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A Very Brief Overview of Hailey-Hailey Disease with Various Available Treatment Options

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Abstract

Hailey-Hailey disease is one of the rare genetic hereditary skin disease which is characterized by the presence of flaccid blisters and extensive rashes at various sites on skin like neck, groins, armpits, etc. It occurs equally in both males and females due to a point mutation in *ATP2C1* gene which is indirectly responsible for cellular adhesion through SPCA1 (Secretory Pathway Calcium/manganese-ATPase) protein encoding. Proper diagnosis can differentiate Hailey-Hailey disease from other similar skin diseases. As the symptoms are remittent, there is no complete cure. However, life style modifications can help the patient by providing comfort. In this paper, we will briefly discuss about Hailey-Hailey disease along with various treatment options available.

Keywords: Hailey-Hailey disease; Flaccid blisters; *ATP2C1* gene; SPCA1 protein

Introduction

Skin is the primary defence organ in the body and performs several functions like providing protection, holding body fluids, synthesis of vitamin D in presence of sunlight, etc. However, the skin is so sensitive and gets easily damaged by different allergens like microbes showing rashes, redness, erythema which can lead to skin diseases. Even genetic mutations can also sometimes result in various hereditary skin diseases. One of such is Hailey-Hailey disease which occurs due to point mutation in *ATP2C1* gene. In 1933, two dermatologist brothers Hugh Edward and William Howard (commonly known as Hailey brothers) identified a skin disease and described about it completely in 1939. Later, the disease was named after them as Hailey-Hailey disease [1].

It is a very rare hereditary disease with a prevalence of 1 in 50,000 people and is characterized by intense formation of flaccid blisters and rashes at various sites on skin and occurs equally in both males and females. As it is hereditary, it can be passed on to generations. So, it is also known as familial benign chronic pemphigus or simply familial benign pemphigus. However, Hailey-Hailey disease is not an autoimmune disorder [2,3].

Characteristic Feature

Hailey-Hailey disease can occur at any age but mostly seen during the third or fourth decade (30 to 45 years). Symptoms may vary from person to person. It is characterized by presence of outbreaks of rashes and blisters in the skin, usually in the folds of the skin and also over large areas of the body. These rashes may cause itching or burning sensation. Most common sites of the rashes are the armpits, groins, neck, under the breasts and between the buttocks. These rashes and blisters become painful and often break resulting in formation of new blisters over raw skin continuing the unending cycle of outbreaks which give brick wall appearance.

According to Human Phenotype Ontology (HPO) derived from Orphanet, a European rare disease database, about 80-99% of the affected patients exhibit acantholysis, erythema, hyperkeratosis, skin erosions and skin vesicles as more common symptoms besides blistering. Moreover, secondary bacterial, fungal and/or viral infections are common which may cause unpleasant smell. Multiple white bands in finger nails can also be seen. Heat, sweating and friction often exacerbates the disease, and most patients have worse symptoms during the summer months. In certain cases, outbreaks are triggered by certain foods, hormone cycles and stress [4].

Development of the Disease

Normally, *ATP2C1* gene which is located on chromosome 3 is responsible for encoding of protein SPCA1 (Secretory Pathway Calcium/manganese-ATPase). This protein is involved in proper pumping of sufficient calcium and magnesium ions into the cells which is necessary for proper formation of intercellular desmosomes and ultimately proper adhering of the skin cells (keratinocytes). Desmosomes are the structures containing calcium binding trans-membrane glycoproteins which are involved in cellular adhesion. But in Hailey-Hailey patients, a mutation in *ATP2C1* gene occurs. This results in insufficient production of SPCA1 protein. Reduced SPCA1 protein implicates in either improper functioning of calcium pump or loss of sensitivity to calcium and manganese ions resulting in malformation of intercellular desmosomes. This leads to loose connection between keratinocytes (skin cells) and ultimately flaccid blisters and rashes appear [5].

Diagnosis

Hailey-Hailey disease is often mistaken for other skin problems like impetigo, thrush, tinea (jock itch) and other blistering conditions. A biopsy and/or family history can confirm the disorder. A biopsy of skin may reveal abnormal formation of keratin tissue (keratinization) and failure of cell-to-cell adhesion (acantholysis). The immunofluorescence test can be performed which shows negative

for antibodies. The lack of oral lesions and intercellular antibodies also distinguishes the Hailey-Hailey disease from others [6].

Treatment Options

At present, there is no complete cure to this disease as it is remittent. The treatment is based on severity and extent of the disease and is directed towards controlling symptoms. Topical corticosteroids like Triamcinolone, Hydrocortisone as 2% ointments or lotions are used more often for a duration of two weeks to control the lesions. In case of severity, systemic corticosteroids like Prednisolone can be used. Topical antibiotics (like Erythromycin, Tetracycline, Clindamycin and Mupirocin), antifungal drugs (like Ketoconazole) can be prescribed for controlling secondary bacterial and fungal infections. Selection of antibiotics can be done based on bacterial culture and sensitivity [7].

Anticholinergic medications such as glycopyrrolate at 0.1 mg/kg can be used to reduce hyperhidrosis (excessive sweating) [8]. Botulinum toxin injections used to inhibit perspiration also showed significant result [9]. They can reduce colonization by microorganisms and flare-ups by reducing sweating in axillae and groins. Studies showed that intramuscular Alefacept may control the mild to moderate forms of the disease. Naltrexone has been helpful in a few patients [10-12]. Vitamin A derivatives such as Acitretin and Etretinate can be used as they inhibit sebaceous gland differentiation and abnormal keratinization. Acitretin is more efficient and is given at a dose of 25 mg daily over a period of 6 months. Drugs that suppress the immune system such as Tacrolimus and Methotrexate, and astringents like oral Magnesium chloride can also help to an extent in some patients [13]. Use of agents that reduce oxidative stress, such as the subcutaneous administration of the melanocortin analogue Nle4-D-Phe7-alpha MSH, also have been reported to improve the skin lesions of Hailey-Hailey disease [14].

Lasers have been reported to be successful. For example, CO_2 laser and Er:YAG lasers 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 non-affected skin to regrow in its place can also control blisters [15]. Photodynamic therapy with aminolevulinic acid is also successful in most of the patients [16]. In severe cases, finally surgery can be performed to remove the affected skin. Skin grafts are usually necessary to repair the wounds [17].

Life Style Modifications

- Avoid triggering factors such as sunburn, sweating and friction.
- Usage of sunscreens and moisturizing creams during day time.
- Apply ointments repeatedly to inflamed patches.
- Wash and dry the affected areas once or twice daily using mild soap and water.
- Wear soft and loose clothing
- Avoid fabrics and other clothing which rub or irritate the affected areas.
- Avoid gaining over weight.
- Try to decrease body fat to minimize friction.
- Try to dry up oozing patches using 1:40 diluted aluminium acetate or vinegar.
- Take bleach baths twice weekly to reduce superficial infections [18].

Conclusion

Though Hailey-Hailey disease is not life threatening, it causes a lot of discomfort to the affected patients. As most of the symptoms of the disease are remittent, there is no complete cure. However, many treatment options are available which are selected based on patient and disease severity condition. But mostly, these are mainly directed towards providing relief to the patients rather than curing the symptoms. Other life style modifications and non-pharmacological therapy can also help by providing relief to some extent.

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