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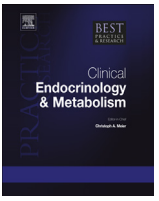

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Classical and non-classical causes of GH deficiency in the paediatric age

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Growth hormone deficiency (GHD) may result from a failure of hypothalamic GHRH production or release, from congenital disorders of pituitary development, or from central nervous system insults including tumors, surgery, trauma, radiation or infiltration from inflammatory diseases. Idiopathic, isolated GHD is the most common sporadic form of hypopituitarism. GHD may also occur in combination with other pituitary hormone deficiencies, and is often referred to as hypopituitarism, combined pituitary hormone deficiency (CPHD), multiple pituitary hormone deficiency (MPHD) or panhypopituitarism. Children without any identifiable cause of their GHD are commonly labeled as having idiopathic hypopituitarism.
MRI imaging is the technique of choice in the diagnosis of children with hypopituitarism. Marked differences in MRI pituitary gland morphology suggest different etiologies of GHD and different

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prognoses. Pituitary stalk agenesis and ectopic posterior pituitary (EPP) are specific markers of permanent GHD, and patients with these MRI findings show a different clinical and endocrine outcome compared to those with normal pituitary anatomy or hypoplastic pituitary alone. Furthermore, the classic triad of ectopic posterior pituitary gland, pituitary stalk hypoplasia/agenesis, and anterior pituitary gland hypoplasia is generally associated with permanent GHD. T2 DRIVE images aid in the identification of pituitary stalk without the use of contrast medium administration. Future developments in imaging techniques will undoubtedly reveal additional insights. Mutations in a number of genes encoding transcription factors – such as HESX1, SOX2, SOX3, LHX3, LHX4, PROP1, POU1F1, PITX, GLI3, GLI2, OTX2, ARNT2, IGSF1, FGF8, FGFR1, PROKR2, PROK2, CHD7, WDR11, NFKB2, PAX6, TCF7L1, IFT72, GPR161 and CDON – have been associated with pituitary dysfunction and abnormal pituitary gland development; the correlation of genetic mutations to endocrine and MRI phenotypes has improved our knowledge of pituitary development and management of patients with hypopituitarism, both in terms of possible genetic counseling, and of early diagnosis of evolving anterior pituitary hormone deficiencies.

Introduction

Growth hormone deficiency (GHD) may result from a failure of hypothalamic GHRH production or release, from genetic or congenital disorders of pituitary development affecting either the somatotrophs or the other pituitary specialized cells. GHD may be also secondary to central nervous system (CNS) insults including tumors, surgery, trauma, radiation or infiltration from inflammatory diseases. It may be isolated or it may occur in combination with other pituitary hormone deficiencies, and is often referred to as hypopituitarism, combined pituitary hormone deficiency (CPHD), multiple pituitary hormone deficiency (MPHD) or panhypopituitarism. Children without any identifiable cause of their GHD are commonly labeled as having idiopathic hypopituitarism (Table 1).

Although the majority of subjects with hypopituitarism are idiopathic in origin, familial inheritance, which may be either dominant, recessive or X-linked accounts for between 5 and 30% of all cases [1]. It may present early in the neonatal period or later in childhood and may be associated with a number of midline defects or extrapituitary abnormalities such as optic nerve hypoplasia, anophtalmia, microphtalmia, agenesis of the corpus callosum, absence of the septum pellucidum, midbrain abnormalities, and olfactory bulbs and tract hypoplasia or agenesis.

The pituitary gland is a complex organ secreting six hormones from five different cell types. The anterior portion of pituitary gland forms from Rathke's pouch around the third week of gestation, and its development is influenced by the expression of numerous transcription factors and signaling molecules. Naturally occurring mutations and transgenic murine models have demonstrated a role for many of these molecules in the etiology of congenital hypopituitarism. These consist of transcription factors and genes, some of which have unknown functions, including HESX1, SOX2, SOX3, LHX3, LHX4, PROP1, POU1F1, PITX, GLI3, GLI2, OTX2, ARNT2, IGSF1, FGF8, FGFR1, PROKR2, PROK2, CHD7, WDR11, NFKB2, PAX6, TCF7L1, IFT72 (ciliopathy), GPR161 and CDON [1–33]. Mutations in any of the genes encoding these components (no functional studies available for IFT72, GPR161, CDON) can lead to congenital hypopituitarism, which is often associated with a wide spectrum of defects affecting craniofacial/midline development.

Many other genes that are required for normal pituitary function and for the control of the growth hormone/insulin-like growth factor axis (secretion and synthesis of GH) have been identified. Abnormalities either in the synthesis or the activity of GH can cause a wide variation in the clinical

Table 1
Etiologies of GHD.

Isolated GHD	Genetic • GH1 Mutations (GHD type 1A) • GHRH Mutations (GHD type 1B) • GH1 Mutations (GHD type II with evolving pituitary deficiencies) • GHD type III (XL Agammaglobulinemia) • GH1 Kowarski Syndrome (Bioinactive GH) • GHS Mutation/Variant • Alstrom Syndrome
CPHD/MPHD	Genetic (Transcription factor defect, gene mutation, deletion or duplication) • Genes implicated in early development of hypothalamic–pituitary region • Genes implicated in early development of brain and hypothalamic–pituitary region - Holoprosencephaly - Septo-optic dysplasia and its spectrum involving eyes - Midline defects (cleft-palate, persistence of craniopharyngeal canal, dental agenesis, …) - Extra brain malformations (ARNT2, CHD7, IGSF1, …) - Overlapping Kallmann syndrome (FGF8, FGFR1, PROKR2, PROK2 CDH7,WDR11, …) - Other conditions • Genes implicated in cellular differentiation • Inducing tumor genes (SOX2, BRAF, …)
CPHD/MPHD	Congenital • Midline brain and pituitary developmental defects • Pituitary aplasia; ectopic posterior pituitary, anterior pituitary hypoplasia and pituitary stalk abnormalities (agenesis, hypoplasia); empty sella • Congenital CNS mass (hamartoblastoma, hamartoma), cyst. encephalocele
IGHD/CPHD/MPHD	• Idiopathic permanent • Idiopathic transitory
IGHD/CPHD/MPHD	Acquired • CNS tumors (craniopharyngioma, germinoma, ependymoma, pituitary adenoma, meningioma, medulloblastoma, glioma, metastatic tumors (rare), Rathke's cleft cyst, arachnoid cyst) • Radiotherapy (cranial irradiation for CNS tumors, other malignancies,BMT) • TBI (accidental, after neurosurgery, subarachnoid hemorrhage) • Infections (meningitis, encephalitis, tuberculosis, hypophysitis) • Autoimmune (hypophysitis, APS, anti Pit1antibodies) • Infiltration (LCH, hemochromatosis, chronic blood transfusions) • Chemotherapy (cancer survivors)

GHD, growth hormone deficiency; CPHD, combined pituitary hormone deficiency; MPHD, multiple pituitary hormone deficiency; CNS, central nervous system; BMT, bone marrow transplantation; TBI, traumatic brain injury; APS, autoimmune polyglandular syndrome; LCH, Langherans cell histiocytosis.

phenotype of these patients; isolated growth hormone deficiency (IGHD) may result from mutations or deletions in GH1 or GHRHR gene [2,3]. Recently a new mechanism of defective spliceosome mRNA processing has been reported to be associated with familial isolated GHD [4].

The advent of magnetic resonance imaging (MRI) has led to a significant improvement in the understanding of the pathogenesis of disorders that affect the hypothalamus-pituitary area and particularly of congenital hypopituitarism. Today there is convincing evidence to support the hypothesis that marked MRI differences in pituitary morphology indicate a diverse range of disorders that affect the organogenesis and function of the anterior pituitary gland, with different prognoses. Specifically, MRI allows for a detailed and precise anatomical study of the pituitary gland by differentiating between the anterior and the posterior pituitary lobes. The MRI identification of pituitary hyperintensity in the posterior part of the sella, now commonly considered as a marker of neurohypophyseal functional integrity, has been the most striking finding for the diagnosis and understanding of anterior and posterior pituitary diseases [34–36].

This article will discuss the current state of knowledge in our understanding of the etiology of hypopituitarism associated with structural hypothalamic–pituitary abnormalities. The role of transcription factors and genes implicated in abnormal pituitary development and pituitary cell differentiation will be underlined, and the lack of a genetic characterization in a high number of patients with congenital conditions will also be considered.

Epidemiology of GHD

Idiopathic isolated GHD is the most common sporadic form of hypopituitarism, and its incidence is estimated to be between 1/4000 and 1/10,000 among live births [37–41]. Although in 5%–30% of cases there is also an affected first degree relative [1], most cases are sporadic and believed to be related to a combination of environmental and/or developmental risk factors, including viral infections, vascular or degenerative changes, drug exposure, young maternal age, as is the case for septo-optic dysplasia [42]. An incidence of growth hormone (GH) deficiency of one in 60,000 live births was first reported in the United Kingdom in early 1974 [37,38]. Another survey of 48,000 Scottish schoolchildren [39] showed different results, reporting an occurrence as high as one in 4018. Although the incidence of GHD is thought to vary significantly between different countries, an exact figure based on recent data and standard criteria has not yet been determined. To date, the most reliable prevalence for short stature associated with childhood GH deficiency is believed to range between approximately one in 3000 to one in 10,000 live births [39–41].

The best current estimate available comes from the UTAH growth study of a United States' population [40]. In this survey, serial measurements of elementary-school children were conducted for 2 consecutive years to assess height and growth velocity and to determine the prevalence of GH deficiency in American children. Trained volunteers measured 114,881 children in the first year of the study; after a second measurement, the growth rates of 79,495 subjects were calculated, leading to an estimated GH deficiency incidence of one in 3480. The prevalence and incidence of GH deficiency appears relatively constant in more recent studies ranging between 1:5000 to 18,646 [43–46].

Pathophysiology of GHD

The understanding of the causes of GHD requires a brief overview of pituitary development, clinical presentation of hypopituitarism, MRI principles and technical requirements and its role in the diagnosis and prognosis, that will be discussed in the next paragraphs.

Pituitary organogenesis and genes causing hypopituitarism

The development of the pituitary gland is strictly related to that of the forebrain in an early stage of embryogenesis. The three pituitary lobes have different embryological origins: anterior and intermediates lobes are derived from the oral ectoderm, while the posterior lobe develops from neural ectoderm.

The first marker of pituitary organogenesis, occurring in the mouse between 8 and 14 embryonic days, is the formation of an upwards evagination of the ectoderm of the primitive oral cavity, known as Rathke's pouch. At the same time, another evagination originates from the neural ectoderm of the dorsal diencephalon, giving rise to an infundibulum (the future posterior pituitary) that maintains close contact with Rathke's pouch during the early stages of pituitary organogenesis. This relationship has a key role for inductive tissue interactions and for the influence exerted by neuroectodermal signaling on the primordial pituitary gland [47].

In recent years, a significant understanding of the molecular mechanisms regulating these processes has been attained, especially in rodents, compared to the relatively smaller amount of existing knowledge about pituitary embryogenesis in humans. However, significant overlaps have been identified between the phenotypes of spontaneous and induced murine mutations and various human clinical syndromes, suggesting that pituitary development in rodents and humans share some common mechanisms. The sequential expression of a complex cascade of transcription factors is mandatory for normal development of the pituitary gland. The lack of one or more of these mechanisms during different phases may lead to various degrees of pituitary dysmorphogenesis and/or function impairment. Early pituitary development is structured in three steps in response to inductive signals from the diencephalon [47], the first step occurring near embryonic day 8.5 in mice with the formation of a placode in the oral ectoderm in response to signaling molecules from the diencephalon. The second step consists of the transformation of the placode into the definitive Rathke's pouch. During the third step, oral ectoderm cells in the pouch differentiate into the different pituitary cell types to form a nascent anterior pituitary gland and pars intermedia.

Several homeodomain transcription factors directing embryologic development of the anterior pituitary have been found to have mutations that result in congenital defects affecting the synthesis of GH and additional pituitary hormones. The human mutations that cause isolated growth hormone deficiency and the associated features are summarized in Table 2 while those causing MPHD including HESX1, SOX2, SOX3, LHX3, LHX4, PROP1, POU1F1, PITX, GLI3, GLI2, OTX2, ARNT2, IGSF1, FGF8, FGFR1, PROKR2, PROK2, CHD7, WDR11, NFKB2, PAX6, TCF7L1, IFT72 GPR161 and CDON [1–33] are summarized in Table 3.

Idiopathic GHD – phenotype

Idiopathic non syndromic GHD is a heterogeneous condition whose pathophysiology remains largely unknown, and the diagnosis during childhood and adolescence is frequently challenging. Once growth hormone deficiency is suspected, testing of the hypothalamic–pituitary axes along with radiological evaluation, should be performed. Evaluation should begin with a detailed past medical history, family history, detailed review of prior growth data and a thorough physical examination. The typical GHD clinical phenotype in childhood is short stature and persistent growth failure associated with frontal bossing, mid-facial hypoplasia, truncal adiposity, small genitalia in the male, and/or hypoglycemia and cholestatic jaundice. However, this presentation tends to be the exception rather than the rule and thus the clinical phenotype may not be particularly notable [48].

A study from the Netherlands analyzed the clinical phenotype of GHD photographs of 137 patients (73 IGHD and 64 MPHD). Standardized frontal and lateral digital pictures were taken of each patient and analyzed using specific software. The analysis revealed that Canthal Index (CI), the relative distance between the eyes, was related to pituitary morphology. Patients with an Ectopic Posterior Pituitary (EPP) had significantly higher CI values than patients without EPP, with a cut-off value being CI > 39 for identifying children with the highest probability of having EPP.

The combination of CI > 39 in the presence of hormonal deficiencies in addition to GHD strongly predicted EPP: 93% of the patients with a CI > 39 and additional hormonal deficiencies had EPP, compared to 77% of patients with additional hormonal deficiencies but a CI < 39, and 29% of patients without any of these criteria. The association between Canthal Index, measured from digital pictures, and EPP could be caused by altered midline development, affecting both the pituitary gland and the facial structures of GHD patients [49].

Idiopathic GHD – etiology

In recent decades, studies have identified a number of conditions or adverse events associated with pituitary disorders and GHD. There are anecdotal data to support a role for intrauterine insults in pituitary gland dysgenesis including prenatal vascular disruption and intrauterine exposure to certain drugs or drug abuse [50–52]. In addition, intrauterine insults and traumatic or vascular head birth-related injuries have been raised as causes of hypopituitarism despite few reports of an association between GHD and malformations involving the brain and pituitary vascular system such as the agenesis of internal carotid artery [53,54].

Indeed, perinatal injury has been reported in more than 80% of patients with hypopituitarism, and some authors have suggested that birth trauma during abnormal delivery such as breech presentation is a common primary cause of idiopathic hypopituitarism [55,56]. Despite the exact role of birth trauma in the etiology of pituitary dysgenesis is unclear [57,58], it remains possible that, in some patients, birth trauma and associated hypoxemia may worsen congenital pituitary dysplasia rather than acting as a primary cause [57]. On the other hand, fetal hypopituitarism and pituitary dysfunction could increase the risk of breech delivery, which in turn leads to mechanical and hypoxic damage to midline structures [59]. This theory is consistent with observations that birth trauma and breech delivery are more commonly reported in association with MPHD. Breech delivery, in fact, was reported as five times more common in patients with structural hypothalamic–pituitary abnormalities compared with patients who had isolated anterior pituitary hypoplasia [56–59].

Published data seem to suggest that many of the so called “idiopathic” cases of IGHD may actually have a congenital origin or genetic cause, although the latter hypothesis remains largely unconfirmed

Table 2
Genetics and phenotypes of isolated growth hormone deficiency.

Disorder/gene	Inheritance	MIM/Locus	Pituitary defects					Pituitary phenotype	EPP	Associated features		
			GH	PRL	TSH	LH/FSH	ACTH			Head/neck	CNS	Findings
Isolated GHD type 1A/GH-1	AR	262400 17q23.3	Yes	No	No	No	No	Normal AP	No	Severe phenotype, midfacial hypoplasia, frontal bossing, cleft nose	–	Severe short stature, severe GHD, micropenis, hypoglycemia, anti GH-antibodies
Isolated GHD type 1B/ GHRHR	AR	612781 7p15-14	Yes	Low	No	No	No	Normal AP/APH	No	Less severe phenotype, frontal bosses, cleft nose	Chiari I, arachnoid cyst	Less severe short stature, low GH, dyslipidemia, hypoglycemia, troncular fat distribution, pubertal delay
Isolated GHD type II/GH-1	AD	173100 17q23.3	Yes	No	#	No	No	Normal AP/APH	No	Variable phenotype, frontal bossing, cleft nose	–	Variable short stature, micropenis, hypoglycemia
5′IVS-3 +1nt E32A*	AD	173100	Yes	Yes	Yes	Yes	Yes	Normal AP/APH	No	Variable phenotype, frontal bosses, cleft nose	–	Evolutive endocrinopathy
Isolated GHD type III/ SOX3**/BTK/ other genes	X-linked	312000 300123 307200 Xq27.1	Yes	No/yes**	No/yes**	No/yes**	No/yes**	Normal/AP**	Yes with persistence of craniopharyngeal canal**	Ocular motor dyspraxia	–	X-linked agammaglobulinemia and IGHD
Isolated partial GHD/GHSR	AR, AD	615925 3q26.31	Yes	No	No	No	No	–	–	–	–	Non severe short stature Variable GH and IGF-I levels
Bioinactive GH/ GH-1	AD	262650 17q23.3	High GH	No	No	No	No	–	No	–	–	Low IGF-I, IGFBP-3 and ALS
Kowarski Syndrome												
Alstrom syndrome												
RNPC3	AR	203800 2p13.1	Yes 50% GHD	No	No	No	No	APH	No	–	Frontal bossing	Severe short stature, Insulin resistance syndromic l obesity metaphyseal dysplasia, hypertension, retinopathy
ALMS1	AR											
IFT172***	AR											

Ad, Autosomal dominant; AR, Autosomal recessive; EPP, Ectopic Posterior Pituitary; CNS, central nervous system; AP, anterior pituitary; APH, anterior pituitary hypoplasia; #exceptionally reported (1 patient) (Ref. [59]); *IGHD type II and apparent functional reversal; **SOX3 amy be associated with IGHD to MPHD with different MRIs findings sometimes Combined pituitary hormone defect; IGHD, isolated growth hormone deficiency; ***No functional studies.

Table 3
Genetics and characteristics of patients with combined or multiple pituitary hormone defects.

Gene	Inheritance	MIM/Locus	Pituitary defects					Pituitary phenotype	EPP	Other abnormalities of pituitary region	Associated features				
			GH	PRL	TSH	LH/FSH	ACTH				Head/neck	Eye	Psychomotor development	CNS	Findings
POU1F1 CPHD-1	AR/AD	3p11 613038	Yes	Yes/no	Yes/no	No	No	Normal AP/APH	No	–	Macrocephaly, frontal bossing, cleft nose, large anterior fontanels, macroglossia	–	–	–	Feet polydactyly
PROP1 CPHD-2	AR	5q35.3 262600	Yes	Yes	Yes	Yes	Yes/no	Normal AP/Large AP/APH	No	Large sella turcica	–	–	–	–	Pubertal delay, risk of evolutive endocrinopathy, ACTH deficiency in 1/3 of cases
LHX3 CPHD-3	AR	9q34.3 221750	Yes	Yes	Yes	Yes	No	APH/Large AP	No	Flat sella turcica	Stubby neck anomalies of cervical vertebrae and limited neck rotation	–	Cognitive delay	Sensorineural deafness	Severe scoliosis skin defect
LHX4 CPHD-4	AD/AR	1q25 262700	Yes	No	Yes	Yes	Yes	Normal AP/APH	Yes/no	Abnormal sella turcica	–	–	–	Chiari I	Abnormal cerebellar tonsils neonatal hypoglycemia, cardiac insufficiency and respiratory distress (death)
HESX1 CPHD-5	AD/AR	3p21.2-p21.1 182230	Yes	Yes/no	Yes/no	Yes/no	Yes/no	Normal AP/APH/AP aplasia	Yes/no	–	–	Yes/no	–	Psychomotor development	SOD and SOD variants, midline abnormalities micropenis, polydactyly
OTX2 CPHD-6	AD	14q22.3 613986	Yes	Yes/no	Yes	Yes	Yes/no	Normal AP APH/PSA	Yes/no	–	Cranial dermoid cysts, microcephaly, cleft palate, feeding difficulties	Microphtalmia anophtalmia, coloboma cataract	Learning difficulties autism disorder	Chiari I, epilepsy	Cerebellar abnormalities, heart conditions (Wolff-Parkinson-White), anterior anus, fifth finger clinodactyly
SOX2	AD	3q26.33 206900	Yes/no	No	Yes/no	Yes	Yes/no	APH normal AP Large AP	Yes/no	Pituitary mass	Microcephaly, frontal bossing, dental anomalies	Microphtalmia anophtalmia coloboma	Mental retardation learning difficulties	Sensorineural deafness, spastic diplegia or quadriplegia	Cardiac abnormalities, vertebral and skeletal abnormalities, esophageal atresia, genital malformations
SOX3	X-linked	Xq27.1 312000 300123	Yes	No	Yes/no	Yes/no	Yes/no	APH	Yes/no	Persistent craniopharyngeal canal	Facial abnormalities	–	Cognitive delay, behavioral abnormalities	–	–

(*continued on next page*)

Table 3 (*continued*)

Gene	Inheritance	MIM/Locus	Pituitary defects					Pituitary phenotype	EPP	Other abnormalities of pituitary region	Associated features				
			GH	PRL	TSH	LH/FSH	ACTH				Head/neck	Eye	Psychomotor development	CNS	Findings
IGSF1	X-linked	300388 Xq26.1	Yes	Yes/no	Yes	Yes	Yes/no	Normal AP	No	–	–	Benign external hydrocephalus	Mild problems with attention control	–	Macrorchidism, overweight habitus, delayed testosterone rise in puberty
ARNT2	AR	615926 15q25.1	Yes/no	No	Yes	Yes/no	Yes	–	No	–	Microcephaly prominent forehead retrognathia	Blindness	Developmental delay	Cerebral palsy, Intractable seizures	Diabetes insipidus dislocation of hips gastroesophageal reflux hydronephrosis death from sepsis
TCF7L1	AD Variable penetrance	2p11.2	Yes/No	slightly in 1 patient	TSH midly elevated in 1 case	no	no	APH	no	no	–	Nystagmus ONH and small chiasm	–	–	Partial agenesis of CC, thin anterior commissure, absent septum pellucidum
CHD7	AD	214800 7q21.11 8q12.2	Yes	No	No	Yes	No	APH	Yes/no	–	Choanal atresia, ogival palate	Exophtalmos	Cognitive delay	Deafness	Pubertal delay, growth delay, CHARGE syndrome, ear abnormalities genital hypoplasia, heart abnormalities, cryptorchidism
GLI3	AD/AR	146510 241800 7p14.1	Yes	Yes/no	Yes	Yes	Yes	APH	No	–	Microphtalmia, cleft nose, palatoschisis, hydrocephalus encephalocele	–	–	–	Encephalic trunk glioma Pallister-Hall syndrome; hypothalamic hamarthoma
FGF8	AR	600483 10q24.32	Yes	Yes	Yes	Yes	Yes/no	APH/PSA Enlarged AP	Yes/no	Empty sella	Craniofacial defects	–	–	Hearing loss	Semilobar holoprosencephaly SOD, absent corpus callosum diabetes insipidus, micropenis, renal hypoplasia, Kallmann syndrome Moebius syndrome
FGFR1	AD	136350 8p11.23	Yes	No	–	Yes	–	APH/PSA	Yes/no	–	Labio-palatoschisis, trigonocephaly, dental agenesis	coloboma	–	–	Ipo-anosmia, micropenis, cryptorchidism, syndactyly, Kallmann syndrome

PROKR2	AD	607123 20p12.3	Yes	No	Yes/no	Yes	Yes/no	APH/PSA	Yes/no	–	Nasopharyngeal stenosis	–	Mental delay	Synkinesis, seizures	Sleep disorders, “morning glory syndrome”, Kallmann syndrome, diabetes insipidus, SOD, flat feet, pectus excavatum, cryptorchidism, neonatal respiratory distress
GLI2	AD	610829 2q14	Yes	–	Yes/no	Yes/no	Yes/no	APH/AP aplasia/	Yes/no	–	Microcephaly. Midface hypoplasia Single incisor, Holoprosencephalylike features	–	–	–	Abnormal corpus callosum Variable mdlline defects Variable phenotype
CDON*	AD?	11q24.2	Yes	No	Yes	No	Yes	APH	Yes			Strabismus		Seizures	Neonatal hypoglicemia and jaundice; HPE
GPR161*	AR	1q24.2	Yes	?	Yes	?	?	APH	Yes	Empty sella	Broad nasal root; hypotelorism; partial alopecia; thick alae nasi	Eye ptosis	Intellectual disability		Short fifth finger; syndactyly; nail hypoplasia; diabetes insipidus

AR, autosomal recessive; AD, autosomal dominant; AP, anterior pituitary; APH, anterior pituitary hypoplasia; PS, pituitary stalk; PSA pituitary stalk agenesis; EPP, ectopic posterior pituitary; CC, corpus callosum; SOD, Septo-optic Dysplasia; ONH, optic nerve hypoplasia; HPE, holoprosencephaly; CNS, central nervous system; *No functional studies available.

in many patients, while the role of epigenetics or environmental factors in determining pituitary dysfunction still needs to be determined.

A noteworthy mechanism of anterior hypopituitarism on a possible vascular basis could be related to pituitary stalk diseases associated with impairment of the blood supply to the anterior pituitary [60–62]. The term "pituitary stalk transection syndrome", applied in a high percentage of cases of birth trauma or breech delivery in patients with GHD and ectopic posterior pituitary, and based on the results of experimental studies showing that surgical section of the pituitary stalk leads to posterior pituitary lobe regeneration at the hypothalamic level, does not appear appropriate [63]. The traumatic origin of such anatomical findings cannot be confirmed on the basis of birth trauma and consequent mechanical section of the pituitary stalk at the time of delivery, because two thirds of these patients are born with no reported adverse perinatal events, with cephalic delivery in approximately 50% and caesarean section in 15% of cases [64]. The precise cause of the high frequency of breech births in cases of agenesis of the stalk and severe hypoplasia of the pituitary remains largely unexplained, though a hypothesis of fetal hypotonia secondary to anatomical and pituitary dysfunction or to other causes leading to breech presentation appears plausible [61,62].

A congenital-genetic origin is supported by various factors such as: the presence of a phenotype appearance compatible with congenital defect; the absence of perinatal adverse events in a large number of cases, the presence of familial cases associated with the same anatomic – functional pituitary characteristics, the association of chromosome defects in some patients, the presence of central nervous system malformations, and findings of ectopia of the posterior pituitary, with absence of local signs secondary to trauma of the stalk in twins who were born with normal delivery but who died during the first month of life [65–71], as well as in patients with syndromes associated with hypothalamic–pituitary abnormalities. These include Fanconi's anemia [72], Poland's syndrome [73], Arthrogryposis multiplex congenital [74], Dubowitz syndrome [75], Worster-Drought syndrome, congenital bilateral perisylvian syndrome, neuronal migration defect, epilepsy, neuromotor retardation [76], situs inversus totalis [77], 18p deletion [78], cat eye syndrome [79] and syndromic midlines defects [80] in the absence of detectable mutations of transcription factors involved in pituitary development as often reported.

Organic GHD

GHD can be secondary to organic lesions which include tumors, infections, infiltrative processes, and trauma (Table 1). Growth retardation/arrest can be the only manifestation of GHD in these patients, and the diagnosis is often delayed. Among CNS tumors, craniopharyngioma is the most common neoplastic lesion of the hypothalamic/pituitary area in children.

Craniopharyngiomas are embryonal tumors which derive from remnants of the Ratchke's pouch. In children their histological type is commonly adamantinomatous with formation of cysts [81]. Activating mutations in the beta-catenin gene have been identified in the majority of these tumors [81]. The diagnosis is often made late either for the appearance of symptoms due to the mass effect of the tumor (headache, nausea, visual impairment), or for endocrine deficits, among which GHD with arrested growth account for more than 75% [81,82]. A paradigmatic case of a boy with GHD, arrested growth due to a large intra- and supra-sellar craniopharyngioma and delayed diagnosis is shown in Fig. 1. Craniopharyngiomas are easily identified by MRI, and treatment is removal of the tumor either via transcranial or via transphenoidal approach. It is still debated whether the best treatment is total resection of the tumor or partial resection followed by radiotherapy [81] being "do no harm" the main objective [83]. Recent findings indicate that proton radiation therapy may be more effective with respect to endocrine dysfunction in children [84].

Tumor development and/or surgical resections close to the hypothalamus and/or pituitary may induce direct anatomical damage to these structures and result in multiple hypothalamic/pituitary dysfunctions. Endocrine dysfunctions are commonly observed also in children treated for brain tumors located outside of the hypothalamic–pituitary area [85]. The most common endocrine disorders within the first five years after diagnosis is GHD in 13–100% of cases (86). A recent report calls for the need of a standardized follow-up program including periodical endocrine evaluation in these patients [86].

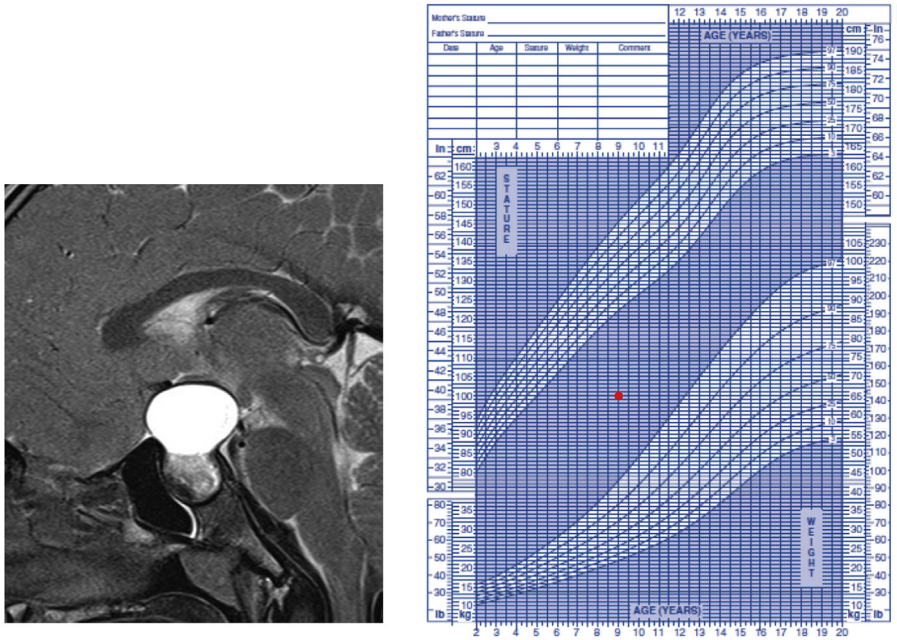

Fig. 1. A 9-year-old boy presenting with severe short stature and intra-sellar and suprasellar craniopharyngioma.

The deleterious effect of cranial irradiation on hypothalamic–pituitary function has long been recognized, with GHD being the first and most common pituitary deficit [87]. Dose of irradiation and time after irradiation are the main risk factors for developing GHD [88,89], as well as tumor stage and number of progressions.

Traumatic brain injury (TBI) is another, often unrecognized, cause of GHD. Endocrine dysfunction after moderate to severe TBI has been reported in 23–69% of adult patients, with GHD being the most common [90]. Few studies have been published on the prevalence of endocrine dysfunction after TBI in children [reviewed in Ref. [91]]. At five years follow-up after moderate to severe TBI more than ¼ of children experienced hypopituitarism. Also in children GHD is the most common endocrine dysfunction, and can be transient, or worsen with time resulting in permanent GHD [92,93]. Thus, children suffering TBI should undergo endocrine follow-up for more than one year.

GHD can be secondary to an autoimmune process either directed against the pituitary or the hypothalamus in patients with lymphocytic hypophysitis or in the context of APS [94–96]. However, the role of anti-pituitary antibodies in the pathogenesis of isolated GHD is still debated. De Bellis et al. [97] have shown the presence of specific antibodies against GH-producing cells in children with isolated GHD and normal MRI. More recently, the same group have reported that among 16 patients with isolated GHD positive for anti-pituitary antibodies against the somatotroph cells and normal MRI, 8 were still GHD and positive for antibodies at the end of treatment with GH [98]. Autoimmunity to PIT1 (pituitary specific transcription factor 1) has also been described as causative of hypopituitarism involving GH, TSH and prolactin in adult patients [99]. These patients had normal or slightly reduced anterior pituitary at MRI. There are no reports of similar cases in children.

More rarely GHD may be secondary to non-autoimmune infiltrative or infectious processes including Langerhans cell histiocytosis [100,101], and exceptionally after meningitis, and encephalitis (Table 1).

Of note is the fact that patients with isolated organic GHD may develop additional pituitary hormone deficit with time. A recent report has shown than among 716 children with isolated GHD of organic origin followed for >3.5 years, 71 (9.9%) developed MPHD [102]. MPHD was more likely to develop in those with severe GHD, especially in those with history of intracranial tumors.

Di Iorgi et al. [103] have shown that many patients presenting in childhood with central diabetes insipidus also had GHD, which was mildly associated with pituitary stalk thickness at diagnosis. Pituitary function was evaluated every 6 months for 2 years and then yearly for 3 years. GHD persisted only in the patients with minimal to moderate pituitary stalk thickness [103]. These findings point to the importance of careful morphologic evaluation in the prognosis of long-term outcome. Thus, long-term surveillance and monitoring of endocrine function is recommended in these patients.

GHD is common after hematopoietic cell transplantation in Fanconi's anemia and some of these patients may have classical GHD, whereas others may have hypothalamic dysfunction leading to "partial" GHD [104]. Growth failure and short stature are among the most common sequelae of childhood cancer therapy and several etiologies may contribute to growth failure including GHD [105,106], exposures to spinal and total-body irradiation, chemotherapy and treatments including glucocorticoids, hypothyroidism, suboptimal nutrition, and renal disease [reviewed in Ref. [105]]. Imatinib, a tyrosine kinase inhibitor, has been associated with growth deceleration and with failure of provocative GH stimulation testing [reviewed in Ref. [101]] and Ipilimumab, an immune system modulator, was shown to potentially cause auto-immune hypophysitis with ensuing anterior panhypopituitarism [reviewed in Ref. [101]].

Role of imaging in the dianostic etiology of GHD

Imaging techniques

Magnetic resonance imaging (MRI) is the gold standard radiological method for evaluating the hypothalamic–pituitary axis because of its inherent tissue contrast, direct multiplanar capability, and lack of invasiveness [34,35].

Standard evaluation of the sellar region includes spin-echo (SE) T1- and turbo/fast spin-echo (TSE) T2-weighted images on sagittal and coronal planes, acquired with a slice thickness of 2–3 mm. Additionally, heavily T2-weighted images [i.e. driven equilibrium (DRIVE), constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA) sequences] acquired on the sagittal plane at sub-millimetric thickness are part of our routine sellar protocol since they provide a better depiction of the suprasellar compartment and in particular of the pituitary stalk. In our experience, T2 DRIVE sensitivity to evaluate the infundibulum is similar to that of post contrast T1-weighted images that therefore can safely be omitted in patients with an isolated growth hormone defect [36].

In addition to high-resolution sellar MR imaging, we always perform at least a Fluid Attenuation Inversion Recovery (FLAIR) and a diffusion-weighted-imaging (DWI) sequence of the whole brain on the axial plane to screen for additional brain abnormalities.

Among advanced MR techniques, Diffusion Tensor Imaging (DTI) can add valuable information in the evaluation and characterization of brain malformations that can be associated with hypothalamic pituitary axis developmental defects. Diffusion tensor imaging (DTI) provides qualitative and quantitative information about white matter micro-structural integrity and organization by measuring the three-dimensional shape and direction of diffusion of water molecules within the brain, voxel by voxel [107].

MR spectroscopy (MRS) is another advanced MRI technique that can be used in selected cases, in particular in the evaluation and characterization of sellar-suprasellar mass lesions. This imaging technique allows noninvasive detection and estimation of different brain metabolites that can be associated with increased cellular growth, neuronal loss, necrosis, or normal tissue [108].

A complete neuroradiological evaluation including whole brain axial DWI and FLAIR along with sagittal T1, coronal T2 and sagittal T2-DRIVE or equivalent, focused on the sellar region, requires approximately 20 min scan time; this protocol should represents the baseline study of all patients with GHD (Fig. 2). Post-contrast imaging or additional advanced MRI techniques, including DTI or MRS, can be acquired on a case-by-case basis. They can further extend the length of the neuroradiological evaluation up to 45–50 min (Table 4).

When MRI is contraindicated, computerized tomography (CT) can be considered a valuable alternative diagnostic tool. Current multislice helical CT provides high-quality multi planar reformatted images for the study of the sellar and parasellar region. In selected cases CT can also be performed in

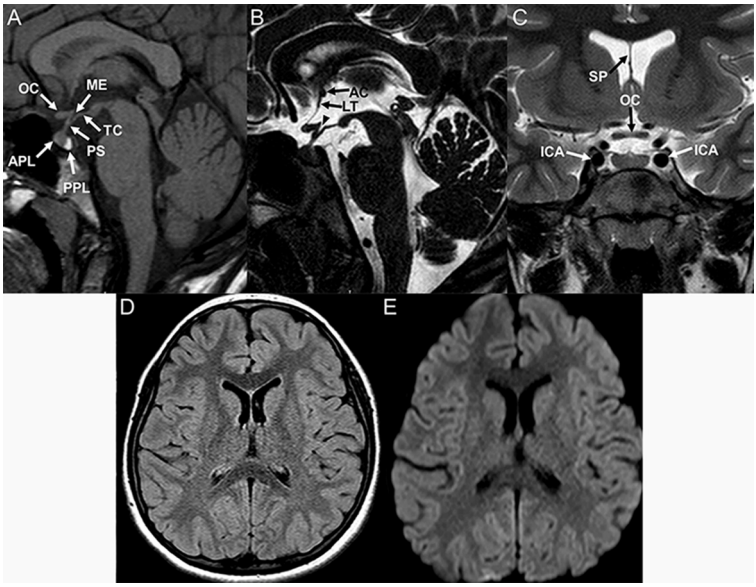

Fig. 2. Baseline MRI study in a 9 year-old boy with GHD and normal MRI findings. A. Sagittal T1-weighted image; B. Sagittal T2-DRIVE image; C. Coronal T2-weighted image; D. Axial FLAIR image;E. Axial DWI image. A. The posterior pituitary lobe (PPL), physiologically bright on T1-weighted image, anterior pituitary lobe (APL), pituitary stalk (PS), median eminence (ME), optic chiasm (OC) and tuber cinereum (TC) are clearly visible. B. The pituitary stalk is optimally depicted with sharp delineation of the infundibular recess of the third ventricle (arrowhead). Additional midline structure such as the anterior commissure (AC) and lamina terminalis (LT) are clearly recognizable. Note the homogeneously low signal intensity of the pituitary gland, that cannot thus be confidently separated into the anterior and posterior lobe. C. On the coronal plane the internal carotid arteries (ICA) are recognizable within the cavernous sinuses. The optic chiasm (OC) and septum pellucidum (SP) are well depicted. D, E. Screening sequences to evaluate the whole brain. There is no evidence of structural and signal abnormalities.

Table 4
Brain MRI protocol in the evaluation of GHD.

Baseline study	Sagittal SE T1	Anterior pituitary morphology, height and lenght. Bright spot discrimination. Midline structures and cranio-cervical junction evaluation. Depiction of high protein content cysts or lipomas
	Sagittal T2 DRIVE	Baseline and follow-up pituitary stalk evaluation. Optic chiasm and nerves morphology. Pineal gland evaluation. Depiction of the relationship between suprasellar mass lesions and surrounding structures
	Coronal TSE T2	Pituitary width and shape evaluation. Pituitary stalk orientation. Optic chiasm and septum pellucidum depiction
	Axial FLAIR	Screening sequence to evaluate the whole brain. In children below the age of 2 years, instead of axial FLAIR, axial T2-weighted image is recommended
	Axial DWI	Screening sequence. Estimation of differences in cell density and tissue structure (i.e.: sellar-extrasellar mass lesions)
Complementary study (performed on a case by case basis)	Whole brain 3D T1	Detailed structural analysis in case of concomitant brain malformations
	Coronal, sagittal and axial post-contrast T1	Pituitary stalk evaluation. Mass lesions characterization. Secondary dissemination
	DTI	Analysis of white matter micro-structural integrity and organization (i.e.: brain malformations)
	MRS	Detection and estimation of normal and abnormal brain metabolites (i.e.: sellar-suprasellar mass lesion characterization)

SE = Spin Echo, DRIVE = Driven Equilibrium, TSE = Turbo Spin Echo, FLAIR = Fluid Attenuation Inversion Recovery, DWI = Diffusion Weighted Imaging, DTI = Diffusion Tensor Imaging, MRS = Magnetic Resonance Spectroscopy.

addition to MRI in order to identify calcifications or to better evaluate bone structures (i.e. in the study of the skull base before trans-sphenoidal surgery or in case of suspected bone lesions).

Normal pituitary and MRI appearance

A detailed knowledge of the normal features of the pediatric pituitary gland is essential in order to properly asses and interpret pathological changes of the hypothalamic–pituitary axis that may be related to GHD.

The pituitary gland is a dynamic structure and undergoes physiological changes in size and shape throughout life [109], depending on age and sex (Fig. 3). Furthermore, even among children of identical age and gender there is wide morphological and dimensional variability [110,111]; the morphology of the gland may also vary from side to side reflecting a physiological asymmetric development of the pituitary fossa, which in turn may be influenced by the variable degree of pneumatization of the underlying sphenoid sinus throughout infancy.

In newborns, the gland typically presents an upward convex margin, very high signal intensity on T1-weighted images and a slightly higher mean height (about 4–5 mm) when compared to the gland height of the following months of age. This morphology and signal intensity correlates with the intense endocrine activity and protein synthesis which typically characterize the neonatal period.

This appearance gradually changes during the first and second months, until the infant configuration, with a flat or slightly concave superior surface and isointensity of the anterior lobe to the white matter on T1- and T2-weighted images, is achieved. In general, the height of the pituitary gland remains stable during the first 2 years of life, whereas its width (transverse measurement) and depth (anterior-posterior measurement) slightly increase; then, a mild but progressive increase in height occurs until puberty, when the pituitary gland undergoes rapid and profound changes in size and

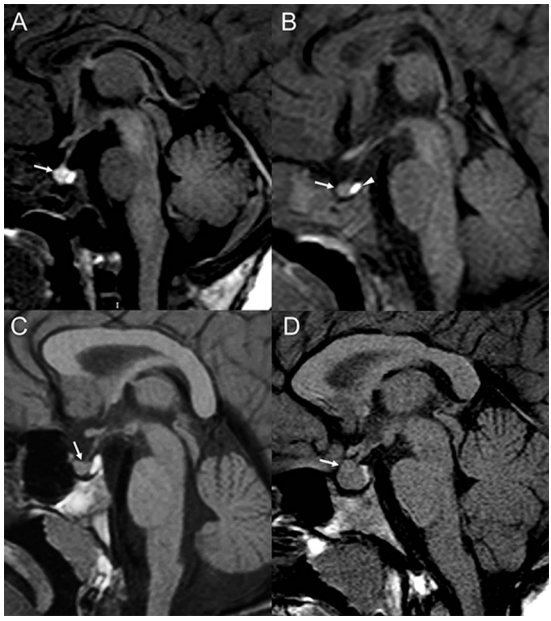

Fig. 3. Normal evolution of the pituitary gland on sagittal T1-weighted images obtained in 4 different subjects. A. Newborn. The anterior pituitary lobe shows an upward convex margin and high signal intensity (arrow). B. Two-months of age. The pituitary gland shows the typical adult pattern with isointensity of the anterior lobe (arrow) to the white matter and hyperintensity of the posterior lobe (arrowhead). C. 6 years. Pre-pubertal appearance of the anterior pituitary lobe with a slightly concave superior margin (arrow). D. Pubertal girl. Marked and symmetrical increase in size of the anterior pituitary lobe that appears nearly spherical (arrow). The height of the gland is about 10 mm.

shape, with marked enlargement [71]. In girls, the gland may swell symmetrically to a height of 10–11 mm, whereas in pubertal boys it may reach 7–8 mm [35,112,113] (Fig. 3).

The spontaneous T1 hyperintensity of the posterior lobe (bright spot) becomes progressively recognizable next to the dorsum sellae during the first and second month of life (Fig. 3) and does not undergo physiological variations in either size or signal intensity during childhood. The bright T1 appearance of the neurohypophysis specifically results from the storage of vasopressin [114] and is considered an important marker of neurohypophyseal functional integrity. However, it may be absent in about 10% of normal individuals; besides, it depends on patient's hydration and may be absent in case of severe dehydration.

Contrast material (gadopentetate dimeglumine) administration determines marked enhancement of the adenohypophysis and of the infundibulo-tuberal region. This is due to lack of the blood brain barrier and to the dense vascularization of these regions.

A normal pituitary stalk usually tapers smoothly along its course. It may reach approximately 3 mm in diameter near the optic chiasm and 2 mm where it inserts into the gland. The pituitary stalk is divided into two parts: one is the neuronal component made up of the track of axons extending from the hypothalamic nuclei down to the axon terminals in the posterior pituitary pouch, while the other is the vascular component that provides blood supply to the anterior pituitary gland from the superior hypophyseal arteries through the pituitary portal system [115].

In every day practice, measurement of the pituitary gland height is the most widely used method to obtain a quick, indirect determination of the gland size; normal pituitary gland height values ranges between 3 and 6 mm in prepubertal children. In order to provide a better assessment of a tridimensional structure such as the pituitary gland, indirect pituitary volume calculation has been proposed using formulas adapted from the formula for the volume of an ellipsoid (i.e., the Di Chiro formula: $V = 1/2$ length $\times$ height $\times$ width). However, because glands are usually not spherical, these methods do not allow a precise calculation of the real size of the gland [116]. To overcome the above mentioned computational bias, direct calculation of pituitary volumes from 3D MRI sequences, can be performed [117,118]. Unfortunately, this method is time consuming and of limited practical use in daily work. Furthermore, estimated pituitary volumes calculated from 3D MRI sequences showed a wide variation of normal ranges [116–118]; for instance, in one study [116] in which the volume of the gland included the posterior pituitary, the average volume of the entire gland resulted smaller at a given age, when compared to another study in which only the volume of the adenohypophysis was taken into account [117]. Larger series are therefore awaited to better elucidate the clinical significance and reproducibility of volumetric results.

MRI findings in idiopathic and genetic forms of GHD

Patients with idiopathic or genetically-determined GHD can present with (a) normal or hypoplastic pituitary gland without anatomical abnormalities of the hypothalamus or pituitary stalk, (b) pituitary dystopia, (c) agenesis of the pituitary gland or (d) enlarged anterior pituitary (pituitary hyperplasia) (Table 5). IGHD is more commonly observed in the first category while MPHD occur in the last three [119]. A primary empty sella is reported in about 10% of IGHD [12].

By definition an hypoplastic anterior pituitary (Fig. 4) is a small adenohypophysis housed within a small or normal pituitary fossa.

Pituitary dystopia, consists of failed conjunction between the anterior and the posterior lobe. Morphologically, it is characterized by: moderate to severe hypoplasia of the anterior pituitary lobe, absence or marked thinning of the pituitary stalk, and ectopic posterior lobe ("ectopic bright spot"). The stalk is usually not identifiable on baseline MRI, although, when present, it may be seen after gadolinium administration or using high resolution, heavily T2-weighted sequences (CISS, DRIVE or FIESTA) (Figs. 5 and 6). The ectopic posterior lobe is usually located at level of the infundibular recess of the third ventricle (median eminence), but it may be found anywhere along the infundibular axis (Fig. 7).

Congenital pituitary gland absence (aplasia) is an extremely rare anomaly that involves variably the anterior pituitary, both the anterior and the posterior pituitary lobes and, in many cases, the pituitary stalk. The characteristic imaging finding of pituitary aplasia is the absence of an identifiable pituitary gland (Fig. 4). In addition, the sella is small and flat, and it is sometimes covered by a layer of dura. The

Table 5
MRI phenotypes in GHD.

Idiopathic or genetically determined GHD	Normal pituitary	No evidence of morphologic, volumetric and signal abnormalities
	Isolated pituitary hypoplasia	Small anterior pituitary (height < 3 mm) housed within a small or normal pituitary fossa
	Pituitary dystopia	Variable degree of anterior pituitary hypoplasia, absence or marked thinning of the pituitary stalk and ectopic posterior lobe
	Pituitary gland agenesis	Absence of an identifiable pituitary gland. Small and flat sella
	Primary empty sella	Deep and enlarged pituitary fossa, mainly filled with CSF. The anterior pituitary appears as a thin layer along its floor. Laminar appearance of the posterior lobe, flattened against the dorsum sellae. Stretched pituitary stalk, posteriorly dislocated
	Anterior pituitary hyperplasia	Anterior pituitary enlargement mimicking a sellar mass lesion (PROP 1 mutations). Tendency to spontaneous regression and evolution into pituitary hypoplasia
Secondary GHD	Secondary empty sella	Pituitary gland loss of volume mainly due to iatrogenic causes with ex-vacuo enlargement of CSF spaces within the pituitary fossa
	Craniopharyngiomas	Sellar-suprasellar prevailingly cystic mass lesion with enhancing walls and calcifications. High protein content cysts. Differential diagnosis with Rathke cleft cyst (no calcifications, no contrast enhancement)
	Suprasellar germinomas	Mild to severe thickening of the pituitary stalk. Absent bright spot. Anterior pituitary enlargement due to invasion of the pituitary parenchyma. Possible concomitant pineal or basal ganglia involvement. Solid contrast-enhancing sellar-suprasellar mass lesion. DWI: reduced diffusivity. Leptomeningeal or subependymal secondary dissemination
	Langerhans cell histiocytosis	Mild to severe thickening of the pituitary stalk. Absent bright spot. Look for extrasellar diagnostic clues (i.e. skull lesions, neurodegenerative changes)
	Lymphocytic-infundibuloneurohypophysitis	Mild to severe thickening of the pituitary stalk. Absent bright spot. Normal or reduced size of the anterior pituitary. Tendency to spontaneous regression on follow-up
	Chiasmatic-hypothalamic glioma	Solid or mixed solid-cystic suprasellar mass lesion with variable degree of contrast enhancement. Sparing of the anterior and posterior pituitary. Pattern of growth along the visual pathway and hypothalamus

differential diagnosis includes severe hypoplasia of the pituitary gland. In patients with neonatal panhypopituitarism, severe symptoms of hypoglycaemia may appear during the 1st hours of life. Symptoms include seizures, apnea, and cardiovascular collapse and arrest [120,121].

The above mentioned conditions may either be isolated or associated with other central nervous system (CNS) malformations, such as septo-optic dysplasia (Fig. 8), holoprosencephaly, anencephaly,

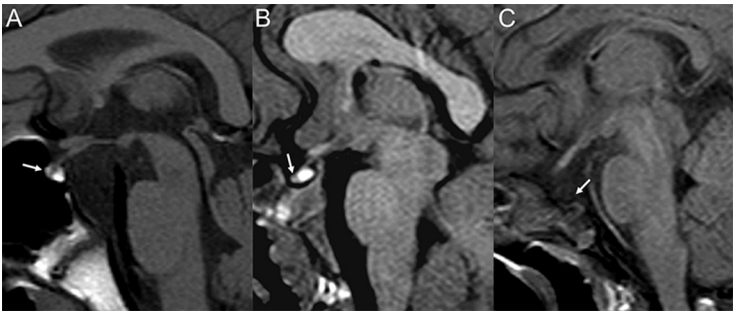

Fig. 4. Pituitary hypoplasia and agenesis. A–C. Sagittal T1-weighted images. A, B. Different degree of anterior pituitary hypoplasia (arrows) in two different children, ranging from moderate (A) to severe (B). The pituitary stalk and posterior lobe are normal. C. Pituitary gland agenesis. Flat pituitary fossa without evidence of the pituitary parenchyma (arrow). The pituitary stalk is not visible.

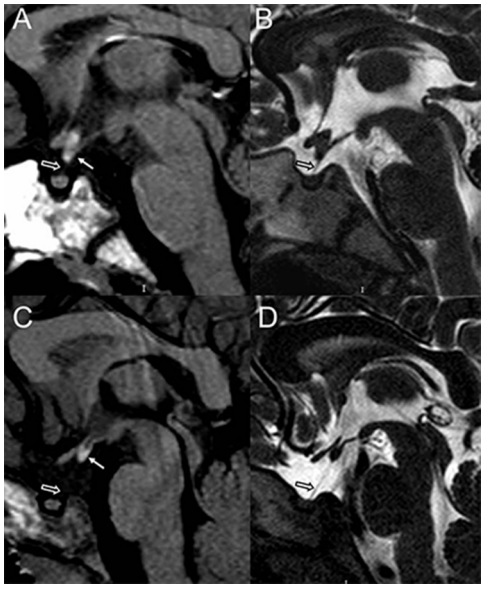

Fig. 5. Pituitary dystopia in two different children. A, C. Sagittal T1-weighted image; B, D. Sagittal T2 DRIVE image. Ectopic posterior lobe located at the level of the median eminence (arrows, A, C). The pituitary stalk is not clearly identifiable on baseline sagittal T1-weighted images (white open arrows, A, C), whereas is demonstrated on T2 DRIVE images (black open arrows, B, D).

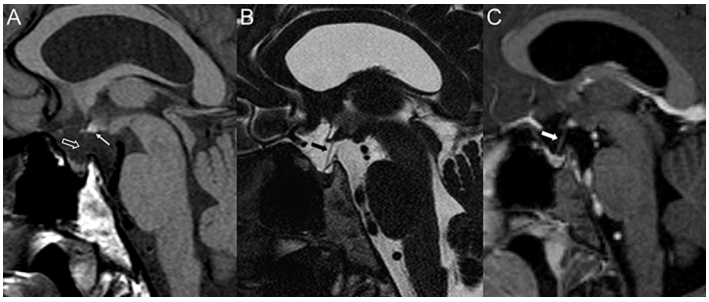

Fig. 6. Pituitary dystopia. A. Sagittal T1-weighted image; B. Sagittal T2 DRIVE image; C. Gd-enhanced sagittal T1-weighted image. Ectopic posterior lobe at the level of the median eminence (thin arrow, A). The pituitary stalk is not visible on the sagittal T1-weighted image (open arrow, A), whereas is clearly demonstrated both on the 3D DRIVE sequence (black thick arrow, B) and on post contrast T1-weighted image (white thick arrow, C).

hypothalamic dysgenesis, corpus callosum dysgenesis (Fig. 8), and Chiari malformation. In such cases additional high resolution morphologic brain sequences (i.e. 3D T1-weighted images) and DTI are recommended for a better characterization of the picture, especially in children with midline developmental defects.

Enlarged anterior pituitary gland or even hypothalamic non-enhancing mass lesions are very rare MRI phenotypes that can occur in about one third of patients with PROP 1 inactivating mutations [22,122]. Histological evaluation of the pituitary masses surgically removed revealed inmunohistochemical and histopathological features characteristic of the pituitary intermediate lobe [123], suggesting that pituitary enlargement in patients with PROP1 mutations may origin in the intermediate lobe, due to arrest of normal anterior pituitary development. It is important to recognize this MRI phenotype since PROP1 mutation associated masses usually regress spontaneously. In such cases MRI follow-up is recommended and neurosurgical interventions should be avoided.

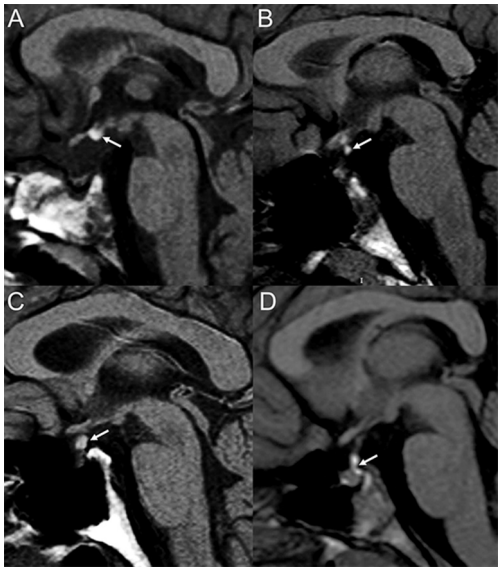

Fig. 7. Posterior lobe ectopia in different children. A–D. Sagittal T1-weighted images. Different locations of the ectopic posterior lobe from the median eminence (arrow, A), to proximal (arrow, B), mid- (arrow, C) and distal stalk (arrow, D).

Primary empty sella

Primary empty sella basically refers to an intrasellar herniation of the subarachnoid spaces through an incompetent sellar diaphragm (arachnoidal diverticulum) with secondary chronic compression of the pituitary gland and enlargement of the pituitary fossa due to rhythmic CSF pulsations. On MRI the pituitary fossa is deep and enlarged, mainly filled with CSF, and contains an anterior pituitary lobe that appears as a thin layer along its floor. The posterior lobe is flattened against the dorsum sellae, with a thin and stretched pituitary stalk (Fig. 9).

Previous studies have reported the prevalence of primary empty sella to be about 5–9% for all ages, with an increase in prevalence with age [124]. Most frequently, this anomaly is an incidental finding, the only exceptions being patients with pseudotumor cerebri (benign intracranial hypertension) in which clinical symptoms and additional MRI findings may orient the diagnosis [125] (Fig. 9) or children with anterior pituitary deficiency [126,127].

In certain circumstances only part of the intrasellar space (less than 50%) is filled with an arachnoid diverticulum with reduced height of the gland on the midline and normal height along the bilateral sellar margins. This condition is usually termed “partially empty sella”. Discrimination between partially empty sella and pituitary hypoplasia is not straightforward. The presence of a small pituitary fossa may help to orient the diagnosis.

MRI findings in organic GHD

Acquired GHD can be determined by clastic lesions leading to a pattern of secondary empty sella or be the consequence of several benign or malignant sellar suprasellar mass lesion, mainly including craniopharyngiomas, suprasellar germinomas, Langerhans cell histiocytosis, Lymphocytic hypophysitis and chiasmatic-hypothalamic gliomas (Table 2).

Secondary empty sella

An intrasellar arachnoid expansion can occur secondary to a reduced intrasellar tissue volume due to different causes including surgical resection, radiation necrosis, pituitary atrophy, or infarction. It is

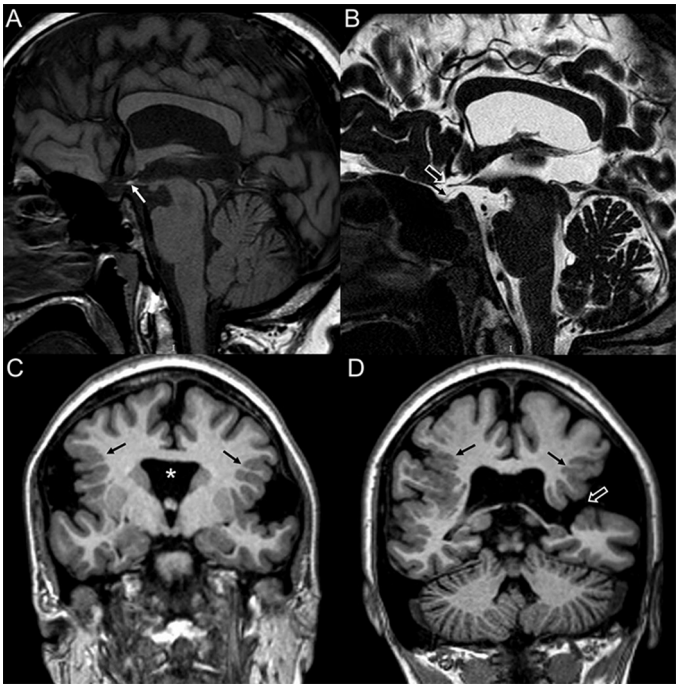

Fig. 8. Pituitary dystopia and septo optic dysplasia plus. A. Sagittal T1-weighted image; B. Sagittal T2 DRIVE image; C, D. Coronal T1-weighted images. Hypoplastic anterior lobe located into a small pituitary fossa and ectopic bright spot located at the level of the median eminence (white arrow, A). The pituitary stalk is not identifiable on baseline sagittal T1-weighted image (A), whereas is demonstrated on T2 DRIVE (black arrow, B). Midline structures evaluation shows dysgenesis of the corpus callosum, marked thinning of the optic chiasm (white open arrow, B) and agenesis of the septum pellucidum (asterisk, C). There is also bilateral perisylvian polymicrogyria (black arrows, C, D) and open lips schizencephaly on the left (open arrow, D).

essentially an "ex vacuo" phenomenon where intracranial subarachnoid space secondarily extends into the sella.

Craniopharyngiomas

Craniopharyngiomas are benign epithelial tumors arising from remnants of the craniopharyngeal duct. They account for 5%–13% of all intracranial tumors and 50% of all suprasellar masses in children [128], with a male predominance. The clinical presentation is generally with headache and visual disturbances. However, up to 80% have evidence of endocrine dysfunction at diagnosis. Affected children show poor growth due to GH deficiency (75% of cases), and may also have gonadotropin deficiency (40% of cases) or ACTH/TSH deficiency (25% of cases).

Pathologically, craniopharyngiomas are categorized into adamantinomatous and squamous-papillary types. Adamantinomatous craniopharyngiomas are cystic or predominantly cystic lobulated tumors, typical of childhood and only occasionally found in adults [129]. Squamous-papillary craniopharyngiomas are typical of adults, and they usually appear as predominantly solid masses.

Craniopharyngiomas may be intrasellar, suprasellar, or a combination of both. The typical suprasellar lesion originates from the infundibulo-tuberal region and extends either in front of or behind the chiasmatic region. Occasionally, craniopharyngiomas may purely grow within the third ventricle. Giant craniopharyngiomas may involve the posterior fossa, or even extend into the paranasal cavities. Evidence of invasion of the third ventricle and identification of the optic chiasm are crucial information for the neurosurgeon. High resolution imaging of the suprasellar region is needed and 3D DRIVE sequences are extremely helpful (Fig. 10).

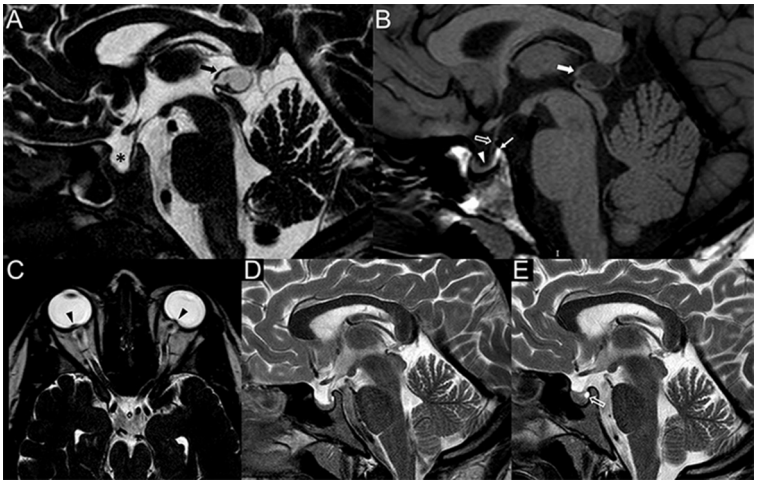

Fig. 9. Empty sella in two different children. A, B. Incidentally discovered primary empty sella and pineal gland cyst in a 9 year-old girl. Sagittal T2 DRIVE image shows a deep pituitary fossa mainly filled with CSF (asterisk, A). On sagittal T1-weighted image the anterior pituitary lobe appears as a thin layer (arrowhead). The posterior lobe is flattened against the dorsum sellae (arrow). The pituitary stalk is thinned and displaced posteriorly (open arrow). There is a concomitant benign pineal gland cyst (thick arrows, A, B). C–E. Empty sella in a child with pseudotumor cerebri. Axial T2-DRIVE image shows bilateral intraocular protrusion of the optic nerve head (arrowheads, C) and mild prominence of the subarachnoid space around the optic nerves (C). There is neither evidence of hydrocephalus nor of intracranial mass lesions in keeping with a condition of idiopathic intracranial hypertension. Sagittal T2-weighted image shows a picture of empty sella (D), no longer visible on a subsequent MRI performed after resolution of symptoms, 6 months later (E). Notice the presence of a small pars intermedia cyst (open arrow, E) barely visible in the prior examination (D).

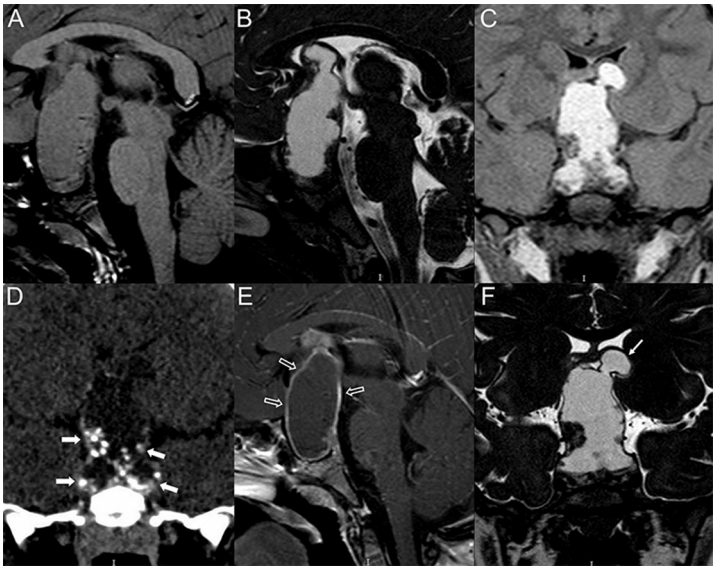

Fig. 10. Craniopharyngioma in a 7-year-old boy with MPHD. A. Sagittal T1-weighted image; B. Sagittal T2-DRIVE image; C. Coronal FLAIR image; D. Coronal MPR CT image; E. Gd-enhanced sagittal T1-weighted image; F. Coronal T2-DRIVE image. Huge sellar-suprasellar cystic neoplasm that is isointense on T1-weighted (A) and hyperintense on T2-weighted and FLAIR images (B,C), with multiple peripheral calcifications (thick arrows, D). The pituitary fossa is enlarged and the pituitary parenchyma is not recognizable. Following gadolinium injection there is linear enhancement of the wall of the lesion (open arrows, E) which also demonstrates a left cranial diverticulum (thin arrow, F).

On MRI, the most common pattern is represented by a cystic lesion that is hypointense on T1- and hyperintense on T2-weighted images, with enhancing walls and subtle calcifications. However, some cysts can show an hyperintense signal on T1-weighted images basically resulting from increased protein concentration [130].

Solid tumor components, often located in the intra- or parasellar region, are iso-hypointense on T1-weighted images, and show variable signal intensity on T2-weighted images, partly due to the presence of calcification. These solid parts typically enhance following gadolinium administration.

CT is superior to MRI in the identification of calcifications, that represent a hallmark of craniopharyngiomas; therefore, CT scans should always be obtained in case of suprasellar tumors. Proton MR spectroscopy can be extremely variable and may show a prominent lipid peak, with only small quantities of other metabolites, a non-specific pattern of increased Choline and decreased N-acetylaspartatate, or absence of any detectable metabolite peak [125].

Germinomas

Intracranial germinomas are rare malignant tumors, accounting for 8–9% of primary brain tumors in children [130], with an incidence peak at 10–12 years. Following the pineal region, the suprasellar region is the second most common location of intracranial germinomas. Synchronous lesions in the hypothalamic and pineal regions account for about 10% of all intracranial germ cell tumors (so called bifocal germinomas). Affected children typically present with diabetes insipidus. However, growth arrest and multiple pituitary hormone deficiencies are common and early findings in pituitary germinomas (almost 100% of cases at follow-up).

Confirmation of the diagnosis requires measurement of serum and CSF tumor markers (α-fetoprotein and/or β-human chorionic gonadotropin) and/or biopsy. However, the role of human chorionic gonadotropin (hCG) and other tumor markers in the early diagnosis of germinomas is not very well understood, and negative result for cerebrospinal fluid hCG does not exclude a diagnosis of germinoma [131]. Of note, biopsy may be avoided in typical bifocal germinomas on neuroimaging.

Small tumors are characterized only by thickening of the infundibulum. With tumor growth, the normal pituitary gland may be compressed by the mass extending into the sella turcica. The tumor may also manifest as a giant sellar mass, without identification of the normal pituitary gland parenchyma.

On MRI (Fig. 11), germinomas are generally isointense to gray matter on T1-weighted images and iso- to hypointense on T2-weighted images. The short T2 relaxation time presumably reflects the diminished free water content of these tumors. Contrast enhancement is usually moderate to marked. Calcification and cystic-necrotic changes are rare.

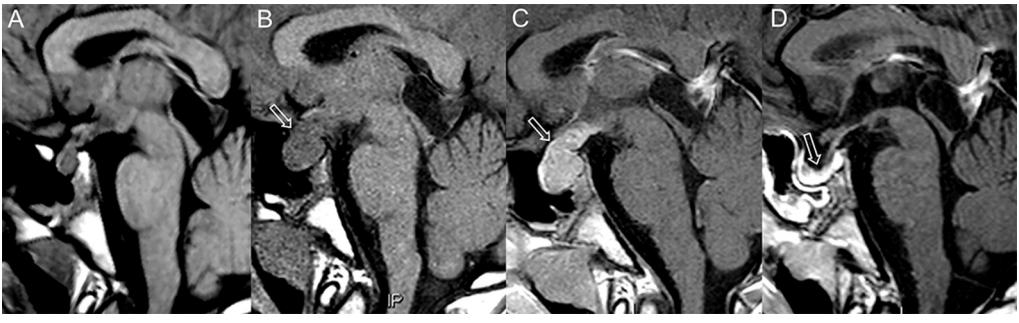

Fig. 11. Suprasellar germinoma in a 11-year-old girl with CDI and GH deficit. A. Sagittal T1-weighted image at admission shows absence of the pituitary bright spot and mild volumetric increase of the pituitary gland; the pituitary stalk is within normal limits. There is a concomitant large pineal gland cyst. B, C. Pre and post contrast sagittal T1-weighted images performed 1 year later clearly show a sellar-suprasellar mass lesion (open arrows, B, C) with dense, homogeneous enhancement. Stable size of the pineal gland cyst. D. Post contrast sagittal T1-weighted image performed 1 months after chemotherapy treatment demonstrates marked volumetric decrease of the lesion (open arrow, D). The pineal gland cyst is stable in size, confirming the benign nature of the lesion.

Diffusion-weighted imaging may shows restricted diffusion reflecting hypercellularity, while proton MR spectroscopy is characterized by predominance of choline peak, residual creatine peak, absence or marked reduction of NAA, and possible lactate and lipid peaks [132].

Midsagittal T1-weighted images obtained in patients with diabetes insipidus characteristically display absence of the "bright spot" corresponding to the posterior pituitary lobe. Sometimes, suprasellar germinomas can infiltrate the anterior optic pathways; germinomas are also prone to give secondary dissemination with typical subependymal or leptomeningeal involvement.

It is important to recognize that, in children suffering from diabetes insipidus showing absence of visualization of the posterior 'bright spot', a small germinoma could not yet be visible on the initial MR images. A close follow-up with repeated imaging studies is therefore fundamental in these patients. Concomitant volumetric increase in the size of the stalk and anterior pituitary on follow-up studies supports the diagnosis of infiltrative/neoplastic disorders, particularly germinoma [133–135]. On the other hand, the association of anterior pituitary hormone deficiency with MRI evidence of progressive reduction in size of the anterior pituitary is suggestive of an inflammatory cause such as lymphocytic infundibulo-hypophysitis [103] (see below).

Langerhans-cell histiocytosis

The most common intracranial manifestation of Langerhans-cell histiocytosis, a rare reactive disorder of the reticuloendothelial system, is the involvement of the hypothalamic–pituitary axis, causing diabetes insipidus. Anterior pituitary dysfunction may be associated [136].

Thin-section sagittal and coronal MR images display a characteristically thickened, intensely enhancing pituitary stalk. It should be remembered that the pituitary stalk lacks a blood-brain-barrier; therefore, it normally enhances with contrast administration. Therefore, a careful evaluation of its thickness is extremely important and 3D DRIVE sequences are highly recommended. Absence of the posterior pituitary bright spot is typically associated [137,138].

The second most common intracranial manifestation of LCH consists of focal or confluent areas of T2/FLAIR hypersignal, that typically involve the cerebellar white matter and dentate nuclei, sometimes the pontine tegmentum and, occasionally, the basal ganglia (Fig. 12). These areas have been interpreted as indicative of a neurodegenerative process, since histopathologic examination revealed neuronal loss and axonal degeneration along with a profound T-cell inflammation [137]. An high frequency of pineal cysts and enlarged pineal glands has been reported in patients with LCH. This finding remains nonspecific and may reflect direct pineal infiltration by LCH or hyperplasia of the gland. Brain MRI evidence of concomitant soft tissue or skull lesions can be an helpful diagnostic clue in order to orient a correct etiological diagnosis, given the lack of specificity of the sellar MRI pattern [133,134].

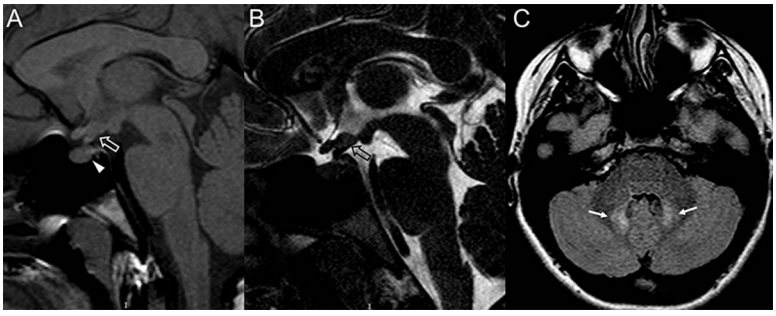

Fig. 12. Langerhans cell histiocytosis. A. Sagittal T1-weighted image; B. Sagittal T2-DRIVE image; C. Axial FLAIR image. The posterior bright spot is not visualized (arrowhead, A). The pituitary stalk is thickened (open arrows, A, B). Brain survey with axial FLAIR reveals signal abnormalities in the dentate nuclei region (arrows, C) in keeping with degenerative changes.

Lymphocytic infundibulo-hypophysitis

Lymphocytic hypophysitis is an autoimmune mediated chronic inflammation of the pituitary gland better defined in adults with enlargement of anterior pituitary gland as compared to children where involvement of pituitary stalk by inflammation is the most frequent finding associated with central diabetes insipidus; it's called lymphocytic infundibulo-hypophysitis [133–135]. Diabetes insipidus is the most common hormonal deficiency in children, accounting for 85% compared with 14%–20% of adults [137].

Depending on the area involved, lymphocytic hypophysitis can be classified morphologically as lymphocytic adenohypophysitis (anterior pituitary lobe), lymphocytic infundibulo-neurohypophysitis (posterior pituitary lobe and infundibulum), and lymphocytic infundibulohypophysitis (anterior and posterior lobe, and infundibulum) [139].

Lymphocytic adenohypophysitis occurs mainly in women with a strong correlation to pregnancy and the postpartum period. In children and adolescents the term lymphocytic-infundibulohypophysitis distinguishes patients with CDI, anterior pituitary hormone deficiency, reduced anterior pituitary size, and transient or persistent pituitary stalk thickening from adults showing increased posterior pituitary size without anterior pituitary involvement [140].

The term "lymphocytic infundibuloneurohypophysitis" which is used to describe cases of central diabetes insipidus in adults with a thickened pituitary stalk, is applicable to childhood cases only when the pituitary stalk is transiently or persistently thickened, the "bright spot" of the posterior lobe on T1-weighted images is absent, and the size of the anterior pituitary is normal.

On the whole, the MR appearance of lymphocytic hypophysitis is similar to that of suprasellar germinomas or Langerhans cell histiocytosis, with which it may be confused (Fig. 13). The gold standard for unequivocal diagnosis remains pituitary biopsy, however follow-up studies are fundamental and can usually clear the view [132]. A systematic neuroimaging and endocrine follow-up has been recently proven to be highly sensitive in the identification of an inflammatory/autoimmune process as the major cause of CDI in children [134].

Chiasmatic-hypothalamic gliomas

Gliomas arising in the hypothalamus or optic chiasm and nerves account for 3%–5% of all pediatric brain tumors. Patient age is usually 2–4 years at presentation. Affected patients usually complain with

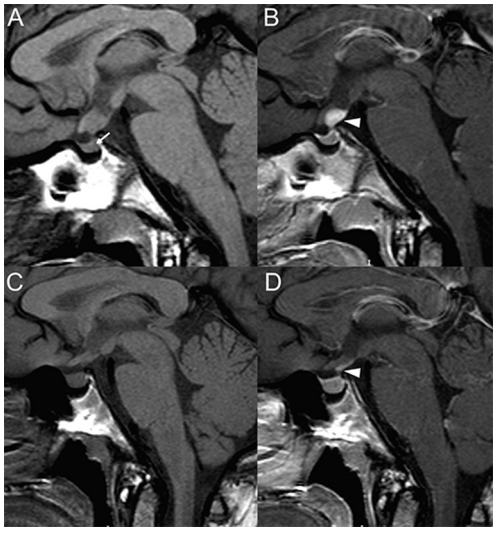

Fig. 13. Lymphocytic-infundibulo-hypophysitis. A, B. Baseline brain MRI. Pre- and post-contrast sagittal T1-weighted images show absence of the bright spot (arrow, A) and thickening of the pituitary stalk (arrowhead, B). C, D. Follow-up MRI at 1 year. Pre- and post-contrast sagittal T1-weighted images show thinning of pituitary stalk (arrowhead, D).

visual loss that progresses slowly, so that tumors are generally large at diagnosis. Endocrine dysfunction is seen in around 20% of cases [35].

Histologically, most of these tumors are pilocytic astrocytomas, but pilomyxoid astrocytomas or anaplastic variants are also possible.

MRI depicts these tumors as multilobular or oval masses (Fig. 14) that are usually hypointense on T1-weighted images and hyperintense on T2-weighted images. Contrast enhancement is generally marked, but may be moderate or even absent is some cases. Cystic-necrotic changes are well recognizable following gadolinium injection. Contrast material administration is mandatory not only to assess the extent of the mass, but also to recognize leptomeningeal seeding in case of pylomixoid forms, which are otherwise undistinguishable from pilocytic forms. Diffusion weighted imaging typically shows increased diffusivity whereas proton MRS demonstrates increased choline and variably diminished NAA levels. Lactate peak is a very frequent finding.

The pituitary gland is typically not involved and the epicenter of the lesion as well the pattern of growth along the visual pathways, can confidently allow a differential diagnosis from other sellar suprasellar mass lesions.

Hypopituitarism and MRI prenatal appearance

Prenatal imaging using MRI technology has provided important insights into morphological abnormalities associated with congenital hypopituitarism. Structures of the hypothalamic–pituitary region, including the pituitary stalk, can be studied in utero by using single-shot fast spin-echo (SS-FSE) T2-weighted images, which are the primary technique for fetal MRI diagnosis.

The whole pituitary gland is recognizable prenatally as a round, ovoid or irregular triangular hypointense structure on the sellar floor, without differentiation between anterior and posterior lobe.

The pituitary stalk, represented by a linear isointense structure connecting the hypothalamic region to the floor of the sella turcica, has been detected on coronal or sagittal section in 100% of fetuses with gestational age later than 26 weeks and in approximately 71% of those between 19 and 25 weeks [35,141]. Ultrasound is the standard imaging tool for prenatal screening, however, and it can make a

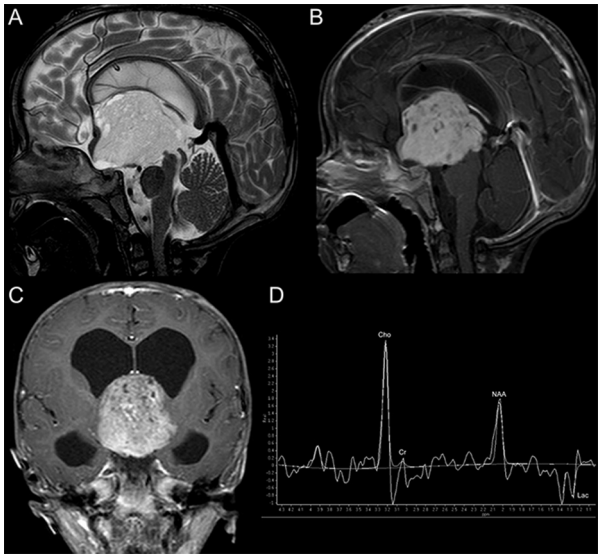

Fig. 14. Chiasmatic-hypothalamic astrocytoma. A. Sagittal T2-weighted image; B. Gd-enhanced sagittal T1-weighted image; C. Gd-enhanced coronal T1-weighted image; D. Single voxel MRS (TE 144ms). Huge chiasmatic-hypothalamic mass. The lesion is well marginated and prevailingly solid with small cystic areas and marked enhancement following contrast administration (B, C). MRS demonstrates markedly increased Choline/Creatine ratio, decreased N-acetylaspartate and a prominent lactate peak.

significant contribution towards the early diagnosis of hypothalamic–pituitary disease. In particular, the absence of the septum pellucidum, detectable from a gestational age of 22 weeks as fusion of the frontal horns of the lateral ventricles, is a clue for the diagnosis of septo-optic dysplasia [141]. In the light of reported data, MRI may play a complementary role in diagnosis when abnormalities have previously been demonstrated sonographically and could be helpful both for the early management of neonatal hypopituitarism and for counseling prospective parents. Indeed, the identification of pituitary aplasia in familial forms [121], or other conditions associated with midline defects, without evidence of gene mutations, early post-natal death and life-threatening presentation could be helpful.

MRI value and follow-up

Marked differences in MRI pituitary gland morphology suggest different etiologies of GHD and different prognoses. Indeed, the correlation of genetic mutations associated with GHD, CPHD and MPHD to endocrine and MRI phenotypes has improved our knowledge of pituitary development and counseling (Fig. 15).

MRI as a predictor of pituitary function and outcomes

Numerous studies have reported higher rates of pituitary dysgenesis in patients with MPHD than with IGHD [34–36,65,67,68,142–145], while the great majority of patients with idiopathic isolated GHD have normal pituitary gland anatomy [127]. The MRI identification of the triad of ectopic posterior pituitary, anterior pituitary hypoplasia and pituitary stalk agenesis has a great value in the identification of patients at risk for evolving pituitary hormone deficiencies [35,36,65–68,119,142–151]. The presence of a vascular component of the stalk has prognostic significance since patients with agenesis

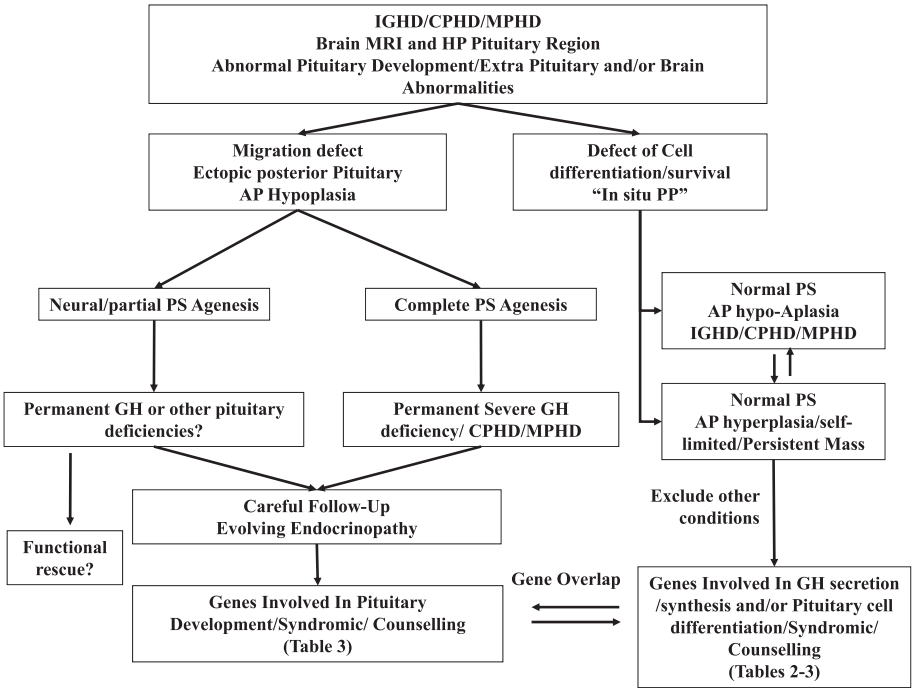

Fig. 15. Differential diagnosis and follow-up of congenital GHD with abnormal pituitary development. IGHD, isolated growth hormone deficiency; CPHD, combined pituitary hormone deficiency MPHD multiple pituitary hormone deficiency; MRI, magnetic resonance imaging; HP, hypothalamic–pituitary; AP, anterior pituitary; PP, posterior pituitary; PS, pituitary stalk.

of the pituitary stalk run a greater risk of developing MPHD than those who show a vascular residue of the stalk [61,62]. Patients in whom a pituitary stalk cannot be identified after Gd-DTPA have a risk of evolving pituitary hormone deficiencies that is 27 times greater than those with a residual vascular pituitary stalk [61,62]. Although absence of the stalk has been identified as a risk factor for MPHD in several studies, such association was not supported by others [152]. Indeed, a hypothalamic-located, small ectopic posterior pituitary surface area was predictive for the development of MPHD [152,153].

There is also evidence that pituitary dysgenesis is rare in children born small for gestational age (SGA) with either isolated growth hormone deficiency (IGHD) or who are not tested for GH function [119,154]. Among 1844 patients with ISS and SGA, one hundred fifty one displayed pituitary abnormalities and pituitary hypoplasia was the most common. In a recent study [119], ectopic posterior pituitary was documented in short patients born SGA or in patients with idiopathic short stature, raising the question about the misclassification bias based on GH response to stimulation tests (false-negative results) and the discontinuation of GHD after adult height achievement [119].

MRI as a predictor to rhGH treatment

Data suggest that MRI scans can help in predicting an individual patient's likely response to therapy. The relationship between pituitary MRI features and final outcome has also been studied, showing that structural hypothalamic–pituitary abnormalities are determinant parameters in the prediction of growth response and adult height [34,80,146–149].

MRI evidence of congenital developmental abnormalities at MR imaging is a stronger predictor than the maximal stimulated GH response of height gain during rhGH treatment [34,146,147]. In a study of 146 short children, GHD patients with normal MRI had similar characteristics to children with short stature of unknown cause, including target height and age at evaluation [147]. Both groups achieved a comparable final height after a mean 4.6 years' GH treatment, which was also similar to untreated children with short stature of unknown cause. Further data from a study in 69 GHD children showed that normal pituitary development – according to MRI – was linked with significantly worse response to 3 years' GH treatment compared with patients who had abnormal results in their MRI scans [146]. Hence, short stature in patients with a normal MRI scan may be due to other factors, such as genetic variation, and these patients may be unlikely to respond to GH therapy. In addition, hormonal status does not significantly affect adult height prognosis either before or after puberty, as reported in two cohorts of subjects with childhood onset IGHD and MPHD associated with structural hypothalamic–pituitary abnormalities [148].

MRI as a predictor of pituitary function after adult height achievement

The diagnosis of GHD in young adults is not straightforward and represents a major clinical challenge. The key predictors of persistent GHD are the severity of the original GH deficiency, the presence of additional pituitary hormone deficits, severely low IGF-I concentration, and structural HP abnormalities [142,145,150,151]. We have shown that patients with GHD and congenital hypothalamic–pituitary abnormalities might not require re-evaluation of GH secretion, whereas patients with isolated GHD and normal or small pituitary gland should be retested well before the attainment of adult height [150]. MRI findings of the hypothalamic–pituitary area in patients with GHD may be the most important criterion upon which the decision to re-evaluate the patient should be based, rather than response to pharmacological stimulation.

Two recent Consensus Statements on the management of young adults with childhood onset GHD during transition phase [155,156] state that patients with severe GHD in childhood – with or without two or three additional hormone deficits – possibly due to a defined genetic cause, those with severe GHD due to structural hypothalamic–pituitary abnormalities, with CNS tumors, or patients having received high-dose cranial irradiation all have a high likelihood of permanent GHD after adult height attainment.

A subgroup of subjects with idiopathic GHD of childhood-onset presenting with congenital structural hypothalamic–pituitary abnormalities confirms that GHD patients – defined “a priori” as those with GH response <5 μg/L and with anterior pituitary hypoplasia, pituitary stalk agenesis and posterior

pituitary ectopia at the level of the median eminence – are probable candidates for permanent GHD in adult life [150], while those with less severe MRI features have an uncertain diagnosis or a likelihood of normal GH response after stimulation tests [153]. In our study on the reassessment of the GH status in young adults with childhood-onset GHD, four patients with isolated GHD and three with CPHD or MPHD showed a discordant response with "normal" GH peak after insulin while IGF-I levels were compatible with severe GHD [158]. The absence of data on long-term metabolic impacts in patients with structural hypothalamic–pituitary abnormalities reported in these two studies [153,158] raise a question about what is "normal GH peak" after adult height achievement and have important clinical implications in the diagnosis and prognosis of GHD during the transition. By applying the criterion of peak GH values of less than 3 μg/L, 5 μg/L or 6 μg/L [155–158], several misdiagnosed GHD subjects would be wrongly excluded from a potentially beneficial renewal of GH replacement treatment. Indeed, pituitary function should be periodically assessed in subjects with pituitary stalk agenesis and IGHD or CPHD, as they may develop additional pituitary hormone deficiencies, including ACTH deficiency and deterioration of metabolic parameters [159].

Practice points

- Clinical phenotype may not be particularly notable in idiopathic GHD; patients with pituitary anomalies such as EPP may show facial dysmorphic features.
- Idiopathic GHD often has a congenital-genetic origin, though intrauterine insults may have a role in worsening pituitary function.
- GHD can be secondary to organic lesions (tumors, infections, infiltrative processes, and trauma). Growth retardation can be the only manifestation in these patients at disease onset.
- MRI is the gold standard radiological method for evaluating children with GHD.
- One or more survey sequences of the entire brain should always be performed to screen for additional brain abnormalities.
- Standard sagittal and coronal T1 imaging is the method of choice for first-level exam in GHD patients.
- High resolution T2 DRIVE sequence is highly recommended to better depict the suprasellar compartment, and in particular the pituitary stalk; T2 DRIVE sensitivity in evaluating the pituitary stalk is similar to that of post contrast T1-weighted images, that can safely be omitted in patients with isolated GHD.
- Advanced imaging modalities such as MRS or DTI can be helpful to better characterize sellar-suprasellar mass lesions or brain malformations that can be associated with hypothalamic pituitary axis developmental defects.
- MRI evidence of congenital developmental abnormalities in GHD is a strong predictor of height gain during rhGH treatment, and is associated with increased MPHD risk.
- GHD patients with anterior pituitary hypoplasia, pituitary stalk agenesis, and posterior pituitary ectopia are probable candidates for permanent GHD in adult life.

Research agenda

- Further experience on large cohorts is required to better define the diagnostic yield of T2 DRIVE sequence in patients with GHD.
- Larger series are awaited to better elucidate the clinical significance and reproducibility of volumetric pituitary computations.
- Next generation sequencing panels may be helpful in defining genetic origin in patients with MPHD and brain/pituitary anomalies.
- Functional studies and transgenic murine models may help demonstrating the role of transcription factors in the etiology of congenital hypopituitarism.

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References

[1] Phillips 3rd JA, Cogan JD. Genetic basis of endocrine disease. 6. Molecular basis of familial human growth hormone deficiency. J Clin Endocrinol Metab 1994;78:11–6.
*[2] Alatzoglou KS, Webb EA, Le Tissier P, et al. Isolated growth hormone deficiency (GHD) in childhood and adolescence: recent advances. Endocr Rev 2014;35:376–432.
*[3] Wit JM, Oostdijk W, Losekoot M, et al. Mechanisms in endocrinology: novel genetic causes of short stature. Eur J Endocrinol 2016;174:R145–73.
[4] Argente J, Flores R, Gutiérrez-Arumí A, et al. Defective minor spliceosome mRNA processing results in isolated familial growth hormone deficiency. EMBO Mol Med 2014;6:299–306.
[5] Webb EA, AlMutair A, Kelberman D, et al. ARNT2 mutation causes hypopituitarism, post-natal microcephaly, visual and renal anomalies. Brain 2013;136:3096–105.
[6] Joustra SD, Heinen CA, Schoenmakers N, et al. IGSF1 deficiency: lessons from an extensive case series and recommendations for clinical management. J Clin Endocrinol Metab 2016;101:1627–36.
[7] Gregory LC, Gevers EF, Baker J, et al. Structural pituitary abnormalities associated with CHARGE syndrome. J Clin Endocrinol Metab 2013;98:E737–43.
[8] Gaston-Massuet C, McCabe MJ, Scagliotti V, et al. Transcription factor 7-like 1 is involved in hypothalamo-pituitary axis development in mice and humans. Proc Natl Acad Sci 2016;113:E548–57.
[9] Lucas-Herald AK, Kinning E, Iida A, et al. A case of functional growth hormone deficiency and early growth retardation in a child with IFT172 mutations. J Clin Endocrinol Metab 2015;100:1221–4.
[10] Karaca E, Buyukkaya R, Pehlivan D, et al. Whole-exome sequencing identifies homozygous GPR161 mutation in a family with pituitary stalk interruption syndrome. J Clin Endocrinol Metab 2015;100:E140–7.
[11] Bashamboo A, Bignon-Topalovic J, Rouba H, et al. A nonsense mutation in the hedgehog receptor CDON associated with pituitary stalk interruption syndrome. J Clin Endocrinol Metab 2016;101:12–5.
[12] Patat O, van Ravenswaaij-Arts CMA, Tantau J, et al. Otocephaly-dysgnathia complex: description of four cases and confirmation of the role of OTX2. Mol Syndromol 2013;4:302–5.
[13] Sergouniotis PI, Urquhart JE, Williams SG, et al. Agnathia-otocephaly complex and asymmetric velopharyngeal insufficiency due to an in-frame duplication in OTX2. J Hum Genet 2015;60:199–202.
[14] Vincent A, Forster N, Maynes JT, et al. OTX2 mutations cause autosomal dominant pattern dystrophy of the retinal pigment epithelium. J Med Genet 2014;51:797–805.
[15] Williamson KA, Fitz Patrick. The genetic architecture of microphthalmia, anophthalmia and coloboma. Eur J Med Genet 2014;57:369–80.
[16] Franca MM, Jorge AAL, Carvalho LRS, et al. Novel heterozygous nonsense GLI2 mutations in patients with hypopituitarism and ectopic posterior pituitary lobe without holoprosencephaly. J Clin Endocrinol Metab 2010;95:E384–91.
[17] Demurger F, Ichkou A, Mougou-Zerelli S, et al. New insights into genotype-phenotype correlation for GLI3 mutations. Eur J Hum Genet 2015;23:92–102.
[18] Netchine I, Sobrier M-L, Krude H, et al. Mutations in LHX3 result in a new syndrome revealed by combined pituitary hormone deficiency. Nat Genet 2000;25:182–6.
[19] Pfaeffle RW, Savage JJ, Hunter CS, et al. Four novel mutations of the LHX3 gene cause combined pituitary hormone deficiencies with or without limited neck rotation. J Clin Endocrinol Metab 2007;92:1909–19.
[20] Pfaeffle RW, Hunter CS, Savage JJ, et al. Three novel missense mutations within the LHX4 gene are associated with variable pituitary hormone deficiencies. J Clin Endocrinol Metab 2008;93:1062–71.
[21] Gregory LC, Humayun KN, Turton JP, et al. Novel lethal form of congenital hypopituitarism associated with the first recessive LHX4 mutation. J Clin Endocrinol Metab 2015;100:2158–64.
[22] Voutetakis A, Argyropoulou M, Sertedaki A, et al. Pituitary magnetic resonance imaging in 15 patients with Prop1 gene mutations: pituitary enlargement may originate from the intermediate lobe. J Clin Endocrinol Metab 2004;89:2200–6.
[23] Turton JPG, Reynaud R, Mehta A, et al. Novel mutations within the POU1F1 gene associated with variable combined pituitary hormone deficiency. J Clin Endocrinol Metab 2005;90:4762–70.
[24] Gregory LC, Gaston-Massuet C, Andoniadou CL, et al. The role of the sonic hedgehog signalling pathway in patients with midline defects and congenital hypopituitarism. Clin Endocrinol 2015;82:728–38.
[25] McCabe MJ, Gaston-Massuet C, Tziaferi V, et al. Novel FGF8 mutations associated with recessive holoprosencephaly, craniofacial defects, and hypothalamo-pituitary dysfunction. J Clin Endocrinol Metab 2011;96:E1709–18.
[26] Correa FA, Trarbach EB, Tusset C, et al. FGFR1 and PROKR2 rare variants found in patients with combined pituitary hormone deficiencies. Endocr Connect 2015;4:100–7.
[27] Xu H, Niu Y, Wang T, et al. Novel FGFR1 and KISS1R mutations in Chinese Kallmann syndrome males with cleft lip/palate. Biomed Res Int 2015. http://dx.doi.org/10.1155/2015/649698.
[28] Asakura Y, Muroya K, Hanakawa J, et al. Combined pituitary hormone deficiency with unique pituitary dysplasia and morning glory syndrome related to a heterozygous PROKR2 mutation. Clin Pediatr Endocrinol 2015;24:27–32.
[29] Reynaud R, Jayakody SA, Monnier C, et al. PROKR2 variants in multiple hypopituitarism with pituitary stalk interruption. J Clin Endocrinol Metab 2012;97:E1068–73.
[30] McCabe MJ, Gaston-Massuet C, Gregory LC, et al. Variations in PROKR2, but not PROK2, are associated with hypopituitarism and septo-optic dysplasia. J Clin Endocrinol Metab 2013;98:E547–57.

[31] Quentien MH, Delemer B, Papadimitriou DT, et al. Deficitin anterior pituitary function and variable immune deficiency (DAVID) in children presenting with adrenocorticotropin deficiency and severe infections. J Clin Endocrinol Metab 2012;9:E121–8.
[32] Takagi M, Nagasaki K, Fujiwara I, et al. Heterozygous defects in PAX6 gene and congenital hypopituitarism. Eur J Endocrinol 2015;172:37–45.
*[33] Castinetti F, Reynaud R, Saveanu A, et al. Mechanisms in endocrinology: an update in the genetic aetiologies of combined pituitary hormone deficiency. Eur J Endocrinol 2016;174:R239–47.
[34] Maghnie M, Ghirardello S, Genovese E. Magnetic resonance imaging of the hypothalamus-pituitary unit in children suspected of hypopituitarism: who, how and when to investigate. J Endocrinol Invest 2004;27:496–509.
*[35] Di Iorgi N, Allegri AE, Napoli F, et al. The use of neuroimaging for assessing disorders of pituitary development. Clin Endocrinol 2012;76:161–76.
[36] Di Iorgi N, Morana G, Gallizia AL, et al. Pituitary gland imaging and outcome. Endocr Dev 2012;23:16–29.
[37] Lacey KA, Parkin JM. Causes of short stature. A community study of children in Newcastle upon Tyne. Lancet 1974;12:42–5.
[38] Parkin JM. Incidence of growth hormone deficiency. Arch Dis Childhood 1974;49:904–5.
[39] Vimpani GV, Vimpani AF, Lidgard GP, et al. Prevalence of severe growth hormone deficiency. Br Med J 1977;2:427–30.
[40] Lindsay R, Feldkamp M, Harris D, et al. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994;125:29–35.
[41] Rona RJ, Tanner JM. Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch Dis Childhood 1977;52:197–208.
[42] Murray PG, Paterson WF, Donaldson MD. Maternal age in patients with septo-optic dysplasia. J Pediatr Endocrinol Metab 2005;18:471–6.
[43] Bao XL, Shi YF, Du YC, et al. Prevalence of growth hormone deficiency of children in Beijing. Chin Med J (Engl) 1992;105:401–5.
[44] Werther GA. Growth hormone measurements versus auxology in treatment decisions: the Australian experience. J Pediatr 1996;128:S47–51.
[45] Thomas M, Massa G, Craen M, et al. Prevalence and demographic features of childhood growth hormone deficiency in Belgium during the period 1986–2001. Eur J Endocrinol 2004;151:67–72.
[46] Migliaretti G, Aimaretti G, Borraccino A, et al. Incidence and prevalence rate estimation of growth hormone treatment exposure in Piedment paediatric population in the years 2002–2004: data from the GH registry. J Endocrinol Invest 2006;29:438–42.
[47] Bancalari RE, Gregory LC, McCabe MJ, et al. Pituitary gland development: an update. Endocr Dev 2012;23:1–15.
[48] Secco A, Di Iorgi N, Napoli F, et al. The glucagon test in the diagnosis of growth hormone deficiency in children with short stature younger than 6 years. J Clin Endocrinol Metab 2009;94:4251–7.
[49] de Graaff LC, Baan J, Govaerts LC, et al. Facial and pituitary morphology are related in Dutch patients with GH deficiency. Clin Endocrinol 2008;69:112–6.
[50] McMahon CL, Braddock SR. Septo-optic dysplasia as a manifestation of valproic acid embryopathy. Teratology 2001;64:83–6.
[51] Orrico A, Gallia L, Zappellab M, et al. Septo-optic dysplasia with digital anomalies associated with maternal multidrug abuse during pregnancy. Eur J Neurol 2002;9:679–82.
[52] Lubinsky MS. Hypothesis: septo-optic dysplasia is a vascular dysruption sequence. Am J Med Genet 1997;69:235–6.
[53] Kjellin IB, Kaiserman KB, Curran JG, et al. Aplasia of right internal carotid artery and hypopituitarism. Pediatr Radiol 1999;29:586–8.
[54] Stagi S, Traficante G, Lapi E, et al. Agenesis of internal carotid artery associated with isolated growth hormone deficiency: a case report and literature review. BioMedCentral Endocr Disord 2015;15:58. http://dx.doi.org/10.1186/s12902-015-0037-y.
[55] Surtees R, Adams J, Price D, et al. Association of adverse perinatal events with an empty sella turcica in children with growth hormone deficiency. Hormone Res 1987;28:5–12.
[56] Maghnie M, Triulzi F, Larizza D, et al. Hypothalamic-pituitary dwarfism: comparison between MR imaging and CT findings. Pediatr Radiol 1990;20:229–35.
[57] Maghnie M, Altobelli M, Di Iorgi N, et al. Idiopathic central diabetes insipidus is associated with abnormal blood supply to the posterior pituitary gland caused by vascular impairment of the inferior hypophyseal artery system. J Clin Endocrinol Metab 2004;89:1891–6.
[58] Fujita K, Matsuo N, Mori O, et al. The association of hypopituitarism with small pituitary, invisible pituitary stalk, type 1 Arnold-Chiari malformation, and syringomyelia in seven patients born in breech position: a further proof of birth injury theory on the pathogenesis of “idiopathic hypopituitarism”. Eur J Pediatr 1992;151:266–70.
[59] Maghnie M, Larizza D, Zuliani I, et al. Congenital central nervous system abnormalities, idiopathic hypopituitarism and breech delivery: what is the connection? Eur J Pediatr 1993;152:175.
[60] Maghnie M, Genovese E, Arico' M, et al. Evolving pituitary hormone deficiency is associated with pituitary vasculopathy: dynamic MR study in children with hypopituitarism, diabetes insipidus, and langerhans cell histiocytosis. Radiology 1994;193:493–9.
[61] Maghnie M, Genovese E, Villa A, et al. Dynamic MRI in the congenital agenesis of the neural pituitary stalk syndrome: the role of the vascular pituitary stalk in predicting residual anterior pituitary function. Clin Endocrinol 1996;45:281–90.
[62] Genovese E, Maghnie M, Beluffi G, et al. Hypothalamic-pituitary vascularization in pituitary stalk transection syndrome: is the pituitary stalk really transected? The role of gadolinium-DTPA with spin-echo T1 imaging and turbo-FLASH technique. Pediatr Radiol 1997;27:48–53.
[63] Kikuchi K, Fujisawa I, Momoi T, et al. Hypothalamic-pituitary function in growth hormone-deficient patients with pituitary stalk transection. J Clin Endocrinol Metab 1988;67:817–23.

*[64] Triulzi F, Scotti G, di Natale B, et al. Evidence of a congenital midline brain anomaly in pituitary dwarfs: a magnetic resonance imaging study in 101 patients. Pediatrics 1994;93:409–16.
[65] Maghnie M, Triulzi F, Larizza D, et al. Hypothalamic-pituitary dysfunction in growth hormone-deficient patients with pituitary abnormalities. J Clin Endocrinol Metab 1991;73:79–83.
[66] Argyropoulou M, Perignon F, Brauner R, et al. Magnetic resonance imaging in the diagnosis of growth hormone deficiency. J Pediatr 1992;120:886–91.
[67] Chen S, Leger J, Garel C, et al. Growth hormone deficiency with ectopic neurohypophysis: anatomical variations and relationship between the visibility of the pituitary stalk asserted by magnetic resonance imaging and anterior pituitary function. J Clin Endocrinol Metab 1999;84:2408–13.
[68] Pinto G, Netchine I, Sobrier ML, et al. Pituitary stalk interruption syndrome: a clinical-biological-genetic assessment of its pathogenesis. J Clin Endocrinol Metab 1997;82:3450–4.
[69] Siegel SF, Ahdab-Barmada M, Arslanian S, et al. Ectopic posterior pituitary tissue and paracentric inversion of the short arm of chromosome 1 in twins. Eur J Endocrinol 1995;133:87–92.
[70] Larizza D, Maraschio P, Maghnie M, et al. Hypogonadism in a patient with balanced X/18 translocation and pituitary hormone deficiency. Eur J Pediatr 1993;152:424–7.
[71] Hamilton J, Chitayat D, Blaser S, et al. Familial growth hormone deficiency associated with MRI abnormalities. Am J Med Genet 1998;80:128–32.
[72] Dupuis-Girod S, Gluckman E, Souberbielle JC, et al. Growth hormone deficiency caused by pituitary stalk interruption in Fanconi's anemia. J Pediatr 2001;138:129–33.
[73] Larizza D, Maghnie M. Poland's syndrome associated with growth hormone deficiency. J Med Genet 1990;27:53–5.
[74] Parano E, Trifiletti RR, Barone R, et al. Arthrogryposis multiplex congenita and pituitary ectopia. A case report. Neuropediatrics 2000;31:325–7.
[75] Oguz KK, Ozgen B, Erdem Z. Cranial midline abnormalities in Dubowitz syndrome: MR imaging findings. Eur Radiol 2003;13:1056–7.
[76] Bas F, Darendeliler F, Yapici Z, et al. Worster-Drought syndrome (congenital bilateral perisylvian syndrome) with posterior pituitary ectopia, pituitary hypoplasia, empty sella and panhypopituitarism: a patient report. J Pediatr Endocrinol Metab 2006;19:535–40.
[77] Halasz Z, Bertalan R, Toke J, et al. Laterality disturbance and hypopituitarism. A case report of co-existing situs inversus totalis and combined pituitary hormone deficiency. J Endocrinol Invest 2008;31:74–8.
[78] Hasi-Zogaj M, Sebold C, Heard P, et al. A review of 18p deletions. Am J Med Genet Part C 2015;169:251–64.
[79] Melo C, Gama-de-Sousa S, Almeida F, et al. Cat eye syndrome and growth hormone deficiency with pituitary anomalies: a case report and review of the literature. Gene 2013;15(529):186–9.
[80] Secco A, Allegri AE, di Iorgi N, et al. Posterior pituitary (PP) evaluation in patients with anterior pituitary defect associated with ectopic PP and septo-optic dysplasia. Eur J Endocrinol 2011;165:411–4.
[81] Müller HL. Craniopharyngioma. Endocr Rev 2014;35:513–43.
[82] Hopper N, Albanese A, Ghirardello S, et al. The pre-operative endocrine assessment of craniopharyngiomas. J Pediatr Endocrinol Metab 2006;19(Suppl. 1):325–7.
[83] Gleeson H, Amin R, Maghnie M. "Do no harm" – workshop on the management of craniopharyngioma. Eur J Endocrinol 2008;159(Suppl. 1):S95–9.
[84] Vega RM, Kim J, Hollander H, et al. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. Cancer 2015;121:1694–702.
[85] Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumors. Endocr Relat Cancer 2004;11:589–602.
[86] Clement SC, Schouten-van Meeteren AYN, Kremer LCM, et al. High prevalence of early hypothalamic-pituitary damage in childhood brain tumor survivors: need for standardized follow-up programs. Pediatr Blood Cancer 2014;61:2285–9.
[87] Darzy KH, Shalet SM. Hypopituitarism following radiotherapy revisited. Endocr Dev 2009;15:1–24.
[88] Merchant TE, Rose SR, Bosley C, et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. J Clin Oncol 2011;29:4776–80.
[89] Gan H, Phipps K, Aquilina K, et al. Neuroendocrine morbidity after pediatric optic gliomas: a longitudinal analysis of 166 children over 30 years. J Clin Endocrinol Metab 2015;100:3787–99.
[90] Tanriverdi F, Schneider HJ, Aimaretti G, et al. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. Endocr Rev 2015;36:305–42.
[91] Reischneider K, Auble BA, Rose SR. Update of endocrine dysfunction following pediatric traumatic brain injury. J Clin Med 2015;4:1536–60.
[92] Kaulfers AM, Backeljauw PF, Reifschneider K, et al. Endorine dysfunction following traumatic brain injury in children. J Pediatr 2010;157:894–9.
[93] Casano-Sancho P, Suarez L, Ibanez L, et al. Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment? Clin Endocrinol 2013;79:853–8.
[94] Caturegli P, Newschaffer C, Olivi A, et al. Autoimmune hypophysitis. Endocr Rev 2005;26:599–614.
[95] Bensing S, Fetissov SO, Mulder J, et al. Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1. Proc Natl Acad Sci 2007;104:949–54.
[96] De Bellis A, Sinisi AA, Pane E, et al. Involvement of hypothalamus autoimmunity in patients with autoimmune hypopituitarism: role of antibodies to hypothalamic cells. J Clin Endocrinol Metab 2012;97:3684–90.
[97] De Bellis A, Salerno M, Conte M, et al. Antipituitary antibodies recognizing growth hormone (GH)-producing cells in children with idiopathic GH deficiency and in children with idiopathic short stature. J Clin Endocrinol Metab 2006;91:2484–9.
[98] De Bellis A, Bellastella G, Maiorino MI, et al. Longitudinal behavior of autoimmune GH deficiency: from childhood to transition age. Eur J Endocrinol 2016;174:381–7.

[99] Yamamoto M, Iguchi G, Takeno R, et al. Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans. J Clin Invest 2011;121:113–9.
[100] Maghnie M, Bossi G, Klersy C, et al. Dynamic endocrine testing and magnetic resonance imaging in the long-term follow-up of childhood langerhans cell histiocytosis. J Clin Endocrinol Metab 1998;83:3089–94.
[101] Maghnie M, Cavigioli F, Tinelli C, et al. GHRH plus arginine in the diagnosis of acquired GH deficiency of childhood-onset. J Clin Endocrinol Metab 2002;87:2740–4.
*[102] Child CJ, Blum WF, Zimmerman A, et al. Development of additional pituitary hormone deficiencies in paediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes. Eur J Endocrinol 2016;15:1203–8.
*[103] Di Iorgi N, Allegri AEM, Napoli F, et al. Central diabetes insipidus in children and youg adults: etiological diagnosis and long-term outcome of idiopathic cases. J Clin Endocrinol Metab 2014;99:1264–72.
[104] Petryk A, Kanakatti Shankar R, Giri N, et al. Endocrine disorders in Fanconi anemia: recommendations for screening and treatment. J Clin Endocrinol Metab 2015;100:803–11.
[105] Barnes N, Chemaitilly W. Endocrinopathies in survivors of childhood neoplasia. Front Pediatr 2014;2:101. http://dx.doi.org/10.3389/fped.2014.00101. eCollection 2014.
[106] Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. J Clin Oncol 2015;10:492–500.
[107] Poretti A, Meoded A, Rossi A, et al. Diffusion tensor imaging and fiber tractography in brain malformations. Pediatr Radiol 2013;43:28–54.
[108] Rossi A, Gandolfo C, Morana G, et al. New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours. Pediatr Radiol 2010;40:999–1009.
[109] Elster AD. Modern imaging of the pituitary. Radiology 1993;187:1–14.
[110] Cox TD, Elster AD. Normal pituitary gland: changes in shape, size, and signal intensity during the 1st year of life at MR imaging. Radiology 1991;179:721–4.
[111] Dietrich RB, Lis LE, Greensite FS, et al. Normal MR appearance of the pituitary gland in the first 2 years of life. Am J Neuroradiol 1995;16:1413–9.
[112] Elster AD, Chen MTM, Williams III DW, et al. Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. Radiology 1990;174:681–5.
[113] Tsunoda A, Okuda O, Sato K. MR height of the pituitary gland as a function of age and sex: especially physiological hypertrophy in adolescence and in climacterium. Am J Neuroradiol 1997;18:551–4.
[114] Bonneville F, Cattin F, Marsot-Dupuch K, et al. T1 signal hyperintensity in the sellar region: spectrum of findings. Radiographics 2006;26:93–113.
[115] Tortori-Donati P, Rossi A, Biancheri R. Sellar and suprasellar disorders. In: Tortori-Donati P, editor. Pediatric neuroradiology. Berlin: Springer; 2005. p. 855–91.
[116] Fink AM, Vidmar S, Kumbla S, et al. Age-related pituitary volumes in prepubertal children with normal endocrine function: volumetric magnetic resonance data. J Clin Endocrinol Metab 2005;90:3274–8.
[117] Marziali S, Gaudiello F, Bozzao A, et al. Evaluation of anterior pituitary gland volume in childhood using three-dimensional MRI. Pediatr Radiol 2004;34:547–51.
[118] Takano K, Utsunomiya H, Ono H, et al. Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. Am J Neuroradiol 2004;20:312–5.
[119] Pampanini V, Pedicelli S, Gubinelli J, et al. Brain magnetic resonance imaging as first-line investigation for growth hormone deficiency diagnosis in early childhood. Hormone Res Paediatr 2015;84:323–30.
[120] Cervantes LF, Altman NR, Medina LS. Case 102: pituitary aplasia. Radiology 2006;241:936–8.
[121] Sobrier ML, Maghnie M, Vie-Luton MP, et al. Novel HESX1 mutations associated with a life-threatening neonatal phenotype, pituitary aplasia, but normally located posterior pituitary and no optic nerve abnormalities. J Clin Endocrinol Metab 2006;91:4528–36.
[122] Akcay A, Ulucan K, Taskin N, et al. Suprasellar mass mimicking a hypothalamic glioma in a patient with a complete PROP1 deletion. Eur J Med Genet 2013;56:445–51.
[123] Zygmunt-Górska A, Starzyk J, Adamek D, et al. Pituitary enlargement in patients with PROP1 gene inactivating mutation represents cystic hyperplasia of the intermediate pituitary lobe. Histopathology and over 10 years follow up of two patients. J Pediatr Endocrinol Metab 2009;22:653–60.
[124] Cacciari E, Zucchini S, Ambrosetto P, et al. Empty sella in children and adolescents with possible hypothalamic-pituitary disorders. J Clin Endocrinol Metab 1994;78:767–71.
[125] Degnan AJ, Levy LM. Pseudotumor cerebri: brief review of clinical syndrome and imaging findings. Am J Neuroradiol 2011;32:1986–93.
[126] Lenz AM, Root AW. Empty sella syndrome. Pediatr Endocrinol Rev 2012;9:710–5.
*[127] Maghnie M, Lindberg A, Koltowska-Häggström M, et al. Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (pfizer international growth database). Eur J Endocrinol 2013;168:211–7.
[128] Rossi A, Cama A, Consales A, et al. Neuroimaging of pediatric craniopharyngiomas: a pictorial essay. J Pediatr Endocrinol Metab 2006;19:299–319.
[129] Eldevik OP, Blaivas M, Gabrielsen TO, et al. Craniopharyngioma: radiologic and histologic findings and recurrence. Am J Neuroradiol 1996;17:1427–39.
[130] Morana G, Maghnie M, Rossi A. Pituitary tumors: advances in neuroimaging. Endocr Dev 2010;17:160–74.
[131] Wang Y, Zou L, Gao B. Intracranial germinoma: clinical and MRI findings in 56 patients. Childs Nerv Syst 2010;26:1773–7.
[132] Di Iorgi N, Napoli F, Allegri AEM, et al. Diabetes insipidus – diagnosis and management. Hormone Res Paediatr 2012;77:69–84.
[133] Chernov MF, Kawamata T, Amano K, et al. Possible role of single-voxel (1)H-MRS in differential diagnosis of suprasellar tumors. J Neurooncol 2009;91:191–8.

[134] Di Iorgi N, Morana G, Napoli F, et al. Management of diabetes insipidus and adipsia in the child. Best Pract Res Clin Endocrinol Metab 2015;29:415–36.
[135] Di Iorgi N, Morana G, Maghnie M. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clin Endocrinol 2015;83:449–55.
[136] Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. N Engl J Med 2000;343:998–1007.
[137] Demaerel P, Van Gool S. Paediatric neuroradiological aspects of Langerhans cell histiocytosis. Neuroradiology 2008;50:85–92.
[138] Gabbay LB, Leite Cda C, Andriola RS, et al. Histiocytosis: a review focusing on neuroimaging findings. Arq Neuro-Psiquiatria 2014;72:548–58.
[139] Kalra AA, Riel-Romero RM, Gonzalez-Toledo E. Lymphocytic hypophysitis in children: a novel presentation and literature review. J Child Neurol 2011;26:87–94.
[140] Maghnie M, Genovese E, Sommaruga MG, et al. Evolution of childhood central diabetes insipidus into pan-hypopituitarism with a large hypothalamic mass: is 'lymphocytic infundibuloneurohypophysitis' in children a different entity? Eur J Endocrinol 1998;139:635–40.
[141] Righini A, Parazzini C, Doneda C, et al. Prenatal MR imaging of the normal pituitary stalk. Am J Neuroradiol 2009;30:1014–6.
[142] Murray PG, Hague C, Fafoula O, et al. Likelihood of persistent GH deficiency into late adolescence: relationship to the presence of an ectopic or normally sited posterior pituitary gland. Clin Endocrinol 2009;71:215–9.
[143] Mehta A, Hindmarsh PC, Mehta H, et al. Congenital hypopituitarism: clinical, molecular and neuroradiological correlates. Clin Endocrinol 2009;71:376–82.
*[144] Deal C, Hasselmann C, Pfäffle RW, et al. Associations between pituitary imaging abnormalities and clinical and biochemical phenotypes in children with congenital growth hormone deficiency: data from an international observational study. Hormone Res Paediatr 2013;79:283–92.
[145] Quigley CA, Zagar AJ, Liu CC, et al. United States multicenter study of factors predicting the persistence of GH deficiency during the transition period between childhood and adulthood. Int J Pediatr Endocrinol 2013;2013(1):6. http://dx.doi.org/10.1186/1687-9856-2013-6.
[146] Zenaty D, Garel C, Limoni C, et al. Presence of magnetic resonance imaging abnormalities of the hypothalamic-pituitary axis is a significant determinant of the first 3 years growth response to human growth hormone treatment in prepubertal children with non acquired growth hormone deficiency. Clin Endocrinol 2003;58:647–52.
[147] Coutant R, Rouleau S, Despert F, et al. Growth and adult height in GH-treated children with nonacquired GH deficiency and idiopathic short stature: the influence of pituitary magnetic resonance imaging findings. J Clin Endocrinol Metab 2001;86:4649–54.
[148] Maghnie M, Ambrosini L, Cappa M, et al. Adult height in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies. J Clin Endocrinol Metab 2006;91:2900–5.
[149] De Luca F, Maghnie M, Arrigo T, et al. Final height outcome of growth hormone-deficient patients treated since less than five years of age. Acta Paediatr 1992;85(10):1167–71.
*[150] Maghnie M, Strigazzi C, Tinelli C, et al. Growth hormone (GH) deficiency (GHD) of childhood onset: reassessment of GH status and evaluation of the predictive criteria for permanent GHD in young adults. J Clin Endocrinol Metab 1999;184:1324–8.
[151] Adan L, Souberbielle JC, Brauner R. Diagnostic markers of permanent idiopathic growth hormone deficiency. J Clin Endocrinol Metab 1994;78:353–8.
[152] Murray PG, Hague C, et al. Associations with multiple pituitary hormone deficiency in patients with an ectopic posterior pituitary gland. Clin Endocrinol 2008;69:597–602.
[153] Léger J, Danner S, Simon D, Garel C, Czernichow P. Do all patients with childhood-onset growth hormone deficiency (GHD) and ectopic neurohypophysis have persistent GHD in adulthood? J Clin Endocrinol Metab 2005;90:650–6.
[154] Arends NJ, V d Lip W, Robben SG, et al. MRI findings of the pituitary gland in short children born small for gestational age (SGA) in comparison with growth hormone-deficient (GHD) children and children with normal stature. Clin Endocrinol 2002;57:719–24.
[155] Clayton PE, Cuneo RC, Juul A, et al. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol 2005;152:165–70.
[156] Ho KK. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH research society in association with the European society for pediatric Endocrinology, lawson Wilkins society, European society of Endocrinology, Japan endocrine society, and endocrine society of Australia. Eur J Endocrinol 2007;157:695–700.
[157] Maghnie M, Aimaretti G, Bellone S, et al. Diagnosis of GH deficiency in the transition period: accuracy of insulin tolerance test and insulin-like growth factor-I measurement. Eur J Endocrinol 2005;152:589–96.
[158] Secco A, di Iorgi N, Napoli F, et al. Reassessment of the growth hormone status in young adults with childhood-onset growth hormone deficiency: reappraisal of insulin tolerance testing. J Clin Endocrinol Metab 2009;94:4195–204.
[159] di Iorgi N, Secco A, Napoli F, et al. Deterioration of growth hormone (GH) response and anterior pituitary function in young adults with childhood-onset GH deficiency and ectopic posterior pituitary: a two-year prospective follow-up study. J Clin Endocrinol Metab 2007;92:3875–84.