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The challenging diagnosis of pituitary stalk interruptionsyndrome: a case report

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Abstract

Pituitary stalk interruption syndrome (PSIS) is a rare congenital abnormality affecting thehypothalamic pituitary complex. It is characterized by a peculiar radiological triad which includes thin or interruptedpituitary stalk, hypoplasia or aplasia of the adenohypophysis and absent or ectopic neurohypophysis seen on magnetic resonance imaging (MRI). Patients affected by PSIS may show a wide range of clinical manifestations depending on the variable involvement of pituitary specialized cells, ranging from isolated to multiple pituitary hormone deficiency. The exact aetiology of PSIS is still uncertain, even if genetic causes arelikely to be involved in some cases, especially mutations in genes implicated in pituitary and neuronal development. Prognosis may vary according to several factors, the most relevant of which is diagnostical-timing, being strictly related to the start of hormonal replacement therapy.This report describes an emblematic PSIS case diagnosed in a 15-year-old girl with primary amenorrhoea and short stature. Her past medical history was not significant. Accurate diagnostic investigation including bone age examination, basal hormonal evaluation and growth hormone stimulation dynamic tests were performed, revealingcombined pituitary hormone deficiency (CPHD). MRI findings confirmed a picture of PSIS. The case highlights the importance of accurate history taking and careful monitoring of growth and pubertal development, which is crucial to avoid diagnostic delay and to allow promptly hormonal replacement therapy.

Keywords: hypopituitarism, multiple pituitary hormone deficiency, delayed puberty, short stature, pituitary stalk interruption syndrome

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Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disorder belonging to the holoprosencephaly(HPE) wide spectrum (1). It is characterized by specific radiological findings: thin or interrupted pituitary stalk, hypoplasia or aplasia of the adenohypophysis and absent or ectopic neurohypophysis (2), detected by magnetic resonance imaging (MRI).The presence of these abnormalities can cause a variable involvement of pituitary cells leading to insufficient synthesis or release of one or more peptide hormones, ranging from isolated growth hormone deficiency (IGHD) to combined pituitary hormone deficiency (CPHD) (3). Therefore, clinical expression of PSIS is highly variable, from hypoglycemia and jaundice as neonatal signs to short stature and delayed puberty as later manifestations, depending on the severity of the loss of function of pituitary specialized cells.

Even if perinatal suffering with pituitary involvement was firstly suspected to play a primary role in PSIS genesis, newer findings seem to indicate genetic defects as the main cause of PSIS (1).

Case Report

We present the case of a 15-year-old girl who was admitted to our outpatient clinic of pediatric endocrinology for delayed puberty. The patient was born at term, adequate for gestational age, to non-consanguineous parents.Her personal medical history did not show any remarkable information except for physiologic jaundice. No growth data were available. At the time of the first visit, she presented with a stature of -2.68 standard deviation score (SDs), below the target height (164.65 cm; + 0.2 SDs), with normal sitting height ratio (0.49). Immature face appearance, low-set ears, trident hairline and shortened 4^{th} and 5^{th} metacarpal were observed *(Figure 1).* Tanner stage was B3, P1.

Fig.1 Physical examination of a 15-year- old girl referred to the PediatricEndocrinology Unit for delayed puberty showing evidenceof immature face appearance

Bone-age was compatible with 13 years, according to Greulich and Pyle method.Laboratory investigations revealed low cortisol levels and adrenocorticotrophic hormone (ACTH), within the lower limits, together with low thyroid-stimulating hormone (TSH), and free thyroxine (FT4), suggestive for central hypothyroidism (*Table 1*).Celiac disease was excluded. Karyotype was 46, XX. In order to evaluate hypothalamic-pituitary function, dynamic tests were performed. Luteinizing hormone releasing hormone (LH-RH) test (*Table 2*) revealed pubertal levels of both LH and follicle-stimulating hormone (FSH) with detectable levels of estrogens, associated with a

pubertal ultrasonographic pattern of uterus and ovaries. The growth hormone (GH) / insulin-like growth factor-1 (IGF-1) axis evaluation showed decreased GH secretion (both at arginine and glucagon stimulating tests) (*Table 2*). Pathological cortisol levels were also detected within glucagon stimulating test, confirming secondary adrenal insufficiency (*Table 2*). Normal values of urinary osmolarity and specific gravity excluded posterior pituitary gland compromission.

Table 1. Main basal biochemical findings

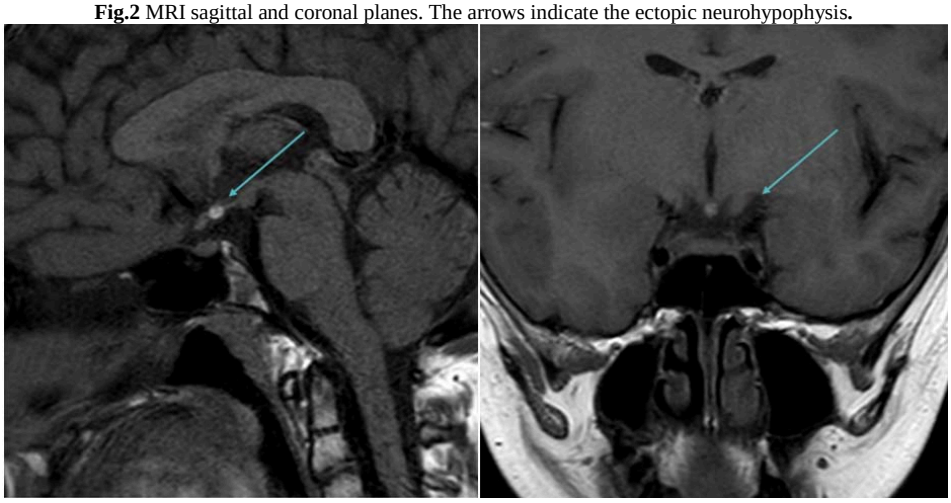
	Value	Normal Range
Cortisol	1.38	>10-12 μg/dL
ACTH	14,7 pg/ml	7.2-63.3 pg/ml
TSH	7.230	0.270-4.200
FT4	7.73 pmol/L	12.00-22.00
Prolactin	648 ng/ml	102 - 496 ng/ml
IGF-1	15.6 ng/ml	127-554 ng/ml
Oestradiol	8.42 pg/ml	

Table 2. Dynamic tests results.

	Value
FSH Time (T) 0’ (LH-RH test)	5.12 mIU/ml
FSH T30’ (LH-RH test)	8.42 mIU/ml
FSH T60’ (LH-RH test)	9.26 mIU/ml
LH T0’ (LH-RH test)	2.20 mIU/ml
LH T30’ (LH-RH test)	11.10 mIU/ml
LH T 60’ (LH-RH test)	10.50 mIU/ml
GH T0’ (arginine stimulation)	0.04 ng/ml
GH T30’ (arginine stimulation)	0.03 ng/ml
GH T60’ (arginine stimulation)	0.06 ng/ml
GH T90’ (arginine stimulation)	0.06 ng/ml
GH T120’ (arginine stimulation)	0.09 ng/ml
GH T150’ (arginine stimulation)	0.03ng/ml
GH T180’ (arginine stimulation)	<0.3ng/ml
GH (glucagon stimulation) T0’	0.11ng/ml
GH (glucagon stimulation) T30’	0.08 ng/ml
GH (glucagon stimulation) T60’	0.10 ng/ml
GH (glucagon stimulation) T90’	0.10 ng/ml
GH (glucagon stimulation) T120’	0.07 ng/ml
GH (glucagon stimulation) T150’	0.04 ng/ml
GH (glucagon stimulation) T180’	0.04 ng/ml
Cortisol (glucagon stimulation)T0’	0.78 ug/dl
Cortisol (glucagon stimulation)T120’	1.55 ug/dl
Cortisol (glucagon stimulation)T1500’	1.60 ug/dl

MRI with detailed study of hypothalamic-pituitary region was performed showing PSIS distinctive findings (*Figure 2*): small adenohypophysis (approximately 7x11x4mm), ectopic neurohypophysis (4mm formation in the infundibular site), pituitary stalk not clearly visible.

Fig.2 MRI sagittal and coronal planes. The arrows indicate the ectopic neurohypophysis**.**



CPHD due to PSIS was consequently diagnosed. Hormonal replacement therapy was immediately started, beginning with hydrocortisone, followed by levothyroxine and GH. Genetic evaluation is still pending.

Discussion

Our case is a representative example of PSIS with pubertal-age onset since the diagnosis was made at the age of fifteen years.Even though the patient was referred to our center because of suspected delayed puberty, biochemical tests showed the presence of CPHD involving all the pituitary trophic hormones except for gonadotropins. This could be explained as part of the wide-ranging symptoms secondary to GH deficiency, as GH has been hypothesized to play a complementary role to gonadotropins for the onset of menarche (4). However, the role of hyperprolactinemia cannot be excluded, even if the detected level did not seem to be high enough to influence puberty. The diagnostic delay in this case could have impaired her response to replacement therapy or, at worst, hesitated in acute adrenal insufficiency, threatening patient life.

The risk of developing acute or severe consequence of hypopituitarism points out the necessity of an accurate clinical and auxological follow-up during pediatric age, considering possible neonatal signs. Moreover, the detection of high levels of prolactin seems to confirm that recent hypothesis of prolactin playing a predictive role in PSIS diagnosis (5) and could support early PSIS identification. The underlying origin of PSIS has not been univocally defined yet. Nevertheless, several gene mutations of transcription factors involved in pituitary embryogenesis (6,7) and HPE-related genes (8) as well as copy number variation (9) have been showed to have a relevant role in PSISpathogenesis (7).However, incomplete penetrance and wide phenotypic expressivity have been detected, leading to the idea that a combination of complex patterns of polygenic inheritance and gene–environment

interactions could be at the basis of PSIS genesis (1). Moreover, taking into consideration the complex genetic heterogeneity and extreme variablephenotypic presentation, it has been suggested to possibly consider PSIS not only as a specific entity but also as part of more complex genetic syndromes (10), requiring standardized genetic investigation.

Our case highlighted the importance of accurate history taking and careful monitoring of growth and pubertal development, which is crucial to avoid diagnostic delay of this rare syndrome, which requires prompt detection to gain the maximum therapeutic benefit.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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