Endocrinología, Diabetes y Nutrición 68 (2021) 137–140

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Megacolon in the context of long-standing Cushing syndrome☆

Megacolon en el contexto de síndrome de Cushing de larga evolución

The development of Cushing's syndrome produces a range of signs and symptoms secondary to chronic exposure to excess glucocorticoids. The syndrome may be due to the abnormal endogenous production of glucocorticoids (induced by ACTH-secreting pituitary tumours, adrenal tumors) or to the exogenous administration of glucocorticoids.[1] Cushing's syndrome is more common in women than in men, with an incidence of 0.7–2.4 cases per million inhabitants per year.[2,3] The typical clinical picture consists of a series of morphological and anthropometric, metabolic, cardiovascular, musculoskeletal, reproductive, dermatological, neuropsychiatric and infectious disorders.[4–6] The involvement of the gastrointestinal system is exceptional, however.[4]

We report a case of Cushing's syndrome due to bilateral adrenal nodular hyperplasia with long-standing hypopotassemia and persistent constipation, with the development of a megacolon, that improved after hypercortisolism was brought under control.

The case corresponded to a 66-year-old male with arterial hypertension (AHT) known since 2008 and associated with hypopotassemia since 2015, two years before evaluation at our centre. The patient history included persistent constipation with chronic laxative use in recent years. He had been admitted twice in recent months due to paralytic ileus attributed to hypopotassemia. The patient had received multiple antihypertensive drugs over time, and had been treated in recent months with furosemide, spironolactone, olmesartan/hydrochlorothiazide, manidipine, doxazosin and atenolol. Assessment of the patient prior to our evaluation revealed marked bilateral adrenal hyperplasia on the CAT scan, and the hormone study showed a normal aldosterone/plasma renin activity ratio (aldosterone 3 ng/dl, [normal range (NR) 1.1–50.6]; plasma renin activity 0.88 ng/ml/h [NR 0.35–1.8]), elevated 24-h urinary cortisol levels <2 times the normal value on a single occasion, and isolated elevated plasma cortisol.

At initial evaluation, the patient presented hypotension and symptomatic bradycardia in the context of atrial flutter with variable ventricular conduction at 45 bpm, in addition to evidence of intestinal pseudo-obstruction with a globose abdomen, generalized pain in response to palpation, tympanism and metallic sounds. Severe proximal muscle atrophy of the lower extremities was also noted. In view of this situation, the patient was admitted to a monitored unit, and positive chronotropic drugs were administered. The placement of a pacemaker was avoided following heart rate stabilization within 48—72 h. Transthoracic echocardiography revealed evidence of hypertensive heart disease with severe left ventricular hypertrophy and left atrial dilatation. Bradycardia was attributed to basal beta-blocker treatment. Following suspension of the latter, the cardiological course proved favourable.

However, the abdominal symptoms persisted, and the plain abdominal X-ray study showed important left colon distension, with a maximum diameter of 11.2 cm (Fig. 1a), requiring intermittent rectal catheterization and daily enemas to relieve the abdominal bloating.

The study was completed with the suspicion of Cushing's syndrome based on the patient phenotype and elevated urinary free cortisol levels. The arterial hypertension and hypopotassemia were considered to be an expression of the mineralocorticoid activity inherent to hypercortisolism. From the hormonal perspective, we confirmed hypercortisolism with suppressed ACTH (2 pg/ml [NR 3.5–60.5]): elevated urinary free cortisol on 3 occasions (1100, 1750 and 2633 nmol/24 h [NR 100–379]), elevated plasma cortisol after dexamethasone 1 mg (721 nmol/l [NR 172–497]), and basal 281 nmol/l (NR < 21) and nocturnal salivary cortisol 117 nmol/l (NR < 5.7). The serum TSH and free T4 levels were normal. A CAT scan of the chest and abdomen revealed large sigmoid colon dilatation together with greatly enlarged adrenal glands, of hyperplastic appearance (Fig. 1b and c). Colonoscopy revealed no cause of obstruction.

Based on the suspicion of Cushing's syndrome due to bilateral adrenal gland hyperplasia, and considering the severe systemic condition (hypertensive heart disease, megacolon, amyotrophy with functional impairment), bilateral adrenalectomy was planned after treatment with ketoconazole for 21 days in an attempt to mitigate the systemic effects of hypercortisolism. The diagnosis of macronodular adrenocortical hyperplasia in both adrenal glands was confirmed, and hormone replacement therapy was started.

Initial postoperative management was complicated by the persistence of hypopotassemia despite oral and intravenous supplementing, together with a new episode of intestinal pseudo-obstruction, though after the first week the patient started to progress favourably. Over follow-up

☆ Please cite this article as: Márquez López L, Beltrán Romero LM, Mangas Cruz MÁ, Pumar López A, Acosta Delgado D. Megacolon en el contexto de síndrome de Cushing de larga evolución. Endocrinol Diabetes Nutr. 2021;68:137–139.

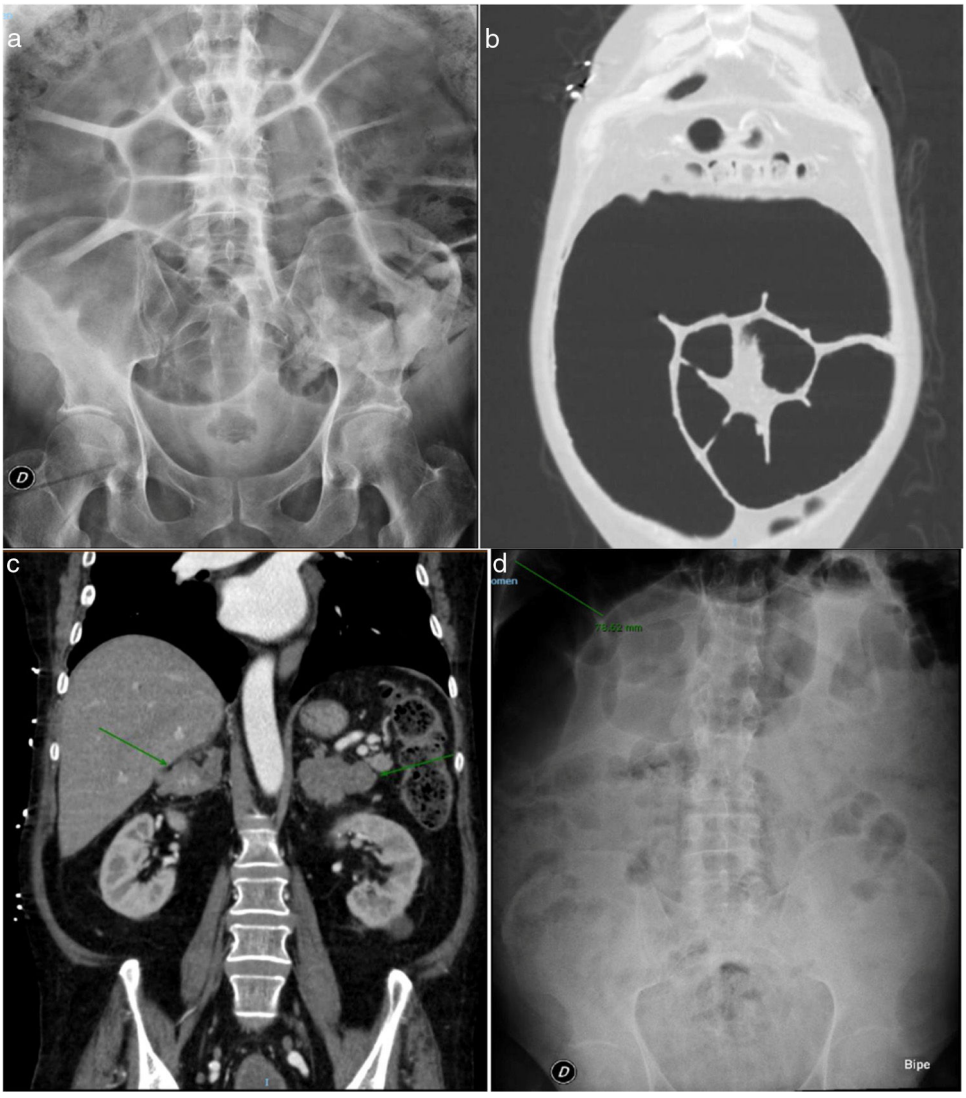

Figure 1 a) Plain abdominal X-ray view. Large left colon distension with a maximum diameter of 11.2 cm. b) CAT scan of the chest and abdomen. Large sigmoid colon dilatation. c) CAT scan of the chest and abdomen. Greatly enlarged adrenal glands of hyperplastic appearance. d) Plain abdominal X-ray view. Colon calibre reduction to 7.8 cm following bilateral adrenalectomy.

after admission, the patient showed very good blood pressure control (systolic blood pressure 110—130 mmHg and diastolic blood pressure 70—80 mmHg), sinus rhythm was maintained at a good frequency without the need for beta-blockers, the constipation had been significantly reduced, without the need for laxatives or the administration of enemas (which had previously proved essential), and the colon diameter was reduced to 7.8 cm (Fig. 1d). The Coloproctology Unit was consulted regarding the need for surgery, but the decision was made to continue patient monitoring given the continued gradual improvement.

Gastrointestinal symptoms in Cushing's syndrome are very uncommon, and mainly consist of abdominal pain.[4] However, in the context of exogenous glucocorticoid use there have been reports of gastritis, ulcers, gastrointestinal bleeding (1.5%),[7] pancreatitis,[8] fatty liver, and hollow organ perforation.[9] Specifically, 6 cases of diverticular perforation have been described in patients with clinical signs analogous to those of our patient, though with no evidence of a megacolon. These conditions have been related to persistent hypopotassemia, severe hypercortisolism, advanced age, malnutrition, uremia or immune deficiencies.[10]

In our case, we wish to underscore two aspects: severe hypopotassemia (minimum value: 1.8 mEq/l [NR 3.5−5.1]) and bowel involvement with a megacolon.

Hypopotassemia can be explained by the mineralocorticoid action of high glucocorticoid levels, as well as by the possible overproduction of steroids with mineralocorticoid activity occurring in macronodular hyperplasia, resulting in hyperactivity not only in the fascicular zone but also in the glomerular zone of the adrenal cortex.

In turn, although the megacolon might be explained by the chronic use of laxatives and, indeed, has been reported as a side effect of drugs such as diuretics (which favour hypopotassemia) or calcium antagonists (due to their effect upon smooth muscle), we have found no reported cases of an iatrogenic megacolon of this calibre. We therefore consider the main cause of the megacolon and hypotonia to

have been Cushing's syndrome (due to the catabolic proteolytic effect of glucocorticoids upon the intestinal smooth muscle), together with chronic hypopotassemia, no other similar cases having been found in the literature. The partial response after bilateral adrenalectomy supports the hypothesis of chronic damage established upon the colon wall.

In sum, we have reported a case of hypercortisolism associated with a megacolon, the cause of which may be related to the structural damage induced by cortisol overproduction and chronic hypopotassemia.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Priapism associated with cabergoline in a young adult☆

Priapismo asociado al uso de cabergolina en un adulto joven

Prolactinomas are the most prevalent pituitary adenomas. While these lesions are more common in women (gender proportion 10:1), in males they tend to manifest in the form of macroprolactinomas. Although such lesions may manifest through a mass effect as headaches and vision disturbances, central hypogonadism is the main manifesting syndrome regardless of tumour size. Dopamine agonists such as cabergoline constitute an effective treatment for prolactinomas, achieving a normalization of prolactin levels and a decrease in tumour size. Their side effects include cardiac valve alterations and, less commonly, compulsive behaviour and hypersexuality.[1] Only one case of priapism as a side effect of cabergoline has been reported in the literature to date.[2] We report another case in a young adult with macroprolactinoma.

An 18-year-old male with a history of type 1 diabetes mellitus since 10 months of age presented with a weight gain of 10 kg over the past year (weight 79.5 kg, height 1.70 cm), incomplete pubertal development (Tanner stage III–IV, testicular volume 12 cc) and a bone age of 16.5 years. The laboratory tests revealed hypogonadotropic hypogonadism with total testosterone levels of 2.41 ng/mL (2.6–10 ng/mL), LH 1.68 IU/L, and FSH 3.33 IU/L. Hyperprolactinemia (192 μg/L) was also observed, with all other pituitary hormone levels and IGF-1 within normal ranges (228.6 ng/mL). Magnetic resonance imaging showed the presence of a macroadenoma measuring 12 × 9 mm in size, with no suprasellar extension, causing contralateral displacement of the pituitary stalk, in the absence of headache and vision disturbances in confrontation visual field examination. Cabergoline 0.25 mg twice weekly was started as treatment.

After six months of treatment, the patient showed a marked decrease in prolactinemia (0.59 μg/L) associated with clinical (Tanner stage IV–V, testicular volume 16 cc) and laboratory test pubertal development (total testosterone 8.89 ng/mL [2.6–10 ng/mL], LH 3.43 IU/L, and FSH 5.14 IU/L), as well as a weight loss of 8.6 kg and a 1-cm increase in height. Despite the good clinical course, over the following months he experienced weekly episodes of painful, very prolonged erections, always in the absence of sexual stimulation, and had to report to the emergency

☆ Please cite this article as: Mesa A, Conget I, Viñals C. Priapismo asociado al uso de cabergolina en un adulto joven. Endocrinol Diabetes Nutr. 2021;68:139–140.