithelial cell rests (remnants of that portion of the stomodeum that contributed to the development of the buccal mucosa) [16–19].

Nowadays, genetic and epigenetic studies showed different mutation and pathway signaling between both craniopahryngioma subtypes, so there might be new therapeutic strategies in the next future to treat or control tumor growth and progression [15].

21.2.1.1 Clinical Presentation

Clinical presentation in children is related to mass effect or endocrine disturbances. Initial symptoms of craniopharyngioma are frequently unspecific, and the diagnosis can be made relatively late. The most frequent symptoms before the diagnosis in children are headache (68%), followed by visual impairment (55%), growth failure (36%), nausea (34%), neurologic deficits (23%), polydipsia/polyuria (19%) and weight gain (16%) [12, 20, 21]. The period from initial symptoms to the diagnosis does not correlate with tumor size, hypothalamic involvement, functional capacity or survival [22]. It is important to investigate children that show weight gain and growth retardation because they may be early signs of craniopharyngiomas in children. Acute presentation with signs and symptoms of raised ICP or acute vision loss secondary to obstructive hydrocephalus are associated with bad prognosis with lower 10-year overall survival [22].

21.2.1.2 Diagnosis

Imaging: craniopharyngioma can be located in the sella, and/or partially or entirely suprasellar. Craniopharyngioma classic CT scan image in a child is an enhancing sellar/suprasellar mass that is calcified (90% of craniopharyngiomas calcify in children) and cystic. When two out of these three features are present, craniopharyngioma is the most likely diagnosis [23, 24]. Usually the solid focus is in the sella and

cystic components arising above it [24]. On MRI usually demonstrates T1 high intensity, reflecting the protein or cholesterol content of the "motor oil-like" fluid found in the tumor cysts [25]. Other causes of T1 hyperintensity in craniopharyngiomas have been described—fat, hemorrhage, or even mild calcification [26]. On T2-weighted sequences, including Fluid Attenuated Inversion Recovery (FLAIR), the solid portion is again usually heterogeneous, whereas the cysts are invariably hyperintense. The use of contrast show almost invariable contrast enhancement of the solid portion and the peripheral rim of the cystic portion on both CT and MR (Fig. 21.1).

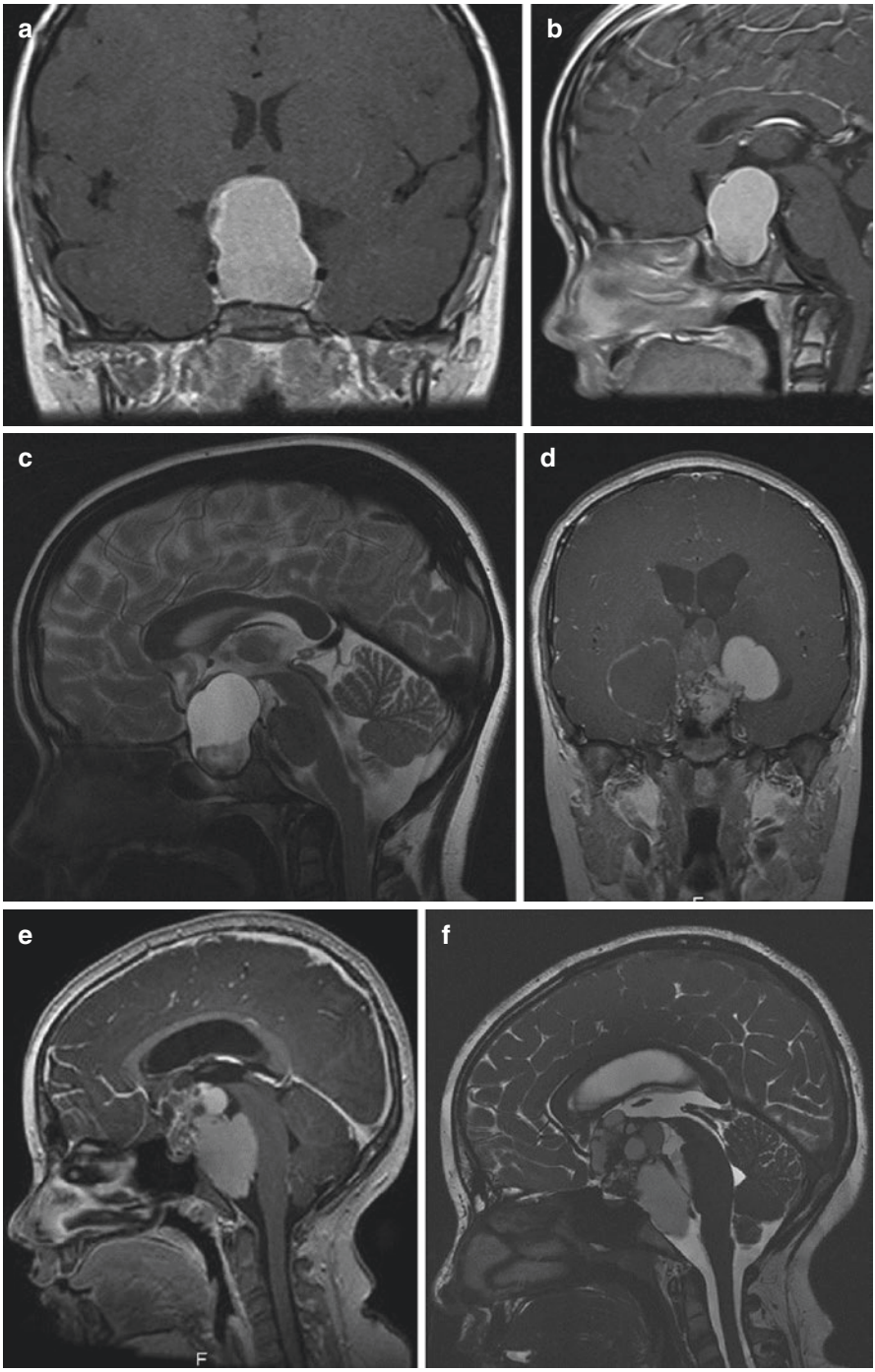
The most common differential diagnosis of craniopharyngioma are pituitary adenoma, hypothalamic or optic pathway glioma, Rathke's pouch cyst and Epidermoid tumor. Pituitary adenomas are noncalcified lesions, have a tendency to expand into the sella and have less superior extension. If cystic component is present it usually has low intensity signal on T1 images [27]. Hypothalamic or optic pathway gliomas rarely have a sellar component (only large lesions), rarely calcify, are usually isointense on T1 and usually lack a cystic component [24]. Large Rathke's cleft cysts typically do not contain a solid component, do not enhance, and are not calcified. With small lesions it may be difficult to differentiate [28]. Epidermoid tumors are rare in the suprasellar region and may be identified by restricted diffusion as they have high signal. Peripheral rim enhancement is less common in epidermoids [29].

Hormonal and hypothalamic assessment: endocrine deficits might be present in 52%–87% of children at the time of presentation as the result of disturbances to the hypothalamic-pituitary axes. They affect growth hormone secretion (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%) [30]. 17%–27% have been reported to have diabetes insipidus neurohormonalis [31–33]. So all hypothalamus-pituitary axis, urine output and water intake must be tested at the time of diagnosis.

Symptoms of hypothalamic dysfunction have been found in 35% of craniopharyngioma patients at diagnosis. They are obesity, behavioral changes, disturbed circadian rhythm and sleep irregularities, daytime sleepiness, and imbalances in regulation of body temperature, thirst, heart rate and/or blood pressure [33]. Rapid weight gain and severe obesity are serious neuroendocrine complications due to hypothalamic involvement and difficult to control. 12%–19% of patients reported to be obese at presentation [31, 32, 34, 35] and often occur years before diagnosis [36].

Ophtalmological examination: Craniopharyngiomas commonly induce visual impairment in children so ophthalmological examination and referral might be done

Fig. 21.1 Craniopharyngioma MRI features: (**a**) 7 years old boy with sellar and suprasellar craniopharyngioma and no hypothalamus involvement, mostly cystic, coronal T1-weighted image; (**b**) (same patient) sagital T1-weighted image with contrast enhancement; (**c**) (same patient) Sagital T2-weighted-image; (**d**) 9 years old girl, with sellar, suprasellar and parasselar craniopharyngioma with suspected hypothalamus involvement, coronal T1-weighted image with contrast enhancement; (**e**) (same patient) sagital T1-weighted image with contrast enhancement; (**f**) (same patient) sagital T2-weighted image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at diagnosis [37, 38]. Almost 50% of children may have visual impairment at diagnosis: decreased visual acuity (41.3%), visual field loss (38.3%), papilledema (25.8%) and optic nerve atrophy (44.8%). Abnormalities in orthoptic examination such strabismus, diplopia and cranial nerve deficits were seen in 12.5% of cases [37].

21.2.1.3 Treatment

Treatment of craniopharyngiomas in children is under continuous debate because the optimal treatment strategy for craniopharyngioma is controversial [39, 40]. Although craniopharyngiomas are benign lesions and, historically, gross total resection has been the preferred treatment approach, tumor's proximity, encasement and invasion to vital structures such as hypothalamus, frontal lobe, ventricles, cranial nerves, and circle of Willis makes complete tumour resection unfeasible and unsafe in many cases and may lead to high rates of hypothalamic-pituitary and/or optic impairment [41–45].

Perioperative fatal complications are reported in up to 3% of craniopharyngioma surgery [52]. The rate of neuroendocrine hypothalamic dysfunction increases seriously following radical surgical treatment, up to 65%–80% in some series [30, 33, 34]. The degree of obesity of affected craniopharyngioma patients is positively correlated with the degree of hypothalamic damage [53–55] and rapid weight gain typically occurs during the first 6–12 months after treatment [35, 55, 56]. The prevalence of severe obesity is higher in comparison with pretreatment status, reaching up to 55% [30]. Obesity and eating disorders result in increased risks of metabolic syndrome [57] and cardiovascular disease [55], including sudden death events [58], multisystem morbidity and death [59].

The rate of post-surgical pituitary hormone deficiencies increases due to the tumor's proximity or even involvement of hypothalamic-pituitary axis [30, 32, 33, 36, 60–64]. Transient post-surgical diabetes insipidus occurs in up to 80%–100% of all cases [30, 34, 60] and the rate of permanent post-surgical diabetes insipidus ranges between 40% and 93% [30, 32–35, 60, 61, 65]. Growth hormone deficiency following treatment is found in about 70%–92% of patients [30, 36, 53, 66, 67].

Last twenty years many groups reviewed their results retrospectively to design new strategies in order to reduce mortality and morbidity secondary to surgical treatment [13, 40, 46–51].

Some classifications emerged based on preoperative clinical and imaging but focused in craniopharyngioma relationship/invasion of hypothalamus and sparing during surgical procedures [13, 21, 49, 68–71]. Nowadays it is accepted that craniopharyngioma with no hipothalamus involvement and "safety" neurovascular dissection might be treated by surgery with the goal of complete removal. When hypothalamus sparing is not possible more conservative surgical management is the rule with association of radiotherapy for tumour remnant. This new approach for craniopharyngioma treatment has shown good long-term disease control and survival with much less morbidity and mortality mainly related to hypothalamus sparing [13, 40, 41, 48–51, 53–56, 62, 63].

Surgical technique may be by craniotomy (pterional transsylvian fissure, interhemispheric transcallosal, midline subfrontal, supraorbitary subfrontal), by endoscopic transnasal transsphenoidal approach or expanded endonasal approach but also by transventricular endoscopic approach. There are also some radiotherapy approaches to craniopharyngioma adjuvant treatment. Detailed description of surgical technique and radiotherapy options are beyond the scope of this chapter.

Overall survival rates reflect the benign origin of craniopharyngiomas but also the complexity and consequences of treatment options, mainly when hypothalamus is affected. Overall survival described in children series show: from 83% to 96% at 5 years, 65%–100% at 10 years and averaging 62% at 20 years. It is not only survival but also quality of life affected by craniopharyngiomas when there is hypothalamus involvement so treatment recommended strategy, in this cases, is limited hypothalamus-sparing surgery followed by radiotherapy [46].

21.2.2 Pituitary Adenomas

Pituitary adenomas are very rare in children. Data from autopsy studies show that pituitary adenomas were present in 17–25% in general population and data from radiological imaging studies show similar incidence, up to 20% of people [72–74]. Only 3.5 to 8.5% of pituitary adenomas are diagnosed in people under 20 years of age accounting for 3% of all intracranial tumours in children [75–78]. However many adenomas presenting in early adult life probably originated in childhood [79].

Pituitary adenomas in children, in comparison to adenomas in adults, are more frequently functioning (80–97%). Adrenocorticotropin (ACTH)-secreting adenomas (Cushing disease) are the most common in early childhood, followed by prolactin (PRL)- prolactinoma- and growth hormone (GH)- secreting adenomas [80]. Prolactinomas predominate in older children and adolescents [3, 81, 82]. Except for corticotroph adenomas, the majority of pituitary adenomas are macroadenomas (diameter > 1 cm) and are frequently invasive.

Although the majority of these tumors are sporadic they can be part of a genetic condition predisposing to pituitary and other tumors. Even sporadic tumors have genetic abnormalities: most pituitary tumors are monoclonal lesions and modifications in expression of various oncogenes or tumor suppressor genes. In recent years many genetic defects have been identified, including genes involved in cell signaling or cell growth and proliferation [79, 81, 83–87]. Other factors and genetic events seem to be implicated in pituitary cell clonal expansion, and oncogene activation is necessary to propagate tumor growth [3, 83, 85]. Familial cases account for 5% of pituitary adenomas [79, 81, 86, 87]. Some genetic syndromes have been associated with pituitary adenomas: MEN-1, McCune- Albright, Carney complex and familial isolated pituitary adenomas (FIPA) [88].

Clinical and laboratory diagnosis depend on tumour secreting hormone (adenoma subtype). Pituitary MR imaging is the modality of choice for detecting pituitary adenomas. Main sequences are T1 weighted spin-echo MRI of the pituitary

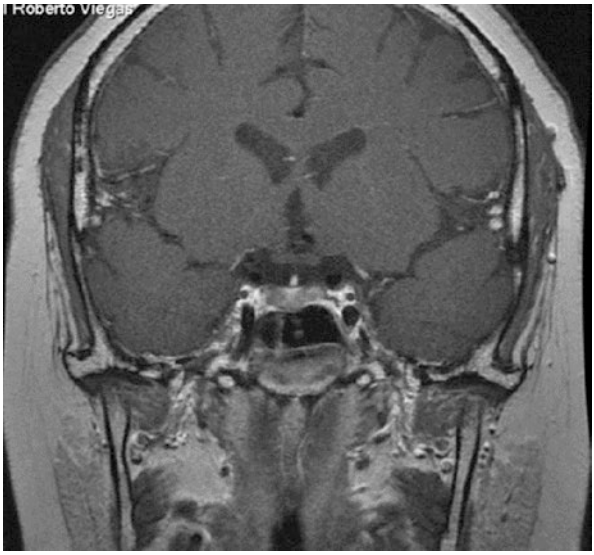

Fig. 21.2 Pituitary adenoma MRI features. Coronal T1-weighted image with contrast enhancement showing hypointense adenoma surrounded by contrast enhanced pituitary gland

before and after administration of gadolinium (Gd). Adenohypophysis (anterior pituitary gland) is normally iso-intense with the rest of the brain. Adenomas appear as hypoenhancing lesions because normal pituitary issue enhance faster than adenoma (Fig. 21.2). Deviation of the pituitary stalk away from the side of the tumor and an asymmetrical increase in the vertical height of the gland are less specific signs for adenoma diagnosis [89]. Dynamic MR techniques rely on rapidly repeated scans, which capture the wash-in and wash-out of contrast to demonstrate a time-dependent pattern of early gland enhancement, followed by delayed adenoma enhancement, optimizing visualization of the lesion [88].

Prolactinoma (Prolactin-secreting adenomas): It arises from acidophilic cells of adenohypophysis. These cells are derived from the same embryonic lineage as the somatotropes and thyrotropes so tumours might secrete also GH and, rarely, TSH [3, 89]. Prolactinomas are the most common adenoma in children accounting for 48%–52% of tumors in general but is much more prevalent in second decade. In fact, ACTH-releasing tumors (Cushing disease) are much more common in the first decade than prolactinomas (71% vs 16%) [90]. Prolactinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood [3]. Girls are more affected than boys (1.9:1 to 4.5:1, depending on age) [79].

Clinical presentation in prepubertal children is a combination of headache, visual disturbance, and growth failure. Due to suppression of gonadotropin secretion by hiperprolactinemia or local compression/destruction of pituitary gland pubertal females frequently present with symptoms of pubertal arrest, hypogonadism and, sometimes, galactorrhea. Clinicians may ask but also express the breast to rule out galactorrhea because teenagers may not spontaneously talk about this symptom and it may not occur spontaneously. In males macroadenoma are more frequent at presentation so may present with headaches and/or visual impairment. Presentation

may be also pubertal arrest or growth failure but is less frequent maybe due to the fact that gonadotropin release is sensitive to the effects of hyperprolactinemia, enabling earlier detection of the tumor in females [89, 91–93].

Basal prolactin levels has a high diagnostic value and correlates with the size of the tumour [80, 94, 95] but, due to pulsatile secretion, at least two determinations on different days and 2–3 samples separated by 20 min should be obtained [96, 97]. It is important to rule out physiologic (nipple stimulation, chest wall lesions, physical or emotional stress), iatrogenic (medication as phenothiazines, metoclopramide, centrally acting antihypertensive) and pathologic causes (tumors and infiltrative disease of the pituitary, infundibulum, hypothalamus) of secondary hyperprolactinaemia [79, 89]. Supranormal PRL levels below 100 ng/mL may be attributable to the so-called "stalk effect", above 100 ng/mL, prolactinoma is relatively assured and certain above 200 ng/mL—although results below these thresholds do not exclude the possibility of a true secreting prolactinoma [88, 97, 98].

Management of prolactinoma is mostly medical with dopamine agonists in order to reduce prolactin levels and reduce tumor volume, unless there is an acute threat to vision, hydrocephalus, cerebrospinal fluid leak or other surgical emergency [79, 89]. D2 agonists can achieve control of PRL in 80–90% of patients in the majority of cases in the first 6 months of therapy [97, 99]. There are mainly two options of medication, cabergoline (0.5–3.5 mg/week) or bromocriptine (2.5–15 mg/day). In the first year of treatment, up to 80% microadenomas and 25% of macroadenomas my show tumour volume reduction. Medical treatment must be continued at least two years after normal prolatin values and tumor desappearance on MR.

If hyperprolactinaemia persists after 3 months of maximal dose treatment and tumour reduction is <50% can be concluded tumour resistance to medical treatment and pituitary surgery should be considered. Radiotherapy may be an option after medical and surgical treatment failure [96, 97].

Corticotropinomas (ACTH-secreting adenomas, Cushing disease): adenomas causing Cushing's disease are the most common pituitary adenomas in prepubescent children [3] accounting for 54.8% of adenomas from age 0 to 11 years, and 29.4% from 12 to 17 years [80]. Beyond the first 5 years of life, ACTH-secreting adenomas account for 80–90% of children who develop Cushing's syndrome [89]. Male predominance is observed in prepubertal subjects [101, 102] accounting for 63% of cases [103]. Corticotropinomas are significantly smaller than other types of pituitary tumors (usually 3 mm or less) and rarely invade the cavernous sinus or grow into the subarachnoid space [3]. There are also case reports of tumors that originate in the posterior lobe [101].

The classic presentation is one of rapid weight gain with striae, hypertension, headaches, growth failure, pubertal failure or arrest, delayed pubertal development and amenorrhea despite often significant virilization and hirsutism and premature pubarche in prepubertal children [3, 89]. Insulin resistance is common, although frank diabetes occurs infrequently [89]. Features of paediatric Cushing disease show some differences compared with adult patients [79] as children and younger adolescents do not typically report problems with sleep disruption, muscle weakness, or problems with memory or cognition [3]. Instead of depression, memory

problems, and sleep disturbances, children with Cushing's syndrome frequently tend to be obsessive and are high performers at school [89].

The diagnosis of an ACTH-secreting adenoma needs the demonstration of ACTH-dependent hypercortisolaemia of pituitary origin [79]. Although microadenoma is the cause of most Cushing syndrome differential diagnosis must be done with primary adrenal tumors (more frequently seen in first 3 years of life), ectopic ACTH production (bronchial or thymic carcinoids), and, very rarely, ectopic CRH-producing tumors [89]. First step in diagnosis is to confirm Cushing's syndrome with several 24-h urine free cortisol (UFC) measurements and correct values for body surface area and normal range of each laboratory. Failure of the serum cortisol to suppress to less than 3 mg/dL the morning after receiving low dose of dexamethasone at midnight is another important data [89].

To establish that the Cushing's syndrome is due to an ACTH-secreting pituitary adenoma more tests are needed: stimulation of ACTH and cortisol following injection of ovine-CRH (increase after injection) and suppression of cortisol by more than 50% after high dose of dexamethasone given at midnight. The latter test has a sensitivity that is 85% and able to be done as an outpatient [89].

If laboratorial tests suggest corticotropinoma and the pituitary MRI shows adenoma the diagnosis is already done. If MRI is negative, then ovine-CRH-stimulated bilateral inferior petrosal sinus sampling can be used to confirm that the ACTH is coming from the pituitary gland and can also assist in lateralizing the tumor with approximately 75% accuracy. The sensitivity of this test at confirming pituitary ACTH dependence is 97% [89] (Fig. 21.3).

Cushing disease treatment in childhood is always surgical mainly by transsphenoidal adenomectomy [3]. The cure rate is significantly greater in those patients

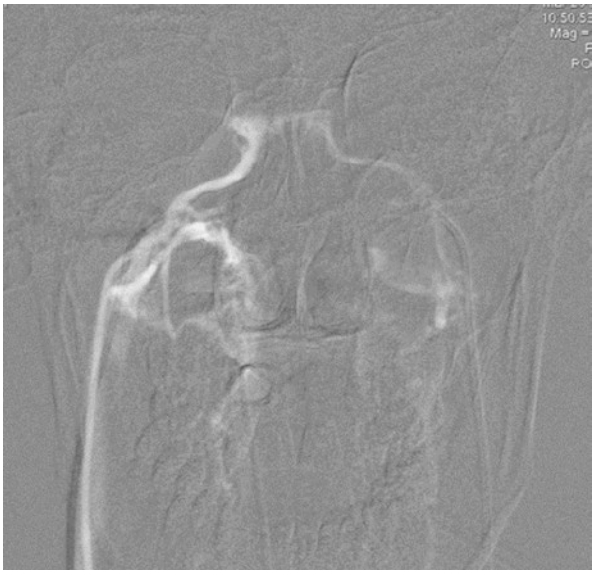

Fig. 21.3 Inferior petrosal sinus sampling for Cushing's disease diagnosis

who have noninvasive microadenomas and is successful in over 90% of the cases, with a recurrence rate of less than 10% [3, 89]. If the tumor is surgically unresectable, or after a second recurrence, fractionated radiation or gamma-knife therapy will produce normalization of cortisol in the majority of patients, although delayed plurihormonal hormone deficiency is expected [3, 89, 104, 105]. Cure rate of radiotherapy is approximately 70–80% of children [106]. Bilateral adrenalectomy may be considered for inoperable or recurrent cases; however it is associated with a significant risk of development of Nelson's syndrome [3, 107].

Somatotropinomas (GH-secreting adenomas, gigantism/acromegaly): Somatotroph GH-secreting adenomas account for 5–15% of pediatric pituitary tumors with a higher prevalence in males (59%) and median ages at symptom onset of 9 years and at diagnosis of 14 years [79, 108]. Approximately 90% of cases are macroadenomas, 30–60% being invasive [3]. Excess GH production in children may result from an adenoma or secondary to somatotroph hyperplasia, which occurs by stimulation of somatotroph in certain genetic conditions such as McCune-Albright syndrome, MEN-1 or Carney complex. Almost very rare, another cause of GH excess can be hypothalamic or ectopic tumors that secrete GHRH or by dysregulation of GHRH signaling that may occur as a result of a local mass effect [3, 89].

Somatotrophs are believed to have the same ancestral embriologic lineage as the lactotrophs and thyrotrophs so may stain for and secrete any or all of these hormones but it does not imply that the tumor secretes this hormone in clinically significant amounts [3, 89].

Clinical presentation varies depending on whether the epiphyseal growth plate is open or not [3, 79, 88, 89]. Before epiphyseal closure or fusion, acceleration of growth velocity with prominent height deviation above 2SDs may be the rule, a condition also known as "gigantism". As epiphyseal fusion approaches clinical symptoms become similar to those in adults (acromegaly) such as coarse facial features, broadened nose, large hands and feet, obesity, organomegaly, sweating, nausea and glucose intolerance [3, 79, 89]. Unlike adults, there have been no reports of a significant increase in colonic polyposis or malignancy or thyroid nodules [89]. Since somatotropinomas are often macroadenomas, headaches and visual disturbances are also frequently reported [3, 89, 109, 110]. Weight gain and delayed puberty can also occur [79].

Diagnosis is based on clinical, laboratorial and imaging results. Laboratorial diagnosis is based on the detection of increased IGF-I and GH levels for age and gender in blood tests. Further investigation include oral glucose tolerance test. Somatotropinomas patients show failure of GH suppression or a paradoxical rise in GH after an oral glucose load of 1.75 g/kg although this test alone may result high false positive rate [89, 111]. Identification of a pituitary adenoma on MRI scan is needed for final diagnosis [79, 100].

First-line of treatment for somatotropinomas is transsphenoidal surgery for intrasellar microadenomas and noninvasive macroadenomas with biochemical control reported in 70% of microadenomas and 50% in noninvasive macroadenomas [100, 108, 112]. In large and invasive tumors surgery might be indicated to maximal

removal and decompression but persistent disease is very common so medical therapy and/or radiotherapy may be necessary [3]. Pharmacologic agents such as long-acting somatostatin analogs (octreotide or, more recent, lanreotide) are often indicated both before and after surgery, when surgical cure is unlikely or when surgery fails to achieve biochemical control, and have been shown to be effective at shrinking tumor size and normalizing IGF-1 levels in 56% of cases [79, 100, 113–119]. D2 agonists can be used in patients with associated hyperprolactinaemia, or as adjuvant therapy if no biochemical control observed under high doses of somatostatin analogs [79, 100, 108, 112, 118]. Pegvisomant (GH receptor antagonist) has shown to be effective therapy for normalization of IGF-1 levels with less side effects [120]. Some groups has shown very good results in combined therapy with pegvisomant and long-acting somatostatin analogs [121]. Unfortunately there is limited data on pegvisomant treatment in children [3].

With the development of improved GH assays, the definition of cure of GH-secreting tumors has become increasingly rigorous, from an initial definition of an unsuppressed GH value of less than 10 mg/dL to the current definition that requires a return of the IGF-I levels to normal, with glucose-induced suppression of GH to less than 1 mg/dL (immunoradiometric assay) [89].

Radiotherapy is considered to be the third-line therapy. Hypopituitarism may occur in 30–50% of patients after radiotherapy [79]. Follow-up and monitoring of patients consists in measurement of IGF-I and post-oral glucose tolerance test GH levels together with MRI pituitary imaging [79, 100, 108, 112].

Thyrotropinomas (TSH-secreting adenomas): Thyrotropinomas are very rare during childhood and adolescence accounting for 0.5–2.8% of pituitary adenomas in children [79, 81, 122]. Only few cases reported in literature and described as macroadenomas (almost 90%) with symptoms as headache, visual disturbance, and symptoms and signs of hyperthyroidism [79, 89]. Laboratory tests show elevated free T4 and T3 with no TSH supression. The differential diagnosis might be with isolated central thyroid hormone resistance. Medical suppression of thyroid hormone synthesis may result in increased tumor growth [89].

Again transsphenoidal surgery is the treatment of choice for these tumors but may require adjunctive radiation therapy because its invasiveness and volume. Treatment with octreotide can normalize thyroid hormone levels in 80–90% and produce tumor shrinkage in up to 50% [123, 124].

Gonadotropinomas (FSH/LH-secreting adenomas): extremely rare in children, with few cases in literature, mostly FSH-secreting adenomas so clinical presentation is related to FSH secretion with precocious puberty, ovarian cyst or macroorchidism [81, 125]. Diagnosis is based on signs and symptoms, high levels of FSH and inhibin B, normal or low LH and testosterone, an increased FSH response to gonadotropin-releasing hormone stimulation and detection of a pituitary mass on MRI [125]. Nevertheless diagnosis is usually delayed until the appearance of symptoms related to tumour mass or pituitary hormone deficiency [79].

Non-functioning pituitary adenomas (no hormone secretion): non-functioning pituitary tumors are very rare in children accounting for only 4 to 6% of pediatric cases. In adults they represent 33 to 50% of the total number of pituitary

lesions [77, 126, 127]. These tumors are believed to arise from gonadotroph cells and are frequently macroadenomas at diagnosis, may be invasive and presenting with growth and/or pubertal failure, symptoms of hyperprolactinaemia or hypogonadism especially in young females or with headaches and visual disturbances [3, 79, 89, 122, 128]. In some cases large adenomas may obstruct the foramen of Monro and cause hydrocephalus, but also may expand to cavernous sinus resulting in cranial nerve palsies or cavernous sinus syndromes [3].

Non-functioning pituitary adenomas may show hormone deficiencies: GH deficiency in up to 75%, LH/FSH in 40%, or ACTH and TSH deficiency in 25% [129]. Hyperprolactinemia is seen in less than 20% of patients secondary to stalk compression. Diabetes insipidous is only seen 9 to 17% of cases [3].

Surgery is the first line treatment in symptomatic or growing tumours but observation in small ones. Recommendation for surgical excision of intrasellar tumor or cyst depends on the tumor size, location, and potential for invasiveness [3, 89].

21.3 Other Sellar Tumours

As described at the begining of this chapter pituitary tumors are very rare in children. Craniopharyngioma and adenomas are the most frequent tumors in pituitary fossa, accounting for 90–95% of cases. Other lesions are even rarer than pituitary tumors in children. Some of them are described in summary.

Rathke cleft cyst: are non-neoplastic cystic lesions containing mucoid material in the sellar region accounting for less than 1.2% of pituitary lesions [130–132]. As craniopharyngiomas both have their origin from the remnants of the embryonic Rathke pouch [131, 132] and both may represent a continuum from the simpler Rathke cleft cyst to the more complex craniopharyngiomas [133]. Little data are available on the presentation or treatment outcomes but headache, hypopituitarism and growth delay were the most frequent presentation in a large serie [134]. On CT scanning, cysts usually are hypodense, non-enhancing by contrast and lack of calcification. In MRI, the cyst signal often is similar to cerebrospinal fluid on T1- and T2-weighted images [135]. Surgery is the treatment of choice when symptomatic.

Epidermoid and dermoid cysts: Epidermoid and dermoid cysts result from the inclusion of epithelial elements during embryogenesis. The contents of dermoid lesions are desquamated epithelium, sebaceous material, and, sometimes, dermal appendages, whereas epidermoid cysts contain a white cheesy material (keratin) within a thin capsule [136]. They appear as hypodense cysts with no enhancement in CT or hypointense in MRI [137] and show restriction to diffusion in diffusion-weighted images.

Chordomas: are slow-growing tumors of midline that arise from notochordal remnants in the clivus, usually producing sphenoid basis destruction and invasion. Chordomas of the sellar region are rare but may extend along the entire skull base and the sella (usually is destroyed instead of expanded), so location, bone destruction, and calcification differenciate from pituitary adenomas. Symptoms are

headaches, visual deficit, neck pain, diplopia, and nasopharyngeal obstruction. Surgery is the treatment of choice associated with adjunctive radiotherapy due to complete removal difficulty [135–137].

Germinomas: are malignant intracranial tumors of granulomatous infiltrate around germ cells. They are the most frequent tumour of germ cell tumours group and usually appear at pineal region in children and adolescense (with male preponderance) but another locations may be hypothalamus, anterior III ventricle and intrasellar (not clear gender preponderance) [138, 139]. Diabetes insipidous is a common symptom seen in 80% of cases [136]. Another signs and symptoms may be visual symptoms, including failure of upper gaze and obtundation, delayed sexual development, hypopituitarism and precocious puberty [140–142]. Nowadays a combination of biopsy, chemotherapy and Radiotherapy are the gold standard of treatment with good prognosis depending on dissemination previous to diagnosis [139, 140].

Teratoma: are classified in three different subtypes included in the germ cell tumours group: mature, imature and mature with mailgnant transformation [138]. These tumors are found most commonly in the pineal region, followed by the suprasellar and hypothalamic regions, and rarely in the sellar region [136]. They derive from the pluripotential cells from all three embryologic layers (ectoderm, mesoderm, and endoderm): mature teratoma from two fully differentiated embryologic layers, immature teratoma by embryonic elements from one or two layers. Teratomas can involve the pituitary gland primarily or secondarily, by invasion [136]. Signs and symptoms are similar to germinomas (*see previous description*). Teratoma appear in imaging assessments as a well-delineated mixed cyst with calcification [136]. Treatment may be a combination of surgery alone when mature subtype or surgery plus chemotherapy plus radiotherapy in imature and mature with malignant transformation [139].

Langerhans cell histiocytosis: Langerhans cell histiocytosis is a histiocytic disorder derived from myeloid progenitor cells that express CD34 surface antigen belonging to the monocyte-macrophage complex [136, 143] with an incidence of 3–4 cases/million/year in children younger than 15 years old and male peponderance (2:1) [144]. Anterior pituitary dysfunction is less frequent than diabetes insipidous that may be present in 10–50% of cases. The most common findings on MRI are pituitary stalk thickening and absense of neurohypohysis bright spot in T1-weighted images [136]. The diagnosis may be based on symptoms, imaging techniques (to rule out systemic disease) and surgical biopsy of other involved sites. Biopsy of pituitary stalk is reserved to growing lesions or no other diagnosis possibility [145]. The main treatment is chemotherapy.

Arachnoid cyst: pathogenesis is not known but it is believed to arise from an arachnoid herniation into the pituitary fossa as a result of incompetence of the diaphragma sellae (embriology defect, after trauma or adhesive arachnoiditis) so true sellar arachnoid cyst is very rare [136]. MRI show cystic lesion with same intensity as cerebrospinal fluid in all sequences and no contrast enhancement [135, 137, 142] (Fig. 21.4).

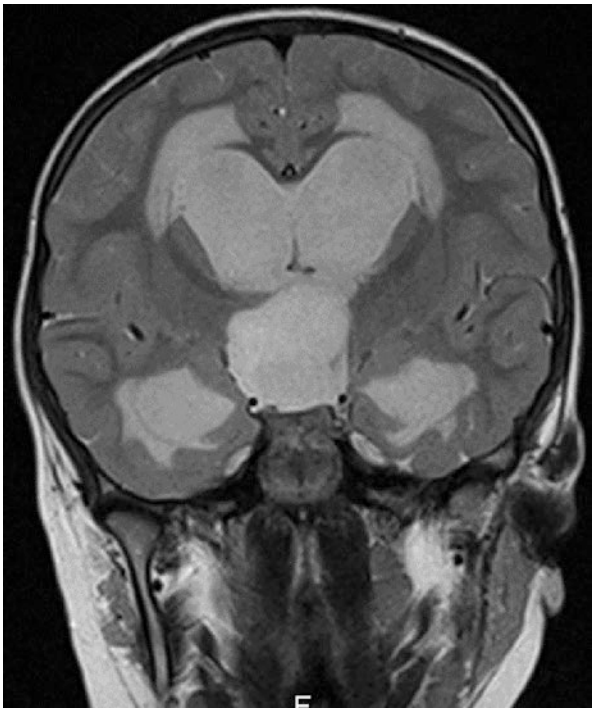

Fig. 21.4 Sellar and suprasellar arachnoid cyst. Coronal T2-weighted image

Optic pathway glioma: Optic pathway gliomas account for 3–5% of all pediatric CNS tumors and represent the most common intrinsic optic nerve tumor [146]. 30% are associated with neurofibromatosis type 1 [136, 146]. Presentation in children varies depending on location into the optic pathway [146]. The most common symptoms are visual loss, headache, and proptosis [136]. Patients with lesions extending to the hypothalamic region may present with hydrocephalus, diencephalic syndrome, precocious puberty or endocrinological deficits [146]. The diencephalic syndrome associates emaciation, growth acceleration, hyperkinesis and euforia [135, 146]. Imaging examinations show a tumor with origin in chiasm or optic nerve, classically a hypointense lesion on T1 images with contrast enhancement. Although optic pathway gliomas are low-grade tumors, their behavior can be aggressive, and their management is often challenging including observation, surgery, chemotherapy and radiation [146].

Other extremely rare lesions in pituitary fossa: inflamatory diseases (sarcoidosis, xanthogranuloma), tumours (astrocytoma, ependymoma, gangliocytoma, hamartoma, metastasis, lymphoma, meningioma), vascular lesions (aneurysm) or infectious diseases (pituitary abscess, tuberculosis, fungal infections) [136].

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