Contribution of Magnetic Resonance Imaging in Non-Tumoral Hypopituitarism in Children

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Key Words

Pituitary · Magnetic resonance imaging · Growth hormone deficiency, children · Diabetes insipidus

Abstract

Background: Magnetic resonance imaging (MRI) is of paramount importance for evaluating the hypothalamo-pituitary axis in children. **Methods:** We summarize the main points of the MRI technique, and describe the normal appearance of the hypothalamo-pituitary axis as a function of age and pubertal status. The most frequent causes of non-tumoral hypopituitarism include anterior pituitary deficiency (growth hormone deficiency may be isolated or associated with other anterior pituitary hormone deficiencies, with or without other malformations, and related to a known genetic abnormality in some cases), isolated hypogonadotropic hypogonadism and posterior pituitary deficiency with or without anterior pituitary hormone deficiency (central diabetes insipidus may be observed without tumor development). **Results:** We describe in detail the appearance of the adenohypophysis, the pituitary stalk and the neurohypophysis, correlations with hormone deficiencies, the abnormalities that may be associated and progression over time for each condition. **Conclusion:** An accurate description of hypothalamo-pituitary axis abnormalities is necessary for accurate diagnosis and prognosis evaluation, with certain features suggestive of particular diseases and some prognostic data correlated with phenotype.

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Magnetic resonance imaging (MRI) is the imaging method of choice for evaluating the hypothalamo-pituitary axis in children. It can be used to detect abnormalities and, in some cases, to evaluate the underlying disorder. Evaluation of the hypothalamo-pituitary axis is of paramount importance in some conditions in which the clinical and biological findings are uncertain, as in neonates, for example. The different normal and pathological patterns of the hypothalamo-pituitary axis observed in children will be depicted but this review will not discuss the place of MRI in the diagnostic strategy of growth hormone (GH) deficiency.

Magnetic Resonance Imaging Technique

MRI of the hypothalamo-pituitary axis includes thin (1- to 1.5-mm-thick) T1-weighted slices focusing on the hypothalamo-pituitary area in the coronal and sagittal planes. Contrast medium injection is not essential, and the use of this technique depends on the clinical context and findings in the absence of contrast injection. A contrast agent is systematically injected if accurate imaging of the pituitary stalk is required, as is the case for children presenting hypopituitarism without a spontaneously visible pituitary stalk and for cases of central diabetes insipidus (CDI).

The whole brain must be examined because other abnormalities may be associated with pituitary abnormali-

Fig. 1. T1-weighted midline sagittal slice in a fetus (**a**), a neonate (**b**), a 7-year-old boy (**c**) and a 13-year-old girl (**d**). Note the physiological hyperintensity of the adenohypophysis and the bulbous shape of the pituitary gland in neonates and fetuses. At puberty (**d**), the pituitary gland is hypertrophied.

ties. T2-weighted axial slices may be useful. The olfactory bulbs and sulci are studied on T2-weighted coronal slices in cases of isolated gonadotropin deficiency.

Normal Appearance of the Hypothalamo-Pituitary Axis in Children

The pituitary gland originates from two structures in the embryo: the adenohypophysis develops from the ectodermal stomodeum, whereas an evagination of the diencephalon gives rise to the neurohypophysis. The fetal pituitary gland consists of the pars distalis (anterior lobe), the pars nervosa (posterior lobe) and the pars intermedia.

The pars intermedia undergoes involution during the third trimester of pregnancy. The residual lumen between the pars distalis and the pars intermedia decreases in size, forming Rathke's cleft, a narrow, non-visible cleft between the anterior and posterior lobes [1, 2].

In fetuses and infants under the age of 2 months, the entire pituitary gland is bright on T1 sequences, resulting in very similar signals for the adenohypophysis and the neurohypophysis. The brightness of the adenohypophysis may be accounted for by intense cellular activity in the pituitary gland during this period of development. High levels of protein synthesis may account for the short T1 values of the pituitary gland [3]. Moreover, the pituitary gland is bulbous in shape in this period, probably due to

cellular hypertrophy [4]. Its upper margin later becomes flatter. At puberty, physiological pituitary hypertrophy is observed, with significant changes in the size and shape of this gland (convex upper margins) in girls, and changes in its size alone in boys [5] (fig. 1). After puberty, the pituitary gland decreases in size.

The T1 hypersignal of the neurohypophysis (visible at the posterior part of the sella turcica and observed in children and adults) has been attributed to storage of the neurophysin vasopressin complex [6]. A lack of T1 hypersignal has been reported in 10% of healthy subjects [7], but this percentage is clearly an overestimate, resulting from the technical conditions of MRI 20 years ago.

The signal of the normal pituitary gland and stalk is markedly enhanced by the intravenous injection of contrast medium. The anterior and posterior lobes differ in their vascularization: the superior hypophyseal arteries supply the median eminence. The neurohypophysis and stalk are supplied by the inferior hypophyseal arteries. The hypophyseal portal vessels supply the anterior lobe [1]. The timing of enhancement has been studied by Maghnie et al. [8].

Data are available concerning the height [9] or volume [10] of the normal pituitary gland as a function of age. The pituitary gland gradually increases in size until puberty. A pituitary gland less than 3 mm high is considered small. At puberty, the pituitary gland displays physiological hypertrophy and may be 8 mm high in boys and 10 mm high in girls [11]. No data are available concerning the normal dimensions of the pituitary stalk in children, but it is widely accepted that the maximum transverse diameter does not exceed 2 mm in children.

Non-Tumoral Hypopituitarism

Non-tumoral hypopituitarism includes the following.

Anterior pituitary deficiency: GH deficiency may be isolated (IGHD) or associated with other anterior pituitary hormone deficiencies which, in some cases, maybe related to a known genetic abnormality or associated with other malformations. Other isolated pituitary hormone deficiencies may be observed, the most common of which is isolated hypogonadotropic hypogonadism.

Posterior pituitary deficiency: CDI may be observed in the absence of tumor development.

Anterior Pituitary Deficiency

Detailed MRI analysis of the hypothalamo-pituitary axis is required for the detection of possible morphological abnormalities.

The adenohypophysis may appear normal (with reference to published data), hypoplastic (with a small height and usually with a concave upper border) or, very rarely, enlarged (an upper threshold of 5 mm can be used as the threshold for height during the prepubertal period). The height of the adenohypophysis should always be analyzed as a function of the child's pubertal status.

The bright neurohypophysis signal may be normally located or ectopic, in the pituitary stalk or at the level of the median eminence. Its position in the stalk should be noted.

The pituitary stalk can be normal, thin or not visible.

Detailed phenotypic description of this type is absolutely essential. Indeed, the type of hormone deficiency and the prognosis seem to differ as a function of the appearance of the hypothalamo-pituitary axis.

Pituitary height is thought to be directly related to GH levels, as GH-secreting cells are the most abundant cell population in the pituitary gland [12]. However, no correlation has been found between the size of the pituitary gland and the severity of the endocrine defect [13]. A hypoplastic adenohypophysis is a nonspecific sign observed in both groups of children, in those with IGHD and in those with multiple pituitary hormone deficiencies (MPHD). However, the prevalence of a normal adenohypophysis in patients with IGHD is twice that in those with MPHD [14]. In children with IGHD and hypoplastic adenohypophysis, the pituitary gland may spontaneously increase significantly in height after completion of spontaneous pubertal development [15, 16]. An enlarged anterior pituitary gland has also been reported in some patients with rare molecular defects involving mutations in the *Prop 1* and *LHX 3* genes [17–19].

The ectopic posterior lobe (EPL) is always located at the median eminence if the stalk is not visible, but may be found anywhere along the stalk if the stalk is hypoplastic (fig. 2). The implications of EPL location are still unknown. However, it has been reported that patients in whom the pituitary stalk is visible and the EPL is found along the stalk may display increased GH secretion abilities in adulthood (after completion of GH therapy), whereas patients in whom the EPL is found at the median eminence continue to present severe GH deficiency [20]. Anterior pituitary hypoplasia is commonly reported in patients with an EPL and its prevalence is higher for a

Fig. 2. T1-weighted midline sagittal slices showing hypoplastic adenohypophysis and ectopic posterior lobe. **a** An 18-month-old boy with GH deficiency and short stature (-3 SD). The neurohypophysis is ectopic (arrow) on the proximal part of the stalk. The stalk is visible and appears very thin. **b** A 4-year-old girl with multiple pituitary hormone deficiencies. The neurohypophysis is ec-

topic at the median eminence (arrow) and the stalk is not visible, even after contrast injection. **c** A 2-year-old boy with multiple pituitary hormone deficiencies. The neurohypophysis is ectopic at the median eminence (arrow) and the stalk is not visible. Note the persistent craniopharyngeal canal (thin arrow) and the Chiari I malformation (arrowhead).

non-visible stalk than for a thin stalk [21]. The association of an EPL and a non-visible stalk is significantly more common in MPHD patients than in IGHD patients [22–24]. Dynamic contrast-enhanced MRI studies in patients with EPL and hypoplastic adenohypophysis have shown that the portal system is partially preserved, suggesting that the ectopic position of the posterior lobe may be due solely to the undescended neural component of the pituitary stalk [25].

The origins of EPL with a non-visible or hypoplastic pituitary stalk remain controversial and few theories have been developed. According to the trauma theory, breech deliveries may lead to transection of the stalk [26]. Perinatal asphyxia of any origin may result in hypoxic lesions, damaging the hypothalamo-hypopituitary axis [27]. According to the malformative theory – currently the most widely accepted theory – a defect in embryogenesis is responsible for abnormalities of the hypothalamo-hypopituitary axis. This theory is supported by the fact that other cerebral developmental abnormalities are often observed in association with the pituitary abnormalities, and by the existence of familial cases of GH deficiency with EPL [21, 28]. The term ‘pituitary stalk transection’, initially proposed for this condition, therefore appears to be inappropriate.

MRI with gadolinium injection is more sensitive for the demonstration of the pituitary stalk in cases in which this structure is not visible on unenhanced images [25]. The presence of an ectopic posterior lobe is highly specific and predictive of GHD [12].

Associated cerebral abnormalities must be carefully sought because pituitary hormone deficits may also be present as part of a syndrome [28, 29]. In our series of 60 patients with GH deficiency and EPL, 31 (52%) presented associated malformative abnormalities. The most common malformations were cerebral, craniofacial and ocular, but cardiac, renal, intestinal, limb and skin abnormalities were also observed. Some of the children presented syndromes such as Currarino syndrome, Pallister-Hall syndrome (fig. 3) and Fanconi anemia [28]. Midline CNS malformations are observed with a high frequency and include optic nerve hypoplasia, Chiari I malformations (fig. 2c) and medial deviation of the carotid arteries [30]. MRI can also reveal callosal, septal or vermian agenesis, aqueductal stenosis, persistent craniopharyngeal canal, solitary median maxillary central incisor. This last malformation is difficult to diagnose clinically in newborns and may be associated with nasal pyriform aperture stenosis readily visible on computed tomography. Conversely, the discovery of such a developmental defect in a newborn should lead to cerebral MRI,

Fig. 3. A 5-year-old boy with Pallister-Hall syndrome. T1-weighted midline sagittal slice (a) and T2-weighted coronal (b) slice. The adenohypophysis is small (large arrow), and the neurohypophysis is ectopic (thin arrow) at the median eminence. The hypothalamic hamartoma is visible (arrowhead) behind the neurohypophysis on the floor of the third ventricle and its intensity is similar to that of the cerebral parenchyma on T1 and T2 sequences. No contrast enhancement was observed within the hamartoma.

Table 1. Anterior pituitary deficiency: MRI findings and the genes implicated in humans

Pituitary deficiency	MRI	Genes ¹
GH	Normal	GH-N
GH, partial Prl	Normal or hypoplastic AH	GHRH-R
GH, Prl, $\pm$ TSH	Normal or hypoplastic AH	PIT-1
GH, Prl, TSH, LH, FSH, $\pm$ ACTH	Normal or hypoplastic or hyperplastic AH	PROP-1 ²
GH, Prl, TSH, LH, FSH, ACTH	Hypoplastic/normal AH, EPL	HESX1 ³
GH, Prl, TSH, LH, FSH	Hypoplastic/hyperplastic AH	LHX3 ⁴
GH, Prl, TSH, LH, FSH, ACTH	EPL	LHX4 ⁵
GH, Prl, TSH, LH, FSH, ACTH	EPL	Sox 3 ⁶

¹ So far, genetic abnormalities have been identified in a small proportion of patients but many genes remain unknown.

² When the adenohypophysis (AH) is hyperplastic, a space-occupying lesion is visible between the anterior lobe and the neurohypophysis. The pituitary stalk is displaced anteriorly without lateral deviation. This pattern is more common in young patients, suggesting that involution of the intermediate lobe may be delayed in humans with *Prop1* gene defects [19].

³ The phenotype may closely resemble that of septo-optic dysplasia.

⁴ Possibly associated with a rigid and short cervical spine with limited head rotation.

⁵ Possibly associated with Chiari malformation, persistent craniopharyngeal canal and shallow sella turcica.

⁶ Mental retardation and callosal agenesis may be observed.

to search for abnormalities of the hypothalamo-hypopituitary axis [31, 32]. These findings account for a wide genetic heterogeneity in ectopic posterior lobe syndrome. Familial cases of GH deficiency with an ectopic posterior lobe have been reported with various transmission patterns: autosomal recessive or dominant, X-linked forms.

Such cases account for about 12% of all cases of GH deficiency. Considerable phenotypic variability may be observed within a given family [1, 28, 33].

Positive cerebral MRI findings have prognostic value in patients with GH deficiency. Children with GH deficiency and CNS midline abnormalities (associated with

Fig. 4. Kallmann syndrome in a 16-year-old boy with anosmia, pubertal retardation, ear abnormalities and syndactylia. T2-weighted coronal slice (a). The olfactory bulbs are not visible. Control (b) with highly visible olfactory bulbs (arrowheads). The morphology of the hypothalamo-pituitary axis is normal.

EPL or pituitary hypoplasia) have been shown to have significantly greater height gain after GH treatment than children with normal or hypoplastic pituitary gland (or with isolated CNS midline malformation), which is probably related to a more severe form of GH deficiency [34]. These findings highlight the great phenotypic variability of GH deficiency, as also demonstrated by the different patterns of growth response to GH replacement treatment during childhood.

Genetic defects of the GH axis have been identified and correlations between phenotype and genotype have been established [1, 19, 35–37] (table 1). However, these identified genetic defects account for very few cases of childhood hypopituitarism, notably forms associated with EPL.

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism and congenital olfactory deficit are common findings in Kallmann's syndrome, which may display X-linked or autosomal inheritance. Other abnormalities, such as cleft lip or palate, dental agenesis, renal abnormalities, hearing loss and cerebellar dysfunction may be associated. The morphology of the hypothalamo-pituitary axis appears normal on MRI scans. Some cases of pituitary hypoplasia have been reported. In case of olfactory deficit, the olfactory bulbs are absent or hypoplastic. The olfactory sulci may be normal, absent or hypoplastic. In no instance is an olfactory sulcus absent when a bulb is present [21, 38, 39] (fig. 4).

Posterior Pituitary Deficiency

CDI is rare in children. MRI can be very useful in searches for the cause of this condition [40]. In a series of 79 children with CDI, 52% were idiopathic. Where causes were identified, they included: Langerhans' cell histiocytosis (LCH) in 15%; intracranial tumors (germinoma, craniopharyngioma, post-resection) in 23%; familial DI in 6%; post-traumatic CDI in 3%, and autoimmune polyendocrinopathy in 1% of cases [41].

The loss of the posterior pituitary bright spot is a sensitive marker for CDI [42]. However, there are two exceptions, in which the posterior lobe remains visible: familial CDI, when evaluated during infancy or early childhood, and chronic neurogenic hypernatremia.

Familial CDI is caused by mutations of the gene encoding a preprohormone and involves the progressive postnatal degeneration of arginine vasopressin (AVP)-producing neurons. The abnormal preprohormone could not be processed correctly and would eventually destroy the AVP-producing neurons. The accumulation of this preprohormone might account for the persistent posterior pituitary bright spot and for the variable appearance of MRI scans of members of the same family [40, 43, 44]. It has been suggested that these patients are able to store small amounts of AVP, but cannot release it normally [45].

Chronic neurogenic hypernatremia is observed in children presenting midline abnormalities of the brain, such as holoprosencephaly, callosal agenesis or septal agenesis. The underlying mechanism remains unclear, but there appears to be a defect in hypothalamic function,

Fig. 5. Central diabetes insipidus and pituitary stalk thickening according to Léger et al. [48].

leading to the failure of the osmoreceptors, whereas the synthesis and storage of AVP remain intact [46, 47].

The size of the adenohypophysis is variable in patients with CDI. An increase in intrasellar content is suggestive of germinoma, which is associated with pituitary stalk thickening (PST). Hypoplasia of the adenohypophysis is observed in almost half of all cases and is often associated with thickened pituitary stalk. Anterior pituitary hormone deficiency, concerning GH deficiency and thyrotropin in particular, is observed in half of all patients with idiopathic CDI. Panhypopituitarism is less common. A gradual decrease in the size of the adenohypophysis is associated with an increase in the risk of an additional endocrine defect, i.e. GH deficiency [41, 48].

The pituitary stalk is considered enlarged if at least part of the stalk is found to have a diameter of >2.0 mm [48]. PST is observed in almost one third of children with CDI [49]. CDI with PST may be related to germinomas (15%) or LCH (15%) or may remain idiopathic (70%) [41, 48]. MRI should always be performed after gadolinium injection in patients with CDI, to make it possible to check for abnormal enhancement within the stalk. PST may be the first sign of a germinoma or of stalk infiltration, as in LCH.

CDI with PST remains idiopathic in most cases. PST may be observed anywhere along the stalk, or may in-

Fig. 6. Central diabetes insipidus and idiopathic pituitary stalk thickening. T1-weighted midline sagittal slices after contrast injection at 4.5 years (a) and 7.5 years (b). The adenohypophysis is hypoplastic, no hypersignal for the neurohypophysis is visible and there is a marked thickening of the pituitary stalk at the median eminence (arrowhead), enhanced at 4.5 years and decreased in size at 7.5 years. The enhancement of stalk thickening is no longer observed in children at this age.

volve the entire stalk (fig. 5). Biopsies in some adult patients demonstrate lymphocytic inflammation. Some patients have circulating antibodies against AVP neurosecretory cells, suggesting a possible autoimmune process. Spontaneous regression of PST has been observed in some children. Conversely, some patients show a progressive increase in PST, with the adenohypophysis remain-

ing hypoplastic. Changes in the size of PST and in the size of the adenohypophysis (possibly associated with changes in PST enhancement) are observed during the first 2 or 3 years, with the appearance of the hypothalamo-pituitary axis remaining unchanged thereafter. The natural history of idiopathic CDI with PST is unpredictable (fig. 6). MRI and determinations of the tumor marker human chorionic gonadotropin (HCG) in serum and cerebrospinal fluid should be performed at diagnosis. MRI and determination of the tumor marker HCG in serum will be repeated every 3–6 months during the first 3 years after the onset of CDI (frequency depending on whether the pituitary stalk progressively increases in size). Determination of the tumor marker HCG in cerebrospinal fluid will be performed during the follow-up only in the cases with an increasing size of the lesion. Malignant processes are unlikely to occur after 3 years. Careful MRI evaluation should then be performed once per year for 2 years and every 2–5 years thereafter, depending on the size and progression of the lesion. Biopsy is not recommended in cases of PST in which the lesion is <7 mm in diameter and is well delimited [48, 50].

Other exceptional causes of PST in children include tuberculosis and sarcoidosis [51, 52].

Conclusion

MRI is essential for the evaluation of the hypothalamo-pituitary axis in children, and a detailed description of hypothalamo-pituitary axis abnormalities should be produced. This description has diagnostic (visibility of EPL, absence of olfactory bulbs in Kallmann's syndrome, absence of visibility of the neurohypophysis in CDI) and prognostic (some prognostic data are correlated with the phenotype) implications. MRI findings also extend the phenotypic profile associated with non-tumoral GH deficiency and should help to increase our understanding of genotype-phenotype relationships in these patients. However, the etiology remains unknown in many cases. Careful phenotypic description of these patients may facilitate the identification of cases of anterior pituitary deficiency requiring further investigation in collaboration with molecular biologists.

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