Coexistence of Glucocorticoid Resistance and Pseudohypoparathyroidism

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ABSTRACT

We report for the first time the case of a young man who developed both glucocorticoid resistance and resistance to parathyroid hormone. Treatment with high doses of dexamethasone together with administration of calcium and calcitriol resulted in a significant improvement in the patient's condition. In this paper, we discuss in detail diagnostic and treatment strategies used on the patient and the impact on the course and outcome of both disorders. We associate the development of both these disorders with a possible inherited defect in the signal pathways common to glucocorticoid and parathyroid hormone receptors.

Keywords: Clinical picture, glucocorticoids, hormonal resistance, pseudohypoparathyroidism

Coexistencia de la Resistencia a Glucocorticoides y el Pseudohipoparatiroidismo

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RESUMEN

Por primera vez se reporta el caso de un joven que desarrolló resistencia a glucocorticoides y resistencia a la hormona paratiroidea. El tratamiento con altas dosis de dexametasona, junto con la administración de calcio y calcitriol, trajo como resultado una mejoría significativa de la condición del paciente. En este papel, se analiza en detalle el diagnóstico así como las estrategias de tratamiento del paciente, y su impacto en el curso y resultado de ambos trastornos. Se concluye que el desarrollo de ambos trastornos se halla asociado a un posible defecto hereditario en las vías de transducción de señales comunes a los receptores de las hormonas glucocorticoides y las hormonas paratiroideas.

Palabras claves: cuadro clínico, glucocorticoides, resistencia hormonal, pseudohipoparatiroidismo

INTRODUCTION

Although insulin resistance is commonly found in clinical practice (1), resistance to other hormone occurs much less frequently and the prevalence may be higher than described in the literature. The underestimation of these clinical entities partially results from physicians' inadequate knowledge about their existence.

Glucocorticoid resistance is characterized by an inability of glucocorticoids to produce their biological effects at the level of target tissues (2, 3). This results in a compensatory increase in the secretion of adrenocorticotrophic hormone (ACTH) and cortisol, which in some patients may protect against the signs of adrenal cortex insufficiency (4, 5). Increased plasma ACTH levels also stimulate mineralocorticoid and androgen productions, leading to increased renal sodium absorption and to androgen excess. Therefore, patients with diagnosed glucocorticoid resistance are often characterized by arterial hypertension and hyperandrogenism coexisting with symptoms of glucocorticoid deficiency (4–6).

Pseudohypoparathyroidism (PHP) comprises a heterogeneous group of disorders, characterized by hypocalcaemia, hyperphosphataemia, increased plasma levels of parathyroid hormone (PTH) and a decreased sensitivity to biological effects of this hormone (7). Depending on a response to PTH injections, PHP may be classified either as Type I with an abnormally low increase in cAMP after administration of PTH and Type II in which a PTH-induced increase in cAMP is preserved (7).

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Type I is further divided into three subtypes: Ia, Ib and Ic (8, 9). In the most frequent Type Ia and in Type Ic, patients have physical features of Albright hereditary osteodystrophy, including obesity, short stature, rounded face, short neck, brachydactyly, ectopic ossifications and mental retardation (8, 9). In these variants, resistance to PTH is often accompanied by a resistance to thyroid stimulating hormone (TSH), gonadotropins, ACTH, growth hormone releasing hormone or glucagon (9,10). In turn, subjects with Types Ib and II have a resistance limited only to PTH and therefore they do not present with the phenotype of Albright hereditary osteodystrophy (7, 8).

This article presents a case of a male with resistance to both PTH and glucocorticoid hormones. We describe in detail diagnostic and treatment strategies applied to the patient and their impact on the course and outcome of both these disorders.

CASE REPORT

The first clinical symptoms in this patient appeared at the age of 6 years, when he underwent isosexual precocious puberty. Since the age of 11 years he experienced asthenia and adynamia. At the age of 23 years, he developed arterial hypertension and therefore was treated by a general practitioner with β-receptor antagonists and calcium channel blockers. Because this treatment resulted in only a moderate reduction in blood pressure, the patient was admitted to clinic with a suspicion of secondary hypertension. On admission, he complained of asthenia, adynamia, muscular cramps and weakness, paresthesias as well as frontal baldness. Both systolic and diastolic blood pressure were markedly increased (180/105 mmHg) and slight hyperpigmentation of the head, neck and palmar folds was noticed. Echocardiography revealed left ventricle hypertrophy, while on examination of the eye, funduscopy revealed grade I hypertensive retinopathy. Because plasma potassium levels were reduced (3.1 mmol/L, reference values: 3.5–5.3 mmol/L) and both adrenal glands were slightly enlarged on ultrasonography, the clinical and laboratory picture suggested the presence of either Cushing's syndrome or primary aldosteronism. The overnight dexamethasone test (1 mg at 23.00) revealed unsuppressed plasma cortisol levels (12.3 µg/dL, normal values below 1.8 µg/dL). Urinary free cortisol assessed in three 24-hour specimens was each time increased (485, 524 and 511 µg/day; reference values: 20–90 µg/day). Moreover, ACTH (149 pg/mL), dehydroepiandrosterone sulfate [DHEA-S] (550 µg/dL) and testosterone (12.1 ng/mL) levels were raised (reference values for these hormones: 20.0–60.0 pg/mL, 80–450 µg/dL and 3.8–11.0 ng/mL, respectively). Interestingly, diurnal plasma ACTH and cortisol rhythms were preserved albeit at the increased levels (ACTH: 6.00 – 135 pg/mL, 12.00 – 98 pg/mL, 18.00 – 85 pg/mL, 24.00 – 62 pg/mL; cortisol: 6.00 – 25.1 µg/dL, 12.00 – 20.3 µg/dL, 18.00 – 18.6 µg/dL, 24.00 – 15.6 µg/dL). Moreover, after the intravenous administration of insulin (0.1 U/kg), he developed

hypoglycaemia, followed by a normal increase in cortisol levels (by 15.8 µg/dL). Supine plasma renin activity was suppressed (0.15 ng/mL/hour; reference values: 0.3–2.8 ng/mL/hour), while supine plasma aldosterone was slightly increased (182 pg/mL; reference values: 30–150 pg/mL). After standing for four hours, plasma renin activity and plasma aldosterone increased to 0.6 ng/mL/hour and 510 ng/dL, respectively. Slightly decreased plasma calcium levels (2.05 mmol/L, reference values: 2.20–2.60 mmol/L) were considered secondary to the inhibitory action of glucocorticoid excess on intestinal calcium absorption. On magnetic resonance imaging, the size of both adrenal glands was mildly increased but without evidence of focal lesions. Dual-energy X-ray absorptiometry (DEXA) revealed slightly increased bone mineral density in the lumbar spine, femoral neck and wrist (Z-values between +0.8 to +1.1). The patient was diagnosed with glucocorticoid resistance and prescribed dexamethasone (at the initial daily dose of 1 mg) which had to be increased to 2 mg daily to induce a rapid disappearance of tiredness, hair regrowth and a normalization of blood pressure. The resultant clinical improvement was associated with a normalization of urinary free cortisol (85 µg/day), plasma aldosterone levels and plasma renin activity. After six months of therapy, the dose of dexamethasone was reduced to 0.5 mg once daily in the evening. Despite these benefits and the lack of evidence of glucocorticoid excess, muscular problems and paraesthesias persisted. Two years later, the patient again contacted the clinic because of perioral tingling and paraesthesia, myalgia and muscular weakness, and periodical attacks of carpopedal spasms. On two occasions he developed tetany, which resolved after intravenous injections of calcium gluconate. He had positive Chvostek's and Trousseau's signs. He was also found to have hypocalcaemia (plasma calcium levels corrected for albumin – 1.9 mmol/L; ionized calcium – 0.88 mmol/L, reference values: 0.9–1.3 mmol/L), hyperphosphataemia (2.2 mmol/L; reference values: 0.8–1.5 mmol/L) and normomagnesaemia (1.15 mmol/L; reference values: 0.8–1.3 mmol/L). Plasma intact PTH, assessed using an immunoradiometric assay, was increased (145 pg/mL; normal values: 15–75 pg/mL), 25-hydroxyvitamin D plasma levels (78 nmol/L) were in the upper limits of normal (15–80 nmol/L), while calcitriol levels were decreased (9.6 pg/mL, reference range: 18–60 pg/mL). Thyrotropin, free thyroxine and free triiodothyronine plasma levels were within normal limits. Phosphate excretion in urine did not increase after the administration of exogenous PTH. Computed tomography revealed calcification of the basal ganglia. The clinical picture and laboratory results supported a diagnosis of PHP and therefore the patient was prescribed with 1 g of calcium carbonate daily and calcitriol at the starting dose of 0.5 µg daily, which was then up-titrated to 1 µg daily. After two weeks of their administration, the patient's clinical status and plasma levels of total and ionized calcium, phosphates and PTH normalized.

DISCUSSION

In this article, we report the case of coexistence of glucocorticoid resistance and PHP. To the best of our knowledge, no previous study described a similar association between the two disorders.

Taking into account the very rare prevalence of glucocorticoid resistance and PHP (4,7), the presence of both these clinical entities in the same patient may not be a simple coincidence. However, this possibility cannot be totally excluded. Parathyroid hormone receptors are members of G protein-coupled receptors, being transmembrane proteins, which are capable of activating adenylyl cyclase and a phosphatidylinositol-calcium second messenger system (11). In turn, the glucocorticoid receptor, which is present in an unbound form in the cytosol, plays a role in the regulation of gene transcription. After binding to the intracellular glucocorticoid receptor, the complex of glucocorticoid and its receptor translocates to the nucleus, where some target genes are regulated positively and others negatively by the complex through diverse mechanisms (2, 3). In the majority of patients described so far, PTH resistance has coexisted with resistances of other G protein-coupled receptors (10). Our study, however, is the first one to have revealed the presence of hormonal resistance to two receptors of different chemical structure in the same patient. Therefore, it cannot be excluded that signal pathways affected by PTH and glucocorticoid receptor stimulations may to some extent overlap.

Some clinical symptoms of glucocorticoid resistance in our patient (hypertension, hyperandrogenism) suggested the presence of Cushing's syndrome. However, in opposition to this syndrome, ACTH and cortisol levels, although increased, exhibited a normal diurnal pattern. Moreover, the patient had a slightly increased bone mineral density, which may be explained by both inability of cortisol to produce its catabolic effect and by an anabolic effect of adrenal androgens. The important issue of glucocorticoid resistance is the fact that its clinical presentation differs markedly among patients, even among those belonging to the same family (6). On one hand, there are patients with the asymptomatic course of the disease, while other subjects demonstrate symptoms of severe deficiency of glucocorticoids associated with substantial mineralocorticoid and androgen excess (4, 5). This variability probably depends on various degrees of the receptor insensitivity and various degrees of sensitivity to mineralocorticoids and adrenal androgens (6). Clinical manifestations of this syndrome in the patient were moderate and limited to asthenia, adynamia, muscular complaints, paresthesias, slight skin hyperpigmentation, arterial hypertension and frontal baldness. The axial component of glucocorticoid resistance in the index patient was asthenia. We attribute this symptom to the impaired action of glucocorticoids in the central nervous system because similar tiredness is typical for Addison's disease (12). In the treatment of glucocorticoid resistance, we had to use dexamethasone at relatively high doses (2 mg daily). Only these doses were capable of stimulating not only wild but also mutated glucocorticoid receptors, which allowed us to fully inhibit ACTH secretion, and as a consequence also mineralocorticoid and adrenal androgen production. Other benefits of dexamethasone are its negligible mineralocorticoid action (13) as well as a reduction of the risk of the development of ACTH-producing adenomas (5). Because this treatment strategy normalized plasma DHEA-S and arterial pressure, there was no need to administer any antiandrogens or hypotensive agents. In some patients, however, a dexamethasone-induced decrease in blood pressure was unsatisfactory and these patients required antihypertensive treatment, preferably with a mineralocorticoid receptor antagonist, spironolactone or eplerenone (4, 5). Contrary to many patients with glucocorticoid resistance who suffer from oligozoospermia-induced infertility, the fertility in the index patient was preserved. Oligozoospermia in glucocorticoid resistant subjects seems to result from an inhibitory effect of androgens on follicle stimulating hormone (FSH) release and from hyperplasia of testicular adrenal rests stimulated by high ACTH levels (6). This was not the case in the index patient, probably because plasma DHEA-S and testosterone levels were only slightly above the upper limits of normal, while ACTH levels were only moderately elevated.

Another syndrome of hormonal resistance described in the patient was PHP, which was not accompanied by the symptoms of Albright hereditary osteodystrophy. This means that the patient suffered from either Type Ib or Type II of PHP. Recently, it has been found that Type Ib results from an epigenetic defect that results in switching of the maternal GNAS1 allele to a paternal pattern of methylation for exon 1A (7). In turn, Type II seems to be a consequence of a defect in the protein kinase A pathway (10), which probably affects further stages in PTH receptor signalling. Unfortunately, we could not investigate the content of cAMP in urine after the administration of PTH, which is required to distinguish between both these types of PHP. It should be mentioned, however, that the differentiation between them does not determine the treatment approach.

Parathyroid hormone resistance in the patient did not negatively affect bone mineral density. In most subjects with PHP Type Ib (and probably also with Type II), PTH resistance was limited to the kidneys, therefore after a longer time they develop bone abnormalities resembling those observed in primary hyperparathyroidism, including osteitis fibrosa cystica, known under the name of pseudohypohyperparathyroidism (9). These changes were not observed in our patient, which can be explained either by a coexistence of increased plasma levels of androgens or by a simultaneous resistance of the bone PTH receptor. Low plasma levels of calcitriol despite high-normal levels of 25-hydroxyvitamin D probably resulted from a lack of renal 1α-hydroxylase due to impaired renal action of PTH (14).

The aim of the treatment of PHP is to restore calcium-phosphate homeostasis. Presently, it is assumed that treat-

ment is required even if the disease is asymptomatic and its only manifestation is an increased PTH concentration (10). This aim is reached by the administration of calcium salts, active vitamin D metabolites and phosphate binders inhibiting phosphate absorption (9). In PHP subjects, despite calcium supplementation, calciuria remains low, therefore calcium supplementation is not associated with the risk of the development of nephrolithiasis (7). Long-term follow-up of the index patient clearly indicated that calcium carbonate and calcitriol, if administered in respective high doses, are safe and effective drugs in the treatment of PHP.

To sum up, this is a report, for the first time, of the presence of PTH and glucocorticoid resistance in the same patient. Treatment with respectively high doses of dexamethasone together with administration of calcium and calcitriol made it possible to effectively control these clinical entities in the patient.

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