SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
JCMS Case Reports
Volume 8: 1–3

DOI: 10.1177/2050313X20984121
journals.sagepub.com/home/sco
SAGE

Improvement in Hailey–Hailey disease with a combination of low-dose naltrexone and oral magnesium chloride: A case report

Darosa Lim[1], Annie Belisle[2] and Sandra Davar[1]

Abstract

Hailey–Hailey disease is a rare autosomal dominant acantholytic disorder due to mutation in the *ATP2C1* gene and presents with flaccid blisters in intertriginous regions. Its chronic and relapsing course may negatively impact patients' quality of life. Multiple medical and interventional treatments have been described with various efficacy. Low-dose naltrexone and oral magnesium chloride represent emerging treatments. Sustained improvement in Hailey–Hailey disease has been reported with the former in case series, while others have shown variable results. Oral magnesium chloride has been reported in four patients with possible results after 2–4 weeks. Two recent cases suggest that the combination of both treatments may have a synergistic effect. Herein, we present a 63-year-old woman with long-standing and recurrent bilateral inguinal Hailey–Hailey disease who significantly improved with low-dose naltrexone and oral magnesium chloride, representing the third case described with this combination.

Keywords

Hailey–Hailey, familial benign chronic pemphigus, naltrexone, magnesium

Introduction

Hailey–Hailey disease (HHD), or familial benign chronic pemphigus, is a rare autosomal dominant dermatosis caused by mutation in the *ATP2C1* gene which encodes a calcium ATPase localized in the Golgi apparatus (hSPA1C).[1,2] The reduced hSPCA1 activity alters calcium intracellular sequestration and leads to impaired processing and translocation of junctional proteins required for adhesion of keratinocytes, thus resulting in acantholysis.

HHD usually presents between the second and fourth decade of life and is characterized by a chronic relapsing course of flaccid vesicles, crusted erosions, fissures and vegetations in intertriginous regions.[3] It may have a significant impact on patients' quality of life and cause psychological distress.[4] Multiple treatments with various efficacy have been described, including topical corticosteroids and calcineurin inhibitors, oral antibiotics, retinoids, immunosuppressive agents and procedural methods such as lasers and dermabrasion.[5] Herein, we present a case of long-standing and recurrent inguinal HHD who significantly improved with a combination of low-dose naltrexone and oral magnesium chloride.

Case report

A 63-year-old woman was followed at the Dermatology clinic for recalcitrant plaques in the groins. She was known for hypothyroidism under Synthroid. Her mother had a similar clinical presentation. Since the age of 35 years, the patient presented recurrent episodes of friable plaques with painful erosions in the inguinal folds without complete clearance. Other intertriginous regions and genital area were not involved. The rash worsened with heat and sweating. Bilateral macerated erythematous plaques with erosions were noted in the inguinal regions extending to lateral labia majora (Figure 1). HHD was highly suspected, but the differential diagnosis

[1]Division of Dermatology, Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada
[2]Department of Pathology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada

Corresponding Author:
Darosa Lim, Division of Dermatology, Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM), 1051 Sanguinet street, Montreal, QC H2X 3E4, Canada.
Email: darosa.lim@umontreal.ca

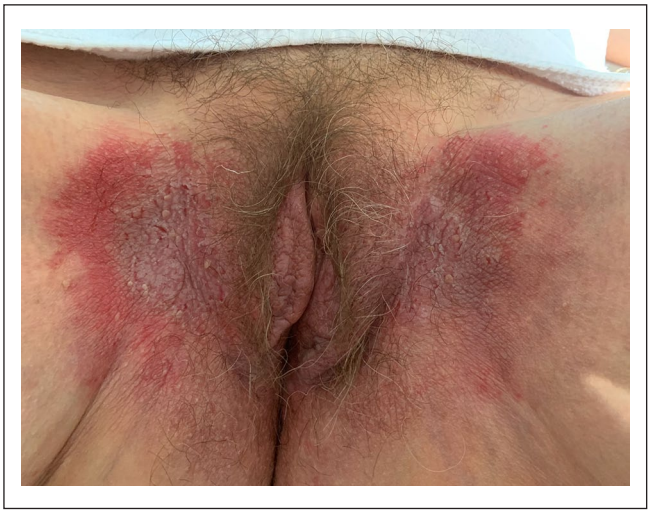

Figure 1. Hailey–Hailey disease with bilateral eroded macerated erythematous plaques in inguinal regions.
This picture was taken during an exacerbation in the last year, and the patient's rash was considerably worse at first consultation (no pictures available).

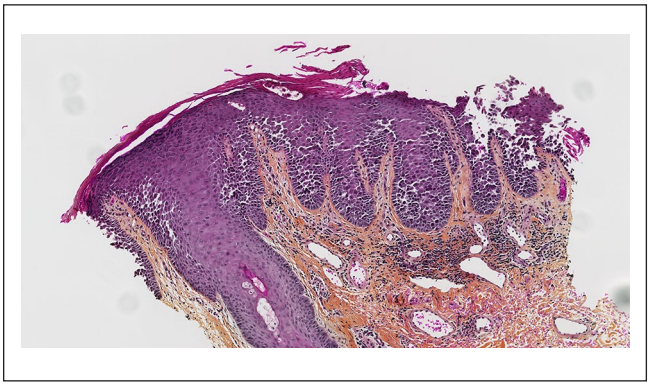

Figure 2. A hematoxylin phloxine saffron–stained section at 10× magnification shows multi-layered intraepidermal acantholysis with few dyskeratosis and parakeratosis, and perivascular lymphocytic infiltrates in the superficial dermis.

may include Darier's disease, intertriginous candidiasis, tinea cruris and pemphigus vegetans. Skin biopsy revealed acantholysis at multiple levels in the epidermis, resembling a "dilapidated brick wall" with few dyskeratosis and parakeratosis (Figure 2). A diagnosis of HHD was made.

Management with wearing lightweight clothes to avoid friction and topical corticosteroids, tacrolimus 0.1%, lidocaine (for symptoms) and zinc paste led to partial improvement only. The patient was hesitant to start systemic treatments such as retinoids due to possible side effects. Her quality of life was, however, greatly affected as the disease continued to worsen. After thorough discussion, naltrexone was prescribed in March 2019. Dosage was started at 1.5 mg/day, titrated to 4.5 mg/day within 6 weeks and then at 6 mg/day after 6 months. Within a year of treatment, exacerbations decreased in frequency (around 5–6 episodes) and severity. Dipropionate betamethasone 0.05% cream twice a day was added, if needed, during exacerbations. In February 2020, the patient decided to start oral magnesium chloride solution at 300 mg/day nightly in addition to her naltrexone after reading a case report on HHD treated with this combination.[6] Within 6 months of this combination, further decrease in episode frequency was observed, with only one exacerbation during summertime which was less severe than initial episodes. A timeline of management is presented in Figure 3. No adverse effects of the treatment were noted. There was complete clearance outside of HHD episodes, and the patient's quality of life significantly improved.

Discussion

Management of HHD remains challenging as it tends to be chronic and relapsing, and numerous treatments were reported without consensus on standard treatment.[3,5] General measures are avoidance of exacerbating factors such as friction and sweating, and treatment of secondary infections. Topical treatments include corticosteroids, calcineurin inhibitors, vitamin D analogs and antibiotics such as tobramycin and gentamicin which have been shown to induce a readthrough of nonsense mutations.[7] Systemic options include antibiotics, retinoids and immunomodulators (methotrexate and cyclosporine). Procedural therapies have been reported with botulinum toxin, lasers and dermabrasion.

Low-dose naltrexone and oral magnesium chloride represent emerging treatments.[5,8] It is believed that naltrexone, a μ-opioid receptor antagonist, modulates opioid receptors expressed in keratinocytes, resulting in increased cellular adhesion.[9] Moreover, it exerts anti-inflammatory effects by antagonizing toll-like receptor 4.[10] Improvement in HHD with low-dose naltrexone has been reported in case series with sustained response after a follow-up of 3–12 months, while others showed a variable response.[9,11–14] Dosage for good response varied mostly between 3.0 and 4.5 mg/day, sometimes up to 6.0 mg/day. Interestingly, one patient with a good response was under concomitant oral magnesium, which may have been synergistic according to authors.[9] Flares may continue to occur as part of HHD fluctuation but are usually milder and less frequent. The treatment is mostly well tolerated with nausea, dizziness and vivid dreams (only one episode) reported seldomly.[9,14]

On the other hand, magnesium chloride inhibits calcium-extruding activity in keratinocytes, favoring calcium accumulation for desmosome assembly.[15] Its efficacy has been described in three patients who were almost cleared of HHD after 2–4 weeks of treatment with 70 mL of 33 mg magnesium chloride dissolved in 1 L of water.[15,16] Two of them were also under topical corticosteroids or clotrimazole with fusidic acid cream. In addition, one patient responded to 300 mg of magnesium citrate combined with 8000 units of vitamin D3 daily.[17] No significant adverse effects were noted except for the unpleasant taste of the magnesium solution.

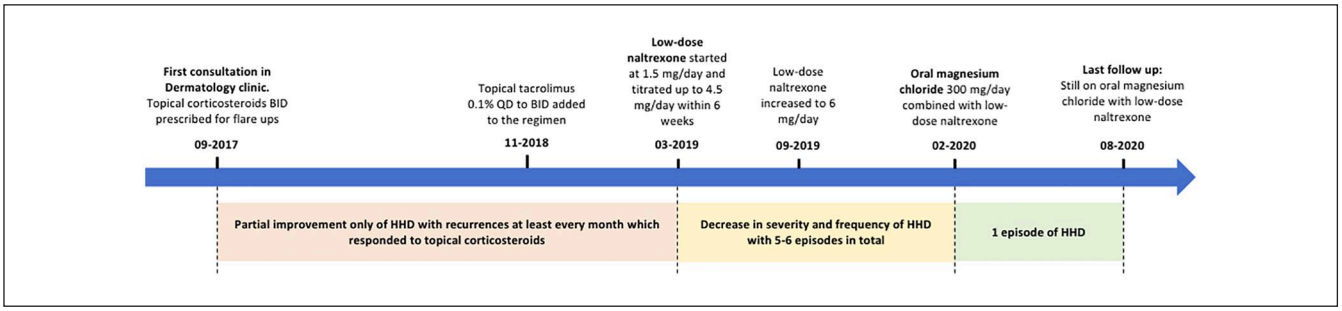

Figure 3. Timeline of management and response to treatments.
HHD: Hailey–Hailey disease.

More recently, significant improvement was reported in a man with recalcitrant HHD within 2 weeks of naltrexone at 4.5 mg combined with magnesium chloride at 286 mg daily, started simultaneously.[6]

In this case of long-standing and recurrent HHD, systemic treatments have not been started earlier as follow-ups were seldom initially and the patient was hesitant to start treatment due to possible side effects (such as with retinoids). Other topical treatments could have been tried, including vitamin D analogs and antimicrobial agents. Nonetheless, after thorough discussion with the patient and considering her preferences, low-dose naltrexone was a well-tolerated therapeutic option, which led to improvement in her HHD. Furthermore, oral magnesium appears to have a synergistic effect with low-dose naltrexone as it was added 1 year after the latter with further decrease in frequency and severity of HHD episodes in the following 6 months. Thus, combination of low-dose naltrexone and oral magnesium chloride represents an interesting alternative treatment with low adverse effect profile and may lead to significant improvement in severe HHD.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent

The patient provided written consent for publication of the case report.

ORCID iD

Darosa Lim https://orcid.org/0000-0003-2707-8134

References

1. Hailey H and Hailey H. Familial benign chronic pemphigus. *Arch Dermatol* 1939; 39: 679–685.
2. Hu Z, Bonifas JM, Beech J, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. *Nat Genet* 2000; 24(1): 61–65.
3. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. *Br J Dermatol* 1992; 126(3): 275–282.
4. Gisondi P, Sampogna F, Annessi G, et al. Severe impairment of quality of life in Hailey-Hailey disease. *Acta Derm Venereol* 2005; 85(2): 132–135.
5. Ben Lagha I, Ashack K and Khachemoune A. Hailey-Hailey Disease: an update review with a focus on treatment data. *Am J Clin Dermatol* 2020; 21(1): 49–68.
6. Alajmi A, Jfri A and Lovett A. Hailey-Hailey disease treated successfully with naltrexone and magnesium. *JAAD Case Rep* 2019; 5(9): 760–762.
7. Kellermayer R, Szigeti R, Keeling KM, et al. Aminoglycosides as potential pharmacogenetic agents in the treatment of Hailey-Hailey disease. *J Invest Dermatol* 2006; 126(1): 229–231.
8. Jfri A, Litvinov IV and Netchiporouk E. Naltrexone for the treatment of Darier and Hailey-Hailey Diseases. *J Cutan Med Surg* 2019; 23(4): 453–454.
9. Albers LN, Arbiser JL and Feldman RJ. Treatment of Hailey-Hailey Disease with low-dose naltrexone. *JAMA Dermatol* 2017; 153(10): 1018–1020.
10. Lee B and Elston DM. The uses of naltrexone in dermatologic conditions. *J Am Acad Dermatol* 2019; 80(6): 1746–1752.
11. Cao S, Lilly E and Chen ST. Variable response to naltrexone in patients with Hailey-Hailey Disease. *JAMA Dermatol* 2018; 154(3): 362–363.
12. Ibrahim O, Hogan SR, Vij A, et al. Low-dose naltrexone treatment of familial benign pemphigus (Hailey-Hailey Disease). *JAMA Dermatol* 2017; 153(10): 1015–1017.
13. Jasans-Barcelo M, Curman P, Hagstromer L, et al. Improvement of Hailey-Hailey disease with low-dose naltrexone. *Br J Dermatol* 2020; 182(6): 1500–1502.
14. Riquelme-Mc Loughlin C, Riera-Monroig J, Morgado-Carrasco D, et al. Low-dose naltrexone therapy in benign chronic pemphigus (Hailey-Hailey disease): a case series. *J Am Acad Dermatol* 2019; 81(2): 644–646.
15. Borghi A, Rimessi A, Minghetti S, et al. Efficacy of magnesium chloride in the treatment of Hailey-Hailey disease: from serendipity to evidence of its effect on intracellular Ca(2+) homeostasis. *Int J Dermatol* 2015; 54(5): 543–548.
16. Barde NG, Mishra DB and Ingole SO. Oral magnesium chloride: a novel approach in the management of Hailey-Hailey disease. *Indian J Dermatol Venereol Leprol* 2017; 83(2): 259–262.
17. Gu K and Silver S. A case of Hailey-Hailey Disease managed with oral magnesium citrate and high-dose vitamin D(3). *J Cutan Med Surg* 2018; 22(3): 362–364.