

ments, when indicated, was recommended at discharge, as well as the possibility of a parenteral hydrocortisone regimen before administering future doses of COVID-19 vaccines. In certain situations of acute stress, it is recommended to double or triple the usual dose of corticosteroids in this type of patient, the indication being clear in cases of surgery, severe or moderate infections, vomiting, diarrhoea and fever of more than 38 °C. In milder situations, such as upper respiratory tract infection, fever less than 38 °C and general malaise, it is more debatable and may not be necessary for most patients.⁵ Likewise, there is no clear indication for increasing the dose before the routine administration of vaccines. More studies are necessary since patients with autoimmune adrenal insufficiency are candidates for routine vaccination to avoid serious infections that can trigger the aforementioned crises.

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Non-endocrine hyperaldosteronism. When hormones are supporting players



Hyperaldosteronismo no endocrino. Cuando las hormonas son actores secundarios

The discovery of persistent hypokalaemia in a young patient without evidence of self-induced or clearly obvious losses (from diuretics, laxative abuse or vomiting) includes evaluation of the renin-aldosterone axis. The detection of an excess of aldosterone makes primary aldosteronism the first suspicion, but it includes a wide diagnostic range that is not always evident. We present the case of a female patient referred for study due to hypokalaemia with very high aldosterone levels. We describe her diagnostic course until the surprising final diagnosis.

After undergoing tests, the 31-year-old patient was sent to another centre to detect low potassium levels (K): 3.11 mmol/l in an episode of orthostatic dizziness treated in the emergency department. She had no history of interest, except for asthma treated intermittently with budesonide inhalers. She underwent extensive tests that included analytical tests, a normal colonoscopy, an abdominal CT scan with normal adrenal glands and kidneys, and even a psychiatric consultation ordered by Nephrology to rule out surreptitious vomiting. She denied recent use of budesonide or previous or current use of diuretics or laxatives. Physi-

cal examination was unremarkable, with normal phenotype, body mass index (BMI) of 21 kg/m² and blood pressure (BP) of 95/60 mmHg, with no other findings of interest. Various ions in plasma and urine tests were performed, with plasma potassium levels without supplementation between 2.85 and 3.3 mmol/l, calorie counts in the normal range (40–55 mmol/24 h) and very high plasma aldosterone levels with concomitant elevated renin. The most recent test showed the following values: K 3.27 mmol/l; sodium (Na) 140 mmol/l; orthostatic aldosterone 1478 pmol/l (upper limit of normal [ULN] 997); plasma orthostatic renin activity 11.9 ng/mL/h (ULN 4.8); diuresis of 1.650 ml with Na 188 mmol/24 h and K 45 mmol/24 h. She had received empirical treatment with spironolactone, which was poorly tolerated due to dizziness and polyuria. Reassessment with 24 mEq/day of daily oral potassium supplementation showed orthostatic aldosterone of 1.680 pmol/l with renin (mass) of 352 mU/l (ULN 46.1) and K 3.6 mmol/l. An extended blood and urine test was requested to maintain potassium supplements, which are shown in Table 1. Given the results, a possible renal loss was suggested with criteria compatible with Gitelman syndrome without hypomagnesaemia. Sequencing of the *SLC12A3* gene showed a homozygous mutation (variant c.812T>C) in the *SLC12A3* gene, present in heterozygous form in both parents, without clinical expression in both or consanguinity.

The evidence of a persistent hypokalaemic alkalosis in a young patient without simultaneous arterial hypertension (AHT) prompts us to rule out the surreptitious intake of laxatives, diuretics or self-induced vomiting, as

Table 1 Results of the simultaneous analysis of blood and urine after oral potassium supplementation.

	Creatinine (Cr)	Bicarbonate	Sodium	Potassium (K)	Chloride	Calcium	Magnesium (Mg)	Aldosterone	Renin mass
Plasma (P)	0.62	31.5	141	3.4 (KP)	100	9.9	1.92 (MgP)	1.420	564.9
Urine (U)	74 (CrU)	–	151	37 (KU)	141	3.1	5.5	–	–
Units	mg/dl	mmol/l	mmol/l	mmol/l	mmol/l	mg/dl	mg/dl	pmol/l	mU/l
Fractional excretion (FE) (%)	–	–	–	0.91%	1.17%	0.26%	2.4%	–	–
Urine ratio	–	–	–	50	–	0.042	–	–	–
Units ratio	–	–	–	mmol/g Cr	–	mg/mg Cr	–	–	–
Criteria ^a	–	>25	–	KP <3.5 Ratio >18	FE >0.5%	Ratio <0.07	MgP <1.70 FEMg <4%	Elevated	Elevated

^a For the diagnosis of Gitelman syndrome ¹⁰. Hypomagnesaemia may not appear in up to 50% of cases.

was initially suggested in this case. All these situations that cause direct intestinal or urinary potassium depletion are aggravated by the secondary activation of the renin-angiotensin-aldosterone system (RAAS) in response to hypovolaemia, which perpetuates hypokalaemia¹.

The excess of aldosterone, characteristic of primary aldosteronism, causes hypokalaemia with metabolic alkalosis due to renal loss, but with low or undetectable levels of renin (or its activity) and habitual elevation of BP. Another hormonal excess with a mineralocorticoid effect and the same biochemical profile, although without hyperaldosteronism, is seen in cases of severe Cushing's syndrome, in which cortisol escapes the inactivation of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), usually associated with malignant ectopic production of adrenocorticotrophic hormone (ACTH) and without the Cushing phenotype due to the explosiveness of its course², and in the inhibition of this same enzyme (11 β -HSD2) due to the abusive consumption of liquorice³. The non-tumour excess of other precursors of steroidogenesis as a cause of mineralocorticoid excess is detected in paediatric patients. It is associated with congenital enzyme deficiencies, in particular, that of 11 β -hydroxylase, with an excess of 11-deoxycortisol and DOCA (both with mineralocorticoid effect)⁴, and of defects in androgen synthesis (17 α -hydroxylase and 17,20-lyase), with associated gonadal dysfunction⁵, also without aldosterone excess. The hyperproduction of precursors of steroidogenesis associated with neoplastic processes without Cushing's syndrome is exceptional and, like all the previous ones, occurs with low levels of renin and aldosterone and high BP⁶.

This patient's hyperreninemic hyperaldosteronism did not respond to any of these patterns, and the possibility of a renal tumour of the renin-producing juxtaglomerular apparatus (reninoma), despite the absence of AHT, had also been ruled out by radiological tests. These tumours usually appear in young patients and generally present with severe AHT⁷, while the patient under study first had syncopal symptoms, and her BP was in the low range of normal.

The study of the renal dynamics of ion handling pointed to the diagnostic suspicion of a primary renal salt-wasting tubular disorder with secondary hyperaldosteronism. Despite the absence of hypomagnesaemia, low calciuria, age, and mild symptoms suggested Gitelman syndrome. Confirming this diagnosis requires demonstrating the presence of inactivating biallelic mutations in the *SLC12A3* gene. In this case, a novel homozygous mutation was found, despite the absence of consanguinity in the parents. This gene encodes the thiazide-sensitive sodium-chloride cotransporter in the apical membrane of the distal convoluted tubule⁸, so its inactivation causes the activation of the RAAS due to hypovolaemia, and aldosterone acts on the mineralocorticoid receptor in the cortical collecting tubule, activating the epithelial sodium channel (ENaC). This activation stimulates electrogenic reabsorption of sodium with secretion of potassium and hydrogen ions into the tubular lumen. Bartter syndrome responds to the same hormonal profile and is caused by mutations that affect sodium transport in the thick ascending portion of the loop of Henle. Still, the phenotype is usually more severe than in Gitelman syndrome, with earlier diagnosis and accompanied by hypercalciuria or nephrocalcinosis⁹.

In summary, we present a case of genetically confirmed Gitelman syndrome, detected in a department of endocrinology in the tests performed on a patient referred for hyperaldosteronism of uncertain origin. It is associated with the peculiarity of not presenting hypomagnesaemia, which attenuates the clinical picture by not producing neuromuscular symptoms (spasms, tetany), which delays diagnosis and presenting a homozygous mutation instead of a compound heterozygous one.

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