Hailey-Hailey disease treated successfully with naltrexone and magnesium

Ali Alajmi, MD, Abdulhadi Jfri, MD, and Audrey Lovett, MD, FRCPC

Montreal, Canada

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INTRODUCTION

Hailey-Hailey disease (HHD), or benign familial pemphigus, is an autosomal dominant genodermatosis that usually presents between the second and fourth decades of life as painful blisters and erosions in the intertriginous areas. It is characterized by a remitting, relapsing course, and recurrent episodes of superinfection. HHD is caused by mutations in the ATP2C1 gene.

Although HHD is not life threatening, it has a significant negative impact on patient quality of life. Many treatments exist, but none is highly effective. We report a case of a patient with recalcitrant HHD dramatically improving with the combination of oral magnesium chloride supplementation and naltrexone.

CASE REPORT

A 54-year-old man with a 30-year history of HHD was assessed in an interdisciplinary genodermatosis clinic. Given the typical clinical findings and a strong family history of this condition, a skin biopsy was never performed by his previous dermatologists. The condition began in the inguinal folds and then progressed to the axillae. Initially, he would present with 1 mild flare every 2 years. The flares increased in frequency in his early forties. His condition has been persistent in the last 2 years. He has taken multiple courses of oral antibiotics. Also, he has been on intermittent topical antibiotics and corticosteroids. He did not tolerate topical calcineurin inhibitors. A spot treatment with CO2 laser led to reduction in blistering of the treated site. Unfortunately, the cost of the full treatment was prohibitive. Botox injections were tried with mild improvement in the axillae only.

Before presentation, he was given naltrexone, 4.5 mg daily. Pain was reduced but no noticeable improvement in the appearance of the lesions was seen. Naltrexone was discontinued after 1 month of use because of a new progressive rash outside of his folds.

On skin examination, bilateral axillae and groin were diffusely red and eroded. Multiple psoriasiform and mildly crusted small plaques were present on the limbs and on the trunk. A punch biopsy was performed of a psoriasiform plaque on the arm. Betamethasone valerate 0,05% ointment was prescribed to the lesions outside of the folds and a compounded mixture of Ihle paste, ketoconazole 1%, and hydrocortisone 1% cream to apply to the intertriginous lesion. We also prescribed magnesium chloride, 286 mg orally once daily. The patient was to return to his dermatologist for continued care.

Genetic testing was performed of the ATP2C1 gene. A previously reported heterozygous mutation c.899+1 G>T slice site variant of the intron 11 considered to be pathogenic was found confirming the clinical diagnosis of HHD. Histopathologic examination of the psoriasiform plaque found trans-epidermal and suprabasal acantholysis consistent with HHD. No evidence of psoriasiform changes or a drug-induced reaction were found.

The patient was reassessed 2 months later. We learned that the patient deferred taking the
magnesium chloride we prescribed but used the topical treatments. The widespread psoriasiform rash resolved with the topical treatment within 3 weeks. However, the intertriginous lesions did not improve, and he required intravenous antibiotics for a suspected cellulitis of the groin. In the interim, he consulted a colleague dermatologist within our hospital center. This dermatologist determined that the widespread psoriasiform rash was unlikely related to the naltrexone. He recommended to restart naltrexone, 4.5 mg daily, and instructed the patient to continue the magnesium chloride; unbeknownst to him, the patient had not yet taken this treatment. The patient reintroduced naltrexone and started magnesium chloride concomitantly at this time. The patient provided us with photos of his groin before the start of this treatment (Fig 1, A). The combination of naltrexone and magnesium chloride resulted a dramatic improvement over the next 2 weeks with excellent pain control (Fig 1, B).

**DISCUSSION**

Calcium plays a central role in the pathophysiology of HHD. The ATP2C1 gene encodes for hSPCA1, a magnesium-dependent calcium pump protein responsible for maintaining intracellular Ca²⁺ concentrations by sequestering it within the Golgi apparatus. Mutations in ATP2C1 disrupt calcium homeostasis within keratinocytes, which affects multiple cellular functions such as desmosome assembly. The resultant impairment of cell-cell adhesion leads to acantholysis, the hallmark of HHD.

Traditional treatments for HHD are mostly symptomatic and do not target pathophysiologic mechanisms. Topicals, corticosteroids, antimicrobials and calcineurin inhibitors can be beneficial to reduce pain and allow temporary healing of the eroded areas. Oral antibiotics are often necessary for treating bacterial superinfections. Botulinum toxin type A injections have been used as an adjunctive treatment with success to reduce sweating and maceration, thus
reducing the severity of the condition.\textsuperscript{2} Reported anecdotal systemic treatments include acitretin, methotrexate, and cyclosporine.\textsuperscript{3,4} Destructive therapies such as CO\textsubscript{2} laser ablation has been used in recalcitrant cases with some success.

Two emerging medical therapies have been reported in the recent years: low-dose naltrexone (LDN) and magnesium chloride. Naltrexone, a long-lasting opiate receptor antagonist, is thought to improve HHD through its anti-inflammatory properties and improvement of intercellular adhesion.\textsuperscript{5-7} Magnesium chloride possibly improves HHD by regulating intracellular calcium homeostasis by promoting the function of the calcium pump defective in HHD and other similar proteins.\textsuperscript{8} A good response was recently reported using a combination of LDN and magnesium in Darier disease, a genodermatosis caused by mutations in \textit{ATP2A2}, which encodes SERCA2, another type of calcium pump present on the endoplasmic reticulum.\textsuperscript{9}

In our case, magnesium chloride and LDN were taken simultaneously. Consequently, the individual effect of either treatment cannot be clearly assessed. However, the lack of clinical improvement with naltrexone alone leads us to believe magnesium chloride was likely effective here. It is possible that naltrexone also played a role in the response through a synergistic effect. We believe the combination of oral magnesium chloride and LDN to be worthy of additional study as a potential safe and effective treatment of HHD.

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