Endocrinología, Diabetes y Nutrición 72 (2025) 501579

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Adrenal hemorrhage: Case series and review of their management

Hemorragia adrenal: serie de casos y actualización de manejo

Adrenal hemorrhage (AH) is considered a rare entity, as the incidence rates described in autopsy series was 0.14%–1.8% in unselected hospitalized patients; although it is possibly underdiagnosed, as in recent series of hospitalized patients who died in shock, it reaches incidence rates of 15%.[1] Below, we describe a series of consecutive cases of AH treated at our hospital between 2022 and 2023, which illustrate different triggering causes, along with a brief update on its management and follow-up according to scientific evidence and current recommendations.

Case report #1: 58-year-old male previously diagnosed with antiphospholipid syndrome (APS) and thrombotic events related to it. He had presented to the emergency department on several occasions for abdominal pain, vomiting, and diarrhea, hypotension and mild hyponatremia, without other analytical alterations. The CT scan showed bilateral AH (Fig. 1a).

Case report #2: 56-year-old male with a past medical history of 2 previous episodes of deep vein thrombosis in the lower limbs, who presented to the emergency department for acute abdominal pain without other signs or analytical alterations. A CT scan showed an incidental right adrenal mass that doubled in volume in 2 days (Fig. 1b and c). An MRI described possible bilateral AH (Fig. 1d).

Case report #3: 65-year-old woman with a past medical history of knee arthroplasty performed 10 days prior. She reported intense abdominal pain that led her to consult in the emergency department, with hypotension and moderate hyponatremia. She on low molecular weight heparin. The CT scan showed bilateral AH (Fig. 1e).

Case report #4: 75-year-old woman in good health and functional status, who presented to the emergency department with intense abdominal pain after a coughing fit, associated with asthenia and weight loss of 2 kg in the last 2 weeks. Although her blood tests showed no alterations, the abdominal CT scan revealed the presence of a heterogeneous hemorrhagic mass in the right adrenal gland (Fig. 1f and g), radiologically consistent with pheochromocytoma on the MRI (Fig. 1h) and on the ^{123}I-MIBG scintigraphy (Fig. 1i). Altered cortisol secretion was ruled out. Urinary determinations of adrenaline 51 μg/24 h (normal up to 18), metanephrines 1854 μg/24 h (normal up to 302), and normetanephrines 977 μg/24 h (normal up to 528) allowed the diagnosis of pheochromocytoma, which was confirmed in the histopathological analysis of the surgical specimen.

In the first 3 case reports, pheochromocytoma was ruled out by determining fractionated metanephrines in urine. First-hour morning plasma cortisol (0.7, 1.4, and 3.5 μg/dL) and concomitant ACTH (451, 131, and 312 pg/mL) led to the diagnosis of primary adrenal insufficiency (PAI). Replacement therapy with hydrocortisone was initiated, initially at stress doses and subsequently reduced to physiological doses, which is maintained to this day, as persistent corticoadrenal hyposecretion confirmed analytically in the 3 patients. Although initially, mineralocorticoid replacement with oral fludrocortisone was also required, it could be discontinued evolutionarily in all 3 cases.

In case report #2, a thrombophilia study was performed on an outpatient basis, with the finding of APS. In case report #3, anticoagulant therapy with LMWH was assumed as the trigger for the AH since the thrombophilia study turned out negative.

The most common symptoms and signs of AH are intense acute abdominal pain (70—55%), fever (65—40%), hypotension (83—54%), nausea or vomiting (31–55%), and weakness (31%), as illustrated by the described case reports, and more rarely neurological alteration, weight loss, diarrhea, or skin hyperpigmentation, among others.[2–5] The magnitude of the symptoms is related to the intensity of the hemorrhage and the extent of adrenal gland involvement.[6] In the presence of concomitant primary adrenal insufficiency, analytical alterations typical of it appear.[2] The diagnosis of AH requires a high clinical suspicion by health care professionals and is generally made by imaging modalities (CT or MRI, mainly).

The existence of a triggering factor for AH has been evidenced in up to 50% of cases, among them, sepsis, adrenal mass (being the most frequent cause of unilateral AH and pheochromocytoma being the most frequent adrenal mass[1,6,7]), trauma, surgical procedures, coagulopathy, or anticoagulant therapy.[1,6] Case reports #1 and #2 illustrate APS as a triggering coagulopathy, case report #3 anticoagulant therapy, and case report #4 the existence of pheochromocytoma. Regarding APS, AH is the most common endocrinological complication, with a incidence rate of 0.4% and up to 10–26 % in catastrophic APS[8]; and the most common cause is a hemorrhagic infarction, with vascular thrombosis in half of the cases. It occurs in a higher inci-

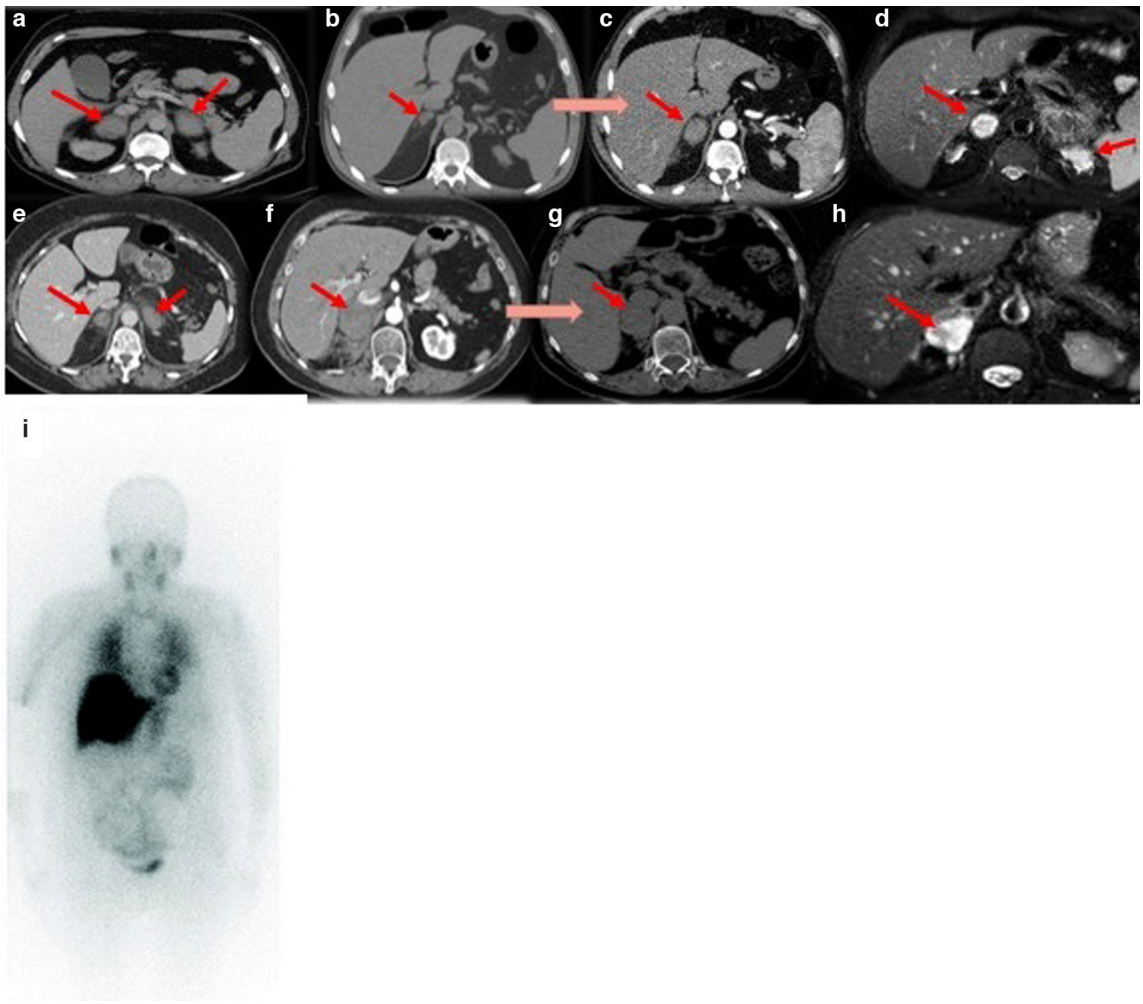

Figure 1 Radiological images of cases reports. Case report #1: CT with bilateral AH (a). Evolutionary growth on CT of case report #2 (b and c), with bilateral hyperintense masses on MRI (d). CT with bilateral AH of case report #3 (e). The initial CT of case report #4 (f) shows a heterogeneous right adrenal mass with hemorrhage, with radiological control showing resolution of the hemorrhage but persistence of the adrenal mass (g), and its image on MRI (h) and on the ^{123}I-MIBG scintigraphy (i), radiologically corresponding to suspected pheochromocytoma.

dence rate in men,[9] such as the cases described. Mortality rate reaches 3.81% when APS, AH, and PAI coexist. The rate of re-thrombosis (established at 3.81%) is the major determinant of long-term morbidity and mortality.[9] The observed rebleeding rate is 3.9% per patient-year.[10]

AH can be unilateral (related to adrenal mass, with indication for exclusion of hormonal hypersecretion by determining morning plasma cortisol after 1 mg of dexamethasone, and urinary or plasma catecholamines) or bilateral, in which case primary adrenal insufficiency appears 16–50% of the time.[6]

Hormonal deficits are related to the location of the hemorrhage, which occurs in the transition zone between the sinusoidal capillaries and the deep plexus, in the reticularis layer, so that the production of sex steroids is the most affected, being deficient in all described cases of AH. Sequentially, due to altered vascularization, the fasciculata layer and, therefore, glucocorticoids are affected, and lastly, the glomerulosa layer with the production of mineralocorticoids.[7] The pattern of hormonal deficits described is represented in the cases of this series: in the 3 cases of bilateral AH, there were decreased values of DHEA-S and cortisol, with preserved production of mineralocorticoids.

Regarding the recovery of hormonal deficits with progression, according to published series, recovery of sex steroids has not been reported, nor of mineralocorticoids if there is initial involvement of them, although they are the least affected. Partial or total recovery of glucocorticoids has been reported in 20% of cases, so it is recommended to determine morning plasma cortisol every 3–6 months for the first 1–2 years, and then annually.[1,9] Similarly, at the follow-up, it is indicated to repeat imaging modalities to exclude underlying adrenal masses and to ensure the resolution or improvement of the hemorrhage.[1,2,9]

Funding

None declared.

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