

Clinical Case Seminar

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Diagnostic difficulties of Addison's disease in children: a case report

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Abstract

Addison's disease is a rare chronic endocrine disorder resulting from primary adrenal insufficiency. Symptoms are non-specific and can arise insidiously, including asthenia, muscular weakness, weight loss, irritability, depression, loss of appetite, dyspepsia, nausea and vomiting. A peculiar clinical sign of Addison's disease is hyperpigmentation of skin and mucous membrane due to overproduction of pro-opiomelanocortin (POMC), precursor of ACTH and MSH (melanocyte stimulating hormone). Without therapy or in the course of triggering events such as infections, surgery or trauma the presentation can be dramatic and may cause an adrenal crisis, a potentially lethal medical emergency. Biochemical investigations are essential for diagnosis and commonly reveals electrolyte abnormalities (hyponatraemia and hyperkalaemia), hypoglycaemia, reduced cortisol levels and increased levels of ACTH. The lack of response to ACTH stimulation test confirms the primary adrenal insufficiency. Treatment for Addison's disease is based on replacing missing cortisol, the most commonly used drug is hydrocortisone often in association with fludrocortisone as replacement for the missing aldosterone. Due to its non-specific presentation, identification of this condition is difficult and can be confused with other disorders, for example eating disorders. We report a case of a young boy with Addison's disease mistaken for anorexia nervosa.

Key Words: Addison's disease, primary adrenal insufficiency, autoimmune adrenalitis, anorexia nervosa, eating disorders

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Introduction

Addison's disease (AD) is a rare condition caused by insufficient production of adrenocortical hormones. It requires a prompt diagnosis and treatment because it can result in adrenal crisis, potentially life-threatening event. In adults autoimmune destruction of adrenal cortex is a major cause of primary hypoadrenalism, otherwhereas, in children, autoimmune adrenalitis represents about 15 percent of the causes (1). Other causes can be infections such as tuberculosis, drugs, tumors or genetic defects. In some cases autoimmune AD can be associated with other autoimmune disorders depicting an autoimmune polyendocrine syndrome (APS) type 1 or 2 or 4 or can be isolated (2,3).

Tab.1 Investigation consistent with a diagnosis of autoimmune Addison's disease

Analyte (unit of measure)	Patient's value	Normal range
SERUM		
ACTH (ST) baseline (pg/ml)	>2000	6-40
Cortisol (ST) baseline (ug/dl)	<0.25	7.3-32.3
Cortisol (ST) T60' (ug/dl)	<0.25	
ACTH 08.00 am (pg/ml)	>2000	6-40
Cortisol 08.00 am (ug/dl)	<0.25	7.3-32.3
ACTH 03.00 pm (pg/ml)	1954.7	3-30
Cortisol 03.00 pm (ug/dl)	<0.25	3.2-15
Cortisol 00.00 (ug/dl)	<0.25	
Sodium (mmol/L)	131	134-145
Potassium (mmol/L)	4.6	3.5-5.2
Aldosterone (pg/ml)	10.8	35-300
Renin (pg/ml)	>320	5.1-38.7
Insulin (uIU/ml)	4.85	2.6-25
Thyroid peroxidase antibodies (UI/ml)	<9	0-34
Antithyroglobulin antibodies (UI/ml)	<10	0-115
Anti-TSH receptor antibodies (UI/L)	0.72	<1
FT4 (pmol/l)	15.9	12-22
TSH (uIU/ml)	3.89	0.27-4.2
Antibodies in T1DM (GAD, ICA, IA2, IAA, ZnT8)	negative	
Adrenal antibodies (21-hydroxylase) (U/ml)	10.4	<0.4
URINE		
Creatinine clearance (ml/min)	144.37	
Free Urinary Cortisol (ug/dl)	<0.25	

ST: stimulation test, T1DM: type 1 diabetes mellitus

Case presentation

A 14 year old boy was admitted to our Neuropsychiatric Centre under suspicion of an eating disorder. In his family history there was no consanguinity between parents and no autoimmune diseases were referred. A maternal aunt had suffered from anorexia nervosa. He had an history of recent weight loss (8 Kg in the previous 2 months), anorexia, fatigue, recurrent abdominal pain, intermittent vomiting, pains and cramps in the lower limbs. It was reported that two years earlier, he had been hospitalized for acute abdominal pain treated with antibiotics in suspicion of appendicitis. More recently, he had been admitted to hospital for a suspected septic shock treated with antibiotic, fluid resuscitation and hydrocortisone. In the last few months he

had been made admitted several times to the emergency room for presyncope episodes, abdominal pain and sporadic vomiting. During his last visit, blood tests showed hyponatraemia and increase in serum urea; physical examination showed hypotension, so he was transferred to our neuropsychiatric department under suspicion of anorexia nervosa.

During the hospitalization the investigation did not reveal any body image distortion and the patient showed a preference for high salt containing foods. On various occasions he presented episodes of hypotension and tachycardia, serum level of sodium remained low despite intravenous rehydration. For these reasons he was transferred to our pediatric department.

On clinical examination he was dehydrated, his blood pressure was 99/65 mmHg, heart rate 113/min, weight 47,5 Kg (25th-50th centile), height 165 cm (50th centile), BMI 17 Kg/m² and he was not pigmented. All routine serum parameters were in the normal range, except sodium, that was 131 mmol/L (range 134-145 mmol/L).

Due to suspicion of adrenal insufficiency, we performed ACTH stimulation test that demonstrated a flat cortisol response. We rancircadian rhythms of cortisol and ACTH and cortisol dosage in 24h urine sample, which were altered (Tab.1). Adrenal antibodies were also positive. In this patient no signs of chronic candidiasis, hypocalcemia, other autoimmune clinical diseases, ectodermal dystrophy were present and the screening for thyroid and pancreas autoimmunity was negative. On the basis of patient's history, combined with biochemical testing, a diagnosis of isolated autoimmune AD was established.

We immediately started replacement steroid therapy (hydrocortisone 12.5 mg/die) and fludrocortisone at 100 mcg.

We also have educated the family regarding emergency treatment in course of acute illnesses in order to prevent adrenal crises.

High-resolution computed tomography of the chest (HRCT) showed a bilateral, but with the prevalence in the right lung, pattern of interstitial lung disease with diffuse ground glass opacities, interstitial thickening, traction bronchiectasis and honeycombing (Figure 1, panel B, C, D). The HRCT pattern was consistent with a diagnosis of amiodarone-induced pulmonary fibrosis (2). Therapy with amiodarone was stopped and replaced with bisoprolol 2,5 mg/daily and a therapy with systemic glucocorticoids (prednisone 25 mg/daily) was started for 15 days. After 4 days the fever has disappeared. Another ABGA performed in breathing room air 4 days after amiodarone discontinuation showed the presence of mild hypoxemia: pH 7.43, PaO₂ 75 mmHg, PaCO₂ 34 mmHg, SpO₂ 95%. After 15 days the patient was discharged. He did not present at the follow-up visit. The patient died five months later in the Pulmonology clinic "Vittorio Emanuele" University Hospital of Catania, Italy during another acute exacerbation of its disease

Discussion

Chronic adrenal insufficiency is a rare condition, often misunderstood due to lack of specific signs and symptoms. If it is untreated and unrecognised it can lead to adrenal crisis, which is a medical emergency, even with fatal consequences (4).

The wide variety in symptoms often causes a delay in diagnosis, because of erroneous attribution to other pathological condition and the main signs such as pigmentation of skin or mucous may be missed or not be present (5). For these reasons AD can be very difficult to diagnose and patients can be evaluated by lots of healthcare professionals such as gastroenterologists or neuropsychiatrists before being correctly diagnosed (6,7) About half of the patients are only diagnosed after an acute adrenal crisis, often precipitated by an infection or other kind of stress. During crisis patients present an acute decline of general conditions with severe dehydration, hypotension or shock. Crisis can be triggered by sepsis, and sepsis can mask signs of adrenal insufficiency and make the diagnosis harder (6).

In this case an eating disorder was initially suspected due to hyporexia, vomiting and weight loss. In teenagers when investigating for fatigue, refusal of food and weight loss, the diagnosis of AD is often underestimated because other diagnosis, such as anorexia nervosa, are more common.

Anorexia nervosa is a functional eating disorder characterized by voluntarily weight loss, induced and sustained by the patient himself, associated with a specific psychopathology which imposes a very low weight threshold. Although it is more frequent in adolescent girls, adolescent boys may also be affected. Anorexia nervosa and AD have many features in common, like refusal of food, weight loss, vomiting, hypotension, hyponatremia, hypoglycemia and hyperpigmented skin (8).

Nevertheless, taking an accurate history, careful physical examination and performing screening biochemical tests such as electrolytes, cortisol and ACTH measurements can help differentiate the two conditions.

The patients affected by anorexia nervosa have a body image distortion, fear of weight gain and are fat phobic. Our patient had salt craving behaviour and preference for high fat containing foods as classically seen in AD. Physical examination in subjects with anorexia nervosa can detect bradycardia even during hypotension, instead tachycardia is common in AD (9). Pigmentation of skin and mucous can be present in both conditions.

In our case despite the presence of very high ACTH levels no signs of hyperpigmentation were present and this can probably be due to the fact that the increment of ACTH was of recent onset and not sufficient to produce hyperpigmentation.

Biochemical evaluation is critical to differentiate between the hypercortisolemic state seen in anorexia nervosa and reduced cortisol levels in AD. Hyponatremia may be present in both conditions but

hypokalemia is commonly seen in anorexia nervosa, while hyperkalemia is typical of AD (10).

It is important to underline that in general the great majority of the young patients with AD the disease is due to genetic forms, and that autoimmune forms are present in about 15% and manifesting as autoimmune polyendocrine (APS) type 1, 2 or 4 or isolated AD. In this patient a diagnosis of isolated autoimmune AD was established.

Without immediate steroid treatment, AD can have fatal consequences. Hydrocortisone doses of 6-8 mg/m²/day, in 3-4 divided doses, might be adequate for replacement therapy.

It is essential to educate patients and their families on how to manage therapy during times of acute stress or illness to prevent potentially deadly adrenal crises. During febrile illnesses, hydrocortisone doses should be 2-3 times higher than baseline levels. It is also crucial to highlight the importance of administering intramuscular hydrocortisone, 50 mg/m²/day, at home when children are unable to tolerate oral hydrocortisone.

In conclusion, AD can be a challenging diagnosis which may be missed because of its non-specific symptoms. A delay in diagnosis can lead to fatal consequences, so it is important that this condition be excluded even in children investigated for eating disorder.

Conflicts of interest: The authors declare no conflict of interest.

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