Medicina de Familia
SEMERGEN
www.elsevier.es/semergen

CLINICAL LETTER

Atypical presentation of Addison's disease with chest pain and dizziness: A case report and literature review

Dolor torácico y mareos como presentación atípica de la enfermedad de Addison: reporte de caso y revisión bibliográfica

Introduction

Addison's disease, also known as primary adrenal insufficiency, is an endocrine disorder characterized by insufficient production of hormones by the adrenal glands, primarily cortisol and aldosterone.[1,2] It is a rare condition, with an incidence of 0.83 cases per 100,000 inhabitants and a prevalence of 4–6 cases per 100,000 inhabitants.[3,4] The average age of onset is 40 years, although it can occur at any age. Currently, the most common cause is autoimmune adrenalitis, followed by tuberculosis, and subsequently other causes such as systemic fungal infections, human immunodeficiency virus (HIV), neoplasms, and drugs.[5,6]

Clinically, it presents with asthenia, muscle weakness, weight loss, gastrointestinal symptoms, hypotension, and hyperpigmentation. In extreme cases, potentially life-threatening adrenal crises may occur.[6] Early diagnosis is challenging due to its nonspecific clinical presentation and low clinical suspicion. Diagnosis is based on a combination of clinical evaluation, laboratory tests, and, in some cases, imaging studies. Confirmation requires measuring serum cortisol, serum ACTH, and, occasionally, conducting ACTH stimulation tests and imaging studies.[1,7]

It is crucial to consider family history and associated autoimmune disorders, as these may influence the patient's predisposition to developing the disease.[4] Treatment involves hormonal replacement therapy, usually with glucocorticoids and, in some cases, mineralocorticoids.[1] This case report highlights an unusual presentation of Addison's disease with atypical chest pain and dizziness, which initially delayed the diagnosis.

Case report

A 36-year-old Spanish male presented to primary care physician with episodes of non-radiating, oppressive chest pain triggered by intense exercise. Each episode lasted about an hour and was accompanied by dizziness that resolved with rest. At the time of consultation, he had no active symptoms. His medical history included autoimmune hypothyroidism, treated with levothyroxine, and he had no cardiovascular risk factors. He denied a family history of cardiovascular diseases or other significant conditions during the initial consultation.

During the physical examination, his vital signs were normal (BP: 110/79 mmHg, HR: 75 bpm, oxygen saturation: 98% on room air), and cardiopulmonary auscultation revealed no abnormalities. An electrocardiogram showed no significant alterations, and the pain was initially attributed to a probable musculoskeletal origin.

A week later, the patient presented to the emergency department due to persistent chest pain when doing exercise, dizziness and had detected hypotension at home (80/40 mmHg). There was no quantifiable weight loss or additional symptoms like asthenia or abdominal pain. He also reported having noticed unusually intense skin pigmentation after a recent trip, especially in areolas, as well as a family history of Addison's disease on his maternal aunt's side. Blood tests revealed hyponatremia (125 mEq/L), hypoglycemia (63 mg/dL), and acute kidney injury (urea: 65 mg/dL, creatinine: 1.64 mg/dL, estimated glomerular filtration rate: 53 mL/min), abnormalities not previously noted in prior tests.

The patient was admitted for a comprehensive evaluation, during which cortisol levels were measured at 2.6 μg/dL and serum ACTH levels at 1040 pg/mL, confirming the diagnosis of primary adrenal insufficiency. Replacement therapy with hydrocortisone and fludrocortisone was initiated, leading to a rapid improvement in both symptoms and laboratory parameters (natremia 129 mEq/L and renal function normalized at discharge).

Additionally, screening for other autoimmune conditions (celiac disease, pernicious anemia, type 1 diabetes) was performed, all of which were negative.

https://doi.org/10.1016/j.semerg.2024.102440

Discussion

Addison's disease is a chronic condition characterized by an insufficient secretion of adrenal cortical hormones relative to the body's needs. It progresses gradually, with acute exacerbations (Addisonian crises) occurring under stress, and without proper treatment, it can be fatal.

Family history is a key factor in evaluating the risk of Addison's disease in patients with compatible symptoms, as a genetic connection to susceptibility has been established. Variants in the HLA gene, such as HLA-DRB1*04:04, have been associated with an increased risk of developing this condition.[2,6]

In over 50% of cases, Addison's disease is associated with other autoimmune conditions, forming part of polyglandular syndrome types 1 and 2. When adrenal insufficiency is autoimmune in nature, other associated diseases, such as chronic thyroiditis, autoimmune hypoparathyroidism, or type I diabetes, should be ruled out.[1]

Symptoms can be categorized according to the hormone deficiencies they cause:

Glucocorticoid deficiency: skin and mucosal hyperpigmentation (evident in exposed areas, palmar creases, knuckles, nails, genital mucosa, areolas, oral mucosa, tongue, and scars), hypoglycemia, asthenia, muscle fatigue, abdominal pain, nausea, diarrhea, constipation, mental fatigue, insomnia, irritability, or depression.
Mineralocorticoid deficiency: arterial hypotension, orthostatic hypotension, dizziness, tachycardia, palpitations, syncope.
Androgen deficiency: loss of axillary and pubic hair, oligomenorrhea, and libido inhibition.

Laboratory findings may include normocytic normochromic anemia, eosinophilia, increased erythrocyte sedimentation rate (ESR), hypoglycemia, hyponatremia, hyperkalemia, and hypercalcemia.

Upon clinical suspicion and biochemical analysis, a baseline plasma cortisol level of <3 μg/dL combined with a baseline ACTH level > 100 pg/mL will confirm the diagnosis of adrenal insufficiency, while a baseline plasma cortisol > 19 μg/dL will exclude it. However, a normal baseline ACTH does not rule out the diagnosis.

If cortisol levels are between 3 and 19 μg/dL, an ACTH stimulation test is performed. After administering 250 μg of synthetic ACTH, cortisol is measured at baseline, 30, and 60 min. A cortisol level > 19 μg/dL at any time is considered normal.

For etiological diagnosis, the detection of adrenal antibodies serves as a diagnostic marker for autoimmune adrenalitis. In cases where the cause is not autoimmune adrenalitis, other tests such as computed tomography (CT) scan can be performed.

Management of an adrenal crisis involves administering an intravenous bolus of 100 mg of hydrocortisone, followed by adding 200–300 mg in normal saline over the next 24 h. Doses above 60 mg/day of hydrocortisone do not require fludrocortisone administration. Electrolyte replacement and treatment of the triggering cause are also necessary.

Maintenance treatment involves oral hydrocortisone at doses of 20–30 mg/day, divided into two-thirds in the morning and one-third in the afternoon, gradually reducing the dose to the minimum that maintains symptom control. Additionally, fludrocortisone treatment should be initiated at 50–200 μg/day in a single daily dose. The dose is adjusted based on blood pressure, plasma renin activity, and blood potassium levels.

Corticosteroid dosage should be increased during stress situations (infections, surgery, etc.).

This comprehensive approach to Addison's disease management focuses on stabilizing endocrine function and preventing severe complications through timely intervention.[5,8]

Conclusions

This case highlights the importance of considering endocrine diagnoses in patients with atypical symptoms, especially in the absence of cardiovascular risk factors. Addison's disease can manifest with cardiovascular symptoms like dizziness and chest pain due to hypovolemia and hypotension, making it crucial to include it in the differential diagnosis when symptoms are not easily explained.[2]

In this patient, despite the absence of electrocardiogram abnormalities, adrenal insufficiency could have contributed to hemodynamic instability.

Appropriate management of Addison's disease not only alleviates symptoms caused by cortisol deficiency but also stabilizes the patient's cardiovascular status.[2,6]

Hyponatremia in the context of dizziness, hypotension, and hyperpigmentation in a patient with a history of autoimmune hypothyroidism and family history of Addison's disease were key clues for the diagnosis. Cases like this underscore the need to consider Addison's disease when patients present with atypical or nonspecific symptoms, particularly if there is a personal or family history of autoimmune disorders.[8]

Diagnosis in primary care settings is feasible and can significantly impact the patient's prognosis.

Informed consent

The participant has provided consent for the submission of the case report to the journal.

Ethical approval

Ethical approval was waived by the local Ethics Committee of Hospital Universitario y Politécnico La Fe in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Fundings and supports

None.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Husebye E, Løvås K. Pathogenesis of primary adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2009;23:147–57, http://dx.doi.org/10.1016/j.beem.2008.09.004.
2. Mitchell AL, Pearce SHS. Autoimmune Addison disease: pathophysiology and genetic complexity. Nat Rev Endocrinol. 2012;8:306–16, http://dx.doi.org/10.1038/nrendo.2011.245.
3. Candel González FJ, Matesanz David M, Candel Monserrate I. Insuficiencia corticosuprarrenal primaria. Enfermedad de Addison. Anal Med Intern (Madrid). 2001;18:492–8.
4. Gombos Z, Hermann R, Kiviniemi M, Nejentsev S, Reimand K, Fadeyev V, et al. Analysis of extended human leukocyte antigen haplotype association with Addison's disease in three populations. Eur J Endocrinol. 2007;157:757–61, http://dx.doi.org/10.1530/EJE-07-0290.
5. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Ann Rev Physiol. 2005;67:259–84, http://dx.doi.org/10.1146/annurev.physiol.67.040403.120816.
6. Napier C, Pearce SHS. Autoimmune Addison's disease. Presse Med. 2012;41:e626–35, http://dx.doi.org/10.1016/j.lpm.2012.09.010.
7. Fernández Serrano F, Collado Sáiz I, del Cañizo Gómez FJ. Insuficiencia suprarrenal primaria como primera manifestación de un síndrome pluriglandular autoinmune. SEMERGEN. 2005;31:31–4.
8. Ngaosuwan K, Johnston DG, Godsland IF, Cox J, Majeed A, Quint JK, et al. Cardiovascular disease in patients with primary and secondary adrenal insufficiency and the role of comorbidities. J Clin Endocrinol Metab. 2021;106:1284–93, http://dx.doi.org/10.1210/clinem/dgab063.

S. Iommi-Diez[a,*], M. Feliu-Sagala[a], S. Almanzo[b]

[a] *Servicio de Medicina Familiar y Comunitaria, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[b] *Departamento de Cirugía, Facultad de Medicina y Odontología, Universidad de Valencia, Valencia, Spain*

[*] Corresponding author.
E-mail address: sarainesiommi@gmail.com (S. Iommi-Diez).