Dermatology Practical & Conceptual

Hailey-Hailey Disease: Case Series and Review of Systemic Medications

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ABSTRACT

Introduction: Hailey-Hailey disease (HHD) is a rare inherited blistering skin disorder characterized by a chronic relapsing course. While it does not pose a serious threat to the patient's health, the quality of life can change. Unfortunately, there is currently no standard treatment for this condition.

Objectives: In this observational retrospective cohort study, our aim was to discover the demographic characteristics and treatment strategies for managing HHD.

Methods: In this retrospective cohort study, we documented the demographic, clinical, and histopathological characteristics beside various treatment employed options of patients diagnosed with HHD at Razi Hospital over the past 14 years.

Results: A total of 32 patients with HHD were enrolled in the study (15 male and 17 female). The mean age of patients was 50.41 ± 13.15 (22-77) years. The average age of disease onset was 37.31 ± 11.88 (15-60) years. Among the participants, 16 individuals (50%) affirm a positive family history of some kind of pemphigoid blisters. The most common site of disease activity was the inguinal area, observed in 14 patients (33.33%). Histopathological examination discovered the existence of suprabasal acantholysis in all of the specimens. Worthily, direct immunofluorescence analysis showed negative results in all skin biopsies. All patients received topical steroids and either topical or systemic antimicrobial agents. In cases of flares, systemic steroids were the most popular and favorable treatment choice during flares.

Conclusion: Indeed, Hailey-Hailey disease, characterized by its chronic inflammatory and rare nature with a relapsing and remitting course, poses a significant challenge for dermatologists. The treatment of HHD has been less than satisfactory and it often presents a challenge and could be misdiagnosed. Among the available treatment options, topical steroids and antimicrobial agents are the most administered therapies.

Introduction

Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, is a rare blistering skin disorder. This genodermatosis follows an autosomal dominant inheritance pattern with complete penetrance and variable expression. While the precise prevalence of HHD remains unknown, it is estimated to affect approximately 1 in 50000 individuals [1,2]. Notably, about 70% of patients may have a positive family history of the condition. Typically, the disease occurs during the second to fourth decade of life [1,3]. One of the challenging aspects of HHD is the vast and unpredictable severity of skin manifestations it may present [2].

The key pathological events in HHD are initiated by a single mutation occurring in one copy of the ATP2C1 gene located on chromosome 3. This gene encodes the P-type Ca2+- transporter ATPase, a protein pump responsible for transporting both calcium (Ca) and manganese (Mn) ions from the cytosol into the Golgi apparatus during each cycle. Consequently, only half of the required Golgi apparatus Ca transporter pumps are produced. As a result of the mutation, the altered protein which inadequately functions in the desmosome causes epidermal acantholysis.

Ultimately, this genetic mutation manifests as blisters and inflamed lesions on the skin mostly on the folds or even on a large area of the body [4-10]. Clinically, Painful blisters frequently rupture, occasionally become infected, resulting in an unpleasant malodor. In some cases, allergic blisters may also present in the involved area. Non-healing erosions gradually progress to scar formation or post-inflammatory hyperpigmentation. Rarely, there is also a risk of squamous cell carcinoma developing within the affected region [1,11-12].

Histologically, HHD often exhibits suprabasal acantholysis, which can be likened to a disrupted brick wall. Dyskeratosis may also be observed. Typically, the dermis remains unaffected; however, there may be lymphatic infiltration around the blood vessels. It is important to note that, unlike pemphigus vulgaris (an autoimmune blistering disorder) anti-desmosome antibodies are not present in HHD [13]. Patients with HHD generally enjoy a normal life span and retain their reproductive capacity. This condition generally affects the skin and follows a chronic relapsing course with flares becoming less frequent as individuals age. While HHD does not pose a serious risk to the patient health, can change the quality of life. Certain factors such as specific foods, hormonal cycles, infection, medication and stress may trigger symptom outbreaks. Additionally, heat and sweating can exacerbate or trigger the condition, while sun exposure may either worsen or improve skin lesions [1].

Despite several studies describing effective treatments, the absence of a standard treatment modality is likely due to the rarity of the disease and the lack of large-scale clinical trials.

Objectives

Due to the scarcity of comprehensive studies focusing on the demographic characteristics of Hailey-Hailey disease, this study pursued to explore the demographic characteristics and treatment approaches employed in patients with HHD who were referred to Razi Hospital over the last 12 years.

Methods

Study Design

This retrospective, observational cohort study received approval from the Ethics Committee of Tehran University of Medical Science (approval ID 9223101036).

Study Population and Outcomes

All patients referred to Razi Hospital with a confirmed diagnosis of HHD through skin biopsy between 2008 till 2022 were included in this survey. Verbal or written informed consent was obtained from each patient before inclusion in the study. The inclusion criteria confirmed a clinicopathologic diagnosis of HHD and the patients agreement for participation. The following data were collected: (1) age of onset, (2) gender, (3) family history, (4) involvement area, (5) histopathological findings and (6) results of direct immunofluorescence (DIF) tests. Patients with missing required data were excluded from the study. The necessary information was retrieved from records available in the dermatology outpatient clinic and the dermato-pathological department. In addition, some data were obtained by contacting or visiting the patients.

Statistical Analysis

All collected data were analyzed using IBM SPSS statistical software version 23. Continuous variables were reported as mean with standard deviation (SD). While categorical variables were described in terms of frequencies. The differences between study groups were examined using the Chi-square test and T-test as appropriate. A significance level of $P < 0.05$ was considered statistically significant.

Results

Patients Characteristics and Clinical Findings

A total of 32 patients with HHD were enrolled in the study (15 male and 17 female). The mean age of patients was 50.41 ± 13.15, ranging from 22 to 77 years. The average age of disease onset was 37.31 ± 11.88 years with an onset range from 15 to 60 years. Notably, 16 patients (50%) reported a positive family history of similar blistering conditions with seven attributing it to their fathers, six to their siblings and four to their mothers.

Regarding the initial areas of presentation, the study detected the following distribution among patients: 19 (45.23%) in the axillary region, 18 (42.85%) in the inguinal region, 2 (4.8%) in the lateral neck region and 3 different patients each presented involvement of the inframammary fold, genital area and perianal area.

However, at the time of data collection, the disease activity was primarily concentrated in the inguinal area, affecting 14 (33.33%) patients. The second most common sites of involvement were the axillary and abdominal regions, each with 7 (16.67%) patients experiencing disease activity. Less frequently, the disease was active in the inframammary region for 5 (11.90%) patients, the genital area for 4 (9.52%) patients, the lumbar and intergluteal regions for 2 (4.76%) patients each and the perianal area for 2 (4.76%) patients.

Histopathological Findings

Histopathological findings were documented for all patients. In the histopathological examination, suprabasal acantholysis was a consistent finding in all patients. Additionally, dyskeratosis was observed in 10 (31.25%) patients, and a brick wall appearance was reported in the specimens of 8 (25%) patients. DIF analysis was conducted on all patients and the results were consistently negative. Anti-IgG was assessed in all patients, Anti-C3 in 92.86% of patients, Anti-IgA in 42.85% of patients, Anti-IgM in 14.28% of patients, Anti-fibrinogen in 7.14% and Anti-total-Ig in 7.14% of patients. In all these assessments, the results were reported as negative.

Treatment

All patients received a treatment regimen consisting of topical corticosteroids (triamcinolone acetonide cream, mometasone cream), topical antifungals (clotrimazole or sertaconazole) and topical antibacterial agents (mupirocin, gentamicin, fusidic acid).

In cases where complications such as eczema herpeticum arose, oral acyclovir was added to the therapeutic regimen. It is worth noting that all patients experienced multiple flares of their condition throughout their lives. For severe flares, treatment included oral prednisolone with doses ranging up to 0.5mg/kg or 0.75mg/kg as required. Following the remission of the flare condition, a gradual tapering of systemic corticosteroids was initiated and typically continued for a duration of 4-6 months. The specific duration of the tapering regimen depended on the severity of HHD in each patient. One of our patients, a 45-year-old male with a known history of HHD for the past 10 years, had been using topical steroids and antifungal agents with only partial improvement. Approximately one year ago, he experienced a severe flare-up of HHD affecting his axillary and inguinal areas.

The patient continued to use topical steroids and antifungal agents concurrently. Within a span of two months, a dramatic response was observed (Figure 1), and after four months, the lesions had completely cleared (Figure 2).

Conclusions

HHD is a rare blistering disorder known for its chronic relapsing feature. In our study, the average age of patients with HHD was 50.41 ± 13.15 (22-77) years. The mean age of onset was 37.31 ± 11.88 (15-60) years. Similarly, in a retrospective study conducted by Zhao et al, on 26 patients with HHD the mean time of disease onset was 35 years [14]. These findings show that HHD tends to present in adulthood

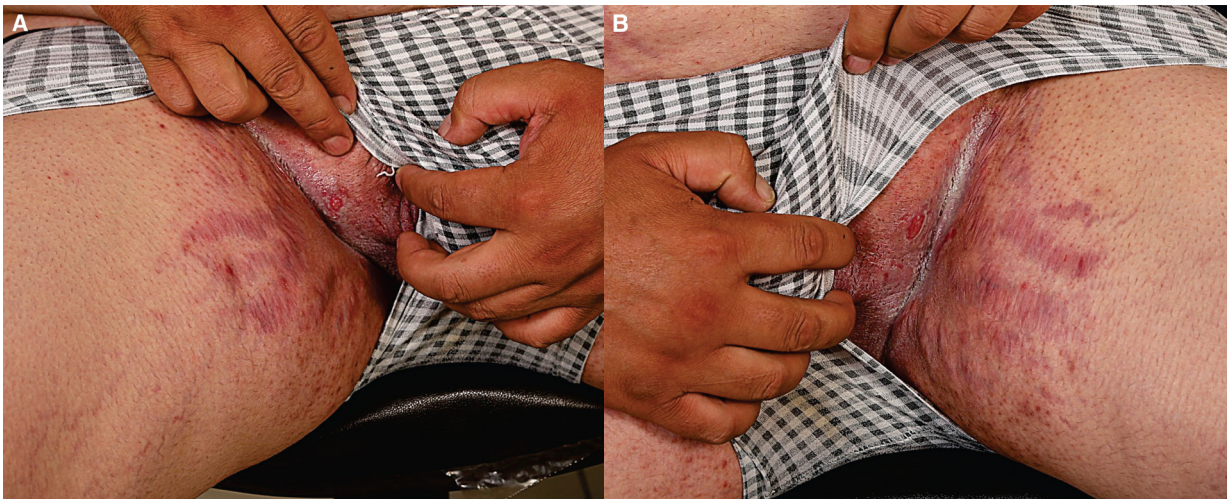

Figure 1. Partial improvement with oral methotrexate with few remaining inguinal ulcers.

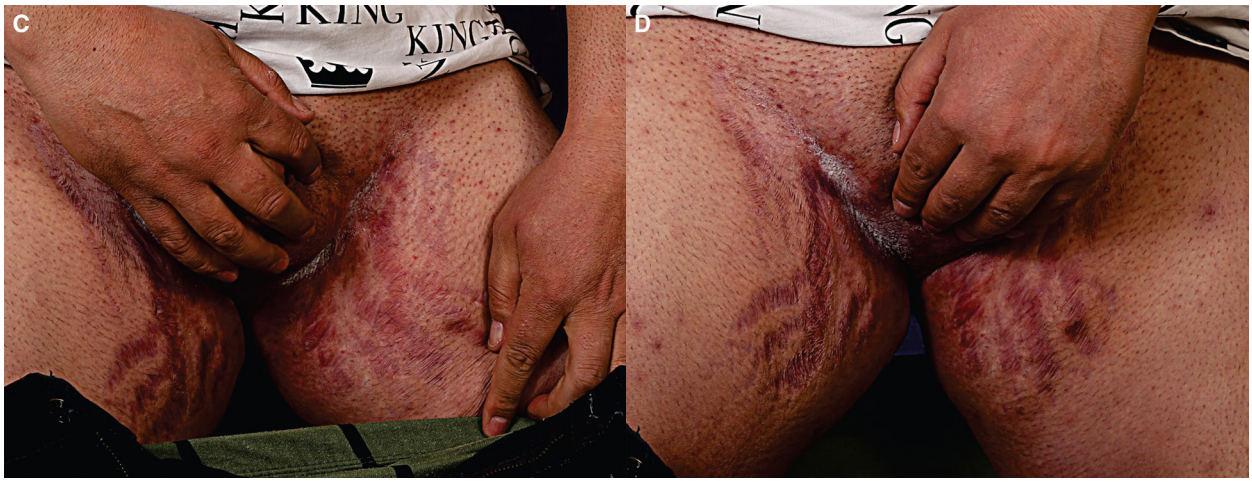

Figure 2. Complete improvement with oral methotrexate after 5 months.

and predominantly affects middle-aged individuals. According to our results, half of our patients had a negative family history of this disease. This inconsistency could possibly be attributed to the variable penetrance of the mutated gene responsible for HHD or the occurrence of de novo mutations in the responsible gene. In contrast, in a survey performed by Zhao et al, positive family history of the disease was stated in nearly all patients [14]. Similarly, in the study by Gisondi, half of the patients had positive family history [15]. The differences in the family history may reflect variations in the genetic inheritance patterns and the presence of mutations in different populations of patients with HHD. Our findings showed that HHD mostly affected the inguinal and axillary areas, which is parallel with the results reported in the survey conducted by Zhao et al [14]. The study performed by Gisondi, lesions were also observed on the back, shoulders and trunk [15]. These differences in lesion distribution among HHD patients may possibly reflect both genetic and environmental factors influencing the various presentation of HHD. The treatment of HHD relies heavily on information derived from case reports and case series. The absence of randomized clinical studies and chronic relapsing course of the disease cause challenges in managing HHD. There is not any gold standard treatment and it remains difficult to directly compare the efficacy of various therapeutic approaches [1,16-18]. First step is certain lifestyle modifications. They are believed to improve the condition. These modifications include:

Heat, sweating and friction avoidance as potential exacerbating factors. Weight loss is recommended to eliminate the friction of the skin.

Personal hygiene and frequent bathing are important to prevent bacterial, fungal and viral superinfections which potentially can worsen HHD lesions.

In severe cases of HHD or during flare-ups, use of topical and systemic medications as well as interventional therapies have successful outcomes [1,16-18].

Oral systemic medications are commonly administered for cases of HHD with recalcitrant and widespread skin involvement [1,17,18]. There is substantial supportive evidence for the efficacy of oral antibiotics, particularly tetracycline, improving skin lesions associated with HHD.

These antibiotics are favored due to their anti-inflammatory properties and safety profiles, making them a first-line choice among systemic medications. However, exacerbation during treatment and relapsing upon discontinuation or failure to respond, have been reported with Tetracycline. In such cases, dermatologists may consider a low maintenance dose or explore alternative medications to manage the condition more effectively.

Systemic corticosteroid can control severe HHD. However, their use is typically limited to short-term periods due to the potential long-term side effects associated with prolonged therapy.

Among the emerging medications for HHD, low-dose naltrexone (LDN) and systemic retinoids have been supported most by the previous case reports and case series [1]. LDN has the potential to modulate the immune system, promote wound healing and alter the cell migration pattern through inhibition of opioid receptors and increasing the levels of enkephalin and endorphin in the body [19]. Strong evidence supports the use of low dose oral acitretin (10-30 mg daily) for managing HHD, due to their role in regulating epidermal proliferation and maintaining calcium homeostasis. There have been some unresponsive cases with oral retinoids though [1,17,18]. Other systemic agents (cyclosporine, thalidomide, glycopyrrolate, azathioprine and biologics such as etanercept) have different efficacy in the management of HHD.

Treatment of HHD is less than satisfying. Further clinical trials with control groups, larger population and longer follow up in addition to genomic studies are needed.

HHD as a hereditary chronic and rare blistering disorder may cause significant morbidity and psychological impact. While numerous therapeutic approaches including topical and systemic medications as well as intervention modalities have been introduced, there is no established gold standard treatment and it could get misdiagnosed. Topical steroids and antimicrobial agents are commonly used, particularly for localized or less severe cases. Systemic steroids may be preserved only for controlling severe recalcitrant flares. There are a few reports supporting the efficacy of systemic immunomodulators with more acceptable safety profiles.

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