



ACTAS Derma-Sifiliográficas

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CASE REPORT

Botulinum Toxin A for the Treatment of Familial Benign Pemphigus[☆]

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KEYWORDS

Benign familial pemphigus;
Hailey-Hailey disease;
Botulinum toxin;
Treatment

PALABRAS CLAVE

Pénfigo benigno familiar;
Hailey-Hailey;
Toxina botulínica;
Tratamiento

Abstract Familial benign pemphigus or Hailey-Hailey disease is a rare bullous disease that presents clinically with recurrent flares of erosions and vesicles that mainly affect the skinfolds. Many topical and systemic therapies have been proposed. Hyperhidrosis is one of the factors that can trigger or aggravate a flare-up, and its treatment is therefore important for controlling the disease and preventing further episodes. We report 3 patients with axillary and/or inguinal benign familial pemphigus that responded favorably to treatment with subcutaneous botulinum toxin.

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Toxina botulínica A en el tratamiento del pénfigo benigno familiar

Resumen El pénfigo benigno familiar (PBF) o enfermedad de Hailey-Hailey es una enfermedad ampollosa poco frecuente que se caracteriza clínicamente por la presencia de erosiones y vesículas, de predominio en flexuras, que cursa en forma de brotes recurrentes para los que se han propuesto múltiples líneas de tratamiento tópicos y sistémicas. Entre los factores inductores o agravantes de los brotes se encuentra la hiperhidrosis, por lo que el tratamiento de ésta será importante para el control de esta enfermedad y evitar la aparición de nuevos brotes. Presentamos el caso de tres pacientes con PBF axilar y/o inguinal que fueron tratados de forma satisfactoria con toxina botulínica subcutánea para el control de su afección.

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Introduction

Familial benign pemphigus (FBP) or Hailey-Hailey disease is a rare, autosomal dominant, hereditary bullous disease that usually affects the skin folds.¹ Its pathogenesis is linked to a lack of cell-to-cell adhesion in epidermal keratinocytes,

which gives rise to recurrent erosions and vesicles despite treatment. The gene responsible is *ATP2C1* located on chromosome 3q21-24. This gene encodes an ATPase protein associated with calcium and magnesium channels in the Golgi apparatus, and abnormalities in this protein, together with epigenetic factors, lead to the loss of epidermal cell integrity found in FBP.^{2,3}

Many topical and systemic treatments for controlling outbreaks of FBP have been described in the literature, some of which are aimed at minimizing exacerbating phenomena such as hyperhidrosis. Botulinum toxin A, a neurotoxin produced by the bacterium *Clostridium botulinum* is used in

[☆] A. López-Ferrer, A. Alomar. Toxina botulínica A en el tratamiento del pénfigo benigno familiar. Actas Dermosifiliogr. 2012;103:532-5.

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Figure 1 Erythematous-violaceous plaques and erosions in the axilla in a patient with Hailey-Hailey disease before treatment with botulinum toxin.



Figure 2 Clinical resolution of the cutaneous symptoms after injection of botulinum toxin.

dermatology to treat certain diseases—including FBP—in which the pathogenesis involves hyperhidrosis.⁴ Various authors have reported on the use of botulinum toxin for this purpose, and we found 9 cases in the literature in which treatment with botulinum toxin produced satisfactory results in FBP.^{5–11}

We report 3 new cases in which FBP proved resistant to the usual treatments but responded satisfactorily to subcutaneous administration of botulinum toxin.

Case 1

A 36-year-old man was referred to our dermatology department in November 2003 because of erosions and vesicles on the axillae and the sides of the neck; the lesions had appeared a year earlier and showed clinical deterioration in the summer months.

The patient had no relevant medical history and reported that his father had been diagnosed with FBP.

Physical examination revealed erythematous plaques with painful erosions in both axillae and on the sides of the neck (Fig. 1). Skin biopsy of an axillary lesion confirmed the diagnosis of FBP. The patient initially received topical treatment with poultices of 1/10 000 potassium permanganate, 0.1% tacrolimus, 2% erythromycin, fusidic acid, and betamethasone, and oral treatment with azithromycin 500 mg/d. Oral treatment was subsequently instated with

25 mg of tretinoin 2 days a week for 6 months, with an incomplete response.

In February 2009, treatment was begun with subcutaneous administration of 80 U of botulinum toxin (Botox) in each axilla. A second dose of botulinum toxin (200 U) was administered after 4 months of follow-up because the patient's condition had deteriorated, with erythematous plaques and erosions in the axilla and right inguinal fold. A third dose was administered in August 2009, leading to improvement of the lesions and making it possible to suspend treatment with tretinoin. A fourth dose was administered in October 2009, although the patient presented no active lesions (Fig. 2). Subsequently, the affected areas were injected every 2 months until June 2010, when it was decided to inject both affected areas and areas at risk of becoming affected. At the 5-month follow-up visit, the patient presented only 1 eroded plaque in the groin and 80 U of botulinum toxin was injected.

Case 2

A 38-year-old woman with a 9-year history of FBP visited our department in July 2009 for assessment of an extensive flare of the disease involving the groin, the area below the left breast, the left axilla, and the side of the neck. The woman was treated by injecting the affected areas with an initial dose of 200 U of botulinum toxin. After 2 months, the lesions in the groin persisted and 80 U of botulinum toxin was injected in that area. The patient was



Figure 3 Erythematous-violaceous plaques and erosions in the submammary folds. The image shows the outlined area to be treated, including affected areas and areas at risk of becoming affected.

asymptomatic until March 2010, when she presented with an intense flare of erythematous plaques and vesicles, and signs of impetiginization in the groin and submammary folds, and a third treatment was administered (Fig. 3). Further injections were administered in April and May 2010 due to persistence of the lesions. In June 2010, the patient continued to present eroded erythematous plaques in both inguinal folds and in the left submammary region; 300 U of botulinum toxin was administered in the entire groin and submammary areas, including the affected areas and healthy areas at risk of becoming affected by the disease. The patient remained asymptomatic for 2 months and the same areas were treated again in September 2010. After 2 months, the patient presented only 1 eroded erythematous plaque below the left breast and mild involvement of both inguinal folds and we decided to treat these areas again with 80 U of botulinum toxin.

Case 3

A 56-year-old woman visited our department in April 2010 with a history of FBP and a flare involving the axillae and groin; 200 U of botulinum toxin was administered in these areas. After 1 month, the patient showed general improvement, but the submammary region was treated again in view of the presence of exudative erythematous plaques. In June 2010, the patient presented with an outbreak of the disease in the perianal region, which had not been previously treated; improvement in the axillae, submammary region, and groin was sustained. On this occasion, all 4 sites were injected (300 U), including both affected areas and areas at risk of becoming affected. After 1 month, the patient presented minimal erythematous plaques and extensive superficial erosion in the axillae, groin and perianal region. At that point, we decided to postpone injection with botulinum toxin and the patient was treated with potassium permanganate poultices, systemic corticosteroids, and topical antibiotics. At the 1-month follow-up visit, the clinical signs had stabilized; in November 2010, the lesions had not recurred.

Discussion

FBP is a bullous disease that takes the form of periodic outbreaks and is exacerbated by heat, friction, and sweating in the affected areas. Several medical and surgical treatments have been described, but none has been shown to alter the course of the disease. The aim of some of the treatments used is to minimize exacerbating factors, such as hyperhidrosis.

We report 3 cases of patients with FBP who, after having received multiple topical and systemic treatments for years without success, were treated with subcutaneous injections of botulinum toxin in the affected areas. In the first case, clear clinical improvement was observed following extensive injection of the affected areas approximately every 2 months until the patient remained asymptomatic for 5 months. In the second case, injections were administered in response to clinical manifestations in both the affected areas and areas at risk of becoming affected. The third case is the only one in which a complete response was not achieved, although the patient reported improved quality of life.

Nine cases have been published in the literature of patients with FBP who were treated with botulinum toxin in the axillary and groin area, with good clinical response.⁵⁻¹¹ As we did with our first patient, Koeysers et al.⁸ periodically administered botulinum toxin and achieved control of the disease in 6 patients with between 3 and 5 treatment sessions. Although the published cases show no recurrence of the disease after complete remission, it would be important to know the subsequent outcome in these patients if we are to establish appropriate guidelines for treatment with botulinum toxin.

Botulinum toxin has been used widely to treat frown lines and hyperhidrosis, but other dermatologic uses have also been reported, such as the treatment of persistent facial flushing, Frey syndrome, dyshidrotic eczema, and anal fissures. It has also been used to promote ulcer healing.^{4,6} In our department, we recently reported treatment of hyperhidrosis using subcutaneous botulinum toxin in a patient with an eccrine hamartoma in the lumbar region.¹²

Many studies have shown the efficacy and safety of botulinum toxin in cosmetic treatment of frown lines and hyperhidrosis, although this is a costly and temporary treatment. In FBP, satisfactory results have only been reported in isolated cases. Controlled studies are needed to determine the efficacy and safety of this treatment in multiple dermatologic diseases, in addition to studies to evaluate its cost-benefit ratio.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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