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Case Series

Low-Dose Naltrexone Therapy in Recalcitrant Hailey-Hailey Disease

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ABSTRACT

Hailey-Hailey disease (HHD), also known as benign familial pemphigus, is a rare genodermatotic disorder characterized by painful blistering and erosions in intertriginous areas. Exacerbations are often triggered by sweating, minor trauma, and secondary infections, leading to significant morbidity and reduced quality of life. This case series presents three biopsy-proven recalcitrant HHD patients treated with low-dose naltrexone (LDN), an off-label, low-cost, and low-risk therapeutic option. The patients, who had failed multiple conventional treatments, were administered LDN hydrochloride starting at 3 mg/day and titrated to 6 mg/day over eight weeks. All three showed marked clinical improvement, including resolution of erosions and ulcerations, reduced pain, and decreased erythema, with sustained results over four months without flare-ups. While these findings suggest LDN may be an effective adjunct or alternative therapy for HHD, further research is needed to confirm its efficacy, long-term safety, and potential applicability in other calcium transport-related disorders.

Keywords: Benign familial pemphigus, Dilapidated brick wall appearance, Genodermatotic, Hailey-Hailey disease, Low-dose naltrexone

INTRODUCTION

Benign familial pemphigus, often known as Hailey-Hailey disease (HHD), is an uncommon genetic condition of the skin. The Hailey brothers initially described the disease in 1939.[1] It is a chronic and recurrent condition. The lesions usually start as flaccid blisters and rupture spontaneously with minimal trauma forming painful erosions over the intertriginous region. Sweating, trauma and infections can all cause flare-ups.[1,2] Managing patients can be difficult. Antibiotics, systemic and intralesional corticosteroids, botulinum toxin type A, laser treatments and systemic immunosuppression are among the various treatments that have been explored; each has had variable and inconsistent results and potential serious side effects.[1] Although low-dose naltrexone (LDN) has been widely promoted on various platforms as an anecdotal treatment for individuals with HHD, it was not until 2016 that one theoretical article was published in peer-reviewed medical literature.[3]

We are reporting that three recalcitrant HHD patients treated successfully with LDN.

CASE SERIES

The dose naltrexone is unavailable in the market, so the 50 mg tablet was crushed and dissolved in 50 mL of distilled water to form a solution with 1 mg/kg concentration which was stored in a sterile container. Patients started on 3 mg/day and titrated monthly as per need. The clinical

response, adverse effects and subjective quality of life are monitored and assessed monthly. The study was conducted for 6 months. Clinical response was measured on the basis of the absence of new lesions, improvement in erythema, healing of involved areas and decrease in pain and discomfort. Thorough clinical examination with laboratory monitoring was done on a monthly basis. Treatment started in the outpatient department (OPD) after obtaining written consent.

Report of cases

Three cases of females aged 75 years, 63 years and 50 years with the history of erythematous, macerated and eroding plaques on the inframammary area, abdominal folds, groin and buttocks for 15 years, 30 years and 10 years, respectively, presented in OPD. Clinical examinations and routine investigations, including complete blood count, erythrocyte sedimentation rate, liver function tests, kidney function tests and serum electrolytes, were done and they were found to be within normal limits. The biopsy was also sent for histopathological examination, which was consistent with the HHD. Figure 1 shows the skin biopsy of the lesions. epidermis showing acantholysis with dilapidated brick wall appearance of stratum malphigi and Widespread acantholysis with dilapidated brick wall appearance of epidermis respectively.

After failing topical corticosteroid and antifungal medications, the patient began using Naltrexone (3 mg/d). Further details of the treatments are in Table 1 for all the cases. All the patients sustained the results by the end of the 6th months of initiation of the therapy. Figure 2a shows the before treatment erosive lesion with greyish slough and maceration in the inframammary area. Figure 2b shows after treatment complete resolution of the lesion with PIH in the right inframammary area. Similarly, Figure 3a depicts before treatment initiation of hyperpigmented patches with maceration in the groin. Figure 3b shows after treatment complete resolution of the lesions of the left groin.

DISCUSSION

HHD is caused by a mutation in the *ATP2 C1* gene on the third chromosome, which encodes the human secretory pathway Ca_2+/Mn_2+-ATPase isoform 1 of the Golgi apparatus.[4,5] A defective pump reduces calcium levels in the Golgi apparatus.[5] Cadherins, which are transmembrane glycoproteins found in desmosomes and adherens junctions, increase cell adhesion in a Ca_2+-dependent way. The prevalence of HHD is approximately 1/50.000.[6]

The illness is frequently resistant to a variety of treatments, including topical and intralesional corticosteroids, retinoids, immunomodulators such as methotrexate and cyclosporine as well as physical and energy-based therapies. To the best of our knowledge, only a few studies have described LDN since 2016.

Naltrexone, an opioid receptor antagonist, was licensed by the Food and Drug Administration in 1984 for the treatment of opioid addiction at a dose of 50–100 mg/day. LDN has been tried for a variety of inflammatory conditions such as Crohn's disease,[7] fibromyalgia,[8] complicated regional pain syndrome, chronic pruritus and multiple sclerosis.[9]

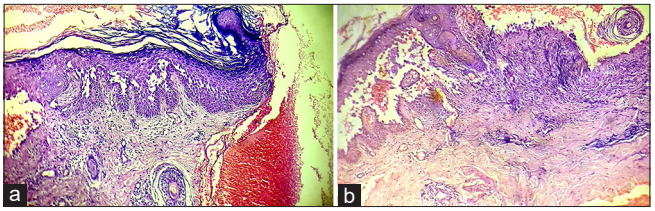

Figure 1: (a) Epidermis with acantholysis and dilapidated wall appearance of the stratum Malpighi. (b) Widespread acantholysis with dilapidated brick wall appearance of epidermis.

Table 1: Treatment and response summary.

Cases	Age (years)	Initial dose of naltrexone (mg/day)	Maximum dose required	Total duration	Response at 4th week	Complete clearance at and healing with PIH	Relapse (until 6th month)	Adverse effect
Case 1	75	3	6 mg/day at 8th week	6 months	No development of new lesions, Reduction in pain and erythema	8th week	NO	NO
Case 2	63	3	4.5 mg/day at 4th week	6 months	Reduced itching, pain and erythema	12th week	NO	NO
Case 3	50	3	4.5 mg/day at 4th week	6 months	No development of new lesions, old lesion stared healing with reduction in erythema pain and discomfort	6th week	NO	NO

PIH: Post inflammatory hyperpigmentation

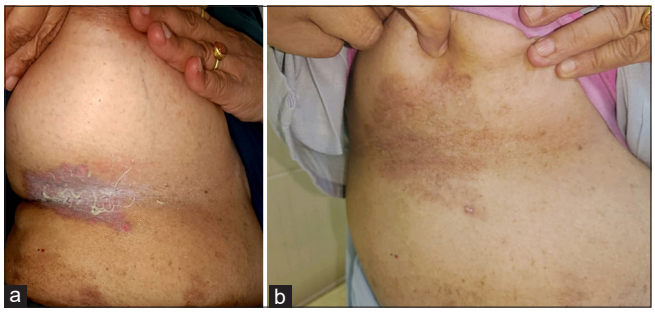

Figure 2: (a) Before treatment erosive lesion with greyish slough and maceration in the inframammary area. (b) After treatment complete resolution of the lesion with PIH in the right inframammary area.

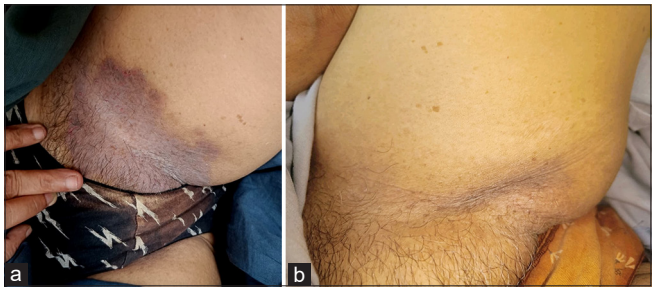

Figure 3: (a) Before the initiation of treatment hyperpigmented patches with maceration in the groin. (b) After treatment complete resolution of the lesions of the left groin.

Opioid receptors from keratinocytes modulate many processes, including wound healing.[9] It could be possible that naltrexone may modulate μ receptors in the epidermis, with increased cellular adhesion and healing of the skin. Naltrexone also functions as a toll like receptor (TLR)-4 antagonist, and downstream signalling pathways are implicated in calcium homeostasis in keratinocytes.[10] Increased calcium allows the differentiation of keratinocytes and wound healing.

A full-dose naltrexone shows side effects such as suicidality, depression, hypersensitivity, headaches and vivid dreams, gastro intestinal (GIT) distress and hepatotoxicity, which are very rare with LDN. No organ system toxicities and abuse has been reported to date. Furthermore, there are no withdrawals with treatment discontinuation.[11]

LDN is a unique treatment for HHD since it has few side effects, improves symptoms quickly and significantly and is reasonably priced. Larger investigations are required to validate early findings and further investigate the process in HHD. LDN could be effective in various faulty calcium transport illnesses like Darrier Disease.

Table 2 depicts the review of the literature with LDN therapy in HHD.[12-16]

Table 2: Review of literature.

Study by	Year	Conclusion
Albers *et al*.[12]	2017	Three cases with severe HHD improved completely within 3 months of therapy
Ibrahim, *et al*.[13]	2017	Three patients exhibited at least an 80% improvement with one patient reporting improvement in his depression
Riquelme-Mc Loughlin *et al*.[14]	2019	The study included 14 patients with a median age of 56.5 years. Six patients with no response, six with response and relapse, two shown sustained improvement for more than a year
Garayar Cantero *et al*.[15]	2019	Case report of 66-year-old women with complete clearance of the disease in 6 weeks of naltrexone 6.25 mg/day therapy initiation
Sousa Gomes *et al*.[16]	2020	A case of a 71-year-old white woman with vulvar HDD responded completely to low-dose naltrexone within 5 months.

HHD: Hailey-Hailey disease

CONCLUSION

Three cases of HHD demonstrate the efficacy of LDN, with complete or near-total disease remission with sustained results by the 6th months. It is an off-label use, low-cost and low-risk option. Concomitant therapy can lead to greater improvements. The clinical evidence supporting its usage is quite preliminary, and more research is required.

Ethical approval: The research/study approved by the Institutional Review Board at Dr.PDMMC Amravati, number PDMMC/SS/ETHICAL/6060/2024, dated 09 May 2024.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
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