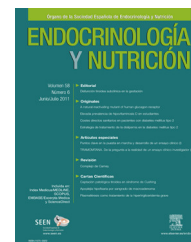




ENDOCRINOLOGÍA Y NUTRICIÓN

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SCIENTIFIC LETTER

Hypoglycemia as a manifestation of iatrogenic adrenal insufficiency due to topical steroids[☆]

Hipoglucemia como manifestación de insuficiencia suprarrenal iatrógena por esteroides tópicos

Hypoglycemia not related to drug treatment for diabetes mellitus is an uncommon diagnosis. In hospitalized patients, its etiology is usually multifactorial, due to the coexistence of acute factors with chronic conditions that increase susceptibility to the development of hypoglycemia.¹

We report the case of a 72-year-old male with a history of high blood pressure, chronic renal failure, and prostatic adenocarcinoma diagnosed in 1995, who was treated with radical surgery and radiotherapy. As sequelae of this treatment, the patient experienced inguinal radiodermatitis and chronic lymphedema, evolving to elephantiasis in the lower limbs. He was taking daily treatment with candesartan 16 mg, lorazepam 1 mg, and enoxaparin 40 mg. The patient was admitted to hospital for a repeat episode of cellulitis in the right lower limb for which empirical antibiotic therapy with ciprofloxacin was started. Vital sign measurements included: temperature, 37.4 °C; blood pressure, 126/87 mmHg; and heart rate, 67 beats per minute. Results of emergency blood tests included: hemoglobin, 12.2 g/dL; WBC, 10,380 mL⁻¹ (90% neutrophils); C-reactive protein (CRP), 140 mg/L (normal range [NR], 0.5–10); glucose, 78 mg/dL; urea, 67 mg/dL; creatinine, 1.65 mg/dL; albumin, 2.3 g/dL; and normal liver enzymes and electrolytes.

Forty-eight hours after admission, a fasting plasma glucose level of 48 mg/dL was found, together with impaired renal function and increases in inflammation markers: WBC, 13,000 mL⁻¹ (92% neutrophils); CRP, 314 mg/L; urea, 111 mg/dL; creatinine 2.76 mg/dL; and estimated glomerular filtration rate, 23.4 mL/min/1.73 m². In the following days, repeat hypoglycemic episodes (plasma glucose levels ranging from 45 to 53 mg/dL) occurred between meals,

associated with sweating and dizziness. A diet of 2500 kcal daily in six meals and continuous intravenous administration of 10% glucose were started, despite which daily hypoglycemia persisted, with the patient reporting marked asthenia, depressive mood, hyporexia, and nausea.

Simultaneously with a plasma glucose level of 50 mg/dL, an insulin level of 3.3 μU/mL, measured by chemoluminescence (NR, 2.6–24.9) and a C-peptide level of 3.25 ng/mL (NR, 0.78–1.9) were recorded. Both levels were inappropriate for the glucose level, but did not allow a diagnosis of endogenous hyperinsulinism (defined by fasting plasma glucose <55 mg/dL, insulin >3 μU/mL, and C peptide >0.6 ng/mL) to be made because of the coexistence of severe renal failure.¹ Mixed moderate malnutrition was also found, and a hyperprotein nutritional supplement by the oral route was provided.

After 20 days of admission, the patient experienced an impairment of his general state with diffuse abdominal pain, blood pressure values of 105/60 mmHg, and electrolyte changes: sodium 128 mEq/L and potassium 6.5 mEq/L. Based on the suspicion of adrenal insufficiency, a plasma cortisol level of 3.4 μg/dL (NR, 4.3–22) was measured in a fasting sample taken during the previous days. Urgent treatment was then started with fluid therapy and hydrocortisone by the intravenous route (starting with bolus of 100 mg, followed by a continuous infusion of 200 mg/day for 48 h). Oral hydrocortisone was subsequently administered, tapered to a maintenance dose of 30 mg daily. No new hypoglycemic episodes occurred thereafter, and blood pressure levels and electrolyte changes normalized. A marked improvement was seen in his general status, and his clinical gastrointestinal symptoms resolved.

The results of the complete laboratory tests were as follows: plasma cortisol, 3.4 μg/dL (NR, 4.3–22.4); adrenocorticotrophic hormone (ACTH), 16.7 pg/mL (NR, 7.2–63.3); thyroid-stimulating hormone (TSH), 24.3 μIU/mL (NR, 0.35–5); free thyroxine, 0.88 ng/dL (NR, 0.8–1.76); and negative thyroperoxidase antibodies; follicle-stimulating hormone, 23.8 U/L (NR, 1.4–18.1); luteinizing hormone, 14.2 U/L (1.5–9.3); total testosterone, 2.76 ng/mL (NR, 2.3–9.9); bioavailable testosterone, 0.64 ng/mL (NR, 1.30–6.82); insulin-like growth factor-1, 73.5 ng/mL (NR, 64–188); and prolactin (PRL), 38.8 ng/mL (NR, 2.1–17.7). Anti-insulin antibodies and the measurement of sulfonyleureas in urine were both negative. A subsequently performed ACTH stimulation test (250 μg by the intravenous route) gave the following results: basal cortisol, 2.2 μg/dL; cortisol at 30 min, 2.6 μg/dL; and cortisol at 60 min,

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2.5 µg/dL (normal cortisol response >20 µg/dL). These results supported the diagnosis of adrenal insufficiency.

A careful medical history found that for over 10 years the patient had been using a cream containing 0.1% triamcinolone, which he applied onto the areas of inguinal radiodermatitis twice daily and which he had discontinued upon hospital admission. On subsequent outpatient follow-up and while the patient continued to receive replacement therapy with hydrocortisone 20 mg daily, normalization occurred in ACTH (40.7 pg/mL), TSH (2.45 µU/mL), and PRL levels (8.49 ng/mL), relating the initial TSH elevation to glucocorticoid deficiency² and PRL elevation to the state of stress and renal function impairment.³ The persistence of a pattern of hypergonadotropic hypogonadism consistent with the existence of primary gonadal failure induced by radiotherapy administered for prostate cancer was however confirmed. The patient had not received hormone blockade therapy.⁴

Steroid treatment suppresses the production of corticotrophic hormone and ACTH, decreasing adrenal cortisol synthesis and causing adrenal gland atrophy. Under basal conditions, exogenous provision may replace the endogenous production of glucocorticoids, but in the event of treatment discontinuation and/or metabolic stress, suppression of the hypothalamic–pituitary–adrenal axis prevents an adequate response, as cortisol synthesis cannot be increased.^{5,6} Adrenal insufficiency then becomes apparent. When steroids are administered by the topical route, the risk of suppression of the adrenal axis and the chance of experiencing adrenal insufficiency when the preparation is discontinued are related to several factors: the use of high potency forms, high doses, long-term use and/or application onto extensive areas or pathological skin.⁷

Adrenal insufficiency is an uncommon cause of clinically relevant hypoglycemic in adults, and very few cases have been reported.^{1,5,6} Cortisol opposes the action of insulin by increasing the bioavailability of hepatic gluconeogenic enzymes and glucagon synthesis. Cortisol deficiency therefore promotes mild fasting hypoglycemia which, however, only tends to occur in metabolic stress situations, especially during infectious processes.^{1,5,6,8,9} In the differential diagnosis of hypoglycemia in outpatients, deficiencies of other contrainsular hormones (growth hormone, glucagon, norepinephrine), organ failures (kidney, liver, or heart failure), exposure to glucose lowering drugs (pentamidine, quinine, quinolones, beta-adrenergic blockers, and angiotensin converting enzyme inhibitors), malnutrition, sepsis, and tumors of non-beta pancreatic cells should be ruled out. Several causative factors are frequently associated, and the exact mechanism of hypoglycemia is difficult to establish.^{1,9,10}

In the reported case, the final diagnosis was iatrogenic, secondary adrenal insufficiency caused by the suppression of the hypothalamic–pituitary–adrenal axis by chronic treatment with topical glucocorticoids. Sudden glucocorticoid withdrawal at a time of high metabolic stress triggered the occurrence of an adrenal crisis of which hypoglycemia was

the initial manifestation. Potential factors considered to be involved in the development of hypoglycemia included infection, quinolone treatment, malnutrition, and exacerbated chronic renal failure, which completed the complex underlying pathogenesis.

Conflicts of interest

The authors state no conflicts of interest.

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