

# Treatment of Hailey–Hailey disease with narrowband phototherapy and acitretin: A case report

SAGE Open Medical Case Reports  
JCMS Case Reports  
Volume 7: 1–3  
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DOI: 10.1177/2050313X19845221  
journals.sagepub.com/home/sco



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## Abstract

The Hailey–Hailey disease, or familial benign chronic pemphigus, is an autosomal dominant genodermatosis affecting mainly intertriginous areas. It manifests itself in painful blisters, erosions, and cracks and has a chronic course with frequent flares, significantly impacting patients' quality of life. Presently, there is no cure, but multiple treatment modalities are available. Most evidence supports treatment with topical steroids and antimicrobials. Treatment of recalcitrant disease has been shown to benefit from the addition of oral antibiotics, Naltrexone, systemic retinoids, botulinum toxin A injections, laser treatment, and surgical excision. We describe a case of refractory Hailey–Hailey disease for which most of the abovementioned options failed, but which demonstrated significant improvement following a combination of oral acitretin and narrowband ultraviolet-B phototherapy. To achieve remission, the patient received 30 sessions three times per week with the increment of 20 mJ/cm<sup>2</sup> per session and oral acitretin 25 mg PO daily.

## Keywords

Hailey–Hailey, phototherapy, retinoids

## Introduction

Hailey–Hailey disease (HHD) or familial benign chronic pemphigus is a rare genetic skin disorder with an autosomal dominant means of transmission. Age of onset is usually between 20 and 40 years. HHD generally affects skin folds, areas of friction, and flexures. Flaccid vesicles or bullae are the primary lesions, but they are hardly noticeable as they easily rupture and leave macerated erosions, sometimes with crusting. Two-thirds of patient have positive family history and one-third expresses new mutation.<sup>1</sup> In pathogenesis, there is a mutation in the ATP2C1 gene on chromosome 3q21 that encodes adenosine triphosphate (ATP)-powered calcium pump protein hSPCA1 of epidermal cells resulting in abnormal keratinocyte adhesion, desmosomal decomposition, and acantholysis.<sup>2</sup> Excessive sweating, heat, skin trauma, and friction contribute to exacerbation of HHD and cause separation of keratinocytes, especially in intertriginous areas. The most common therapeutic options are topical and systemic corticosteroids, antibiotics, topical calcineurin inhibitors, topical vitamin D (Calcipotriol) and their combinations, DMARD (disease-modifying antirheumatic drugs; for example, methotrexate, cyclosporine, dapsone, systemic retinoids, and naltrexone), botulotoxin A injections to reduce sweating, surgical excision, grafting

dermabrasion, and CO<sub>2</sub> laser vaporization.<sup>3</sup> We report using a combination of acitretin and narrowband phototherapy in treatment of HHD unresponsive to other therapies.

## Case report

A 59-year-old male with a 34-year history of HHD was referred to the clinic in 2017 for ongoing management. His family history was significant for HHD—specifically in his sister and brother. For the last 6 years, the patient has experienced frequent flare-ups, especially in the summertime; new lesions appeared on his mid and lower back, and no relief was achieved with topical treatment. On examination, he presented scattered erosions with serous and hemorrhagic crusts over both flanks, axillae, under the breasts, and the mid and lower back (Figure 1). A routine skin biopsy with H&E stain (hematoxylin and eosin stain) revealed full thickness acantholysis. Clinically and histopathologically, the skin condition was compatible with familial benign chronic pemphigus

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**Figure 1.** Mid-back before treatment.

or HHD. The patient was treated with multiple modalities, such as oral and topical corticosteroids, oral tetracycline 500 mg BID, niacinamide 500 mg TID, naltrexone 3 mg, topical glycopyrrolate 1% solution, and magnesium supplements. All of them had very limited or no effect. In May 2018, a trial combination of oral acitretin 25 mg daily and narrowband phototherapy three times per week, with the increment of  $20 \text{ mJ/cm}^2$  (starting with  $100 \text{ mJ/cm}^2$ ) per session, was very successful. Within 2 months, the patient achieved significant improvement with the almost complete clearance of the affected skin in all abovementioned areas (Figure 2). Currently, he is on oral acitretin 25 mg and narrowband phototherapy one to two times per week. After 3 months of follow-ups, the clinical result is still maintained.

## Discussion

HHD is an autosomal dominant genodermatosis. It is caused by a mutation of the ATP2C1 gene localized on chromosome 3q22.1, which encodes the human secretory-pathway calcium/manganese-ATPase isoform 1 (hSPCA1). The hSPCA1 protein transports calcium ions ( $\text{Ca}^{2+}$ ) into the Golgi apparatus, where they are involved in the post-translational modification of the new-synthesized proteins, including structural ones.<sup>2,4</sup> Impaired calcium pump action results in increased intracellular calcium concentration despite the total low calcium content in basal cells.<sup>5</sup> In normal keratinocytes, increased calcium stimulates formation of adherens junctions, while in HHD, this process is downregulated. Actin reorganization and adherens junctions' formation is an integral part of normal cell-to-cell junction in keratinocytes. Impairment of the calcium-induced reorganization of actin filaments was linked to decreased concentrations of ATP level. Abnormally increased cytoplasmic calcium concentration in HHD keratinocytes stimulates a



**Figure 2.** Mid-back after 3 months of treatment.

cascade of energy-consuming processes in keratinocytes, including gene transcription, synthesis of differentiation-specific proteins, migration of junctional proteins to the periphery, and cytoskeletal reorganization resulting in decreasing cellular ATP. In normal keratinocytes, ATP concentration recovers to a baseline level; however, in HHD keratinocytes, cellular ATP remains low. It was suggested that defective ATP synthesis might result from mitochondrial calcium overload. Although small, transient increases in mitochondrial calcium concentration to enhance ATP synthesis, excess mitochondrial calcium accumulation causes calcium overload, which results in uncoupling of oxidative phosphorylation and decreased ATP synthesis. Aging results in increased mitochondrial sensitivity to calcium overload consistent with the onset of HHD in adulthood. Finally, decreased ATP may further exacerbate cellular calcium overload by inhibiting ATP-requiring  $\text{Ca}^{2+}$  ATPases, such as the ATP2A2 and plasma membrane  $\text{Ca}^{2+}$  ATPase, which normally would compensate for decreased ATP2C1 function.<sup>5,6</sup> Narrowband ultraviolet-B phototherapy (NB-UVB) is a unique form of ultraviolet light treatment with irradiation of 311–313 nm, which is more effective than broadband phototherapy in respect to clearing and remission time and safer than PUVA (ultraviolet A plus psoralen). NB-UVB induces apoptosis of T-lymphocytes, targets epidermal keratinocytes, and achieves suppression of disease activity due to combination of immune suppression, alteration of cytokine expression, and cell cycle arrest.<sup>7,8</sup> NB-UVB effectively increases 25-hydroxyvitamin D (25(OH)D) concentration in patients with psoriasis. The beneficial effect of NB-UVB phototherapy may also be exerted through the modulation of the intracellular  $\text{Ca}^{2+}$  homeostasis via cutaneous synthesis of the vitamin D.<sup>9,10</sup> Combination of systemic retinoids with NB-UVB reduces the time for lesions to clear and total radiation dose, improving overall safety, thereby increasing efficacy and reducing the

carcinogenic potential of phototherapy.<sup>11–13</sup> There has been a case in which was reported a beneficial effect of Alitretinoin with NB-UVB in a patient with HHD.<sup>14</sup> Acitretin, a second-generation monoaromatic retinoid, is used in the treatment of severe keratinizing disorders. Acitretin reduces hyperproliferation, abnormal differentiation of keratinocytes, inflammatory infiltrate, and induces apoptosis of keratinocytes and lymphocytes.<sup>12,15</sup> Retinoids exert their physiologic effects by binding to receptors present in the nucleus: a retinoic acid receptor (RAR) family and a retinoid X receptor (RXR) family.<sup>16</sup> Acitretin activates but does not bind to multiple RAR receptors. Retinoids may exert genomic and nongenomic effects on the biophysical properties of voltage-gated calcium channels that may contribute to the normalization of the intracellular Ca<sup>2+</sup> homeostasis in HHD.<sup>17</sup> Our case supports the hypothesis that acitretin and NB-UVB may be effective in treating HHD. More extensive in vitro and clinical trials are necessary to assess the mechanism of action and efficacy of that treatment in the long term.

### 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 informed consent for publication of this case report and associated pictures.

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