# Childhood-onset panhypopituitarism and differential diagnosis of polyuria

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## ABSTRACT

Hypopituitarism is the deficiency of two or more pituitary hormones. Its symptoms depend on the type and degree of hormonal deficit. Proper care of these patients is of fundamental importance to avoid delay in growth and development, death, or changes in the quality of life. The objective of this study is to report a clinical case of a pediatric patient with pan-hypopituitarism and describe the care adopted, as well as the importance of monitoring by the pediatric endocrinologist. The patient was a 14-year-old boy, with pan-hypopituitarism beginning in childhood, secondary to the appearance of germinoma and the treatment performed for it. The first hormonal deficiency presented was diabetes insipidus, followed by multiple deficiencies after chemotherapy and radiotherapy. The patient is under specialized monitoring and takes levothyroxine, desmopressin, somatropin, testosterone, and prednisolone. From the present report, timely diagnosis and adequate approach to a child with pan-hypopituitarism and its follow-up are important to maintain a satisfactory quality of life.

**Keywords:** Hypopituitarism, Transitional care, Germinoma, Medication therapy management, Quality of life.

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## INTRODUCTION

Hypopituitarism corresponds to a deficit of two or more pituitary hormones[1] and persists throughout the person's life[2]. In general, its wide range of etiologies represents a challenge[3]. These can be classified as acquired or congenital, the latter being associated with genetic changes in 5% to 10% of cases[4]. Although studies quantifying its prevalence and main causes are scarce, the pediatric population has a higher incidence of the disease from acquired etiologies, especially central nervous system tumors[5,6].

The clinical condition varies according to the severity of hormone deficits[6], requiring prompt in-depth investigation and timely diagnosis in case of suggestive presentation[2]. There may also be an association with delayed growth and/or development and cardiometabolic, respiratory, and musculoskeletal comorbidities, in addition to the prospect of a negative influence on the quality of life and death if there is no appropriate clinical management[6].

During adolescence, a patient becomes more independent of parental care, leading to the need for a medical approach aimed to maintain treatment. Therefore, it is clear that pituitary disorders during this period require special attention and represent a management challenge to ensure the patient's full development[7].

Thus, this case report is interesting for describing the management of a patient with childhood-onset panhypopituitarism diagnosed late, reinforcing the need for appropriate investigation based on suggestive clinical symptoms and maintaining continuous care by the pediatric endocrinologist.

## CASE REPORT

A 14-year-old male patient was accompanied by his mother to consult with a pediatric endocrinologist for a panhypopituitarism follow-up in August 2019. It was reported that, in December 2014, after moving to another state, the child began to present with polyuria and nocturia and consulted a physician who requested some laboratory tests, such as blood count and fasting glycemia, which showed no changes. Moreover, according to the history, the professional did not continue investigating the condition and referred the child to a psychologist, suspecting that the symptoms were psychogenic. After unsatisfactory results, they sought consultation in May 2015 with a pediatrician, who considered the diagnosis of diabetes insipidus (DI) and referred the patient to a pediatric endocrinologist.

This physician requested tests, which confirmed DI. In this context, polyuria was initially established as 40-50 ml/kg in 24 hours, and previous hypocortisolism and hypothyroidism were excluded. Subsequently, the diagnosis of DI was confirmed due to the association of hypernatremia, serum osmolality greater than 300 mOsm/kg, and urinary osmolality lower than 300 mOsm/kg, in a context of normal blood glucose, nitrogenous slag, potassium, and calcium values[8].

In this scenario, the subcutaneous administration of synthetic vasopressin analog (1-desamino-8-D-arginine vasopressin [DDAVP]) at a dose of 1 unit/m², with consequent urinary concentration, helped differentiate the cause of DI as being central.

The patient was medicated with nasal desmopressin, and a non-contrast cranial magnetic resonance imaging (MRI) showed a hamartoma of approximately 1 cm near the hypophysis. The patient was then referred to a neurosurgeon in the same city. Considering the uncertain diagnosis, a consultation with another neurosurgeon was scheduled. A contrast cranial MRI showed a germinoma.

In July 2015, after consultation with the neurosurgeon, the child was referred to an oncologist pediatrician. Lumbar puncture was requested for tumor markers, beta-HCG, AFP (alpha-fetoprotein) and the patient underwent another MRI. The markers were negative, and the MRI reinforced the hypothesis of suprasellar germinoma (Figure 1).

During the follow-up, a neuroendoscopic biopsy of the suprasellar region was requested, confirming the germinoma diagnosis. Chemotherapy was initiated with etoposide and carboplatin in September 2015, which was completed in November. Subsequently, volumetric modulated arc radiotherapy (VMAT) was performed, with the first phase of 10 x 180 cGy fractions in the ventricular system (DT = 18 Gy) and the second (boost) of seven fractions in a lesion with margins (DT = 30.6 Gy).

Six months after the treatment, the patient presented with fatigue, inappetence, and pain in the legs. He was seen by an endocrinologist, who diagnosed hypocortisolism due to adrenocorticotropic hormone (ACTH) deficit and prescribed prednisolone. Subsequently, the hormonal deficits diagnosed were central hypothyroidism, growth hormone (GH) deficit, and hypogonadism (Figure 2).

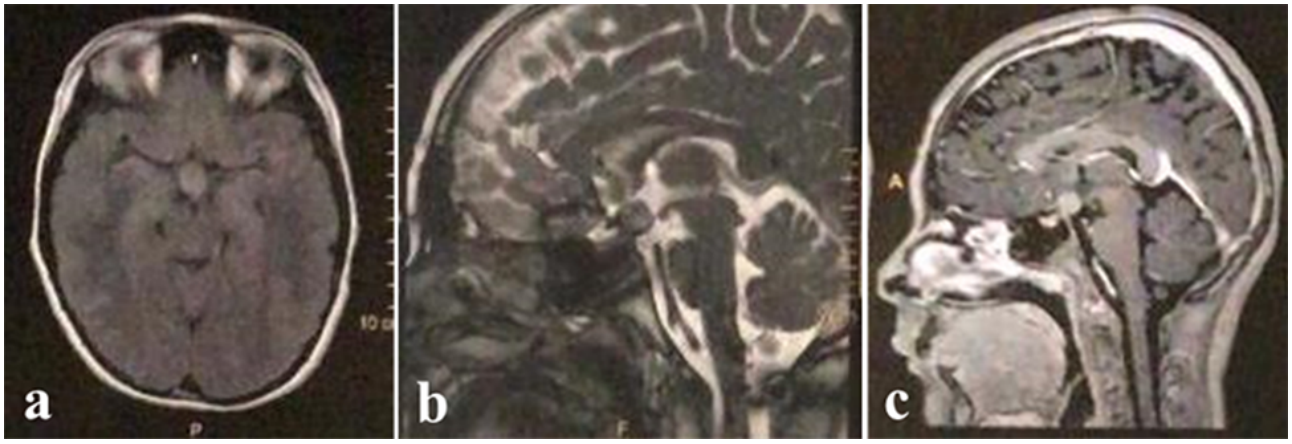


**Figure 1.** Cranial MRI, July 2015. Expansive, rounded lesion in suprasellar region, measuring 1.0 x 1.3 x 0.7 cm, isointense in T1 (a), mildly hyperintense on T2 (b), and with large magnetic contrast enhancement (c). No cleavage planes were seen between the lesion and the pituitary stem. (a) Axial section; (b) and (c) Sagittal section. Source: Authors.

Currently, the patient is on levothyroxine 75 mcg/day, desmopressin nasal spray 0.1 mg/mL (1 jet in each nostril, about twice a day), somatropin 7.2 IU/day, testosterone 100 mg/month, and prednisolone 9 mg in the morning. As for clinical decompensation, according to the information collected, the patient had an episode of adrenal crisis at the beginning of treatment, which did not occur later, demonstrating adequate therapeutic compliance of the patient, as well as parental supervision and support. In addition, considering habits and customs, the patients practiced physical activity (volleyball and swimming) and searched for a healthier diet.

During the physical examination, performed during the first visit with the current pediatric endocrinologist, the following were verified, as shown in Table 1.

As for growth, according to information provided by the patient's mother, there was a considerable increase after the introduction of GH. Furthermore, considering the height of the parents (mother = 178 cm and father = 171 cm), the target height for the patient analyzed was calculated as 181 cm, with a range of 176-186 cm.

For follow-up, new blood and bone age tests were requested. In subsequent consultations, the patient presented with increased height, as shown in Figure 3. BMI values are shown in Figure 4.

### *Ethical aspects*

The patient and his guardian gave their consent to participate in the research. The study was approved by Research Ethics Committee.

## DISCUSSION

The patient described in this report initially had DI secondary to a suprasellar germinoma and, after treatment, developed panhypopituitarism. The importance of timely diagnosis, appropriate investigation, and subsequent follow-up for adequate hormone replacement, maintenance of the quality of life, and prevention and management of acute complications should be emphasized[8].

As for the diagnosis, DI patients clinically present with a complaint of polyuria and polydipsia; moreover, the presence of nocturia in a patient with previous sphincter control should also suggest the possibility of this diagnosis[10]. The patient had a late diagnosis of DI, confused with a psychogenic condition, which delayed the initiation of treatment. Thus, when polyuria is suspected, it is important to investigate it further with complementary tests.

Initially, polyuria must be confirmed, defined by daily values of 120 ml/kg in newborns, 100-110 ml/kg in infants, and 40-50ml/kg in older children. Subsequently, the necessary laboratory tests are aimed at ruling out hydroelectrolytic disorders and establishing hypotonic polyuria. Such tests include serum osmolality, sodium, potassium, glucose, calcium, nitrogenous slag, and urinary evaluation (osmolality, glycosuria, and specific density)[10]. In addition, the previous presence of hypothyroidism and adrenal insufficiency should be evaluated, which may obscure DI due to a decreased free water clearance[11].

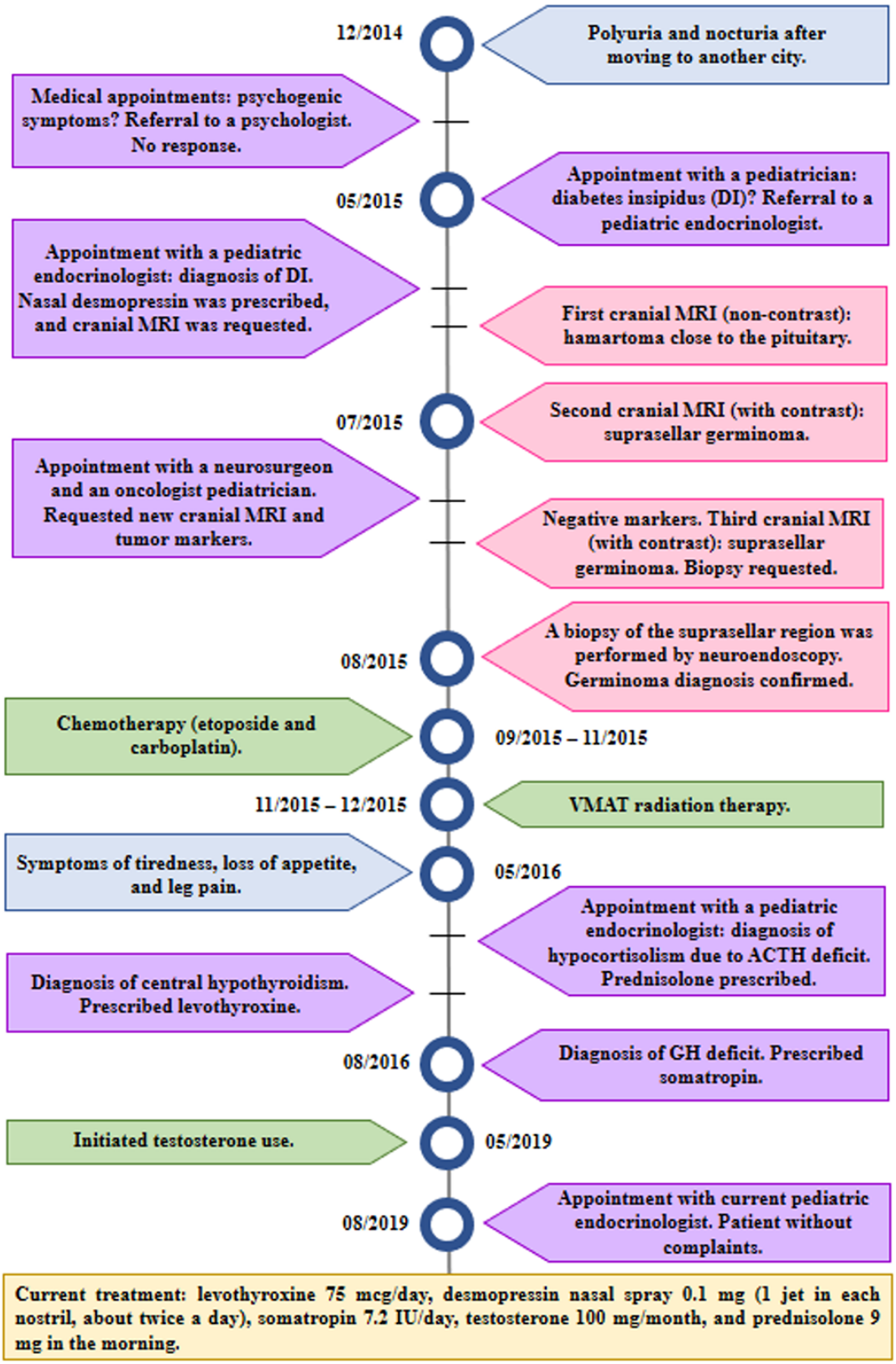


**Figure 2.** Timeline of the clinical case progression. Source: Authors.

**Table 1.** Physical examination data, August 2019.

| Parameter | Result |
|---|---|
| Height | 163.5 cm (z score 0) |
| Body mass index (BMI) | 25.47 Kg/m² (z score +1/+2) |
| Blood pressure | 100 x 60 mmHg (left arm) |
| Tanner staging | G3P3 |
| Testicular volume | 6 cm³ |
| Penis length | 6 cm |
| Presence of axillary acanthosis | - |

Source: the authors

synthetic vasopressin analog, and the resulting urinary concentration corresponds to the central etiology, as shown in the case report. In contrast, in the case of normal serum osmolality and sodium values in the context of hypotonic polyuria, water deprivation testing is required to elucidate the etiology[11].

After identifying that the DI has a central cause, cranial MRI should be performed[10], similar to the management of the present case revealing suprasellar germinoma.

In this scenario, considering the normal pituitary axes prior to treatment, the hormonal deficits initiated after the treatment. From this perspective, irradiation

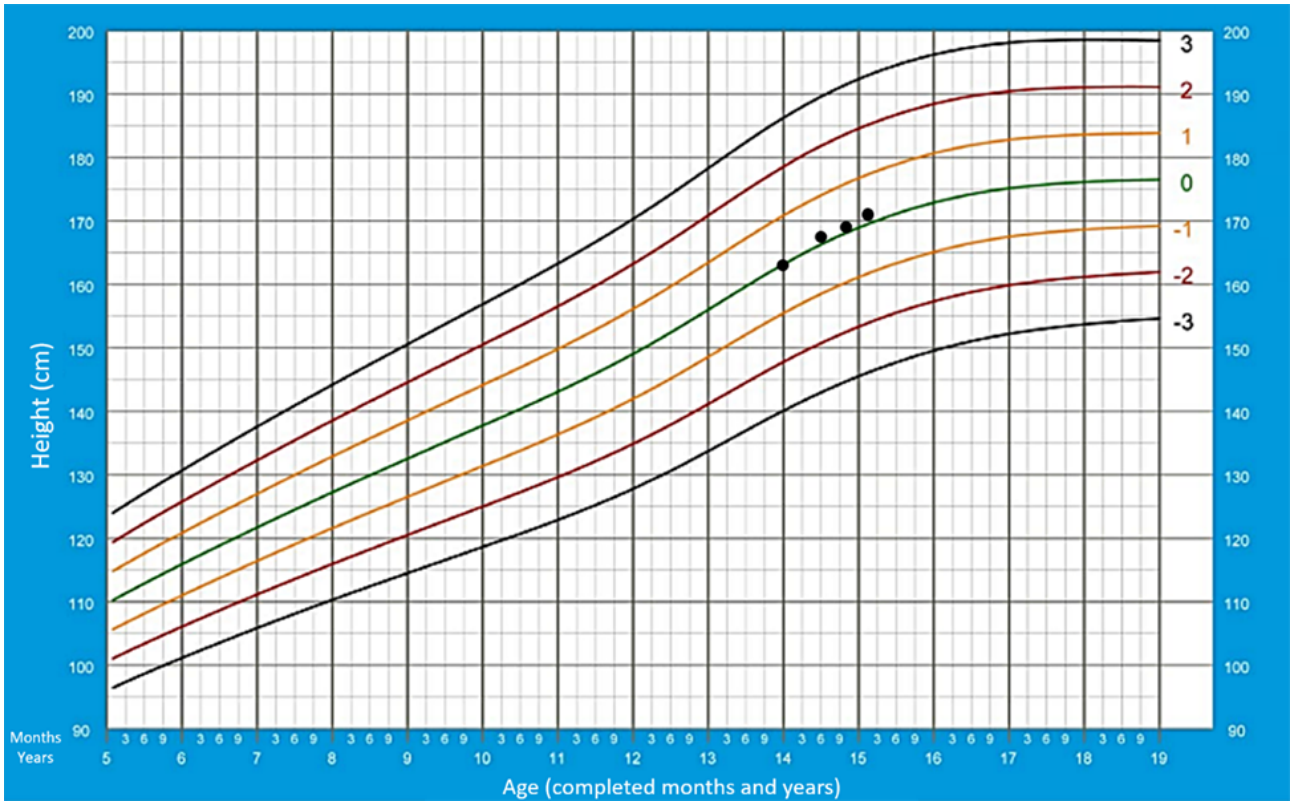


**Figure 3.** Patient's height (in centimeters), from August 2019 (aged 14 years) to October 2020 (aged 15 years and 2 months), according to the "Height-for-age, boys, 5-19 years (z-scores)" WHO chart. Source: Secretariat of Primary Health Care, 2011[9].

Hypotonic polyuria, which characterizes DI, is expressed by low urinary osmolality (lower than 800 mOsm/kg), as well as decreased urinary specific density (lower than 1,010). As for psychogenic polydipsia, it shows low plasma sodium (lower than or equal to 135 mmol/liter) and serum osmolality values (lower than or equal to 280 mOsm/kg)[11].

Moreover, in a condition of high plasma osmolality and hypernatremia, central and nephrogenic DI can be differentiated by subcutaneous administration of

doses in the hypothalamic-pituitary area equal to or greater than 18 Gy can result in GH deficit, and values equal to or greater than 30 Gy can cause thyroid stimulating hormone (TSH), ACTH, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) deficits[12], which occurred in the present case.

Another point that should be assessed refers to the maintenance of the quality of life. The adolescent in the present report maintained good behavior and school performance, healthy relationships, and

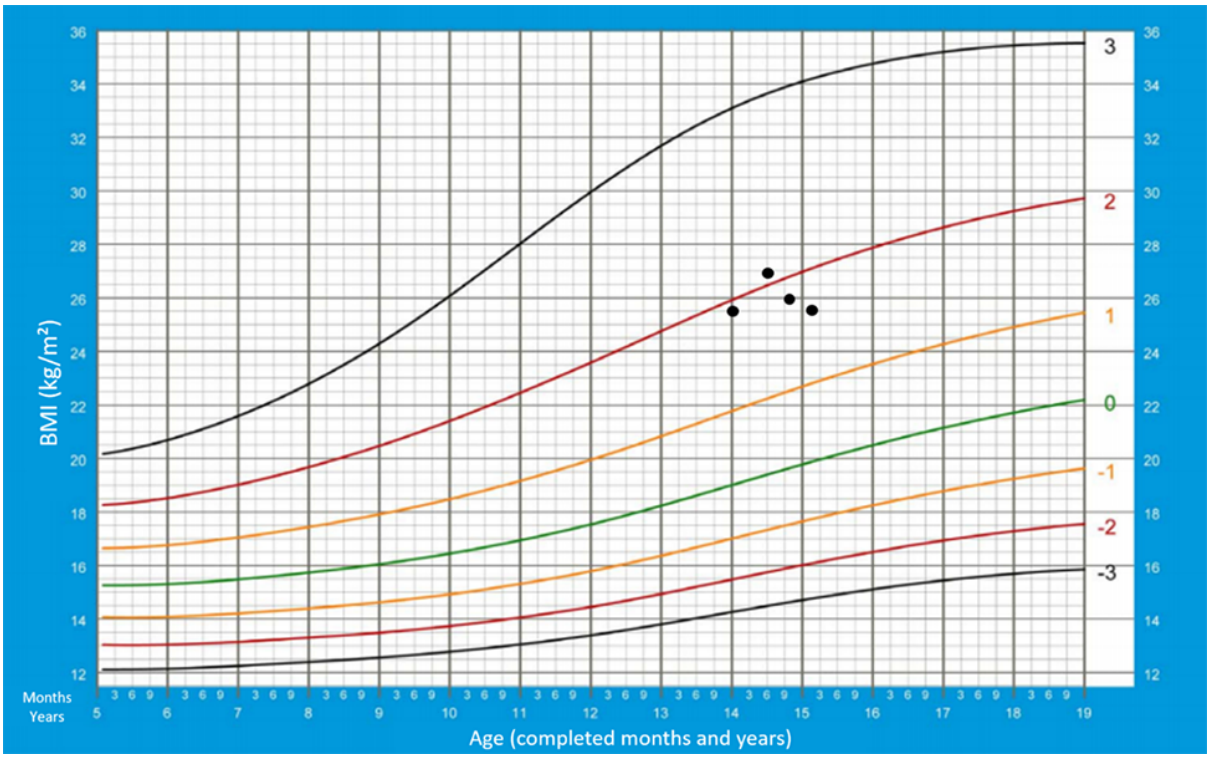


**Figure 4.** Patient's BMI (in kilograms per square meter), from August 2019 (aged 14 years) to October 2020 (aged 15 years and 2 months), according to the "BMI-for-age, boys, 5-19 years (z-scores)" WHO chart. Source: Secretariat of Primary Health Care, 2011[9].

participating in extracurricular sports activities and enjoying healthy eating options. This perspective should be continuously verified since adults with childhood-onset multiple pituitary hormone deficiencies have a poorer quality of life, with more behavioral problems and unemployment, requiring monitoring regarding biopsychosocial issues[5].

In this scenario, the participation of an endocrinologist to manage hormone deficits and periodically evaluate the treatment is essential[6]. As for hormone treatment in the pediatric population, the following drugs and initial doses are suggested, as shown in Table 2:

**Table 2.** Drugs of choice and doses for hormone deficits.

| Deficit | Drug | Doses |
|---|---|---|
| GH | Subcutaneous somatropin[13] | 0.075-0.10 IU/kg/day[13] |
| TSH | Oral levothyroxine (VO)[14] | 100 µg/m²/day, 15 to 30 minutes before the first meal[14] |
| LH and FSH | Intramuscular testosterone (for males)[7] | 50 mg/month7 |
| ACTH | Oral hydrocortisone[7] | 7-9 mg/m²/day[7] |
| ADH (antidiuretic hormone) | Desmopressin[15] | Oral: 100 to 1200 µg, divided into 3 doses a day. Intranasal: 2 - 40 µg, 1 or 2 times a day[15] |

Moreover, considering the decompensation resulting from panhypopituitarism presented by the patient at the beginning of treatment - adrenal crisis - it is important that emergency room physicians recognize it. Adrenal crisis is defined as an acute health condition, combined with hypotension or sinus tachycardia, or a significant electrolyte or hypoglycemic change not attributable to another cause, which resolves after parenteral administration of glucocorticoids. An intravenous (IV) or intramuscular (IM) bolus of hydrocortisone is recommended at a dose of 4 mg/kg[16].

In this scenario, adolescence may represent a challenge, as the patient becomes more independent and gradually assumes responsibility for the treatment. Thus, it is necessary to encourage their autonomy, explaining the risk factors for adrenal crises and medication management[7]. The patients should always carry an instructional card warning about their disease and the possibility of an adrenal crisis.

Finally, considering the relevance of hormone replacement in the management of childhood-onset panhypopituitarism, the importance of immediate clinical suspicion in the face of suggestive presentation and the attention given during the adolescence phase are highlighted. Although there

was a delay in diagnosis, in the reported case, the patient is currently asymptomatic and informed about the subject, showing himself capable of using medications, besides having parental supervision and support. Together with the periodic evaluation of therapy and growth and development monitoring by the pediatric endocrinologist, these facts are fundamental for the maintenance of the adolescent's quality of life.

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**Specific authors' contributions**

- Study conception and design: Vivianne A.N.; R.C.V.L.S.;
- Manuscript writing and critical review with intellectual contribution: Vivianne A.N.; Vinícius A.N.; R.C.V.L.S.;
- Final approval of the version for publication: Vivianne A.N.; Vinícius A.N.; R.C.V.L.S.

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