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CASE REPORT

A critical view about Hypopituitarism in childhood : a case report

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Abstract

Hypopituitarism is a condition defined by adenohypophysis hormones production/action deficiency. It is a challenging diagnosis and it has high mortality rate. The present work shows a case report of a two and a half-year-old female child, weight: 9,05 kg (z-score: -2,97); hight: 80 cm (z-score: -3,07); IMC: 14,14 (z-escore: -1,27) who lives in Federal District - Brazil, with weight-stature deficit and neuropsychomotor developments delay. Association with laboratorial and image exams indicated hypopituitarism. It is up to doctors, pediatricians in special, to be aware of this singular diagnosis.

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INTRODUCTION

Hypopituitarism is a deficiency in the production of one or more hormones in the pituitary gland. This condition results from a variety of genetic or acquired disorders[1].

Complex genetic interactions dictate the normal development of the hypothalamic-pituitary region. Thus, inherited or acquired mutations may cause congenital hormonal deficiencies or late-onset hypopituitarism, whether isolated or as part of a syndrome[1], such as septo-optic dysplasia[2]. Acquired causes include tumors affecting the hypothalamic--pituitary region, local injury secondary to trauma, irradiation and infection[1].

The clinical characteristics of hypopituitarism vary both in severity and in the number of hormones affected. Hormone deficiency is a well-established characteristic of hypopituitarism; therefore, the presence of an affected axis (somatotropic, gonadotrophic, thyrotrophic or corticotroph) requires the evaluation of the other axes at time of diagnosis and over the years.

This article describes a case of hypopituitarism affecting a female child aged two years and six months and advises pediatricians about suspected symptoms and repercussions of the disease on the weight, height and global development of children.

CASE REPORT

S.P.A., a Caucasian female child aged two years and six months, had three episodes of afebrile seizures at home. When she arrived at the emergency department, her blood glucose level was 29 mg/dL; she improved from seizures as her blood glucose level normalized and was hospitalized for further investigation.

The patient was born at term (39 weeks and one day) from an uneventful cesarean section; her weight and length at birth were 3,030g and 48 cm, respectively; her Apgar scores were 8/9; she was described as appropriate for gestational age (AGA). Physical examination was unremarkable, including midline defects. Thirty hours after birth, she had trouble breastfeeding, was hypoactive and suffering from hypothermia. The glucose meter showed a low reading and the child was referred to intensive care with continuous glucose infusion for 72 hours. A critical sample was not collected. She had prolonged jaundice (until 45 days after birth) without the need for phototherapy; mother and daughter had A+ blood type. The neonatal heel prick test result was normal. Global development: the patient sat up at nine months and walked at one year and seven months. At the time of hospitalization, she could walk, talk and play. Her mother said she had never been hospitalized or undergone surgery or trauma.

Family history: Non-consanguineous parents. Mother: healthy, height 159.7cm. Father: healthy, height 169.5cm. Healthy brothers. First cousin took growth hormone (GH) and has altered speech.

On ectoscopy, she was found to have a prominent forehead. Cardiovascular, respiratory and abdominal systems were all normal. Her nails and hair were in good condition. Weight: 9.05 kg (z-score: -2.97); Height: 80 cm (z-score: -3.07); BMI: 14.14 (z-score: -1.27); target height: 158.1 cm.

Initial investigation yielded the following results: TSH 2.66 (RV: 0.27-4.2); T4L: 0.891 (RV: 0.93-1.7); IGF1: 19 (RV: 18-172); Cortisol: 12 (RV: 5.4-25). Hypopituitarism was considered and she was referred to the pediatric endocrinology service.

A critical sample was collected after 20 hours of fasting (glycemia 45mg/dl), TSH 3.41 (RV 0.27-4.2), T4 L 0.797 (RV: 0.93-1.7), GH: 0 .23(RV:> 5); x-ray scans of the hands and wrists showed a bone age of three months (chronological age: 2 years and 6 months); other screening tests for short stature and critical samples were normal. Magnetic Resonance Imaging (MRI) of the sella turcica (Figure 1) showed a shallow sella, no pituitary stalk, hyposignal of the adenohypophysis

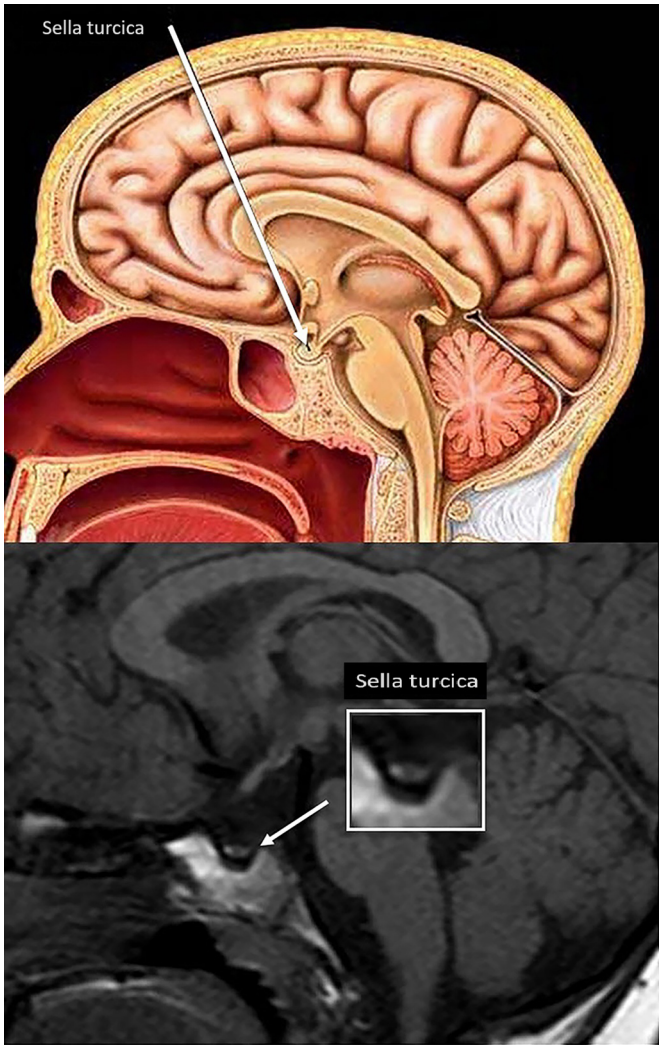


Figure 1. Schematic drawing of the sella turcica. Below, a T1-weighted MRI scan. The sagittal view shows a shallow sella, hyposignal in the adenohypophysis and loss of signal in the neurohypophysis.

and absence of signal of the neurohypophysis in the sella, all findings associated with a diagnosis of hypopituitarism. Treatment with levothyroxine 5 mcg/kg/day and somatropin 0.1 IU/kg/day was started.

Magnetic resonance imaging of the sella turcica showing a shallow sella, no pituitary stalk, hyposignal of the adenohypophysis and absence of signal of the neurohypophysis in the sella. These and clinical findings support a diagnosis of hypopituitarism.

DISCUSSION

The pituitary gland is made up by several cell types, whose secretion products stimulate other peripheral endocrine glands to synthesize and secrete hormones involved in different functions (growth, global development, sexual maturation etc.)[3]. The anterior lobe of the pituitary, also known as adenohypophysis, is of ectodermal origin. It produces growth hormone (GH), gonadotropins (LH and FSH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and prolactin. The posterior lobe, also known as neurohypophysis, is of neural origin. It produces antidiuretic hormone (ADH) and oxytocin[4]. As it starts forming between the 4th and 5th weeks of life with the invagination of Rathke's Pouch, there is a temporally regulated cascade of transcription factors with the expression of hormones from the anterior lobe of the pituitary gland. Changes in transcription factors may cause hormonal deficiencies more frequently, as shown in Figure 2 and Table 1[4].

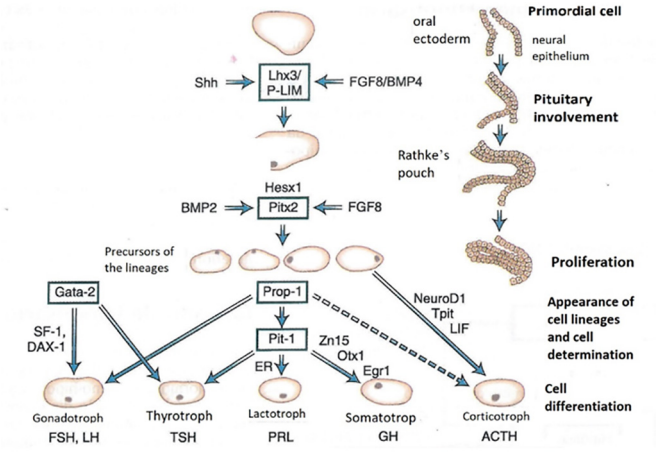


Figura 2. Development model of the anterior lobe of the pituitary gland and cell lineage determination in humans through the transcription factor cascade.

Lhx3 determines the differentiation of GH, Prolactin and TSH cells. PTx works as a universal regulator of the pituitary gland. GATA-2 regulates the expression of the alpha subunit present in gonadotropins and TSH. PROP-1 is the main determinant of pituitary cell lines derived from totipotent stem cells, which determines the expression of PIT-1 and gonadotrophs. The expression of PIT-1 determines the development of GH, prolactin, TSH and the GH receptor.

The clinical signs of hypopituitarism may include short stature, hypothyroidism, sexual maturation disorders, hypoglycemia and signs and symptoms of hypocortisolism, in isolation or combination with other signs[5]. Congenital absence of the pituitary gland (aplasia), partial hypoplasia or ectopic tissue rudiments are rarely found[5]. The latter sign was observed in our patient.

Impairment of the synthesis of one or more pituitary hormones may result from inherited factors (mutations in genes such as PROP-1, POU1F1, HESX1, LHX3 and T-Pit; Lawrence-Moon-Biedl syndrome, Prader-Willi syndrome and Kallman syndrome) and acquired lesions (tumor, trauma, surgery or irradiation)[4,5]. A recently described mutation in the PROP-1[5] gene has been associated with GH and TSH deficiency and pituitary gland enlargement, the most frequent mutation in panhypopituitarism, present in 11% of global, 6.7% of sporadic and 48.5% of familial cases. The case describing the mutation involved a three-year-old white Italian child with jaundice and normal glucose levels at birth. At the age of three years, a linear decline in growth was observed, associated with truncal obesity, doll face and a prominent forehead, but without global development delay. At three years of age, the child's height was 78.7 cm (-4.23 standard deviations) and his weight was 10.8 kg (-2.6 standard deviations); his bone age was one year and two months. Lab tests confirmed thyrotrophic and somatotrophic axis deficiency and hormone replacement therapy was initiated[5].

Congenital hypopituitarism is also an uncommon cause of neonatal cholestasis. Little is known about the hormonal effects of the anterior lobe of the pituitary on liver function. In the literature, an article[6] cites eight cases of newborns with cholestatic jaundice who subsequently developed anterior pituitary hormone deficiency. Signs such as hypoglycemia, ocular abnormalities and micropenis have been frequently described[6]. ACTH, GH, and TSH impairments have been associated with cholestasis; however, some authors described only cortisol as a cause of cholestasis; there is no consensus on the subject yet[7].

Patients with pituitary insufficiency, despite their history, have a high mortality rate, mainly due to respiratory and vascular diseases. Age at diagnosis, female sex and a history of craniopharyngioma are the most evident factors associated with increased mortality[4]. An article[8] described the potential severity of hypopituitarism as it reported the case of a male newborn, born after 41 weeks of gestation weighing 3,320g, with respiratory distress one hour after birth; he was placed on mechanical ventilation, but went into catecholamine-resistant cardiogenic shock. Severe hypopituitarism was considered due to signs including respiratory distress, hypoglycemia and micropenis. After administration of hydrocortisone, there was a significant improvement in hemodynamics. MRI scans showed aplasia of the adenohypophysis and an ectopic posterior gland lobe[8].

Table 1. Appearance of pituitary hormones in the fetus shown according to gestational age.[4]

Appearance in the fetus	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Hormone	FSH, LH	TSH	PRL	GH	POMC
Chromosomal locus in gene	β-11p; β-19q	α-6q; β-1p	6	17q	2q
Protein	α subunits and β glycoprotein	α subunits and β glycoprotein	Polypeptide	Polypeptide	Polypeptide
Arteries	210 204	211	199	191	266 (ACTH 1-39)
Stimulants	GnRH, estrogen	TRH	Estrogen, TRH	GHRH GHS	CRH, AVP gp-130 cytokines
Inhibitors	Sex steroids, inhibin	T3, T4, Dopamine, somatostatin, glucocorticoids	Dopamine	Somatostatin, IGF activin	Glucocorticoids
Target gland	Ovary, testicles	Thyroid	Breast, other tissues	Liver, bone, other tissues	Adrenal
Trophic effect	Sex steroids follicular growth Germ cell maturation H, 5-20 UI/L M (baseline), 5-20 UI/L	Synthesis and secretion of T4	Milk production	Production of IGF--I, growth induction, insulin antagonism	Production of steroids
Normal range	H, 5-20 UI/L, M (baseline), 5-20 U/L	0, 1-5 mIU/L	H<15; M<20 µg/L	<0,5 µg/L	ACTH, 4-22 pg/L

Growth hormone deficiency (GHD) is the most common pituitary axis deficiency in patients with hypothalamic-pituitary disease[4]. Tests for GHD are indicated in patients with 1) severe short stature; 2) short stature associated with reduced growth speed; 3) height above -2 standard deviations for age and sex, associated with low growth velocity; 4) predisposing conditions such as intracranial injury and irradiation of the central nervous system (CNS); 5) deficiency of other pituitary hormones; and 6) signs and symptoms of GHD/hypopituitarism in neonatal life (hypoglycemia, prolonged jaundice, micropenis, midline defects)[9]. History of birth trauma, consanguinity, affected family members and the presence of other hormonal deficiencies have been associated with GHD[3].

Further investigation is warranted in hypoglycemic patients in the following circumstances: 1) healthy newborn with hypoglycemia; 2) recurrent or persistent hypoglycemia (>48 hours of birth); 3) need to infuse glucose at a rate > 14; and 4) association with other abnormalities[10]. Testing must be initiated during hypoglycemic crisis treatment. Obtaining critical blood and urine samples in hypoglycemic patients is extremely important for diagnosis and treatment[11].

Congenital hypothyroidism is categorized as primary when changes occur in the thyroid gland; secondary when they affect the pituitary gland; and tertiary when they occur in the hypothalamus. The last two characterize central hypothyroidism[12]. The main consequences of thyroid hormone deficiency are severe mental retardation, growth failure, ataxia, motor incoordination, strabismus, choreiform movements and sensorineural hearing loss[12]. In Brazil, TSH measurement by immunofluorimetry in dry blood spots is the recommended routine for neonatal screening for congenital hypothyroidism; patients with TSH levels above 10 U/ml are deemed positive in screening[13]. Our patient, however, had an unremarkable heel prick test, which ruled out primary, but not central, congenital hypothyroidism. A prospective study conducted in Argentina[14] demonstrated that the addition of T4 testing in neonatal screening tests enables the diagnosis of central congenital hypothyroidism, which, according to the authors of the study, accounted for 11% of the cases in a population of 22,573 newborns. The importance of establishing a diagnosis of central hypothyroidism lies in the relationship the condition has, in most cases, with potentially fatal pituitary hormone deficiency (adrenal insufficiency and growth hormone deficiency)[14].

In children, gonadotropic hormone deficiency may result in lack of pubertal development, delayed bone maturation and, in boys, micropenis and cryptorchidism[3].

In the pituitary gland, ACTH-producing cells are among the last to have their function compromised by the presence of tumors, trauma (surgical or not) or irradiation. The main signs and symptoms suggestive of ACTH deficiency are anorexia, nausea, vomiting, weight loss, asthenia, skin pallor, and loss of axillary and pubic hair[3].

Our patient has been monitored on an outpatient basis and is progressing well. She has a disease that represents a

diagnostic challenge and requires immediate and long-term treatment to avoid complications. We did not have the supplies needed to run tests for genetic mutations.

REFERÊNCIAS

1. Brook CGD, Clayton PE, Brown RS. Congenital Disorders of the Hypothalamo-Pituitary-Somatotrope Axis. In: Mehta A, Gevers&Mehul ETTD, orgs. Brook's Clinical Pediatric Endocrinology. 6th ed. Oxford: John Wiley & Sons, Ltd; 2009. p. 60-7.
2. Fernandes SY, Gray MCF, Dyonisio ACS. Síndrome de Morsier: relato de dois casos na cidade de Petrópolis. Resid Pediatr. 2020;10(1):44-47.
3. Sociedade Brasileira de Endocrinologia e Metabologia. Projeto Diretrizes - Hipopituitarismo: Diagnóstico. 2006; [acesso em 2019 Set 29];13. Disponível em: https://diretrizes.amb.org.br/_BibliotecaAntiga/hipopituitarismo-diagnostico.pdf.
4. Melmed S, Kleinberg D. Hipófise Anterior, Fatores de Transcrição Hipofisários. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, orgs. Williams Tratado de Endocrinologia. 11ª ed. Rio de Janeiro: Elsevier; 2010. p. 136-7.
5. Penta L, Bizzarri C, Panichi M, Novelli A, Lepri FR, Cappa M, et al. Identification of a novel PROP1 mutation in a patient with combined pituitary hormone deficiency and enlarged pituitary. Int J Mol Sci. 2019;20(8):1-7.
5. Karnsakul W, Sawathiparnich P, Nimkarn S, Likitmaskul S, Santiprabhob J, Aanpreung P. Anterior pituitary hormone effects on hepatic functions in infants with congenital hypopituitarism. Ann Hepatol. 2007;6(2):97-103.
6. Wada K, Kobayashi H, Moriyama A, Haneda Y, Mushimoto Y, Hasegawa Y, et al. A case of an infant with congenital combined pituitary hormone deficiency and normalized liver histology of infantile cholestasis after hormone replacement therapy. Clin Pediatr Endocrinol. 2017;26(4):251-7.
7. Ueda Y, Aoyagi H, Tajima T. A newborn with combined pituitary hormone deficiency developing shock and sludge. J Pediatr Endocrinol Metab. 2017;30(12):1333-6.
8. Ministério da Saúde (BR). Protocolo Clínico e Diretrizes Terapêuticas para Deficiência de Hormônio do Crescimento - Hipopituitarismo. Portal Arquivos [Internet]. 2018; [acesso em 2019 Set 29]. Disponível em: http://portalarquivos2.saude.gov.br/images/pdf/2018/dezembro/14/PCDT-Deficiencia-do-Hormonio-de-Crescimento--Hipopituitarismo.pdf.
9. Universidade Federal do Triângulo Mineiro. Hospital de Clínicas da UFTM. Protocolo Clínico (PC): "Hipoglicemia Neonatal – Condutas Médicas". 2019; [Acesso em 29 setembro 2019]. Uberaba: EBSERH, 2019. Disponível em: http://www2.ebserh.gov.br/documents/147715/0/Hipoglicemia+neonatal++vers%2Búo+final.pdf/10e7a2ba-8c7c--4b2a-870d-241da35b04db
10. Sociedade Brasileira de Pediatria. Diretrizes SBP - Hipoglicemia no Período Neonatal. SBP [Internet]. 2014; [acesso em 2021 Fev 20];(1). Disponível em: https://www.sbp.com.br/fileadmin/user_upload/2015/02/diretrizessbp-hipoglicemia2014.pdf.
11. Cristina LP de P, Garcia LS, Collett-Solberg PF, Liberatore Del Roio R, Pinto RM, Arrais RF, et al. Hipotireoidismo congênito: triagem neonatal. Soc Bras Pediatr. 2018;1-12.
13. Ministério da Saúde (BR). Protocolo clínico e diretrizes terapêuticas para hipotireoidismo congênito. Portaria SAS/MS no 1161, de 18 de novembro de 2015 [Internet]. 2015; [acesso em 2019 Set 29];1-8. Disponível em: http://portalarquivos.saude.gov.br/images/pdf/2015/novembro/26/Hipotiroidismo-congenito---PCDT-Formatado--.pdf.
14. Braslavsky D, Mendez MV, Prieto L, et al. Pilot neonatal screening program for central congenital hypothyroidism: evidence of significant detection. Horm Res Paediatr. 2017;88(3-4):274-80.