# Hailey-Hailey disease and contact hypersensitivity

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## Abstract

Hailey-Hailey disease (HHD) is a genetically determined disorder of autosomal dominant mode of inheritance with high penetrance associated with mutations in the gene *ATP2C1*, which encodes the calcium ion dependent ATPase. Throughout all the skin, including pathologically unchanged skin, abnormal accumulation of $Ca^{2+}$ by the keratinocytes in the granular layer is found. Skin lesions of an erythematous-exudative type (histologically: a vast, incomplete acantholysis above the basal layer of the epidermis) can be induced by various environmental factors: friction, high ambient temperature, increased sweating, UV radiation, and infectious, toxic and allergic agents. The aim is study was to drawing attention in some patients to the possible pathogenetic link between the hypersensitivity to various contact allergens and HHD. Three cases (48-year-old male, 32-year-old female, 42-year-old female) of HHD (medical history of two to nine years) coexisting with hypersensitivity to different contact allergens (nickel sulfate, cobalt chloride, Peruvian balsam, eugenol, aniline, benzocaine, metol) are presented in the paper. The introduction of appropriate preventive measures in patients with HHD and concomitant contact allergy can contribute to alleviating the symptoms of HHD.

**Key words:** Hailey-Hailey disease, pathogenesis, contact hypersensitivity.

## Introduction

Hailey-Hailey disease (HHD), also known as chronic benign pemphigus, is a genetically determined disorder of autosomal dominant mode of inheritance with high penetrance. Clinical signs usually appear in the 3rd or 4th decade of life. Erythematous and exudative lesions in skin folds, flexures and on the nape of the neck are the typical clinical morphology. The histopathological picture of skin lesions is characterized by the presence of extensive, incomplete acantholysis above the basal layer of the epidermis, which leads to generation of blanks and fissures in its lowest layers. Genetics and pathophysiology of HHD are related to mutations within the *ATP2C1* gene, which encodes the calcium ion dependent ATPases SERCA2 (sarco/endoplasmic reticulum $Ca^{2+}$-transport ATPase) and SPCA1 (secretory-pathway $Ca^{2+}$-ATPase). There are identified nearly 100 different mutations within the *ATP2C1* gene so far. The significance of ATP2C1 mutations in HHD pathogenesis and the role of calcium ions ($Ca^{2+}$) in disturbances of intercellular links in the epidermis, though well supplied with documentary evidence, remain however not completely clear [1]. There is no association among types of ATP2C1 mutations and phenotype, i.e. clinical course of the disease, its start, degree of increase, distribution of skin lesions, rate of progression and reaction to different therapeutic methods [1]. What is more, disturbance just of ATP2C1 function is not sufficient for clinical manifestation of HHD. Skin lesions can be provoked by different environmental factors: friction, high temperature, enhanced sweating, UV radiation, and infectious, toxic and allergic factors [2].

The aim of this study was to investigate possible pathogenic relationship among hypersensitivity to different contact allergens (ascertained by patch tests) and HHD in some patients.

## Case reports

### Case I

Man, 48 years old, electrical fitter. Was directed to the Dermatology Clinic due to erythematous and exudative lesions in skin folds and flexures with a history 4 years long. Treatment with corticosteroid, antimycotic and antibiotic ointments did not bring satisfactory results. Additionally, the patient was treated for asthma with

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inhaled drugs, and he has had corneitis and removal of a polyp of the fauces. Family history was negative for HHD. At admission to hospital confluent erythematous and exudative lesions included regions of armpits, groin, chinks, and navel. Histopathology (skin lesions in regions of armpits and groin) pointed to HDD. Direct immunofluorescence test (DIF) was negative. Mycological culture from skin of groin and chinks showed growth of *Candida albicans*. From other regions the result of culture was negative. Patch tests revealed: nickel sulfate (++), cobalt chloride (++), Peruvian balsam (++), eugenol (+), aniline (+). General corticosteroids (methylprednisolone), antibiotics (erythromycin), antimycotics (ketoconazole) and local treatment of the above-mentioned mode of action were employed.

### Case II

Woman, 32 years old, nursery school teacher. Hospitalized in the Dermatology Clinic due to confluent erythematous and exudative lesions on the trunk. The first skin lesions appeared in submammary regions 2 years earlier and they showed resistance to applied local treatment (corticosteroids, antibiotics, antimycotics). Similar skin changes appeared in a prolonged course in the mother and grandmothers, but they did not require diagnostics and treatment due to the small increase. History for concomitant and stayed diseases was negative. There were extensive, confluent erythematous lesions with presence of vesicles, erosions and linear cracks on the skin of the chest and in the interscapular region (Fig. 1). Histopathological examination (skin lesions on chest) pointed to HDD. Direct immunofluorescence test and mycological examination of skin lesions on trunk were negative. Patch tests revealed: nickel sulfate (++), cobalt chloride (++), anesthesine (+++), metol (+). In general treatment corticosteroids (methylprednisolone) and antibiotics (cefuroxime) were used. Corticosteroid ointments were recommended.

### Case III

Woman, 42 years old, office employee. For 9 years she was treated for erythematous and erosive lesions in submammary regions, within strip, groin and on the neck. The patient's mother had a similar type of skin lesions in submammary regions and groin. The patient reported occurrence of skin reactions of eczema type in places of contact with metal decorations and a watch and complained of periodic itching of palms. At admission to the clinic she presented extensive erythematous and exudative lesions in the sacral region, submammary folds, on the abdomen, lateral surfaces of the neck and in the groin. Histopathological examination (skin lesions on chest) confirmed the diagnosis of HDD. Direct immunofluorescence test and mycological examination from skin lesions on the trunk and groin were negative. Patch tests revealed nickel sulfate (++). Systemic antibiotic (cefuroxime: initially intravenous, after 5 days oral continuation due to reaction after catheter) and antihistamines were recommended. Tacrolimus, antibiotic and disinfecting ointments were used in external treatment. Almost complete remission of HHD was achieved in the described cases as a result of employed treatment and preventive maintenance. No recurrence of skin lesions requiring hospitalization or general therapy was found within 0.5 to 5 years observation.

## Discussion

Treatment of HHD is directed at symptoms and usually it relies on local and general application of corticosteroids, antibiotics and antimycotic drugs (often accompanied by staphylococcal, streptococcal and *Candida* infections) [3]. Different immunosuppressive and immunomodulatory drugs are also used: tacrolimus, tacalcitol, cyclosporin A, dapsone, methotrexate, isotretinoin, etretinate, thalidomide, botulinum toxin A, radiotherapy [4-7]. However, identification and elimination of provoking factors should always be the first step in the procedure in patients with HHD. Reactions to drugs, scabies or herpes virus infections can be evoking factors in cases with extensive or generalized lesions [2, 8-10]. However, the cause of severe course of the disease often remains unknown. SERCA2 and SPCA1, whose expression is disturbed in HHD due to mutations within the *ATP2C1* gene, are the main proteins responsible for maintenance of a calcium ion gradient in the epidermis. Disturbance of $Ca^{2+}$ accumulation by keratinocytes from the granular layer occurs throughout the skin of HHD patients, including unchanged skin [11]. It is thought that external factors (friction, UV radiation, changes of temperatures) can influence the decrease of already insufficient SERCA2 and SPCA1 expression. In consequence after occurrence of the harmful factor the concentration of both these proteins can achieve a critical value and be sufficient for

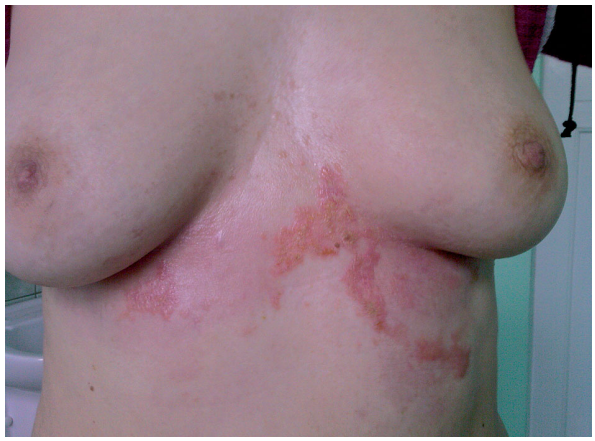

**Fig. 1.** Erythematous and erosive lesions in submammary regions

liberation of pathological changes in the epidermis characteristic for HHD in persons with a mutation. Cellular mechanisms concerning expression of proteins and transport of $Ca^{2+}$ are therefore probably the main reason for incorrect function of desmosomes and acantholysis over the basal layer [12]. The fact that skin lesions typical for HHD appear within an hour after occurrence of the physical stimulus is confirmation of this thesis [13]. External factors may induce a cascade of inflammatory mediators and recruitment of T-lymphocytes. It was found that staphylococci and other germs can boost expression of interleukin-6 in keratinocytes and in consequence decrease hSPCA1 expression in an autocrine way. This process is connected with exacerbation of HHD signs [14, 15]. Reports about the role of contact allergens in HHD pathogenesis are not numerous. Occurrence of allergic reactions to drugs applied in local treatment (neomycin, bacitracin and corticosteroids) is frequent [16-19]. Therefore routine use of patch tests is advocated. However, precaution is advisable as severe vesicular and erosive reactions in the place of contact with adhesive tape were observed [20, 21]. Three cases of HHD characterized by severe, recurrent course accompanied by hypersensitivity to different contact allergens (metals, aromatic substances, dyes) were presented in this paper. Only one patient complained of appearance of palm itching and eczema lesions in places of contact with metal decorations and a watch, which gave positive contact tests with nickel. Nickel included in metal wires stiffening a brassiere could be one of the factors provoking appearance of HHD signs in this woman. Positive results of patch tests were found in the two remaining cases (patient 1: nickel sulfate, cobalt chloride, Peruvian balsam, eugenol, aniline; patient 2: nickel sulfate, cobalt chloride, anesthesine, metol), though they did not report appearance of typical eczema signs. Tests were carried out to search for factors exacerbating the basic disease. In HHD patients with co-existence of contact hypersensitivity it is necessary to take into consideration elimination of the source of allergens in preventive maintenance. Beyond the contact mechanism systemic interaction of allergens (in a contact-sensitized patient) can also affect a co-existing inflammatory state of the skin, e.g. exacerbation of skin lesions due to increased amount of a sensitizing factor in the diet or moderation of signs upon reduction of its consumption [22]. In provocation of skin lesions in HHD patients sensitized to nickel (in the 3 described cases) it is necessary to consider the role of diet based on products containing large amounts of this metal, including: herring, beans, mushrooms, bulb, corn, spinach, tomatoes, pea, lettuce, carrot, cocoa, chocolate, oat, corn, soya bean, tea. Other sources of nickel are smoking of cigarettes and metal implants. A case of systemic contact dermatitis affecting flexures, where the metal part of the catheter was the source of nickel, was also described [23]. Good documentary evidence for cases of "baboon syndrome" evoked by systemic exposure to nickel (oral, respiratory and intravenous way) is provided in the literature [24]. Skin lesions in flexures, groin, on the nates, and in the sacral and anogenital regions usually develop in patients sensitized earlier by contact exposure. To date the reason for the characteristic localization of skin lesions has not been explained. According to some authors it may be related to the "recall phenomenon" – reactivation of skin lesions in places of sun exposure, earlier contact with an allergen, mechanical irritation, or occurrence of other forms of dermatitis [25]. Secretion of nickel mainly by sweat glands, which are particularly numerous in flexural and fold regions, is another possibility. Co-existence in the described patients of hypersensitivity to nickel and HHD may be accidental and result from the fact that nickel is a frequent sensitizing factor, especially in women. It is hard to define also if hypersensitivity to nickel can occur in patients with HHD frequently, as it is a rare disease and to date such research has not been carried out. It is possible to expect that a disabled skin barrier boosts the risk of developing a contact allergy in HHD. Occurrence in our two patients of positive patch tests to numerous allergens is confirmation of this thesis. Therefore, it seems that in all patients with HHD, but not only patients with eczema lesions, it is necessary to perform patch tests. To confirm the significance of systemic exposure to nickel in provocation of HHD lesions it has been suggested to perform oral provocation with this metal, but the patients have not expressed agreement to it. The patients have been informed of detailed prophylactic recommendations concerning all allergens which were positive in patch tests.

The recommendation resulting from diagnostics of contact allergy introduced for preventive maintenance can have an effect on moderating HHD course. However, further studies on the role of contact allergens in this group of patients are required.

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