Magnetic Resonance Imaging in Hypopituitarism in Children

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Introduction

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.
MRI 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.

- CE-MRI is not essential, and the use of this technique depends on the clinical context and findings in the absence of contrast injection.

- Necessary if accurate imaging of the pituitary stalk is required:
  - hypopituitarism without a spontaneously visible pituitary stalk
  - Central diabetes insipidus (CDI).
• The whole brain must be examined because other abnormalities may be associated with pituitary abnormalities.

• 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.
The pituitary gland originates from two structures in the embryo:

- **Adenohypophysis**: ectodermal stomodeum
- **Neurohypophysis**: evagination of the diencephalon.

The fetal pituitary gland consists of:

- **pars distalis** (anterior lobe)
- **pars nervosa** (posterior lobe)
- **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.

**Normal Appearance of the Hypothalamo-Pituitary Axis in Children**
Fetuses and infants <2 months

Entire pituitary gland is bright on T1

• *Reason: intense cellular activity in this period, High levels of protein synthesis*

Bulbous in shape in this period, (cellular hypertrophy)

• Its upper margin later becomes flatter.

At puberty

Physiological hypertrophy, with significant changes in the size and shape of this gland (convex upper margins) in girls, and changes in its size alone in boys.

After puberty

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.

• A lack of T1 hypersignal has been reported in healthy subjects
• Height or volume of the normal pituitary gland a function of age.

• Gradually increases in size until puberty.
• A pituitary gland <3 mm height is considered small. Physiological hypertrophy at this phase (up to 8 mm in boys and 10 mm in girls.)

• 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

• **Anterior pituitary deficiency:**
  (IGHD)
  MPHD, maybe related to a known genetic abnormality or associated with other malformations.
  Other isolated pituitary hormone deficiencies, the most common hypogonadotrophic hypogonadism.

• **Posterior pituitary deficiency:**
  CDI may be observed in the absence of tumor development.
MRI appearance in anterior pituitary deficiency

- Adenohypophysis
- Posterior bright spot
- Pituitary stalk
• The adenohypophysis may appear normal (with reference to published data) hypoplastic (with a small height and usually with a concave upper border) very rarely, enlarged (an upper threshold of 5 mm 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
  - normally located
  - 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.
• Pituitary height, directly related to GH Levels (no correlation between the size of the pituitary gland and the severity of the endocrine defect).

• A hypoplastic adenohypophysis is a nonspecific sign observed in IGHD and in (MPHD).

• However, the prevalence of a normal adenohypophysis in patients with IGHD is twice that in those with MPHD.

• In children with IGHD and hypoplastic adenohypophysis, the pituitary gland may spontaneously increase significantly in height after completion of spontaneous pubertal development.

• An enlarged anterior pituitary gland has also been reported in some patients with rare molecular defects involving mutations in the Prop 1 and LHX3 genes.
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.

The implications of EPL location are still unknown.
EPL along the median eminence with absent stalk and Chiari
• Anterior pituitary hypoplasia is commonly reported in EPL and it is more common in a non-visible stalk than for a thin stalk.

• The association of an EPL and a non-visible stalk is significantly more common in MPHDI patients than in IGHD patients.
EPL Origin

breech deliveries: transection of the stalk.
Perinatal asphyxia: hypoxic lesions, damaging the hypothalamo-hypopituitary axis

Currently the most widely accepted theory
a defect in embryogenesis is responsible for abnormalities of the hypothalamohypopituitary axis. (other cerebral developmental abnormalities are often observed in association with the pituitary familial cases of GH deficiency with EPL)
CE-MRI

• more sensitive for the demonstration of the pituitary stalk in cases in which this structure is not visible on unenhanced images.

• EPL is highly specific and predictive of GHD.
Associated cerebral abnormalities

-Currarino syndrome, Pallister-Hall syndrome and Fanconi anemia.

-Midline CNS malformations (high frequency)
  optic nerve hypoplasia
  Chiari I malformations
  medial deviation of the carotid arteries

- Callosal, septal or vermian agenesis, aqueductal stenosis, persistent craniopharyngeal canal.
Pallister-Hall syndrome: hyoplastic adenohypophysis, EPL in the median eminence and hypothalamic hamartoma
Prognostic value of MRI

- Children with GH deficiency and CNS midline abnormalities (accompanied by EPL or pituitary hypoplasia) have significantly greater height gain after GH treatment.

- If pituitary stalk is visible:
  - EPL along the increased GH in adulthood (after completion of GH therapy)
  - EPL at the median eminence: continue to present severe GH deficiency.
Hypogonadotropic Hypogonadism

- *Kallmann’s syndrome* (*X-linked or AD*)
  Hypogonadotropic hypogonadism and congenital olfactory deficit accompanied by other abnormalities, such as cleft lip or palate, dental agenesis, renal abnormalities, hearing loss and cerebellar dysfunction
- The morphology of the H-P axis appears normal on MRI scans.
- Some cases of pituitary hypoplasia have been reported
Posterior Pituitary Deficiency

- CDI is rare in children.
- MRI can be very useful in finding the cause
  posterior bright spot
  adenohypophysis
  stalk

**In a series of 79 children**

- 52% were idiopathic
- Langerhans’ cell histiocytosis 15%
- Intracranial tumors (germinoma, craniopharyngioma, post-resection) in 23 %
- Familial DI in 6%
- Post-traumatic CDI in 3%
- Autoimmune polyendocrinopathy in 1%
The loss of the posterior pituitary bright spot is a sensitive marker for CDI.

Two exceptions, in which the posterior lobe remains visible:

- Familial CDI, during infancy or early childhood
- Chronic neurogenic hypernatremia.
Familial CDI

Ethiology: 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.
Chronic neurogenic hypernatremia

- Midline abnormalities of the brain; holoprosencephaly, callosal agenesis or septal agenesis.

- The underlying mechanism unclear, but a defect in hypothalamic function leading to the failure of the osmoreceptors, whereas the synthesis and storage of AVP remain intact.
Adenohypophysis in patients with CDI

- Hypoplasia of the adenohypophysis: ½ cases, often associated with thickened stalk.

- PHD, GH & thyrotropin in particular, in ½ of patients with idiopathic CDI.

- Pan hypopituitarism 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

- Increase in intrasellar content: Think of germinoma associated with pituitary stalk thickening (PST).
pituitary stalk in CDI

- PST is seen in 1/3, if at least part of it is > 2.0 mm

- CDI with PST:
  - Germinomas (15%)
  - LCH (15%)
  - Idiopathic (70%) [41]

- CE-MRI should be done in patients with CDI, to check for abnormal enhancement within the stalk.

- PST may be the first sign of a germinoma or of stalk infiltration, as in LCH
Thickening of the proximal part of the pituitary stalk (n = 10)

Thickening of the middle part of the pituitary stalk (n = 6)

Thickening of the distal part of the pituitary stalk (n = 2)

Thickening of the entire pituitary stalk (n = 8)
Conclusion

• MRI is essential for the evaluation of the H-P axis in children, and a detailed description of 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)

  prognostic (some prognostic data are correlated with the phenotype)

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.