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CASE REPORTS

ADRENAL INSUFFICIENCY IN CHILDHOOD: TWO CASES OF A RARE CONDITION

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ABSTRACT

Adrenal insufficiency is a rare condition in children, usually presenting as general and gastrointestinal symptoms and skin hyperpigmentation. Symptoms can appear gradually or suddenly as in Addisonian crisis, a life-threatening condition, with hemodynamic and electrolyte disturbances. Autoimmune Polyglandular Syndromes are rarer conditions characterized by two or more autoimmune endocrinopathies. We aimed to evidence the different presentations of adrenal insufficiency and draw attention for its severity

Two adolescents were referred to pediatric emergency department with asthenia, anorexia, abdominal pain and vomiting. The first patient was hemodynamically unstable, discolored, dehydrated mucous membranes and cutaneous hyperpigmentation. Analytically showed hyponatremia, hyperkalemia, hypochloremia, hypoglycemia and mild metabolic acidosis. Fluid resuscitation and intravenous glucocorticoids were started, with favorable evolution. The second one presented reasonable general condition, sunken eyes, cutaneous hyperpigmentation, maintaining hemodynamic stability. Analytically showed hyponatremia, hyperkaliemia, hypochloremia, hypoglycemia, decreased cortisol and aldosterone and increased corticotropin and renin, along with adrenal antibodies. Investigation showed increased TSH and normal free T4 and anti-peroxidase antibodies. The association of Addison's disease with Hashimoto's Thyroiditis allowed the diagnosis of Autoimmune Polyglandular Syndrome.

These cases highlight the rarity of Addison's disease in pediatric age, whose diagnosis shouldn't be delayed as it can be fatal. Clinical suspicion of this uncommon pathology is essential. Despite the same diagnosis, there were different presentations, including an equally rare Polyglandular Syndrome.

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Introduction

Adrenal insufficiency is a rare condition in childhood. It is classified as primary when the deficit occurs at the level of the adrenal gland, secondary when occurs at the pituitary level and tertiary when there is hypothalamic involvement.[1,2,3]

Primary adrenal insufficiency (PAI) or Addison's disease (AD) has an incidence of 0.8:100.000, with an estimated lower value in the pediatric population.[1,2] It results from abnormalities in the secretion of adrenocorticoid hormones, despite high levels of corticotropin (ACTH).[2] The etiology in childhood can be congenital (congenital adrenal hyperplasia or autoimmune) or acquired, with iatrogenic causes (as mitotane, ketoconazole, phenobarbital and bilateral adrenalectomy) being the most frequent.[1,3,4]

Clinically, it can be acute (Addisonian crisis) or chronic. Symptoms arise when 75% of the glandular tissue is destroyed. The most common are asthenia (100% of cases), anorexia, weight loss, myalgias, abdominal pain and vomiting.[2,3,4] Skin hyperpigmentation, predominantly on the extensor surfaces, is a classic sign of AD, described in 90%.[4] Addisonian crisis is a potentially fatal medical emergency, presenting often with hemodynamic disturbances (hypotension, tachycardia) and electrolyte abnormalities (hyponatremia, hyperkalemia or hypoglycemia), with a favorable response to intravenous glucocorticoids.[1,2,3,5]

AD can be associated with other autoimmune endocrinopathies, in an autoimmune polyglandular syndrome (APS).[2,6] There are 4 types of known APS, I and II being the most studied.[7] Diagnosis requires study of the glandular function and determination of organ-specific antibodies. Therapeutic guidance and prognosis is based on the treatment of each endocrinopathy.[8]

APS type I is more common in childhood with a prevalence of 1:100.000.[8] It results from autosomal recessive mutations in the autoimmune regulatory gene.[4,6,8] Diagnosis requires at least two of the following: chronic mucocutaneous candidiasis, hypoparathyroidism and AD.[2,4,6,8]

APS type II is more prevalent (1:1.000), mostly affecting women in the 3rd-4th decades of life, with a family history of the disease and being extremely rare in childhood.[6,8] Its etiology is not completely clear, appearing to be an autosomal dominant polygenic disease with incomplete penetrance, associated with

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HLA-DR3 and DR4 haplotypes.[4,6,7,8] Clinically, it presents by AD, autoimmune thyroid disease and/or type 1 diabetes (T1D).[2,7,8] The most frequent association is AD and Hashimoto›s thyroiditis, and the presence of the triad is uncommon.[7] There is usually an interval of years to decades between the appearance of the various endocrinopathies, which makes the diagnosis of APS2 difficult.[6,7]

In patients with APS, other associated autoimmune diseases include vitiligo, alopecia areata, hypogonadism and autoimmune gastritis.[6,8]

Case Report

During the period of the study two cases of adrenal insufficiency were identified in the emergency department in a total of approximately ninety thousand children evaluated.

The first case is a 16-year-old female, Caucasian, daughter of non-consanguineous parents. Family history of a sibling with AD. Evaluated in the Emergency Department (ED) with a 1-month history of asthenia, anorexia, unintentional weight loss (16%) and daily vomiting, predominantly in the morning. No abdominal pain, fever, diarrhea or myalgias. On admission, she was hemodynamically unstable, with hypotension and tachycardia. Objectively with reasonable general condition, discolored and dehydrated mucous membranes, and cutaneous hyperpigmentation. Analytically, she had hyponatremia (123 mmol/L), hyperkalemia (6.7 mmol/L), hypochloremia (90 mmol/L) and hypoglycemia (40 mg/dL), acute kidney injury (serum creatinine 1.2 mg/dL and urea 61 mg/dL) with mild metabolic acidosis. Diagnosis of adrenal crisis was suspected and fluid resuscitation was started with normal saline and intravenous hydrocortisone was administered. Additional study revealed decreased cortisol and aldosterone and elevated ACTH and renin (Table 1); adrenal antibodies were detected. Dehydroepiandrosterone sulfate (DHEA), 17-hydroxyprogesterone, delta-4-androstenedione and testosterone were normal. Autoimmune PAI was confirmed and other endocrinopathies were searched and ruled out. During hospitalization, she remained hemodynamically stable, with favorable response to treatment. Discharged three days later, referred for an Endocrinology consultation and medicated with oral hydrocortisone and fludrocortisone. No episodes of outpatient decompensation.

The second case is a 10-year-old female, Caucasian, no known consanguinity. Relevant family history included a maternal aunt with thyroid disease. Observed in the ED for hypogastric pain with 4 days of evolution, nausea and vomiting on the same day. She also reported anorexia and asthenia for 3 months and her mother noticed skin color change. No fever, diarrhea, myalgias or weight loss. Objectively, she was hemodynamically stable, with reasonable general condition, slightly discolored and dehydrated mucous membranes and sunken eyes. Cutaneous hyperpigmentation on the dorsal surface of the fingers (Figure 1) and in the flexor region of the elbows and knees. Generalized pain on deep palpation of the abdomen, without signs of peritoneal irritation. Analytically with hyponatremia (121 mmol/L), hyperkaliemia (5.3 mmol/L), hypochloremia (88 mmol/L) and hypoglycemia (57 mg/dL). Intravenous fluid therapy and hydrocortisone were started. Study revealed decreased cortisol and aldosterone and increased ACTH and renin (Table 1) along with adrenal antibodies. DHEA, 17-hydroxyprogesterone, delta-4-androstenedione and testosterone were unchanged. Abdominal computed tomography showed no abnormalities concerning the adrenal glands. Other endocrinopathies were investigated with findings of primary subclinical hypothyroidism - increased TSH and normal free T4 (Table 1), anti-peroxidase antibodies and ultrasound signs of thyroiditis. Addison's disease associated with Hashimoto's Thyroiditis established a diagnosis of APS2. Oral hydrocortisone and fludrocortisone were started and she was discharged four days later, with symptomatic improvement. During follow up thyroid replacement therapy was started. She maintains clinical stability.

Figure 1. Hyperpigmentation of the fingers (Dorsal Surface).

Discussion

The rarity of Addison's disease in pediatric age, as evidenced in our series, should not lead to a delay in diagnosis, as it can be fatal. In the face of abdominal pain, vomiting, anorexia, asthenia, weight loss and skin hyperpigmentation, PAI should be considered with adequate investigation and therapy started. The appearance of these two cases in a short time in a Pediatric ED reflects the need to maintain clinical suspicion for this uncommon pathology. Despite the same diagnosis, there were different forms of presentation, including an equally rare Polyglandular Syndrome.

In the first case, the disease manifested through an Addisonian crisis, the most severe and life-threatening manifestation of PAI.[2,4,5] Treatment should be started as soon as possible and consists of the administration of a bolus of normal saline (20 mL/kg) and intravenous hydrocortisone (100 mg/m^2/day).[2,3,4,5] These patients require hemodynamic, symptomatic and analytical monitoring.[4] After treatment of the crisis, maintenance therapy should be started.

The second patient presented characteristic symptoms of PAI, without hemodynamic repercussions. For diagnostic confirmation, it is recommended to measure serum cortisol (normal or decreased), ACTH (increased), renin (increased) and aldosterone (decreased), as well as the investigation of anti-adrenal antibodies.[4] As in our case, the absence of symptoms of other endocrinopathies should not delay the diagnosis of APS, and glandular function should be evaluated, and

Table 1. Results of the investigation of adrenal and thyroid functions.

Analytical results	Case 1	Case 2	Reference range
Cortisol (µg/mL)	0.51	1.5	5.5-8.8
ACTH (pg/mL)	3482	2415	9-52
Aldosterone (pg/mL)	<7	31	42-2020
Renin (pg/mL)	1662	>310	1.25–23.1
TSH (µUI/mL)	2.69	42.21	0.35–5
Free T4 (ng/dL)	1.23	0.67	0.54–1.24

auto-antibodies investigated, namely anti-thyroid, anti-pancreatic islets, anti-glutamic-acid-decarboxylase, anti-gastric parietal cells and anti-transglutaminase.[2,6]

APS type 2 is rare in pediatric patients[6], which makes the diagnosis harder. Therapy for adrenal insufficiency should be initiated prior to thyroid supplementation, in order to prevent Addisonian crisis.[4,6,7] In pediatric age, the recommended treatment for AD consists of lifelong administration of oral hydrocortisone (10-20 mg/m^2/day, 3 times daily) and oral fludrocortisone (0.1-0.2 mg/day).[2,4] In situations of physiological stress, such as surgery, trauma or episodes of diarrhea with fever, the hydrocortisone dose should be doubled or tripled, for 24-48 hours.[3,4,5]

Conclusion

These cases evidence that adrenal insufficiency may have a wide range of clinical presentation. Its diagnosis requires a high degree of suspicion, given the nonspecific symptomatology and consequences of late diagnosis.

APS2 is an uncommon pathology, extremely rare in childhood, for which physicians should be aware. It is important to perform clinical and laboratory surveillance of other immune pathologies, in the short and long term, since in APS2 there is usually an interval between them that varies from years to decades. This case of APS2 is particularly relevant due to the very rare age of presentation at 10 years of age.

Compliance with Ethical Standards
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