



HAILEY-HAILEY- A SYSTEMATIC REVIEW**SIVAKRISHNAN S^{1*} AND KAVITHA J²****1:** Assistant Professor, Department of Pharmacy, FEAT, Annamalai University**2:** Associate Professor, Department of Periodontia, RMDCH, Annamalai University
Annamalai Nagar, Chidambaram-608002, Tamilnadu, India***Corresponding Author: Dr. S.Sivakrishnan: E Mail: sivacdm82@gmail.com**Received 27th Dec. 2020; Revised 29th Jan. 2021; Accepted 15th Feb. 2021; Available online 1st Oct. 2021<https://doi.org/10.31032/IJBPAS/2021/10.10.5685>**ABSTRACT**

Hailey-Hailey disease is also known as benign familial pemphigus. In the third or fourth decade, benign familial pemphigus usually occurs, although it can occur at any age. Then it continues to persist life-long. People of all races may be affected by it. Hailey-Hailey disease is caused by ATP2C1 gene mutations and is inherited in an autosomal dominant manner, although rare cases occur occasionally without a family history. Benign familial pemphigus typically begins as a symmetrical painful erosive and crusted skin rash in the skin folds. Diagnosis may require a skin biopsy. This systematic review aimed to collect the early and recently published research articles including PubMed and Google Scholar that confirmed the epidemiology, etiology, pathogenesis, pathophysiology, clinical features, diagnosis, treatment, management and life style modifications of Hailey-Hailey disease. There is no cure for Hailey-Hailey disease. Treatment is aimed at reducing symptoms and preventing flares. Sunlight, heat, sweating and friction often aggravate the disorder.

Keywords: Hailey-Hailey disease, Desmosomes, ATP2C1 gene, Skin grafts, Botulinum toxin**INTRODUCTION**

Hailey-Hailey disease, first identified by the Hailey brothers in 1939, is a rare hereditary blistering skin disease [1]. The condition is characterized by red, raw, and blistered skin areas that occur most

frequently in skin folds, such as the groin, armpits, throat, and under the breasts. These areas that are inflamed may become crusty or scaly and can itch and burn. With exposure to moisture (such as sweat),

friction, and hot weather, skin conditions begin to worsen [2].

Epidemiology

Hailey-Hailey disease (HHD) is a rare disorder. Its prevalence is unclear, since many patients do not have a clear diagnosis or are not seeking care. Within families, the age of onset and clinical symptoms of HHD can differ widely. It is most common to first begin after puberty, but presentation can occur during childhood [3, 4]. Between different ethnic groups, there is no apparent difference in prevalence.

Etiology

ATP2C1 gene mutation [5, 6], encoding the calcium pump, triggers the disease by impairing the adhesion of epidermal keratinocytes.

Pathogenesis

Pathogenesis Hailey-Hailey disease is caused by loss-of-function mutations of the adenosine triphosphate (ATP)-powered, magnesium-dependent calcium pump protein hSPCA1 in the ATP2C1 gene at 3q22.1 [7], with the function of preserving normal intracellular free calcium (Ca^{2+}) concentrations by sequestering Ca^{2+} into the Golgi apparatus [8, 9]. While rare, squamous cell carcinoma [10-12] can develop in patients with Hailey-Hailey disease.

Pathophysiology

- ✓ Mutation in ATP2C1, a calcium pump that is essential for normal

desmosomal protein complex function,

- ✓ Dissociation of the desmosomal cadherin and E-cadherin (adherens junction associated protein) intracellular and extracellular domains
- ✓ Faulty operation of the calcium pump results in desmogleins, which are calcium-dependent adherence proteins (cadherins) [13], having disorganized function.
- ✓ In comparison to pemphigus vulgaris, in which autoantibodies evolve against desmosomal proteins, Hailey and Darier's diseases share similar pathogenesis.

Clinical description

Hailey-Hailey disease is seen in adulthood. It most frequently occurs at intertriginous sites (axillae, groin, and neck). There are flaccid blisters. Weepy or crusted, sharply marginalized erosions with peripheral scales are more common than intact blisters [14, 15]. Severe flare-ups may lead to infection and discharge, which may cause increased pain Pruritic /burning, often malodorous lesions. The affected areas may become particularly problematic if secondarily infected. This may be due to bacterial and/or viral (particularly the cold sore virus) infection, papular, verrucous, annular and vesiculopustular variants are rare, nikolski sign may be positive, 33% of

cases are sporadic, healing accompanied by hyperpigmentation, but scarring is rare, longitudinal leukonychia (in 70% of patients), superinfection by *Candida albicans*, herpes virus and *Staphylococcus aureus* are frequent complications. Cases of complication by squamous cell carcinoma have been reported and symptoms worsen during summer, often disappear during winter

Diagnosis

It is possible to confirm the diagnosis of Hailey-Hailey disease by taking a skin sample (biopsy) for analysis under a microscope. To confirm the diagnosis, a second biopsy is also taken for direct immunofluorescence. The lack of oral lesions and intercellular antibodies distinguishes familial benign pemphigus from other forms of pemphigus. Many people affected have white lines running the length of their fingernails as well. No complications are caused by these lines, but they can be useful for diagnosing Hailey-Hailey disease.

Treatment and management

- ❖ There is no specific treatment
- ❖ The treatment is based on severity and extent of the disease and is directed towards controlling symptoms. Topical medical treatment (like Triamcinolone, Hydrocortisone as 2% ointments or

lotions) can alleviate the symptoms in milder forms.

- ❖ In case of severity, systemic corticosteroids like Prednisolone can be used [16].
- ❖ For the prevention of secondary bacterial and fungal infections, topical antibiotics (such as erythromycin, tetracycline, clindamycin and mupirocin) and antifungal drugs (such as ketoconazole) may be prescribed [17]. It is possible to pick antibiotics on the basis of bacterial culture and susceptibility [18].
- ❖ For the reduction of hyperhidrosis (excessive sweating) [19], anticholinergic drugs such as glycopyrrolate at 0.1 mg/kg may be used.
- ❖ As they inhibit sebaceous gland differentiation and abnormal keratinization [20], vitamin A derivatives such as Acitretin and Etretinate can be used.
- ❖ In certain patients, medications that suppress the immune system such as Tacrolimus and Methotrexate [21-25] and astringents such as oral magnesium chloride [26, 27] can also benefit to an extent.
- ❖ Physical treatments are very effective for more severe forms: CO₂ laser therapy [28] (pulse or

continuous) is often proposed as a first-line treatment. It vaporizes the affected skin; pulsed dye laser enhances the wound healing. Laser resurfacing agents that burn off the top layer of the epidermis, allowing healthy nonaffected skin to regrow in its place can also control blisters [29-34].

- ❖ Botox (botulinum toxin) is an injection which can help alongside topical treatments. It works by reducing sweating and keeping the area dry, and reduce the risk of infection [35-39].
- ❖ Photodynamic therapy with aminolevulinic acid is also successful in most of the patients [40-44].
- ❖ Skin grafts are usually necessary to repair the wounds [45].
- ❖ Other techniques, such as dermabrasion [46-48] may also be required to correct the symptoms of this dermatosis.
- ❖ In many cases naltrexone, taken daily in low doses, appears to help [49, 50].

Life Style Modifications

- ❖ Avoid triggering factors like sunburn, friction and sweating.
- ❖ Sunscreens and moisturizing creams are used during the daytime.

- ❖ Apply ointments to inflamed patches repetitively.
- ❖ Wash and dry the infected areas using mild soap and water once or twice daily.
- ❖ Wearing clothing that is soft and loose
- ❖ Avoid fabrics and other clothes that rub or irritate the areas affected.
- ❖ Stop gaining extra weight.
- ❖ To decrease friction, try decreasing body fat.
- ❖ Try using 1:40 diluted aluminum acetate or vinegar to dry up oozing patches.
- ❖ To reduce superficial infections, take bleach baths twice weekly [51].

CONCLUSION

Benign chronic familial pemphigus is transmitted as a dominant trait, with incomplete penetrance. Though Hailey-Hailey disease is not life threatening, it causes a lot of discomfort to the affected patients. At present, there is no complete cure to this disease as it is remittent. Therapeutic options are limited. The treatment is based on severity and extent of the disease and is directed towards controlling symptoms. But mostly, these are mainly directed towards providing relief to the patients rather than curing the symptoms. Topical treatments, tablet treatments and other treatments such as

botulinum toxin, topical photodynamic therapy, dermabrasion, skin grafts and laser therapy are the several ways of helping patients with Hailey-Hailey diseases. On the other hand, life style modifications also help by providing relief to some extents. Finally, we conclude that the underlying genetic defect cannot be altered; however, treatment and life style modification does help with prevention of flare-ups and may increase the speed of healing.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All the authors contributed equally to the paper.

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