

Hypophysis and Hypothalamus

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Abstract

Pathologies of hypothalamus–hypophysis axis in children express different clinical presentations, regarding endocrine secretions of numerous hormones. Knowledge of embryology, anatomy, and physiology is mandatory to understand the main features of these diseases. MRI is the best tool to assess the anatomical characteristics of the malformative and acquired pathologies. The main clinical expressions are in relation with isolated GH or combined antehypophysis hormones deficiencies, troubles in relation with puberty development, diabetes insipidus; cranial hypertension and visual disturbances may also reveal the disease. Pathologies include developmental disorders, in relation, in most cases with trouble of embryological brain diverticulation, aplasia or hypoplasia of pituitary gland, pituitary stalk interruption. Intra- and suprasellar masses can be a craniopharyngioma, a germinoma, and, mainly after 10 years of life, a pituitary adenoma. Systemic and inflammatory diseases include Langerhans cell histiocytosis, and, rarely in children, lymphocytic hypophysitis, sarcoidosis, and tuberculosis.

1 Introduction

1.1 Embryologic and Anatomical Overview

The pituitary gland is composed of two portions, the anterior adenohypophysis and the posterior neurohypophysis; the development of each is embryologically distinct. At week 4 of embryogenesis, a Rathke's pouch forms on the top of the stomodeum and before the oropharyngeal membrane. The adenohypophysis derives from Rathke's pouch: this one extends through the sphenoid bone development region until it reaches the sella turcica, then converges with the neuroectoderm of the neurohypophysis. In the path passed by Rathke's cyst, a solid cell cord forms, resides

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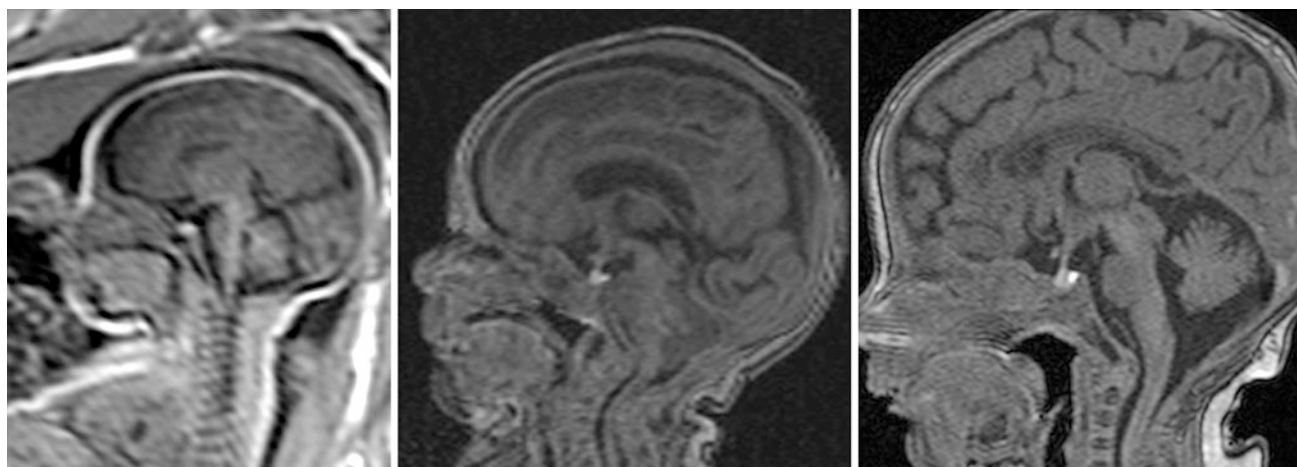


Fig. 1 Normal hypophysis on T1 sagittal plane: antenatal, neonatal (premature baby), with hypersignal within the entire hypophysis and same baby at 2 months

between two centers of chondrification, which develop into the sphenoid bone body and wings, and differentiate into a craniopharyngeal canal. The adenohypophysis is made-up of the pars tuberalis, which surrounds the infundibulum, the pars intermedia, the portion of Rathke's pouch in contact with the neurohypophysis, and the pars distalis, which is the largest portion of the anterior lobe. The residual lumen between the pars distalis and the pars intermedia decreases in size, forming Rathke's cleft, a narrow, non-visible cleft between the anterior and posterior lobes.

The hypothalamus develops from the neuroectoderm of the floor of the embryonic brain and begins its development by days 33–41. There are two major white matter tracts in the hypothalamus: the postcommissural fornix and the mamillothalamic tract. The neurohypophysis forms both the pituitary infundibulum and the posterior lobe proper (Schroeder and Vezina 2011; Yu et al. 2012).

Knowledge concerning genes involved within the formation of these structures becomes larger and larger. Gene defects affecting pituitary transcription factors: HESX1, LHX4, OTX2, or SOX3 are now well-known. The homeobox gene HESX1 is expressed in prospective fore-brain tissue, but later becomes restricted to Rathke's pouch, the primordium of the anterior pituitary gland. Neonates with HESX1 mutation exhibit abnormalities in the corpus callosum, the anterior and hippocampal commissures, and the septum pellucidum (Dattani et al. 1998).

1.2 Physiology and Function

The main function of the hypothalamus is homeostasis. Measurable factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are maintained at a precise value called the set point.

The hypothalamus does so by regulating three interrelated functions: endocrine secretion, autonomic function and emotions. The hypothalamus controls the release of hormones by the pituitary gland. Secretion from the posterior pituitary gland can occur as a result of direct neuronal stimulation via the infundibulum, whereas secretion from the anterior pituitary gland is dependent upon the portal plexus, which carries hypothalamic releasing factors (TRH, CRH, IGF-1 and GH-RH, LH-RH) to the anterior pituitary gland; the precursor of vasopressin is also synthesized in the hypothalamus and then stored in vesicles at the posterior pituitary (Saleem et al. 2007).

The adenohypophysis produces six established hormones: thyroid stimulating hormone (TSH), corticotropin (ACTH), growth hormone (GH), sexual stimulating hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and prolactin (PRL). The first five serve tropic functions by stimulating other organs to secrete hormonally active substances, whereas PRL serves a trophic function on breast tissue. Cells of the anterior lobe also produce propiomelanocortin, which is also made by neurons of the hypothalamus and cells of the intermediate lobe. The posterior lobe or neurohypophysis secretes oxytocin and vasopressin, also called antidiuretic hormone (ADH).

2 Imaging Techniques

2.1 MRI versus CT

MRI is the best tool for imaging hypophysis and hypothalamus. CT may be useful in case of emergency, when MRI is not still available, with clinical signs of acute intracranial hypertension. Calcifications are also better seen

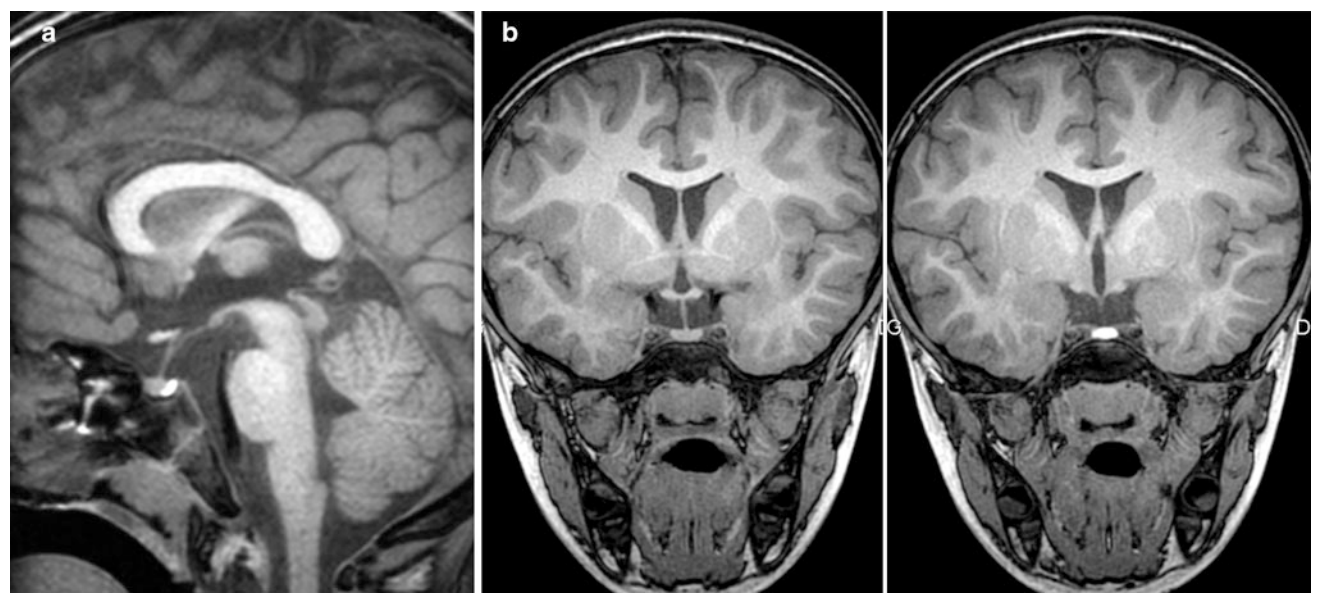


Fig. 2 **a** 3-year-old, normal aspect: T1 sagittal view, isointensity of adenohypophysis and stalk, hypersignal of neurohypophysis. **b** 3-year-old, normal subject: T1 coronal anterior and posterior views, isointensity of adenohypophysis and stalk, hypersignal of neurohypophysis

Fig. 3 14-year-old girl, sagittal and coronal views after contrast injection: homogeneous enhancement with normal prominent pubertal adenohypophysis

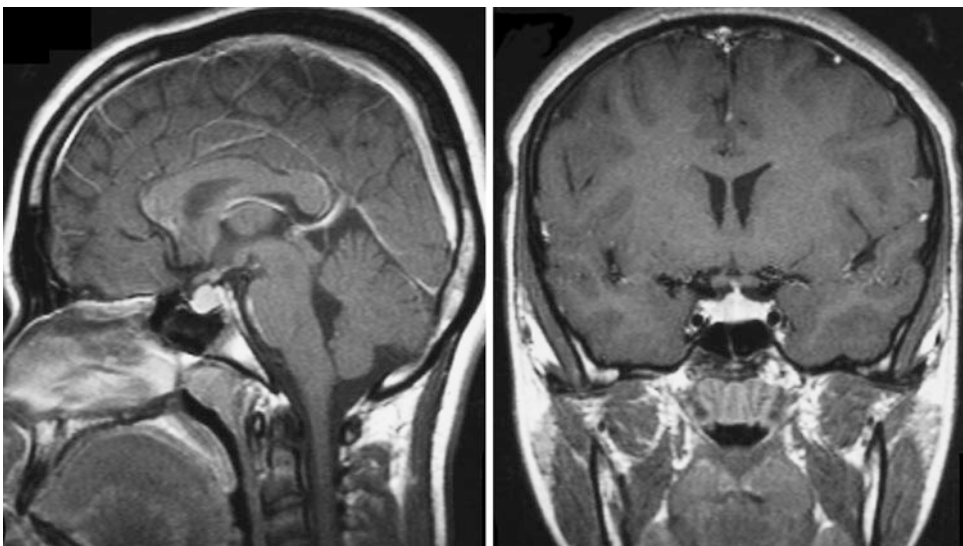


Table 1 Height and volume of antehypophysis regarding the age

Age	Height (mm)	Pituitary volume (mm ³)
<6 weeks	4.5 ± 2	
6 weeks–2 years	3.5 ± 1.2	174 ± 118
2 years–5 years	4 ± 0.7	184 to 214 ± 145
5–10 years	4.5 ± 0.6	226 to 277 ± 188
10–20 years (boys)	5 ± 2	
10–20 years (girls)	8 ± 2	

classically with CT and may help in cases of craniopharyngioma, before and after surgery.

2.1.1 Protocol of MRI

MRI of the hypothalamo-pituitary axis includes thin (1–1.5 mm thick) T1-weighted slices focusing on the hypothalamo-pituitary area in the coronal and sagittal planes. T2-weighted coronal slices are useful to study the hypothalamus, hypophysis and pituitary stalk, chiasm, but also olfactory bulbs and sulci in cases of isolated gonadotropin deficiency; axial slices may be useful for assessment of the neurohypophysis. Constructive interference steady state (CISS) T2-weighted sequence helps also for studying the pituitary stalk. Contrast medium injection is not always mandatory and the use depends on the clinical context and findings in the absence of contrast injection. A contrast agent is systematically injected if accurate imaging of the pituitary stalk is required, as is the case for children presenting hypopituitarism without a spontaneously visible pituitary stalk and for cases of central diabetes insipidus. Enhanced sequences are useful for assessment of cavernous sinus. The whole brain must be examined because other abnormalities may be associated with pituitary abnormalities. Flair, T2-weighted axial slices may be useful (Garel and Leger 2007). MR angiography is useful to evaluate the surrounding vessels: internal carotid arteries and branches, cavernous sinus.

2.1.2 Normal Aspects

The fetal pituitary gland consists of the pars distalis (anterior lobe), the pars nervosa (posterior lobe) and the pars intermedia. The pars intermedia undergoes involution during the third trimester of pregnancy. The normal hypophysis is not clearly depicted by antenatal sonography. With MR fetal imaging, the entire pituitary gland is bright on T1 sequences in fetuses (Garel and Leger 2007).

In infants under the age of 2 months, the entire pituitary gland is bright on T1 sequences, resulting in very similar signals for the adenohypophysis and the neurohypophysis (Fig. 1). The brightness of the adenohypophysis may be accounted for by intense cellular activity in the pituitary gland during this period of development. Moreover, the pituitary gland is bulbous in shape in this period, probably due to cellular hypertrophy (Garel and Leger 2007). The relative signal intensity and pituitary height significantly negatively correlated with postnatal time but not with gestational age at birth (Kitamura et al. 2008).

After the neonatal period, signal of the anterior hypophysis decreases on T1-weighted sequences and reaches the one of the gray matter (Fig. 2). Neurohypophysis remains hyperintense in most of cases and is clearly depicted on thin sagittal and axial slices; this “bright spot” is in relation with the presence of vesicles of ADH, is seen in most of cases and

is a marker of neurohypophyseal functional integrity; it depends on patient’s hydration and may be absent in normal individuals.

The signal of the normal pituitary gland and stalk is markedly enhanced by the intravenous injection of contrast medium. The anterior and posterior lobes differ in their vascularization: the superior hypophyseal arteries supply the median eminence. The inferior hypophyseal arteries supply the neurohypophysis and stalk. The hypophyseal portal vessels supply the anterior lobe; so, dynamic enhancement is not the same for all these structures and is seen later within the anterior lobe in comparison to the median and posterior parts (Garel and Leger 2007).

The pituitary gland gradually increases in size until puberty. Table 1 gives some landmarks regarding the age (Argyropoulou et al. 1991; Dietrich et al. 1995; Kato et al. 2002). A pituitary gland less than 3 mm high is considered small, but pituitary gland shape and size in this age group is highly variable. Shape varies from crescent-like to hemispherical and near spherical, some are dumbbell-shaped. The posterior pituitary bright spot could be elongated or flattened and extended variably in the anterior direction, often beneath the anterior portion of the gland; some authors demonstrated that 3D-measurement of pituitary volume appears to be more robust, giving new references (Fink et al. 2005). At puberty, the pituitary gland displays physiological hypertrophy and may be 8 mm high in boys and 10 mm high in girls. The nearly spherical shape of the pituitary gland in teenage females should be considered a normal developmental feature (Fig. 3). The absence of visual symptoms, homogeneous pituitary enlargement on MR images, and a normal endocrine profile exclude a pituitary adenoma (Aquilina and Boop 2011).

No data are available concerning the normal dimensions of the pituitary stalk in children, but it is widely accepted that the maximum transverse diameter does not exceed 2 mm in children (Dietrich et al. 1995; Garel and Leger 2007).

2.2 Other Techniques

Regarding the variety of hormonal secretions, other manifestations in relation with hypo or hypersecretion may be very protean and it is not possible here to give an exhaustive list of imaging explorations. Bilateral simultaneous inferior petrosal sinus sampling, a very specialized investigation, may be useful in Cushing disease. Skull and sella turcica plain X-rays have no more utility. Bone age determination is still useful in case of growth abnormality. Sonography of thyroid gland, abdomen and pelvis for genitals needs to be performed, regarding the clinical presentation.

3 Diseases

There are several ways to describe the pathologies that may involve the hypothalamus-hypophysis axis. We choose in this chapter to categorize the main disease regarding the endocrine dysfunction, with lack or, in the contrary, hypersecretory states. These pathologies are mainly in relation with developmental disorders, inflammatory/systemic diseases but also due to sellar or suprasellar mass lesions. On the other hand, the first clinical signs can be in relation with a neurodevelopmental delay, an intracranial hypertension or a visual disturbance. In this chapter, we will first describe presentations with primitive endocrine dysfunction of hypothalamus-hypophysis axis, but we have to keep in mind that sellar and suprasellar tumors, described at the end of this chapter, may also be revealed by initial clinical signs in relation with an endocrine dysfunction rather than an occupying space syndrome.

3.1 Anterior Pituitary Deficiency

Anterior pituitary hormone deficiencies may be isolated for one hormone or expressed by a combined pituitary hormone deficiency (CPHD). Some of them are related to a known genetic abnormality or associated with other malformations; in other cases, hypothalamus-hypophysis axis developmental disorders are demonstrated. Some cases are secondary to surgery or radiotherapy. Lastly, some cases remain idiopathic. Isolated GH deficiency (IGHD) is the most frequent one; other isolated pituitary hormone deficiencies may be observed (Garel and Leger 2007). Hormones deficiencies are confirmed by static and dynamic blood samples.

Severe congenital GH deficiency of the newborn is a rare disease, which can cause life-threatening hypoglycemias beginning in the first week of life. In some cases, the cause is monogenic, including mutations of the GH encoding GH-1. The majority of cases are still idiopathic or associated with a significant malformation of the pituitary gland and multiple pituitary hormone deficiency (Binder et al. 2010). In older children, growth retardation with a short stature is the most frequent presentation (Dutta et al. 2009).

3.1.1 Aplasia and Hypoplasia of Pituitary Gland

Aplasia of the hypophysis is extremely rare, without pituitary fossa within the sphenoid bone (Arrigo et al. 2006). Neurohypophysis can be seen on the floor of hypothalamus. Hypoplasia is defined by a small anterior pituitary gland, regarding the normal values in relation with age, within a normal or a dysplastic pituitary fossa. These cases may be isolated (Fig. 4), or associated with other CNS malformations. The endocrine damage is part of the septo-optic

dysplasia, but it is not constant; also, some children may have septal agenesis with an endocrine deficit without visual impairment. Association of a septal agenesis and pituitary stalk interruption syndrome can occur (Belhocine et al. 2005). Other malformations include holoprosencephaly, optic nerve hypoplasia, Chiari I malformation, all of these being part of disorders of diverticulation of the embryonic brain (Fig. 5a, b and c).

Hypoplasia of the pituitary gland must be differentiated from a primitive “empty sella”, which is defined by a sella turcica partially or completely filled with cerebrospinal fluid, with herniation of the sellar diaphragm (Fig. 6). Isolated primary empty sella arises in the absence of previous pituitary surgery or radiotherapy and is quite rare in childhood. The frequency of an empty sella is significantly high in idiopathic intracranial hypertension and nevoid basal cell carcinoma syndrome, but it can be encountered without any hypothalamic disorder in normal children (Takanashi et al. 2001). Dysplastic enlarged sella can be seen in patient with neurofibromatosis 1 (Fig. 7).

3.1.2 Pituitary Stalk Interruption Syndrome

Pituitary stalk interruption syndrome (PSIS), also known as pituitary dystopia, is characterized by the absence of normal pituitary stalk and an ectopic posterior pituitary lobe, seen on T1-weighted MRI as a bright spot localized between hypothalamus floor and pituitary fossa and in some cases with hypoplasia of adenohypophysis (Fig. 8a–d). The stalk may be very thin, better seen with CISS sequence. Hypopituitarism can be CPHD or IGHD. Patients with IGHD have a more preserved hypothalamic pituitary region on MRI than those with CPHD and therefore, the presence of more than one hormonal deficiency could be attributed to more severe abnormalities of the pituitary gland, as has been also previously observed (Acharya et al. 2011). Even if the high rate of extrapituitary birth defects and of familial components supports a role for genetic factors in the pathogenesis, only rare cases have a known genetic cause. HESX1, PROP 1, LHX 3, LHX4, POU1F1 or GLI2 genes mutations accounted for less 5 % of cases and were found in consanguineous or familial cases (do Amaral et al. 2007; Franca et al. 2010; Maghnie et al. 2004; Melo et al. 2007; Reynaud et al. 2011; Simon et al. 2006; Zimmermann et al. 2007). Correlations between involved implicated genes and MRI findings have been given (Garel and Leger 2007). Pituitary stalk can be absent or enlarged: pituitary enlargement consisted of a non-enhancing mass lesion interposed between the normally enhancing anterior lobe and the neurohypophysis. Spontaneous regression of the mass lesion with normalization of the pituitary stalk position was observed (Voutetakis et al. 2006). The initial enlargement of the stalk might be because of growth of functioning adenohypophyseal tissue within the stalk (Berkowitz et al. 2008).

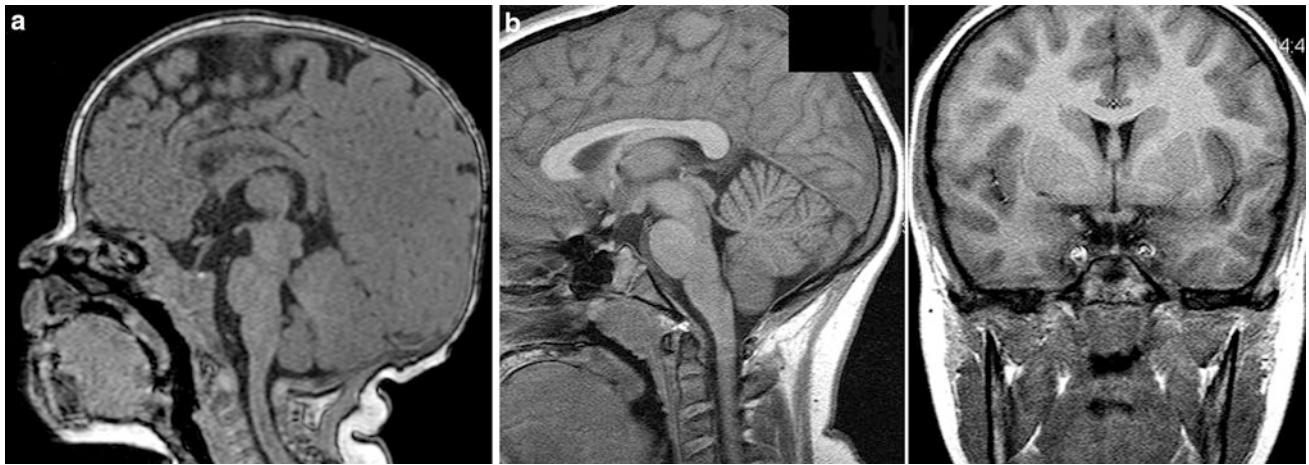


Fig. 4 **a** Neonate with hypoglycemia: aplasia of adenohypophysis. **b** Girl, 10-year-old, GH and gonadotrophins deficiencies: hypoplastic adenohypophysis

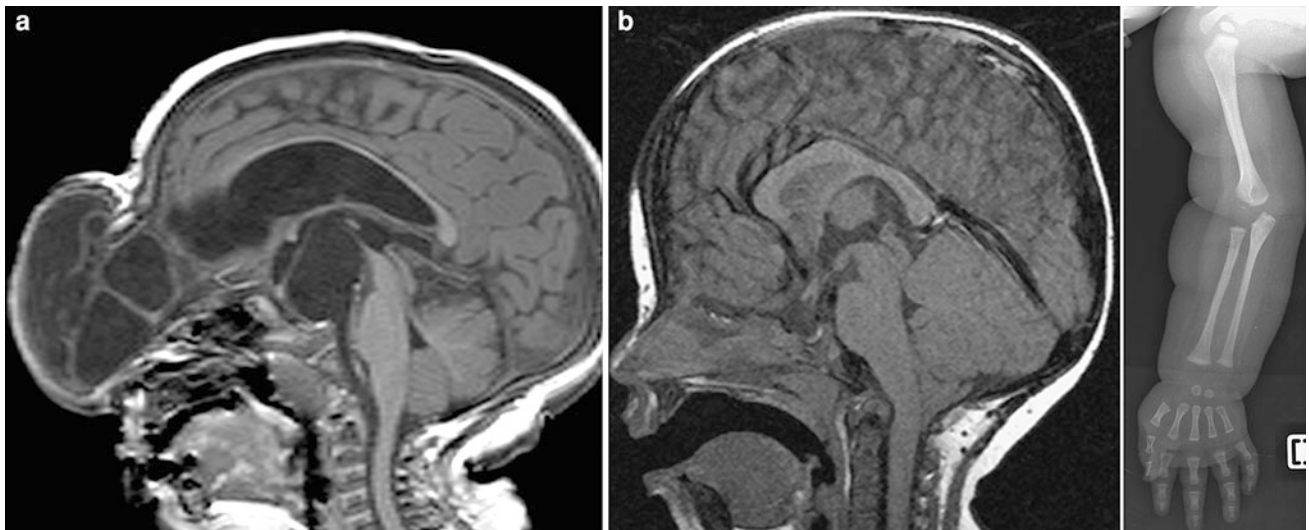


Fig. 5 **a** Boy, one-year-old, midline defect with frontonasal encephalocele, suprasellar arachnoid cyst, hypophysis hypoplasia. **b** 2-year-old, Kenny Caffey syndrome with Chiari 1 malformation, hypoplastic hypophysis, dysplastic bones with subcutaneous fat hypertrophy

Fig. 6 Boy, 17-year-old, short stature: intra sellar arachnoidocele with pseudo empty sella

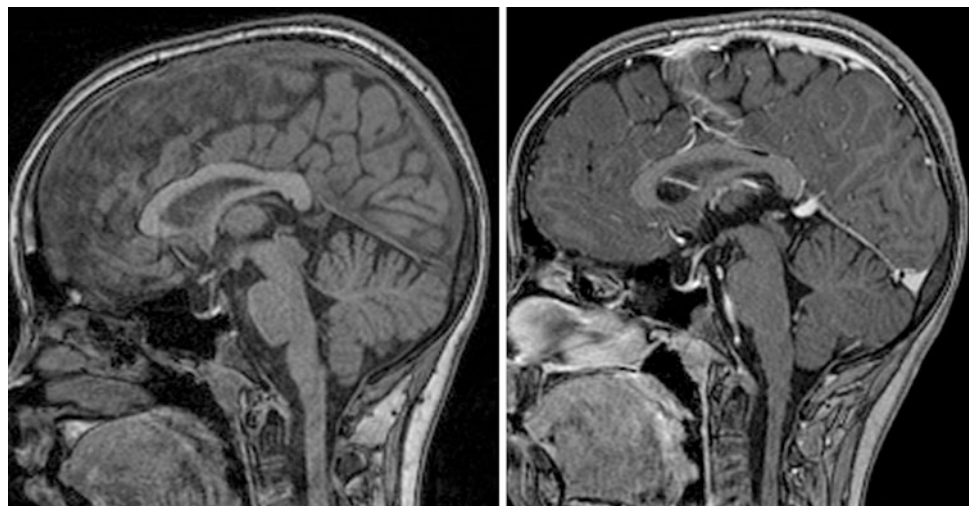
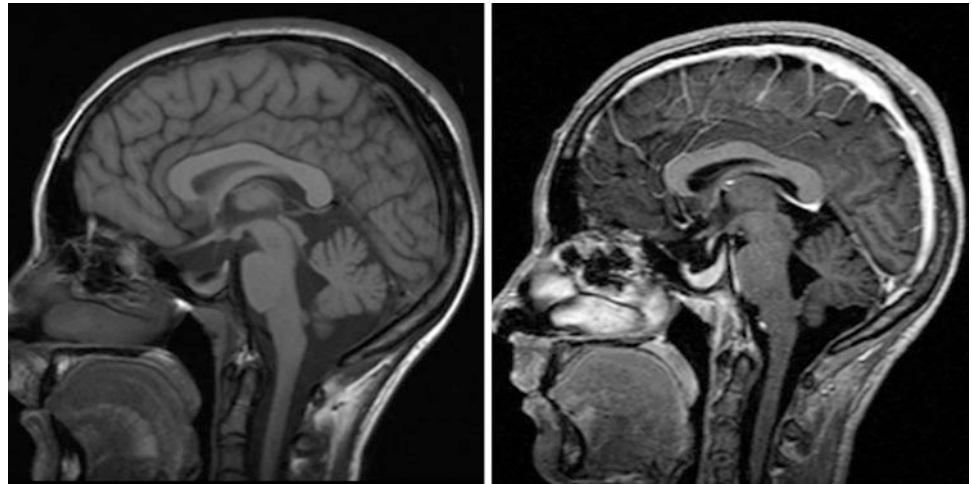


Fig. 7 Girl, 14-year-old, neurofibromatosis type 1, dysplasia of the sphenoid bone with enlarged sella turcica and hypophysis



3.1.3 Other Malformative Abnormalities with Anterior Pituitary Hormone Deficiencies

3.1.3.1 Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism and congenital olfactory deficit are common findings in Kallmann's syndrome, which may display X-linked or autosomal inheritance. Other abnormalities, such as cleft lip or palate, dental agenesis, renal abnormalities, hearing loss and cerebellar dysfunction may be associated. The morphology of the hypothalamo-pituitary axis appears normal on MRI scans, but some cases of pituitary hypoplasia have been reported. In case of olfactory deficit, the olfactory bulbs are absent or hypoplastic. The olfactory sulci may be normal, absent or hypoplastic (Fig. 9). In no instance is an olfactory sulcus absent when a bulb is present (Garel and Leger 2007).

3.1.3.2 Hypoparathyroidism-Retardation-Dysmorphism

Hypoparathyroidism-retardation-dysmorphism syndrome (OMIM no. 241410), is an autosomal recessive disorder almost exclusively reported in children born to consanguineous parents of Middle Eastern origin. The syndrome consists of hypoparathyroidism, dysmorphic features, developmental delay, and intrauterine and postnatal growth failure. The serum IGF-I concentration is low. Neuroimaging demonstrates reduced white matter mass with delayed myelination, a hypoplastic anterior pituitary and hypoplasia of the corpus callosum (Padidela et al. 2009).

3.1.3.3 Prader Willi Syndrome

Prader Willi syndrome is characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, early onset obesity, hyperphagia, and a characteristic clinical phenotype. Hyperphagia, hypogonadotropic hypogonadism, growth hormone deficiency are hypothesized to be due to

abnormalities of the hypothalamus and/or pituitary gland. Hypoplastic pituitary gland, a complete absence of the posterior pituitary bright spot can be seen on MRI, but no relationship between these anomalies and the presence of anterior pituitary hormone deficiencies was found in individuals with Prader Willi syndrome (Fig. 10) (Miller et al. 2008). Other neuroradiological alterations could be a ventricular enlargement, a thin corpus callosum (Iughetti et al. 2008).

3.1.3.4 Other Syndromes

The spectrum of *congenital abnormalities affecting also the skull base* ranges from the persistence of the craniopharyngeal canal, which connects the pituitary fossa and nasopharynx, to large basal cephaloceles with craniofacial defects. Ectopic hypophysis can be found in association with meningo (hypophyso-) encephalocele through the craniopharyngeal canal (Rabelink et al. 2011).

Ectopic posterior pituitary lobe and cortical dysplasia: the coexistence of ectopic posterior pituitary lobe and periventricular heterotopia suggests a common underlying genetic basis. The presence of a heterozygous HESX1 mutation in one case suggests this gene is important in the development of both ectopic posterior pituitary lobe and periventricular heterotopia and supports their place in the spectrum of septo-optic dysplasia (Mitchell et al. 2002).

Pituitary abnormalities have been described in patients with *Fanconi anemia*. PSIS was associated with hypogonadism, thyroid dysfunction, and GH deficiency (Fig. 11). Children with Fanconi anemia tend to have unsuspected small pituitary glands (Sherafat-Kazemzadeh et al. 2007).

3.1.4 Hypogonadism and Hemochromatosis

Pituitary hemochromatosis is an uncommon cause of hypogonadism in children, except in patients with β -thalassemia major due to post-transfusional iron overload. MRI

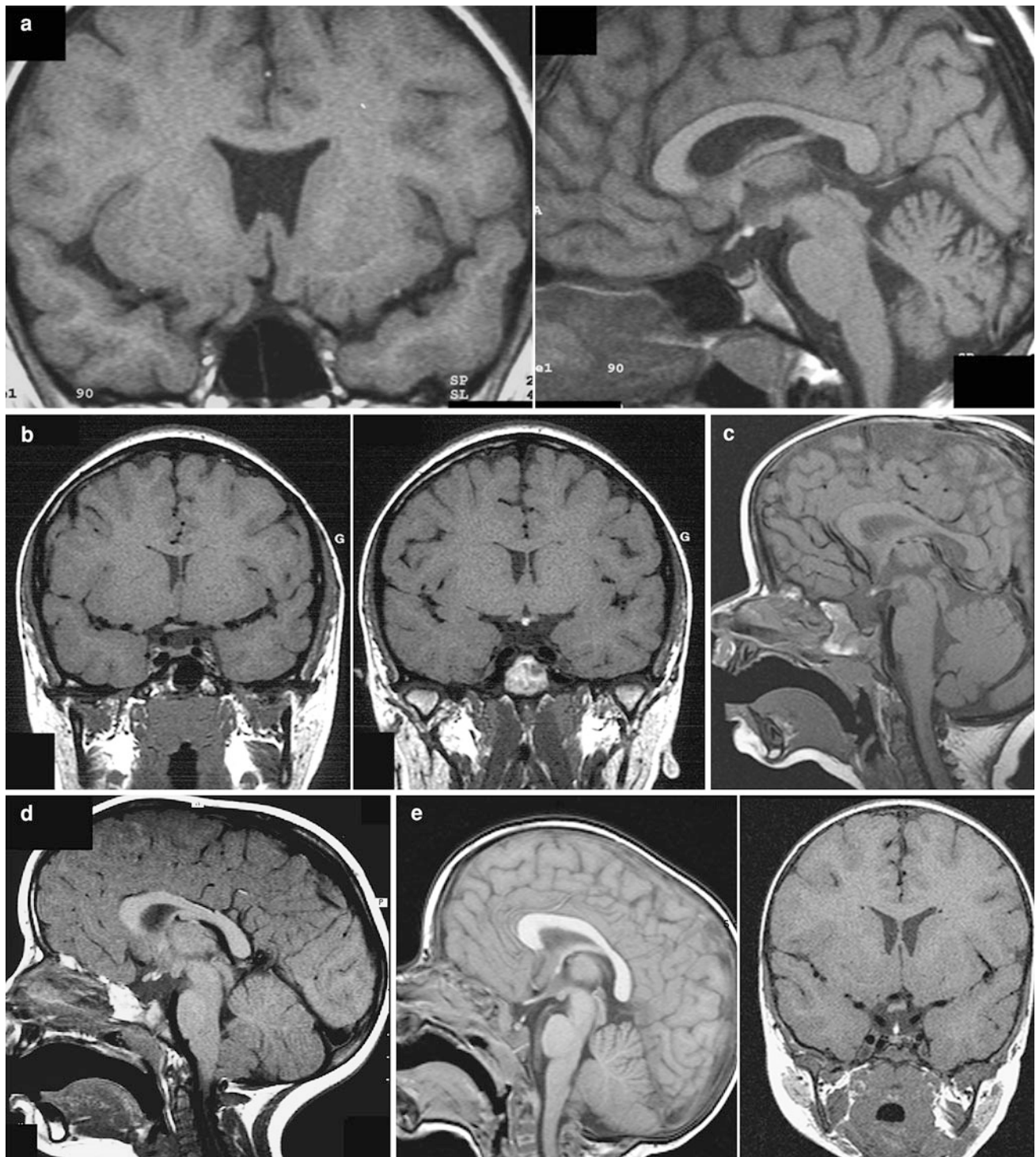


Fig. 8 **a** Girl 17-year-old, short stature with GH deficiency but also biological combined deficiencies: Pituitary stalk interruption with ectopic posterior pituitary lobe; absence of septum lucidum. **b** Girl 9-year-old, short stature, combined pituitary hormone deficiency (thyrotrope and corticotrope) left amblyopia: Pituitary stalk interruption with hypoplasia of the left optic nerve.

c Girl, 5-year-old, short stature: adenohypophysis hypoplasia, interruption of the pituitary stalk, ectopic posterior pituitary lobe. **d** Girl, 3-year-old; short stature with GH deficiency: Pituitary stalk interruption with T1 hyperintense ectopic neurohypophysis within hypothalamus. **e** Boy, 3-year-old, scaphocephaly and short stature: thin pituitary stalk and suprasellar ectopic neurohypophysis

Fig. 9 Boy, 17-year-old, psychomotor development delay, hypogonadism, anosmia, hypertelorism: Kallmann disease without olfactory sulci and tracts, corpus callosum agenesis

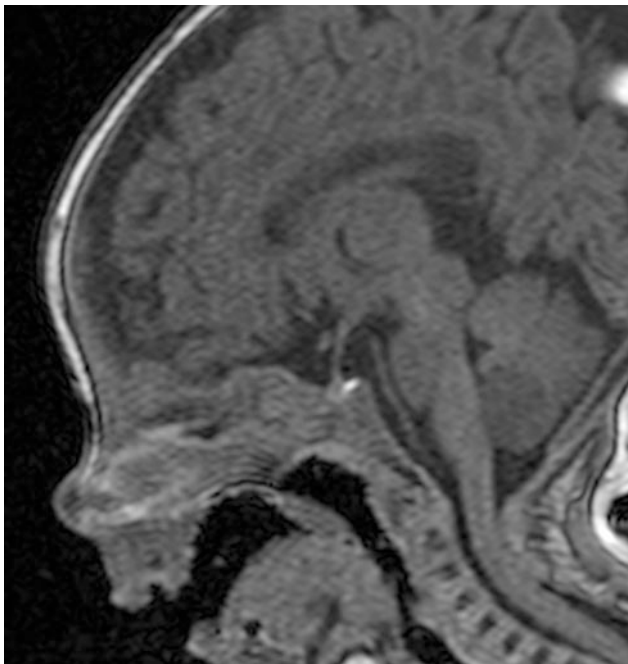
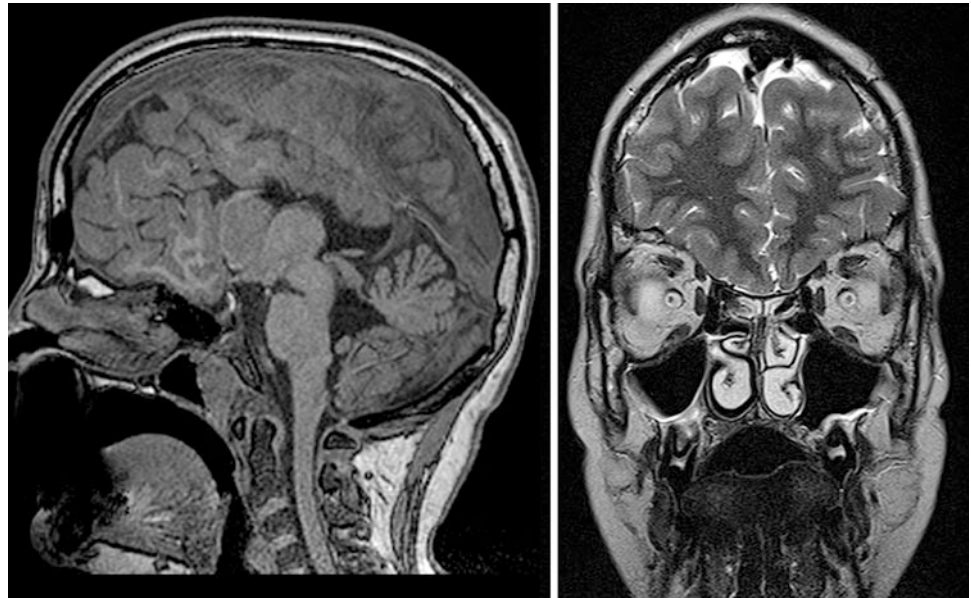


Fig. 10 Boy, neonate, hypotonia, Prader Willi syndrome; hypoplasia of sella turcica

is a good technique for detecting pituitary hemochromatosis, with a markedly decreased signal intensity of the pituitary gland on T2 and T2*-weighted images (Sparacia et al. 2000).

3.1.5 Anterior Pituitary Deficiency without Anatomical Abnormality

A normal pituitary gland on the MRI does not exclude a pituitary endocrine deficit, gland and conversely, some children without biological endocrine abnormalities may have an

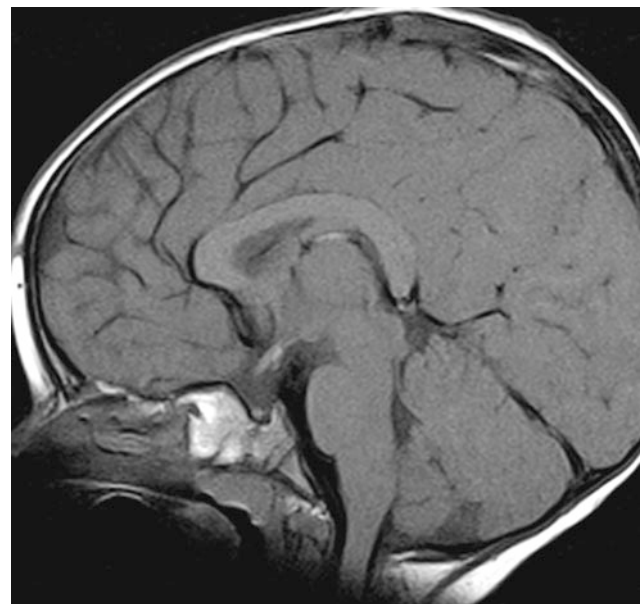


Fig. 11 Boy, 2-year-old, Fanconi disease: hypoplastic hypophysis and pituitary stalk interruption

abnormality of the hypothalamic-pituitary axis on MRI (Wang et al. 2011).

3.2 Central Diabetes Insipidus

Central diabetes insipidus (CDI) is characterized by the absence of secretion of ADH. CDI can be in relation with several diseases: Langerhans cell histiocytosis, inflammatory diseases, intracranial tumor (germinoma, glioma), post

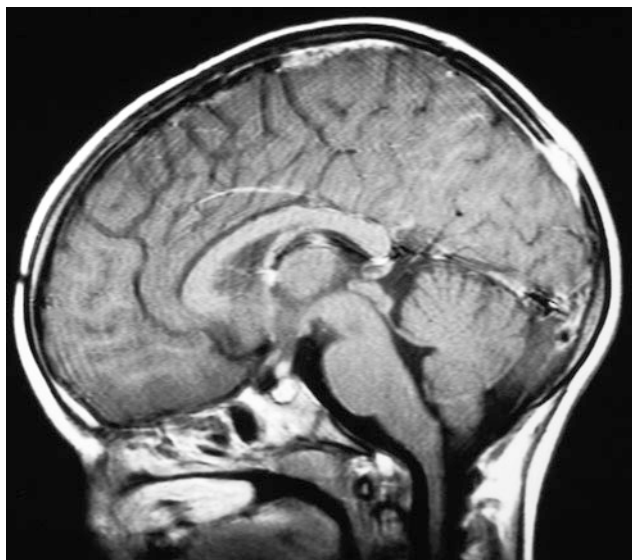


Fig. 12 Boy, 4-year-old, diabetes insipidus: Langerhans cell histiocytosis with enlarged pituitary stalk, occipital osteolysis

traumatic, autoimmune polyendocrinopathy, familial disease, or idiopathic (Maghnie et al. 2000). The natural history of idiopathic CDI with pituitary stalk thickening is unpredictable, and can be the first manifestation of a germinoma. Sampling of HCG in serum will be repeated every 3–6 months during the first 3 years after the onset of CDI, and careful MRI evaluation should then be performed once per year for 2 years and every 2–5 years, thereafter depending on the size and progression of the lesion (Garel and Leger 2007). On MRI, with sagittal or axial T1-weighted images, the loss of the posterior pituitary bright spot is a sensitive marker for CDI. The pituitary stalk is considered enlarged if at least part of the stalk is found to have a diameter superior to 2.0 mm.

3.2.1 Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a clonal proliferative disorder of cells of the mononuclear phagocytic and dendritic cell system that often presents in childhood either as a solitary often-curable bone lesion or as widespread, often multisystemic, sometimes lethal disorder (Demaerel and Van Gool 2008). Infundibular and hypothalamic infiltration occurs in 10–30 % of the patients with multisystemic LCH (Varan et al. 2008). There is a high degree of suspicion for Langerhans cell histiocytosis as etiology of diabetes insipidus, which can be the initial manifestation of the disease. Precocious puberty or hypogonadism, accelerated growth despite growth hormone deficiency, hypothalamic obesity may also occur in LCH (Demaerel and Van Gool 2008; Marchand et al. 2011; Priyambada et al. 2011).

Cerebral imaging demonstrates pituitary stalk thickening, moderate (3.0–7 mm) to marked (>7 mm), with huge

enhancement after contrast media injection (Fig. 12). The coexistence of osteolytic lesions of the orbit, the sphenoid and petrous bones, the cranial vault with soft-tissue enhancing masses is highly suggestive of LCH, previously known as Hand Schüller Christian disease. The stalk lesion can extend to the floor of the third ventricle. Small-sized pituitary gland or atrophic pituitary can be seen. During follow-up, pituitary stalk can increase in volume, decrease, or remaining stable. A normal pituitary stalk can also be seen initially with increase in pituitary stalk volume on follow-up in 50 % of these cases (Marchand et al. 2011). Regression of the pituitary changes, as visualized on MR images, is only rarely accompanied by reversal of the symptomatology and these children are at risk to develop further deficiencies of anterior pituitary hormones (Demaerel and Van Gool 2008). Other lesions within the brain can occur during the evolution: leukoencephalopathy, parenchymal enhancing lesions, gray matter changes in the cerebellar dentate nucleus and in the supratentorial basal ganglia, finally cerebral atrophy (Prayer et al. 2004).

3.2.2 Lymphocytic Hypophysitis

Lymphocytic hypophysitis (LYH) is a rare inflammatory disease of the pituitary gland that usually affects women in their anterior immediate postpartum period, but can also be rarely encountered in children. Symptoms include anterior and/or posterior pituitary insufficiency of varying degrees. Diagnosis can be based on biopsies or inferred from clinical characteristics and typical MRI findings. MRI of the sellar region revealed an homogeneously enhancing mass lesion in the pituitary stalk and the posterior pituitary gland with lack of the hyperintensity signal of the posterior lobe on unenhanced T1-weighted images. Enlargement of the whole pituitary gland with symmetrical suprasellar expansion can be observed, with slightly inhomogeneous enhancement. Differential diagnoses lesions include LYH, idiopathic giant cell hypophysitis and granulomatous hypophysitis caused by conditions such as tuberculosis, sarcoidosis, LCH, primitive abscess, and mycotic infections. Follow-up, spontaneously or after steroids treatment, demonstrates a regression in 50 % of cases (Gellner et al. 2008).

3.2.3 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown cause that most commonly affects young adults and is exceptional in childhood. Neurosarcoidosis occurs in about 10 % of affected patients. The disease has a predilection for the hypothalamus and pituitary gland but any portion of the CNS may be affected. CDI and anterior pituitary failure are the most common feature of neurosarcoidosis. MRI shows granulomatous infiltration of the dura mater or nodular thickening on the infundibular stalk and optic chiasm. The lesion is isointense on T1-weighted

images and hypointense on T2-weighted images. After contrast media injection, there is a thick enhancing infundibulum with intense surrounding meningeal enhancement. Rarely, masslike lesions, particularly in the region of the floor of the third ventricle and optic chiasm can be found (Saleem et al. 2007).

3.2.4 Tuberculosis

A previous study demonstrated a 55 % prevalence of absent posterior pituitary bright spot in pediatric patients presenting with tuberculous meningitis. Those with absent posterior pituitary bright spot demonstrated poorer developmental outcome at 6 months follow-up (Andronikou et al. 2009). Tuberculosis of sellar region is uncommon despite tuberculomas being the most common lesion in neurotuberculosis. Headache, vomiting, visual disturbances, and features of hypopituitarism are common. MRI reveals tuberculomas as hypointense on T1-weighted images and iso to hyperintense on T2-weighted images with perilesional edema; suprasellar extension of the sellar tuberculoma with thickening of pituitary stalk is observed in most of cases (Nayil et al. 2011).

3.2.5 Other Causes of Diabetes Insipidus

3.2.5.1 Familial CDI

Familial CDI is caused by mutations of the gene encoding a preprohormone and involves the progressive postnatal degeneration of ADH producing neurons. This abnormal preprohormone could not be processed correctly, and the accumulation of this preprohormone might account for the persistent posterior pituitary bright spot (Garel and Leger 2007).

3.2.5.2 Chronic Neurogenic Hypernatremia

Chronic neurogenic hypernatremia is observed in children presenting midline abnormalities of the brain, such as holoprosencephaly, callosal agenesis, or septal agenesis. The underlying mechanism remains unclear, but there appears to be a defect in hypothalamic function, leading to the failure of the osmoreceptors, whereas the synthesis and storage of ADH remain intact (Garel and Leger 2007).

3.3 Precocious or Delayed Puberty

3.3.1 Duplication of Pituitary Gland

The duplication of pituitary gland and stalk is a rare malformation. Most of the reported cases were associated with other anomalies, such as agenesis/hypoplasia of corpus callosum, cerebellar hypoplasia, hydrocephalus, absent olfactory bulbs and/or tracts, oropharyngeal masses

including teratomas and various orofacial midline defects (Akin et al. 2011). Other cases demonstrate a wide hypothalamus, named pseudohamartoma (de Penna et al. 2005). Other association with “morning glory disk” anomaly and Moyamoya disease has been described (Loddenkemper et al. 2008). MRI demonstrates the presence of two paramedial pituitary stalks, coming from hypothalamus and connected to two separate anterior and posterior pituitary glands (Fig. 13). Triplication of the pituitary gland is exceptional (Manara et al. 2009).

3.3.2 Hamartoma

Hypothalamic hamartomas are developmental malformations consisting of tumorlike masses located in the tuber cinereum of the hypothalamus. Most patients present in their first or second decade of life, with boys being more commonly affected than girls. These lesions have been divided into two main clinico-anatomic subsets: parahypothalamic and intrahypothalamic hamartomas. Parahypothalamic hamartomas are pedunculated masses that are attached to the floor of the hypothalamus by a narrow base. These lesions seem more likely to be associated with precocious puberty. Intrahypothalamic hamartomas are sessile masses with a broad attachment to the hypothalamus, often associated with gelastic seizures. MR demonstrates a well-defined pedunculated or sessile lesion at the tuber cinereum. The mass is isointense or mildly hypointense on T1-weighted images and iso to hyperintense on T2-weighted images, with no contrast enhancement or calcification (Fig. 14a–c). The absence of any long-term change in the size, shape, or signal intensity of the lesion strongly supports the diagnosis of hypothalamic hamartoma (Saleem et al. 2007). Tuber hamartoma has to be differentiated from septopreoptic holoprosencephaly, where the midline fusion is restricted to the septal region or preoptic region of the telencephalon (Hahn et al. 2010).

3.4 Other Endocrinopathies

Pathological pituitary hyperplasia may occur in several circumstances, including central precocious puberty, ectopic production of hypothalamic-releasing hormones from hypothalamic and nonpituitary tumors, and administration of exogenous oestrogens (Morana et al. 2010). Rapid progression of pituitary hyperplasia may develop in case of peripheral hypothyroidism and evaluation of thyroid function is needed when a homogeneous pituitary mass is revealed by MR imaging; this hyperplasia disappears in a few months after substitutive treatment (Lee et al. 2008).

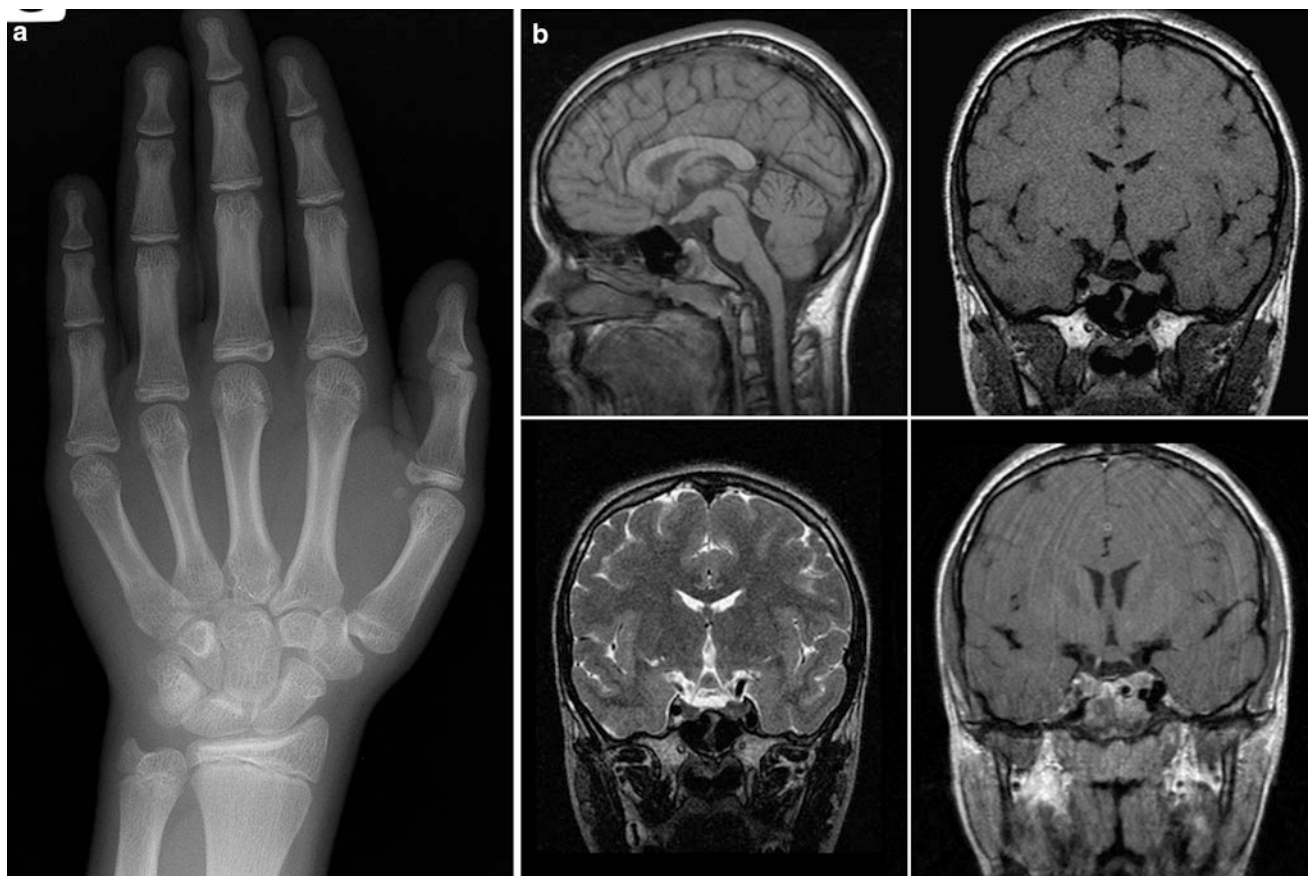


Fig. 13 **a** Girl, 10-year-old, precocious puberty: bone age: 14-year-old. **b** Same patient: duplication of pituitary stalk and hypophysis

3.5 Sellar and Suprasellar Tumors

3.5.1 Pituitary Adenomas

Pituitary adenomas are relatively uncommon in children and account for less than 3 % of all supratentorial tumors. They are more frequent in adolescents than in younger age groups. Hormone secreting tumors predominate, while hormonally inactive adenomas are rare. Prepubertal children more frequently have ACTH-releasing adenomas, while pubertal and postpubertal patients are most likely to have prolactinomas (Morana et al. 2010).

3.5.1.1 Prolactinoma

Depending on size, pituitary adenomas are classified into microadenomas and macroadenomas. Microadenomas are smaller than 10 mm in diameter and lie entirely within the pituitary gland. Most common presenting signs of prolactin microadenomas are primary amenorrhea, then galactorrhea in females and gynecomastia and hypogonadism in males. They can also be associated with delayed puberty. They appear as small, hypointense lesions on T1-weighted images (Fig. 15). Some may only become apparent as non-

enhancing spots within the gland on post-contrast images. Their appearance on T2-weighted images is variable.

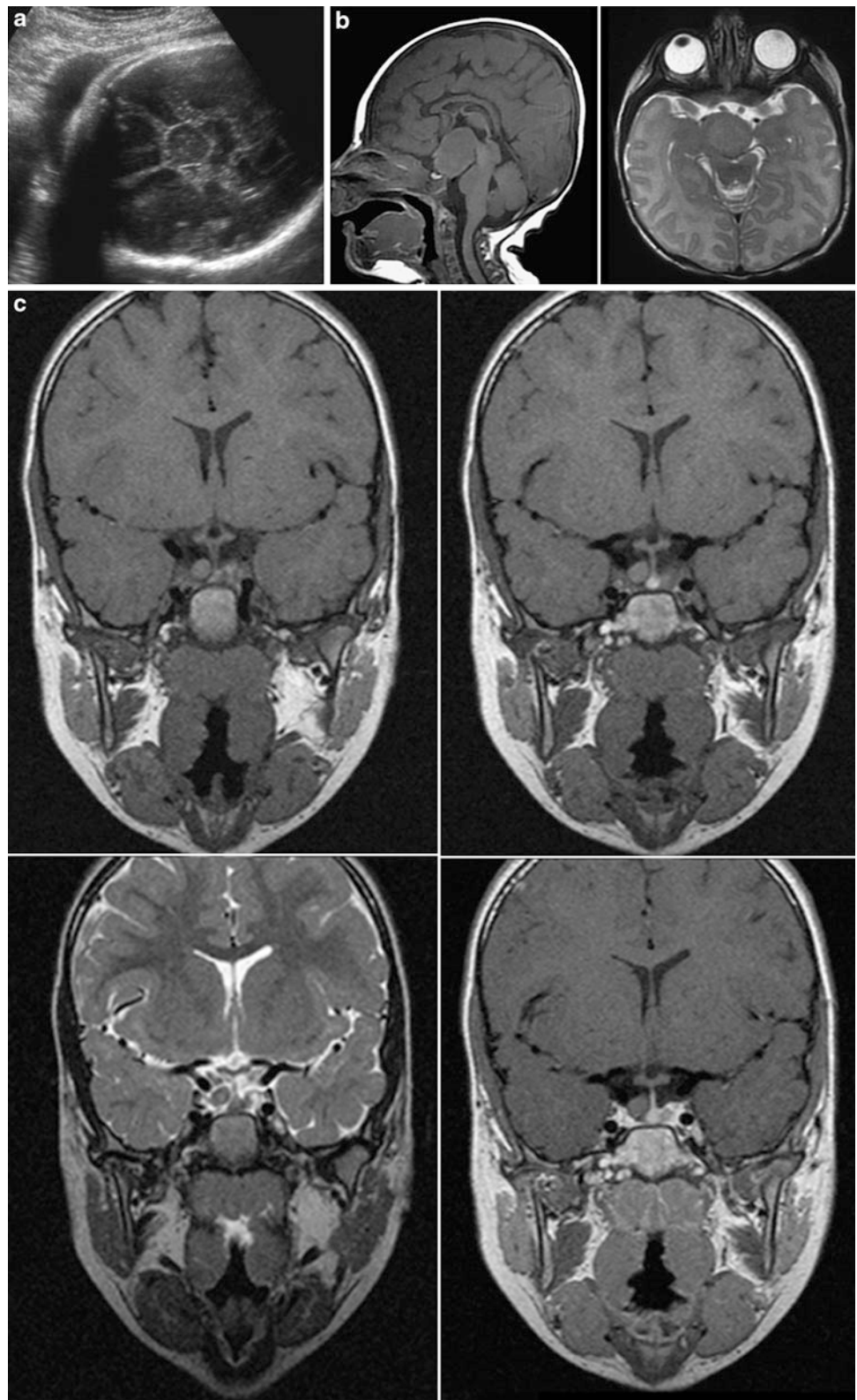
A giant, solid, invasive prolactinoma in a prepubescent child is extremely rare (Dinc et al. 2008; Furtado et al. 2010). Macroadenomas show intermediate signal in unenhanced T1-weighted images and enhance after contrast medium administration (Fig. 16). Invasion of the cavernous sinus is sometimes demonstrated but with normal carotid artery diameter.

Pituitary apoplexy must be considered in case of intense headache and worsening visual acuity. MRI showed a large suprasellar mass with a small sellar component, with heterogeneous hyperintensity on T1-weighted images, suggestive of recent hemorrhage (Fig. 17); sometimes, intrasellar-dependent fluid–fluid levels can be detected, mainly on axial slices. T2* sequences may be useful. Heterogeneous enhancement is often present (Satyarth and Mahapatra 2005).

3.5.1.2 Cushing Disease

Cushing disease (CD) refers only to hypercortisolism secondary to excess production of ACTH from a ACTH-

Fig. 14 **a** Foetus, 34 weeks gestational age, systematic axial US study: hypoechoic mass within the suprasellar cystem. **b** Same partient as 14a, post natal MRI: hypothalamic hamartoma with iso-intensity on T1 and T2 sequences. **c** Girl, 2-year-old, vaginal bleeding and thelarche puberty: small parasagittal suprasellar hamartoma



releasing adenoma. Children with hypercortisolism have subnormal linear growth and excessive weight gain. A high proportion has evidence of excessive virilisation. Striae and

hypertension are seen in half of cases. An elevated midnight cortisol confirms the diagnosis of Cushing syndrome and suppression of morning cortisol levels $>20\%$ in response to an

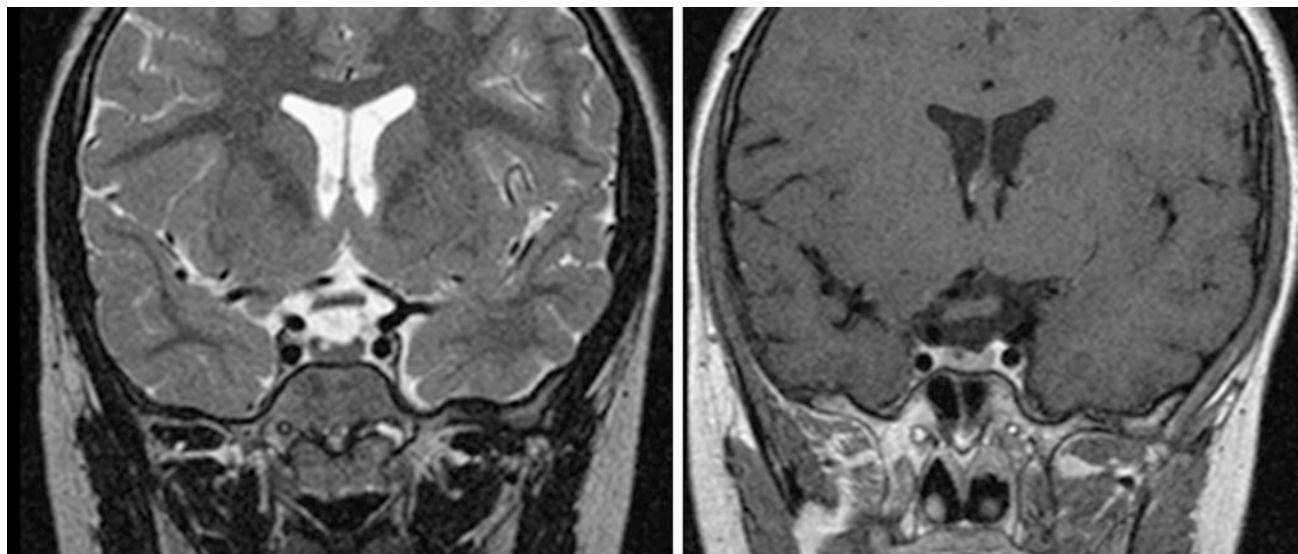


Fig. 15 Girl, 8-year-old, precocious puberty, small lesion with the right part of the adenohypophysis with T2 hyperintensity and lack of enhancement after injection: microadenoma? No surgical confirmation

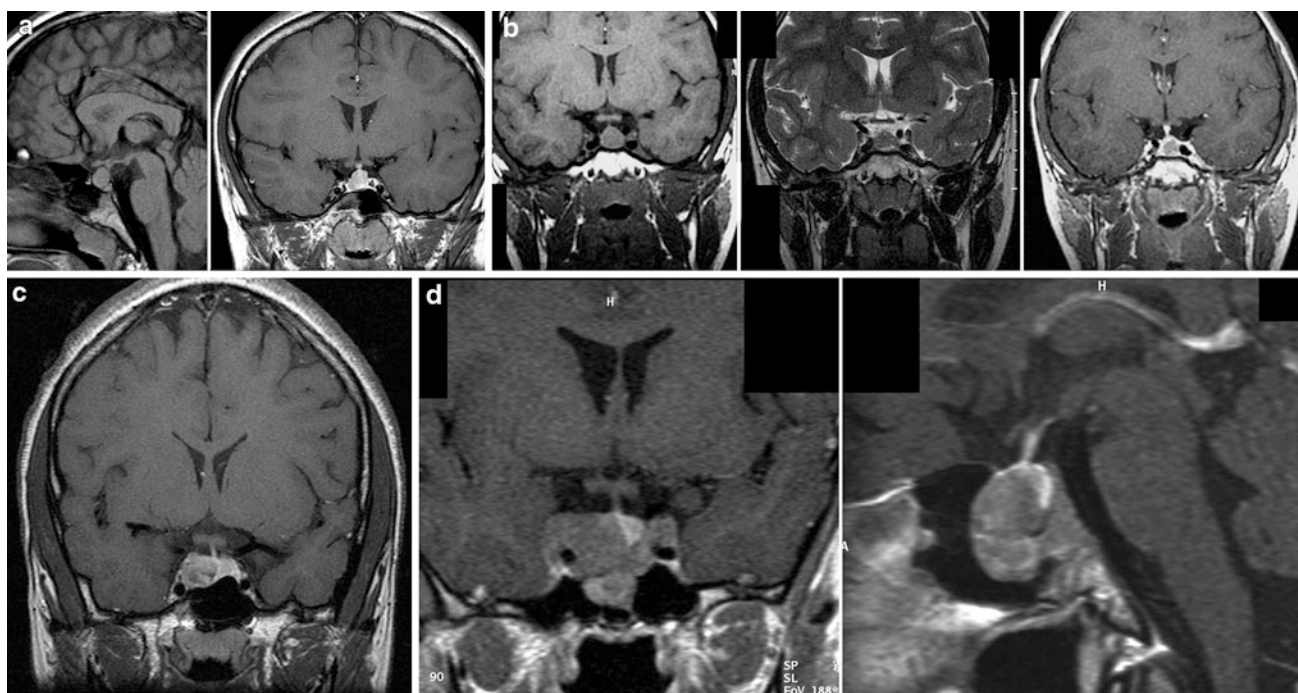


Fig. 16 **a** Girl, 10-year-old precocious puberty, obesity: antehypophysis adenoma with suprasellar extension. **b** Girl, 6-year-old, growth acceleration: prolactinoma without enhancement after contrast media injection. **c** Girl, 14-year-old, secondary amenorrhea, hyper

prolactinemia: prolactinoma: heterogeneous enhancement with extension to the right cavernous sinus. **d** Girl, 15-year-old, headaches: invasive prolactinoma with extension through the floor of sella turcica

overnight, high-dosage dexamethasone test excludes all patients with adrenal tumors and identifies almost all patients with CD.

ACTH-releasing adenomas are frequently small and difficult to localize. In previous studies, nearly half of children with CD (confirmed histologically) had an

identifiable adenoma of the pituitary gland by imaging (Batista et al. 2007; Morana et al. 2010). Most of the corticotrophin adenomas are small (<4 mm), and have similar intensity to those of normal pituitary tissue (Oliveira et al. 2010). A half dose of contrast media with 3T dynamic resonance imaging study seems to increase the sensitivity

Fig. 17 Girl, 14-year-old, galactorrhea and secondary amenorrhea, headache: prolactin adenoma with spontaneous hemorrhage



(Portocarrero-Ortiz et al. 2010). ACTH-producing macroadenomas are rare (Min et al. 2007). Pituitary imaging performed in all the patients showed poor concordance with findings at surgery. In contrast, bilateral simultaneous inferior petrosal sinus sampling, performed in selected centers, demonstrates a good correlation with surgical findings, but the sensitivity regarding the lateralization of the microadenoma is variable (Dias et al. 2010).

In the other hand, CD-like with ectopic ACTH secretion can be in relation with neuro-endocrine tumors: bronchial carcinoid tumor, pancreatic neuro-endocrine tumor, but also Ewing's sarcoma, stromal epithelial tumors of the liver, ganglioneuroblastoma, Wilm's tumor, pancreatoblastoma (More et al. 2011).

3.5.1.3 Others Pituitary Adenomas

McCune–Albright syndrome is characterized by a triad of poly/monostotic fibrous dysplasia, cafe au lait macules and hyperfunctioning endocrinopathies including growth hormone excess. GH secreting pituitary macroadenoma can be responsible of gigantism; treatment of patients with such macroadenoma is difficult because of thickened calvarium and dysplastic skull bone (Bhansali et al. 2003; Subbiah et al. 2011). Hyperthyroidism due to TSH-secreting pituitary adenomas is a very rare disorder in childhood (Nakayama et al. 2010).

3.5.2 Craniopharyngioma

Craniopharyngiomas are benign epithelial tumors accounting for 5–13 % of all intracranial neoplasms in the pediatric age group. These tumors arise from remnants of the craniopharyngeal duct: they may arise anywhere along the infundibular stalk from the floor of the third ventricle to the pituitary gland. They may be intrasellar (25 % of cases), suprasellar, or a combination of both (Morana et al. 2010). Most cases occur between 4 and 12-year-old. The clinical

picture at the time of diagnosis is often characterized by nonendocrine manifestations, such as headache (60 %) and visual disturbances (46 %). However, up to 80 % have evidence of endocrine dysfunction at diagnosis (short stature, inappropriate secretion of ADH, diabetes insipidus, delayed or precocious puberty, even CD. (Sosa et al. 2005; Tomita and Bowman 2005).

3.5.2.1 Imaging

A suprasellar enhancing lesion with a cystic component and calcifications is characteristic of a craniopharyngioma. The most common pattern is represented by a cystic lesion that is hyperintense on both T1-weighted and T2-weighted images due to high protein concentration and/or to the presence of methemoglobin, with enhancing walls and subtle peripheral calcifications. Solid tumor components, often located in the intra or parasellar region, are often heavily calcified and appear isohypointense in T1-weighted images with variable, often low signal intensity on T2-weighted images; these components typically enhance following gadolinium administration (Fig. 18a–f). CT is superior to MRI in the identification of calcifications: calcifications may appear as shell-like deposits along the cyst walls, or may form fine punctuations or lumps within the substance of the lesion. Proton MR spectroscopy may show a prominent lipid peak or doublet of lactate (Morana et al. 2010). The preoperative MR images can classify the tumor according to the degree of hypothalamic involvement as follows: Grade 0, no hypothalamic involvement; Grade 1, the tumor abutting or displacing the hypothalamus; and Grade 2, hypothalamic involvement (Puget et al. 2007). Intrasellar craniopharyngioma are classified into two types according to possible origin regions: the first one, originating in the sella turcica and developing downward to the sphenoidal sinus, and the second one, originating from the residual embryo craniopharyngeal canal (Yu et al. 2012).

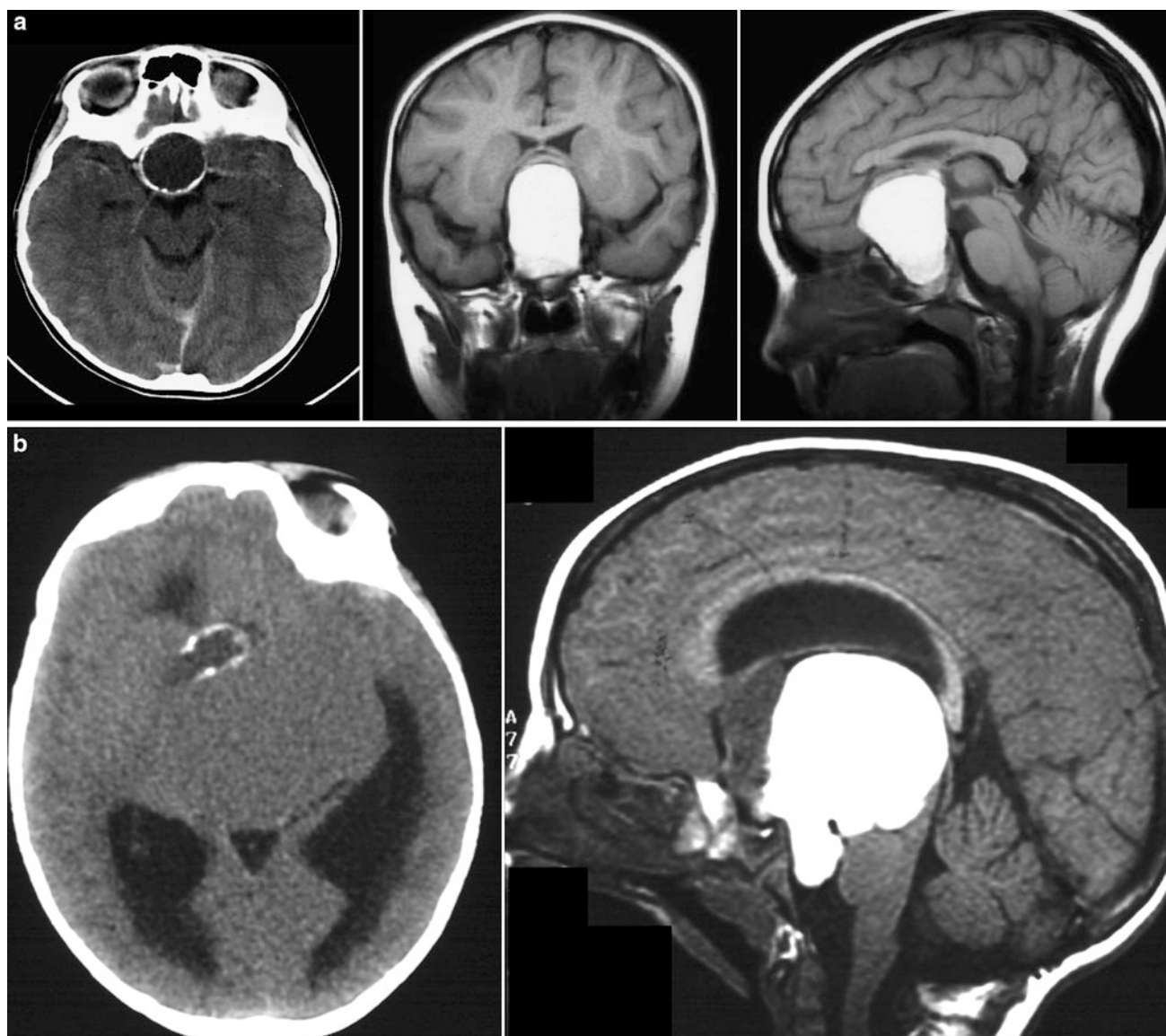


Fig. 18 **a** Girl, 6-year-old, short stature, reduction of the visual field: craniopharyngioma with predominant cystic component, thin wall calcifications seen on CT, spontaneous hypersignal on T1 weighted images in relation with high cholesterol concentration within the cyst. **b** Boy, 5-year-old: short stature, headache and vomiting; craniopharyngioma with hydrocephalus, “egg-shell” calcification on CT, spontaneous T1 hyperintense cystic part on MRI. **c** Girl 9-year old, visual disturbance since several months, papillary edema on fundoscopy: craniopharyngioma with predominantly cystic component,

peripheral rim enhancement after contrast injection. **d** Girl, 4-year-old, anorexia with slimming: craniopharyngioma with multicystic component, hypointense “pop-corn” calcification within the solid enhanced part. **e** Boy, 4-year-old, vomits since 2 weeks, palsy of the right 6th nerve: craniopharyngioma with T1 isointense cystic component, intra sellar solid component. **f** Boy, 4-year-old, same as Fig. 18e, localized MR spectroscopy within the cyst demonstrates a doublet lactate peak

3.5.2.2 Follow-up Evaluation

The extent of tumor resection after surgery influenced the recurrence-free survival, and patients with total resection have a high-rate survival. Postoperative CT and MRI have to search for small residual tumor or calcifications. In case of subtotal resection or residual tumor, radiotherapy is used

(Tomita and Bowman 2005). After radiotherapy, a high incidence of vascular abnormalities is seen in children with craniopharyngioma (temporal cavernomas, moyamoya syndrome, aneurysm or decreases in the caliber of the internal carotid artery. Intracystic bleomycin infusion may contribute to radiation-related vasculopathy (Liu et al. 2009).

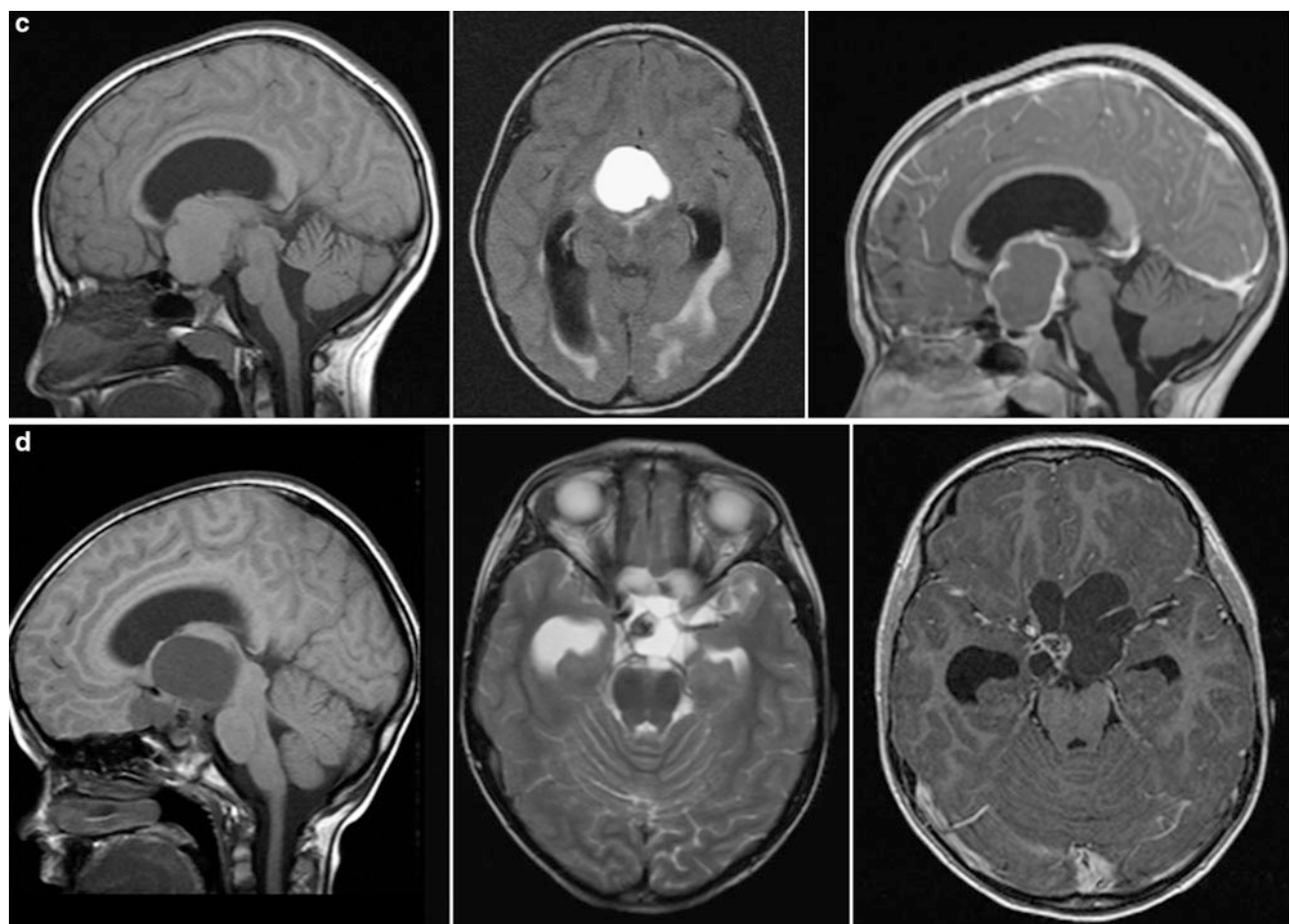


Fig. 18 (continued)

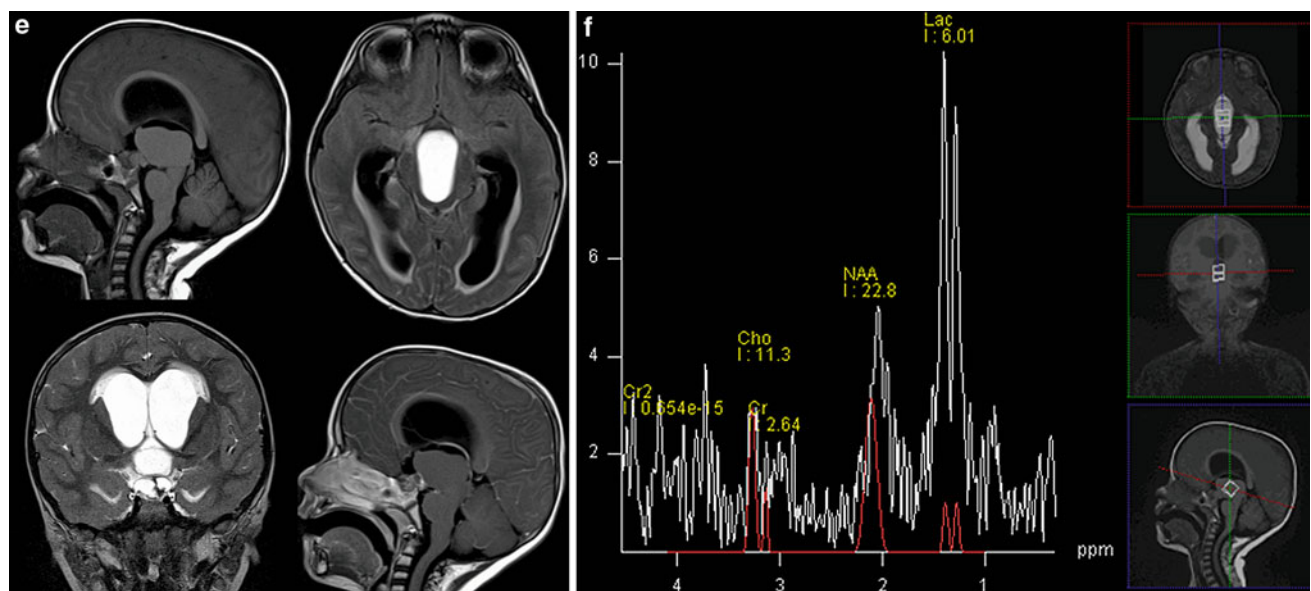


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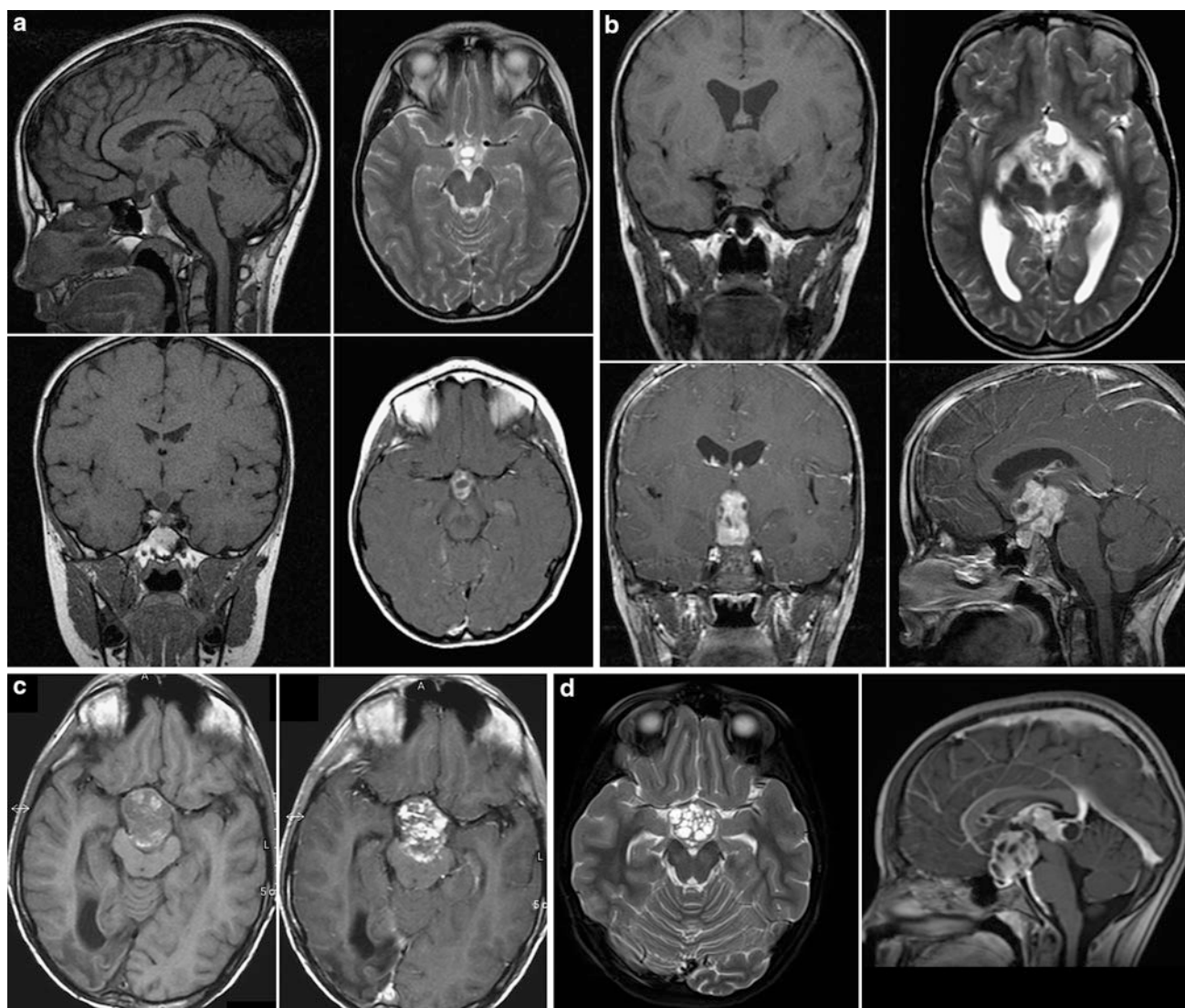


Fig. 19 **a** Girl, 11-year-old with diabetes insipidus: suprasellar germinoma with cysts. **b** Boy, 14-year-old, diabetes insipidus since 6 months: intra and suprasellar germinoma with heterogeneous solid mass. **c** Boy, 11-year-old, oculomotor palsy: suprasellar malignant

germinoma with heterogeneous enhancement. **d** Girl, 9-year-old, headaches and visual disturbances: Synchronous lesions in pineal and suprasellar regions

3.5.3 Germinoma

Intracranial germinoma is a rare malignant tumor, only constituting 0.5–2.0 % of all primary intracranial tumors but constitutes 50–60 % of central nervous system germ cell tumor. Age at diagnosis ranged from 3 to 21 years (mean 12.5 years) with a peak between 10 and 18 years. Almost 60 % of intracranial germinoma are located in pineal region, 30 % in suprasellar region, and 10 % in basal ganglia region. Synchronous lesions in pineal and suprasellar region are also possible. With regard to suprasellar region germinoma, endocrinic syndromes including central diabetes insipidus, abnormality of sexual development (precocious puberty or delayed sexual development) and growth hormone deficiency (Gottschling et al. 2006). Visual

symptoms or headache in relation with intracranial hypertension may be the first signs.

MRI demonstrates a ill-defined margin tumor with irregular shape. It often has necrosis, cysts, and hemorrhage inside the tumor, but has no calcification. The lesion demonstrated hypointense to isointense signal on T1-weighted images and isointense to hyperintense on T2-weighted images with markedly heterogeneous enhancement (Fig. 19). Diffusion-weighted MR imaging shows restricted diffusion (Wang et al. 2010). Craniospinal metastases have to be searched with entire head and spine MR evaluation. As written before, in children suffering from diabetes insipidus showing absence of visualization of the posterior 'bright spot', a small germinoma could not yet be visible on

Fig. 20 **a** Girl, 14-year-old, secondary amenorrhea, then acute headache: enlargement of adenohypophysis, with fluid–fluid level: macroadenoma with pituitary apoplexy was suspected, without surgical confirmation. **b** Same girl as Fig. 20a, six months later, hyperprolactinemia: heterogeneous enhanced mass within the adenohypophysis, biopsy: primitive neuroectodermal tumor

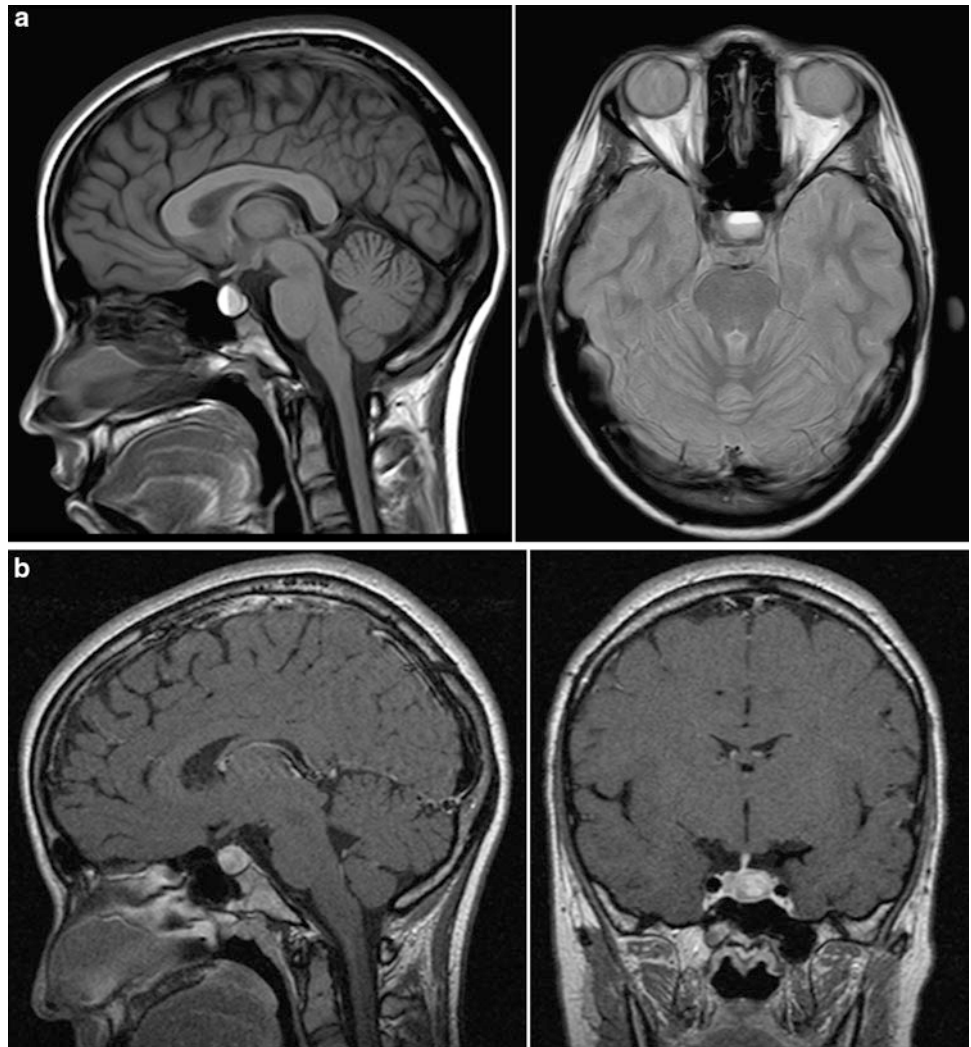
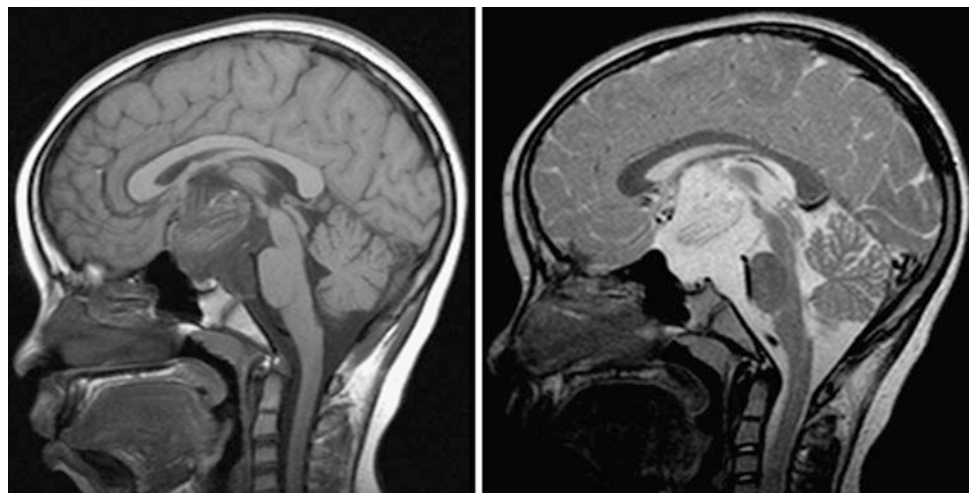


Fig. 21 Girl, 8-year-old, headaches and left visual impairment: suprasellar and pre pontine epidermoid cyst



the initial MR images (Morana et al. 2010). A close follow-up with repeated imaging studies should therefore be carried out in these patients; MRI evidence of an increase in

the size of the anterior pituitary with thickening of the stalk is strongly associated with the presence of a germinoma, whereas a decrease of normal gland parenchyma can

Fig. 22 Boy, 11-year-old, MRI for advanced puberty: incidental lipoma demonstrated, with spontaneous T1 hypersignal posterior to the pituitary stalk

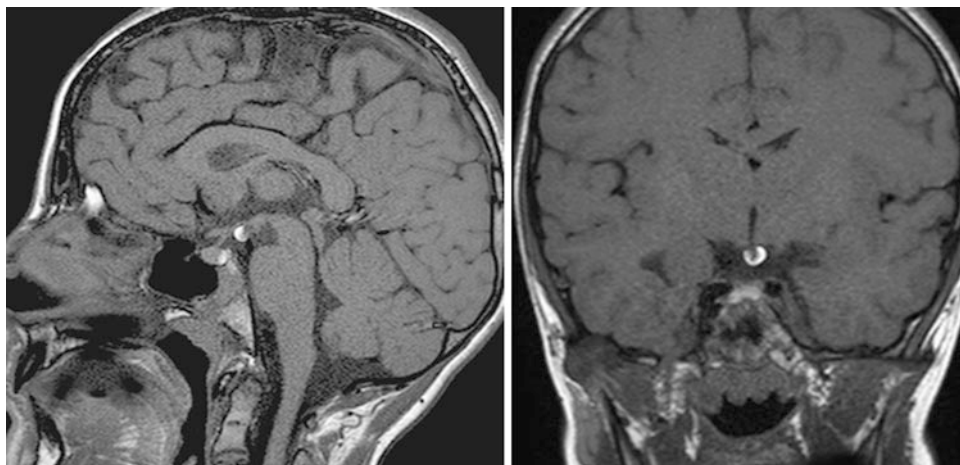
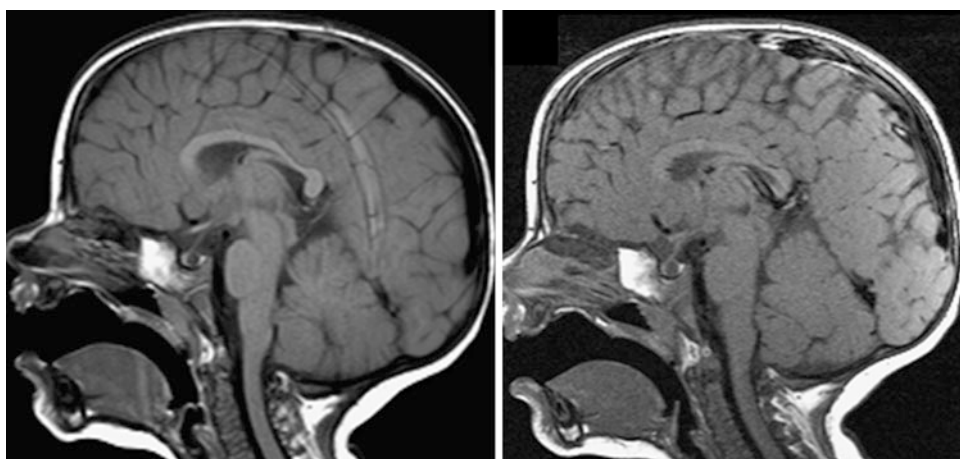


Fig. 23 Girl, 1-year-old, MRI performed for psychomotor development delay: incidental Rathke's cleft cyst



suggest an inflammatory or autoimmune process such as lymphocytic infundibulo-hypophysitis (Edouard et al. 2009; Maghnie et al. 2000).

Confirmation of the diagnosis requires measurement of serum and CSF tumor markers (α -fetoprotein and/or β -human chorionic gonadotropin) and/or biopsy. Germi-noma are highly sensitive to radiotherapy or specific chemotherapy.

3.5.4 Other Tumors

Extremely rare tumors, such as pituitary astrocytomas, granular cell tumors or primitive neuro ectodermal tumors (Fig. 20), may arise within the sella turcica (Huang and Castillo 2005). Pituitary carcinoma is defined as a primary adeno-hypophyseal neoplasm with documented craniospi-nal and/or systemic metastases. They are exceptional in childhood, are hormonally active, and they can have metastases in all parts of the central nervous system (Guzel et al. 2008).

The pituitary stalk is the most common site for the development of supratentorial hemangioblastomas in Von Hippel Lindau disease. Patients with pituitary stalk

hemangioblastomas often remain asymptomatic and do not require treatment (Lonser et al. 2009).

Trilateral retinoblastoma is a rare combination of unila-teral or bilateral retinoblastoma with a midline malignant neuroectodermal tumor (3 % incidence). There are only three published cases of histologically confirmed trilateral retinoblastoma involving suprasellar tumors (Dai et al. 2008).

3.5.5 Dermoid and Epidermoid Cysts of the Suprasellar Cistern

Dermoid and epidermoid cysts are rare benign maldeve-lopmental lesions that arise from epithelial inclusions occurring during neural tube closure. Dermoid and epider-moid cysts consist of a capsule composed of epidermal elements, with dermoid cysts containing dermal derivatives (fat, sebaceous glands, hair). Suprasellar lesions can cause visual abnormalities and endocrinologic disturbances (Saleem et al. 2007). CT and MRI can demonstrate the presence of fat (with characteristic hypodensity with CT, or lack of signal with fat-saturation sequences on MRI; diffusion imaging can also help to characterize the cystic

Table 2 Summary of clinical presentations and pathologies

	HP axis developmental disorders					Intra or suprasellar masses			Inflammatory and systemic diseases	
	Disorders of diverticulation	Pituitary gland aplasia/hypoplasia	Pituitary stalk interruption syndrome	Duplication of pituitary gland and stalk	Hypothalamic hamartoma	Pituitary adenoma	Craniopharyngioma	Germinoma	Langerhans cell histiocytosis	Lymphocytic hypophysitis/Sarcoidosis/Tuberculosis
Growth disturbance	◆	◆	◆	—	—	◆	◆	◆	—	—
Combined antehypophysis deficiency	◆	◆	◆	—	—	—	◆	—	—	◆
Precocious puberty	—	—	—	◆	◆ (+ gelastic seizures)	◆	◆	◆	◆	—
Delayed puberty - hypogonadism	◆	—	◆	—	—	◆	◆	◆	◆	—
Central diabetes insipidus	—	—	—	—	—	◆	◆	◆	◆	◆
Intracranial hypertension	—	—	—	—	—	◆	◆	◆	◆	◆
Visual disturbance	◆	—	—	—	—	◆	◆	◆	—	◆

component by showing a restricted diffusion of water within the hypo-T1 cyst (Fig. 21). Benign lipomas can also be found on the midline (Fig. 22).

3.5.6 Optic Chiasm and Third Ventricle's Floor Glioma

Endocrine syndromes, including precocious puberty and growth hormone deficiency, may reveal gliomas arising from the optic chiasm or the floor of the third ventricle. Children who suffer neurofibromatosis type 1, but also Noonan syndrome should always be carefully examined for clinical signs of precocious puberty (Chateil et al. 2001).

3.6 Rathke's Cleft Cysts and Incidentalomas

Rathke's cleft cyst (RCC) is a benign cystic lesion that is considered to be derived from remnants of Rathke's pouch. The majority seem to remain asymptomatic and only a part of the cyst becomes symptomatic throughout its whole lifetime. The common symptoms in symptomatic RCC are headache (32.1–80 %), endocrine disturbance (30–69.4 %) and visual impairment (14.3–55.8 %) (Wen et al. 2010).

A study evaluating MR imaging studies in a group of 341 patients aged less than 15 years revealed only four pituitary cystic lesions (Takanashi et al. 2005). On MRI, they appear as rounded cysts with variable signal behavior both on T1 and T2-weighted images. On T1-weighted images, about two-thirds are hyperintense to brain and one-third shows low signal intensity, similar to CSF. On T2-weighted images, about 50 % are hyperintense, 25 % isointense, and 25 % hypointense; presence of a hypointense spot within a hyperintense cyst is said to be a characteristic finding. Contrast enhancement is absent (Fig. 23). Regarding differentiation from pituitary adenomas, location is an important factor in that RCC typically lies centrally in the pars intermedia, between the anterior and posterior pituitary lobes, whereas pituitary adenomas are often eccentric and typically located within the adenohypophysis. On diffusion-weighted imaging, RCC is hypointense relative to normal brain parenchyma. It has recently been demonstrated that ADC values of RCC are significantly higher than those of the cystic components of craniopharyngiomas and hemorrhagic components of pituitary adenomas in the subacute phase thus, providing useful information in the differential diagnosis of RCC from other sellar cystic lesions (Kunii et al. 2007).

Incidentalomas may create management difficulties. Incidental identification of a small cyst in the pituitary gland of a child should be considered an incidental finding in the absence of signs or symptoms referable to pituitary dysfunction (Morana et al. 2010; Takanashi et al. 2005).

4 Tips and Tricks for an Easy Diagnosis

Table 2 gives the different diagnosis regarding the clinical presentation and the pathophysiology.

5 Conclusion

Diseases of hypothalamo-hypophysis axis may express a wide variety of symptoms, including endocrine dysfunctions with lack or hypersecretion of one or several hormones, and also in relation with a mass effect. Brain MRI, completed with localized multiplanar thin slices, is the mandatory tool to define the anatomic abnormalities. A normal examination in some presentations does not permit to exclude a lesion, mainly in diabetes insipidus, and has to be repeated in such cases.

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