Raynaud's phenomenon caused by cabergoline during the treatment of a macroprolactinoma: a case report

Fenómeno de raynaud causado por cabergolina durante el tratamiento de macroprolactinoma: reporte de un caso

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Abstract

Digital vasospasm is a known adverse effect of dopamine agonists such as bromocriptine; however, it has rarely been reported with cabergoline. We describe a case of Raynaud's phenomenon as a side effect of treatment with the latter in a 52-year-old woman with a macroprolactinoma, forcing discontinuation. In this context, we conducted a review of the literature, with emphasis on the possible criteria for discontinuation of treatment with dopaminergic agonists in patients with macroprolactinoma.

Keywords: Raynaud, vasospasm, cabergoline, case report, adverse effects.

Resumen

El vasoespasmo digital es un efecto adverso descrito durante el tratamiento con bromocriptina pero apenas notificado con cabergolina. Se presenta un raro caso de fenómeno de Raynaud como efecto secundario al tratamiento con este último fármaco en una mujer de 52 años con un macroprolactinoma, lo que obligó a discontinuar el fármaco. A colación del caso expuesto, realizamos una revisión de la literatura, haciendo hincapié en cuándo, y si se debe, interrumpir el tratamiento con fármacos agonistas dopaminérgicos en pacientes que padecen macroprolactinoma y se someten a tratamiento médico.

Palabras Clave: Raynaud, cabergolina, macroprolactinoma, efectos adversos.

Introduction

Cabergoline (CAB) is the best-tolerated drug in the medical management of prolactinomas, with low adverse effect rates related to treatment discontinuation[1]. Although digital vasospasm has been described with bromocriptine, another dopaminergic agonist (DA), it has rarely been reported with CAB. We present a case of Raynaud's phenomenon as an adverse effect of treatment with CAB that demanded discontinuation in a 52-year-old woman with a macroprolactinoma.

Case presentation

A 52-year-old woman with a history of smoking was referred to our Endocrinology Department during the assessment of a central scotoma; a pituitary magnetic resonance imaging (pMRI) revealed findings of a suggestive pituitary macroadenoma, compromising the anterior region of the optic chiasma. The patient reported mild headache upon waking, without changes in severity with the Valsalva maneuver. The patient denied galactorrhea and had amenorrhea since the age of 48; she also recounted sporadic use of diazepam.

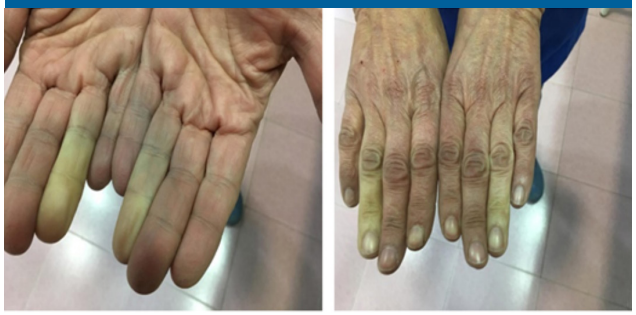
Laboratory evaluation of the hypothalamic-pituitary axis found abnormal serum prolactin and diluted prolactin levels, with 176.75 ng/ml and 96.97 ng/ml, respectively. These concentrations are not necessarily indicative of a prolactinoma, and could also be attributed to pituitary stalk compression. In the ophthalmological assessment, optical coherence tomography and visual field testing revealed compromise of optic fibers in the right eye.

Treatment was started with CAB, gradually increasing the dosage up to 3 mg/week. By the third week, the patient reported only mild symptomatic improvement. However, on day 40 of the treatment, visual alterations had remitted, the serum prolactin level was 0.6 ng/ml, and the pMRI showed a significant decrease in the size of the sella turcica in comparison with the previous imaging. This biochemical and radiological evolution allowed the definitive diagnosis of a pituitary macroprolactinoma with satisfactory response to medical management.

Nevertheless, at this point the patient reported transient episodes of discoloration of her fingers, which had begun to occur 10 days after reaching the 3 mg/week dose of CAB. They were most severe during the first 3 days, predominantly on the fourth finger of either hand; occasionally in association to exposure to cold temperatures. No were identified additional clinical findings or risk factors suggesting other associated disorders (Figure 1). Thus, we established the diagnosis of Raynaud's phenomenon secondary to CAB use, and treatment was suspended.

Up to an 18-month follow-up after discontinuation, the patient remained clinically stable, without any repeated episodes of vasospasm or pMRI changes. However, serum prolactin levels increased gradually, up to 66 ng/ml in the last consultation.

Figure 1. Acral pallor and cyanosis as the key signs of Raynaud's phenomenon secondary to treatment with cabergoline.



Discussion

All patients with macroprolactinomas and most with microprolactinomas require pharmacological treatment; DA are the preferred drugs for these tumors, given their efficacy in normalizing serum prolactin levels and reducing tumor size in most cases[1]. Among DA, CAB is the most frequently used. It is a synthetic derivate of ergoline with affinity for D2 and D1 receptors, as 5-HT1- and 5-HT2-serotonin receptors. Agonism of D2 receptors in the anterior pituitary is essential for inhibition of prolactin secretion. Side effects include cardiovascular, neurological, and gastrointestinal manifestations; the latter being the most frequent one, especially nausea and vomiting. Nonetheless, orthostatic hypotension, headaches, dizziness, vertigo and cardiac valve disease are also common, the latter specially in patients receiving 2 mg/week, which should be echocardiography evaluated annually[2]. Very few cases of Raynaud's phenomenon have been reported with CAB[3], occurring much more frequently with bromocriptine[4–6].

At low doses, DA have vasodilatory properties via activation of D1 receptors, resulting in the aforementioned well-characterized orthostatic hypotension. Nevertheless, at higher doses, activation of adrenergic α1 receptors promotes the peripheral catecholamine release, favoring vasoconstriction[7]. Although CAB displays preferential affinity for D2 receptors—possibly underlying its greater tolerability[1]—the larger doses used in our patient may explain the occurrence of digital vasospasm, which remitted upon discontinuation.

The latest consensus recommendations highlight CAB as the pharmacological treatment of choice for macroprolactinomas, given its greater efficacy and tolerability, as adverse effects tend to be less frequent and severe, and shorter in duration[8,9]. Despite this safety profile, CAB therapy is not innocuous, and discontinuation due to side effects may be a sound decision in some clinical

circumstances. Concerns and controversy surround the suspension of DA in this context, as it may lead to disease relapse, including recurrence of hyperprolactinemia and tumor reexpansion. To date, no specific guidelines are available regarding the interruption of treatment with DA due to adverse effects[8,9].

A meta-analysis evaluating the impact of CAB retirement in patients with prolactinoma found out that subjects who had achieved normalization of prolactinemia and a significant reduction of tumor size with lower doses had increased odds of successful discontinuation. Longer treatment duration was not associated with improved results[10]. In another recent meta-analysis, Xia et al[11] drew similar conclusions, except that longer DA treatment duration was indeed associated with more successful results.

Current clinical guidelines suggest pharmacological treatment may be interrupted in patients who have been treated with DA during at least 2 years, with normal prolactin levels, and no tumor remnants in the pMRI[8,9]. Resistance to DA has also been posited as a criterion for treatment interruption, defined as tumor size reductions under 50% with high doses, between 7-14 mg/week[2,12].

1. DA are the first line of medical treatment for prolactinomas. CAB has been preferred due to higher efficacy and tolerability in comparison with bromocriptine.
2. Raynaud's phenomenon is an infrequent side effect of DA, mediated by the activation of α1 adrenergic receptors, which occurs at higher doses.
3. The optimal duration of treatment with DA, and whether it can be definitively suspended, remains unclear. In general, clinical guidelines propose interruption of pharmacological treatment in patients with normal prolactin levels during at least 2 years, with no tumor remains on pMRI, or with a notable size reduction in comparison with the baseline.

Author contribution

LGF and RAR: Conceptualization; original draft; ARM and JPH: Writing - review & editing.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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