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CASE REPORT

# Delayed diagnosis of adrenal insufficiency in a patient with presumed eating disorder

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## Abstract

Adrenal insufficiency (AI) is a rare condition that can be potentially life-threatening and manifests as an endocrine emergency. The authors present the case of a primary AI in a 13-year-old girl, previously followed in a pediatric and psychology consultation due to weight loss and anorexia, with suspected eating disorder. On admission, the patient had moderate dehydration, asthenia and palmar and gingival hyperpigmentation that raised the hypothesis of adrenal insufficiency. Laboratory results confirmed the diagnosis: hyponatremia, hyperkalemia, high adrenocorticotropic hormone (ACTH) and low cortisol levels. Treatment with hydrocortisone and fludrocortisone was started, with favorable response. The nonspecific nature of the presenting symptoms, underlines the importance of a high level of suspicion. AI is a rare diagnosis that can be misdiagnosed or misinterpreted with more frequent diseases such as eating disorders, delaying timely diagnosis and treatment.

***Keywords:*** Adrenal insufficiency. Addison's disease. Diagnostic challenges. Eating disorders.

## *Diagnóstico tardio de insuficiência adrenal em paciente com transtorno alimentar presumido*

## Resumo

A insuficiência adrenal (IA) é uma patologia rara que pode ser potencialmente fatal e manifestar-se sob a forma de uma emergência endócrina. Os autores apresentam o caso de uma IA primária numa adolescente de 13 anos, previamente seguida em consulta de Pediatria Geral e de Psicologia, por perda de peso e anorexia, em contexto de um possível transtorno alimentar. À admissão a doente apresentava uma desidratação moderada, astenia e hiperpigmentação palmar e gengival, o que levantou a hipótese de se tratar de uma insuficiência adrenal. Os resultados laboratoriais confirmaram o diagnóstico: hiponatrémia, hipercalémia, hormona adrenocorticotrófica elevada (ACTH) e níveis baixos de cortisol. Iniciou tratamento com hidrocortisona e fludrocortisona, com resposta favorável. A natureza inespecífica dos sintomas apresentados sublinha a importância de um elevado nível de suspeita. A AI é um diagnóstico raro que pode ser confundido com doenças mais frequentes, tais como distúrbios alimentares, o que pode atrasar o diagnóstico e o tratamento.

***Palavras chave:*** Insuficiência adrenal. Doença de Addison. Desafios diagnósticos. Distúrbios alimentares.

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## Keypoints

**What is known**

– Adrenal insufficiency is a rare condition in pediatmanifest as an endocrine emergency.
– It can present as a wide range of nonspecific symptoms and can be misdiagnosed with phycological insufficiency is necessary to ensure appropriate gluses, and to optimize growth and development.
– A high degree of suspicion is required to make the cocorticoid dosing, to manage potential adrenal cridiagnosis.

**What is added**

– Prompt treatment is critical and consists of glurics that can be potentially life-threatening and cocorticoid replacement.
– Hydrocortisone is used as a first-line approach in pediatric cases.
– Close monitoring of pediatric patients with adrenal disorders or mimic an eating disorder.

## Introduction

Adrenal insufficiency (AI) is defined by the impaired synthesis of adrenocortical hormones[1]. According to the pathophysiology, AI can be classified as primary, secondary or tertiary.

Glucocorticoid deficiency presents as fatigue, nausea, fasting hypoglycemia, increased insulin sensitivity, muscle weakness, and orthostatic hypotension. These may be of insidious onset. Hyperpigmentation of skin, gingiva, palmar rids or scars is present only in primary AI because it is secondary to high ACTH levels and other pro-opiomelanocortin peptides effects. Mineralocorticoid deficiency presents as a salt-losing syndrome, with dehydration, dizziness, salt craving, weight loss, anorexia, hypotension, and electrolyte abnormalities (metabolic acidosis, hyponatremia and hyperkalemia).

In one third of cases, adrenal crisis (AC) is the initial presentation of AI. Both AC and AI can be potentially life-threatening and lead to shock if not managed quickly[2].

Treatment consists of hormone replacement therapy. The prognosis is favorable with a rigorous adherence to therapy[3].

## Case report

A 13-year-old caucasian girl was referred to a pediatric and psychology consultation, with suspicion of an eating disorder due to weight loss and anorexia with one year of evolution. A restrictive eating pattern was described, with low appetite. In school, her grades dropped and she stopped practicing swimming because of the fatigue.

She was born prematurely, at 34 weeks, from a mono-chorionic and biamniotic gestation. She was previously healthy, with regular growth (weight in $3^{th}$-$15^{th}$ percentile and height in $15^{th}$-$50^{th}$ percentile – WHO Growth Charts), and thelarche at 11 years. Six months before the admission she was in Tanner stage II (M2P2), with no menarche. Her weight progressed towards under the $5^{th}$ percentile (33 Kg) without any repercussion on growth. Her Body mass index (BMI) was 14.67 – z score of -2.07 – WHO Growth Charts.

Use of medication or supplements was denied. There was no family history of immunologic, autoimmune or other diseases.

A thorough investigation had been conducted, which was unremarkable and included complete blood count, electrolytes, celiac disease screening and kidney, liver and thyroid function.

Two months before admission to the ED, she reported asthenia and intermittent episodes of abdominal pain, diarrhea and vomiting. During a holiday travel, this condition worsened, leading to ED admission upon arrival in Portugal. On examination, she weighed 31 Kg (loss of 2 Kg in 6 months), was afebrile, in a stable hemodynamic state (blood pressure [BP] of 103/70 mmHg – in the $41^{st}$/$75^{th}$ systolic/diastolic BP percentile for sex, age and height, heart rate of 99 bpm), had an emaciated appearance, moderate signs of dehydration, constitutional cutaneous brown tone but with slight palmar and gingival hyperpigmentation (Fig. 1). The remaining physical examination was unremarkable. Laboratory tests revealed severe hyponatremia (117 mmol/L reference range (RR): 136-145 mmol/L), mild hyperkalemia (6.4 mmol/L - RR: 3.5-5.1 mmol/L), hypoglycemia (43 mg/dL) and a compensated metabolic acidosis (venous blood gas: pH 7.371, HCO– 20,9 mmol/L, $PCO_2$ 37mmHg). An Intravenous (IV) bolus of 0.9% saline solution 10ml/kg and then a 10% dextrose was given to normalize glycemia, rehydrate and normalize the electrolyte imbalance. She then started IV 0.9% saline solution with 5% dextrose to basic needs. A 10% calcium gluconate was also given in order to stabilize cardiac cell membranes and then inhaled salbutamol was administered to decrease serum potassium levels.

Further analytical study showed high ACTH (> 1250 pg/mL - RR 6-48) and low cortisol levels (1.29 ug/dL at 8 am). It also showed normal

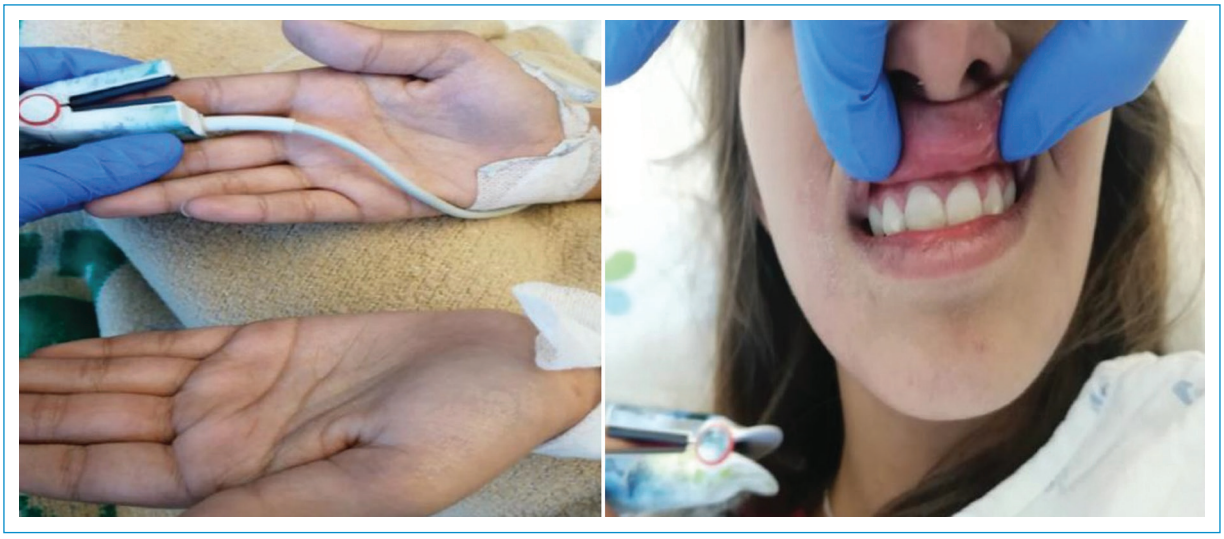

**Figure 1.** Palmar and gingival hyperpigmentation.

17-hydroxyprogesterone levels (0.23ng/mL – RR < 0,32ng/mL) and negative adrenal antibodies (Table 1). Clinical and analytical data were suspicious of an adrenal crisis and a stress dose of IV hydrocortisone (100mg) was administered 8 hours after the admission.

Hospitalization at the Pediatric Intermediate Care Unit was decided for rigorous treatment as well as clinical and analytic surveillance. Therapy was changed to oral hydrocortisone and fludrocortisone after 48 hours and she became progressively less symptomatic with gradual analytical improvement. No other hormonal derangements were found (Table 1). Auto-immunity was positive only for antinuclear antibodies (ANA 1/160), thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies. A subclinical hypothyroidism (high TSH with normal T4L) was also diagnosed, however, during the follow-up, this was corrected with no specific treatment. (Table 1).

She was discharged on the fourth day after admission under hydrocortisone 18 mg/m$^2$/day and fludrocortisone 0,1 mg/day with the diagnosis of primary adrenal insufficiency. Her follow-up keeps on going with regular pediatric endocrinology consultations. One month later, she had gained weight, cutaneous and gingival hyperpigmentation had improved and she had menarche. Nine months later, she was asymptomatic and remains under hydrocortisone 13 mg/m$^2$/day and fludrocortisone 0,1 mg/day. No side effects of the corticoids were noticed or described.

**Table 1.** Complementary laboratory test results

| | Results |
|---|---|
| Anti Ds-DNA antibodies | Negative |
| Anti mitochrondrial M2 antibodies | Negative |
| ANA | Positive 1/160 |
| Anti-parietal cell antibodies | Negative |
| Anti-LKM antibody | Negative |
| ANCA – MPO and PR3 | Negative |
| Anti-adrenal antibodies | Negative |
| IgA anti-endomysial antibody | Negative |
| ENA | All negative |
| T3L | 4.77 pg/ml (RR: 3.0-4.7pg/mL) |
| T4L | 1.02 ng/dL (RR: 0,83-1,43ng/dL) |
| TSH | 9.904 uUI/ml (RR: 0.48-4.17uUI/mL) |
| Anti-Tg antibodies | 143.12 U/mL (RR: < 60U/mL) |
| Anti-TPO antibodies | 159.10 UI/ml (RR: < 60U/mL) |
| FSH | 7.28mUI/mL-Normal |
| LH | 1.84mUI/mL-Normal |
| Estradiol | 103.30pmol/L (RR: 59.1-874.6 pmol/L) |
| 17-Hydroxyprogesterone | 0.23 ng/mL (RR < 0.32ng/mL) |

ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; ENA: anti extractable nu-clear antigens; T3L: free triiodothyronine; T4L: free thyroxine; TSH: thyroid-stimulating hormone; Anti-Tg: antithyroglobulin; Anti-TPO: antithyroid peroxidase; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

## Discussion

The authors report a case of primary AI in a child. Primary AI results from intrinsic disease of the adrenal cortex and patients may present with symptoms of glucocorticoid and/or mineralocorticoid deficiency. Hypothalamic-pituitary-adrenal axis remains intact, under no negative cortisol feedback control, resulting in adrenocorticotropic hormone (ACTH) elevation[1]. The incidence of primary AI in children is unknown. Primary AI is caused by either genetic defects or an acquired disease that affects adrenal function by the following processes: steroidogenic disorders (including congenital adrenal hyperplasia), adrenal damage (such as autoimmune injury like Addison disease or infections), peroxisomal disorders, abnormal adrenal development or drugs. Congenital adrenal hyperplasia, which occurs in approximately 1:14200 live births, is the most common cause of primary AI, followed by autoimmune adrenal failure[4,5].

Secondary AI is caused by a pituitary disease that impairs ACTH synthesis. Tertiary AI is caused by interference with hypothalamic corticotropin-releasing hormone (CRH) production. Patients with secondary or tertiary AI have only glucocorticoid deficiency and no mineralocorticoid deficiency because adrenal glands are intact and still produce mineralocorticoids, especially aldosterone, in response to other stimulus. In addition, they may have other pituitary hormone deficiencies, depending on the etiology (genetic, congenital malformation, pituitary tumors or infiltrative disorders, post-surgery or radiotherapy)[3].

In this case, the most likely etiology was autoim-mune, even with adrenal antibodies being negative. All the other causes were considered, but easily excluded. The diagnosis of Addison's disease should guide investigation of an autoimmune polyglandular syndrome. In this patient, anti-TPO e anti-Tg antibodies were positive, but the subsequent investigation was negative. Despite this fact, the possibility that other autoimmune antibodies may appear only later in life implies maintaining long-term clinical and laboratory surveillance.

AI presents as a wide range of nonspecific symptoms, such as weakness, weight loss, abdominal pain, nausea and vomiting and, as described in this report, it can be misdiagnosed with phycological disorders and can mimic an eating disorder[6]. In adolescents, this entity is more difficult to diagnose due to the biopsychosocial factors frequently involved and nonspecific nature of the symptoms. Sometimes the diagnosis is significantly delayed, which increases the associated morbidity and mortality[7].

Patients may present with hypotension, tachycardia and cutaneous or mucosal hyperpigmentation, however, in pediatric patients these findings are not usually observed[3]. In this case, the patient had a stable hemodynamic state, she already had a constitutional cutaneous brown tone, but a close observation could detect a slight palmar and gingival hyperpigmentation.

Adrenal crisis can result from acute AI or can superimpose a chronic AI during mild intercurrence such as illness, stress, etc. In children, the predominant clinical features are hypotension and electrolyte abnormalities resulting from mineralocorticoid deficiency. These features are more proeminent and possibly life-threatening when compared to symptoms of glucocorticoid deficiency. However, typically, both hormones are deficient and contribute to the clinical presentation. Shock may occur in severe cases and can be fatal[3,8]. This patient showed serum electrolytes imbalance (severe hyponatremia, hyperkalemia, hypoglycemia and compensated metabolic acidosis) and there was no hypotension or shock. In this case, the adrenal crisis was the form of presentation and contributed to establishment of the diagnosis. Attending to the insidious nature of AI, a high suspicion index is needed[9].

To minimize morbidity and mortality, prompt recognition and treatment is critical. A stress dose of hydrocortisone should be administered as early as possible (100 mg IV is the recommended dose for children above 11 years)[3]. In the acute phase of treatment, no mineralocorticoid replacement is needed because hydrocortisone has some mineralocorticoid activity[10].

Admission to an Intermediate or Intensive Care Unit is recommended, especially when there are severe electrolyte disorders and/or hypotension and shock. There should be a close and rigorous monitoring of hemodynamic parameters, water balance, serum electrolytes and glucose.

In our patient, maintenance treatment included physiologic glucocorticoid and mineralocorticoid replacement. Hydrocortisone is used as the first-line approach to glucocorticoid replacement in pediatric cases of AI, due to its shorter duration of action and lower potency, allowing fine titration of optimal individual dose (between 7-20 mg/m$^2$/day) and lower side effects on growth10. Fludrocortisone is used for mineralocorticoid replacement at a dose of 0.05-0.1 mg/day when given in association with hydrocortisone. During some conditions like illness, fever or stress, the dosage of glucocorticoids may need to be increased. Patient education about the recognition of precipitating symptoms and how to act in impending adrenal crisis are also very important[1,10].

The main goal of the treatment and follow-up of children with AI is to control the symptoms of AI with a dose that allows adequate growth, pubertal

development and fertility, which is only achieved with apropriate therapy adherence.

## Conclusion

The diagnosis of AI requires a high degree of suspicion. It can be potentially life-threatening as it can manifest as adrenal crises, an endocrine emergency. The authors intend to alert of this diagnosis in the early stages of disease, namely to its nonspecific symptoms, such as weight loss, that can be misdiagnosed or misinterpreted as eating disorders.

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