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Review Article

A review on Hailey-Hailey disease

家族性良性天疱瘡綜述

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Hailey-Hailey disease (HHD) is a rare autosomal dominant blistering skin disease first described in 1939. It is characterised by vesicular or crusted erosions on the neck and in intertriginous areas. Though it is known that the gene responsible for HHD is located on 3q21-q24, it is only recently found that the disease is a result of the mutations in the Ca^{2+} ATPase *ATP2C1*. A spectrum of mutations have been reported since the identification of the mutation. The disease not only causes itching, unpleasant smell, it might also lead to pain. Thus, the disease may cause significant impact on quality of life. A variety of modalities of treatment have been offered to the patients with various success. This paper reviews the literature to provide a current understanding of the disease.

家族性良性天疱瘡是一種罕見的常染色體顯性大疱性皮膚病，於1939年首次被描述。其特點是頸部及皺折部位皮膚出現小液疱或結痂性皮損。其病變基因位於染色體3q21-q24，新近研究發現此病病因是由於Ca^{2+}ATP酶編碼基因*ATP2C1*突變所致。其後陸續有多種突變基因的報道。本病可引致皮膚痕癢、身帶異味甚至痛楚。可對生活質素頗有影響。予患者的多種療法各有療效。本文回顧有關文獻並就本病提供新近的見解。

Keywords: *ATP2C1*, Hailey-Hailey disease (familial benign chronic pemphigus), SPCA1

關鍵詞：*ATP2C1*，家族性良性天疱瘡，SPCA1

Introduction

Hailey-Hailey disease (HHD), or familial benign chronic pemphigus, is a rare autosomal dominant blistering skin disease first described in 1939 by Howard and Hugh Hailey. They described a skin condition in two sets of brothers from two families. They had recurrent blisters and crusted erosions on the neck in one set and in the axilla and groin in the other set of brothers. The skin biopsies of these patients shared the same features, namely, intradermal vesicles, mild dyskeratosis and hyperkeratosis. Howard and Hugh Hailey believed that the condition they met was a new disease entity and they named the condition 'familial benign chronic pemphigus'.

Sixty-one years after the discovery of the disease, in 2000, the genetic abnormality underlying this entity was elucidated to lie in *ATP2C1* which

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encoded an ATP-powered calcium pump. However, there are no great advances in the treatment of the condition. This article provides an overview of the epidemiology, clinical features, current view on the pathogenesis and current treatment of this disease with special reference to three series of patients in Hong Kong,[1] United Kingdom,[2] and China.[3]

Epidemiology

In Social Hygiene Service, Department of Health, HKSAR, the number of new cases of biopsy-proven HHD per 10,000 new skin cases varies from 0 to 1.58 in HHD with an average of 0.53 per 10,000 new skin cases.[1]

Employing the figures in Social Hygiene Service, the average incidence for the period 1988 to 2005 is 0.017 per 100000 persons. Hailey-Hailey disease is probably under-reported. The actual incidence of HHD in Hong Kong may be greater than this figure. Patients with this disease may be seen and treated outside the Service. Patients with milder form of the disease may ignore the condition and may not seek medical attention. Moreover, physicians may not be aware of this condition and the disease is often misdiagnosed.

The age of onset is usually in the third or fourth decade. In a study of fifty-eight HHD patients from 31 families in United Kingdom,[2] the male to female ratio was 1.42:1. Nine patients had no family history of HHD. In another series of 69 Chinese HHD patients comprising 55 males and 14 females and with a male to female ratio of 3.93:1, there was family history in 39.13% of the patients.[3] In a local study, the male-to-female ratio was 1.83:1.[1] The rate of positive family history in the study was 88%.

Genetics and pathogenesis

By family linkage studies, the HHD region was localised to 3q21-24.[4] In 2000, Hu et al identified mutations in *ATP2C1*, encoding the human homologue of an ATP-powered pump that sequesters calcium into the Golgi in yeast, in 21 HHD kindreds.[5] *ATP2C1* encodes the human secretory pathway Ca^{2+}/Mn^{2+}-ATPase protein 1 (SPCA1) that is found in the Golgi apparatus.

HHD is caused by mutations inactivating one allele of *ATP2C1* and many different mutations have already been described.[5-10] They are scattered throughout the *ATP2C1* gene, indicating no "hotspot" or clustering of mutations in the gene. It has been hypothesised that haploinsufficiency is responsible for the dominant phenotypes in HHD.

Behne et al have shown that human keratinocyte SPCA1 localises to the Golgi.[11] This pump supplies the Golgi apparatus, and possibly other more distal components of the secretory pathway, with both Ca^{2+} and Mn^{2+} required for the correct production, processing, and maturation of membrane and secreted proteins. Ca^{2+} in the lumen of the Golgi controls protein trafficking, cargo condensation, and precursor processing.[12] Mn^{2+} in the Golgi apparatus is needed for N- and O-linked glycosylation of cellular proteins.[13]

A decrease in Ca^{2+} concentration was found in the lumen of the Golgi complex. This leads to an impaired glycosylation, proteolytic processing, folding, trafficking, or sorting of proteins essential for cell-to-cell adhesion, like desmosomal proteins. Consequently, the ability to maintain structurally intact desmosomes may be lost, leading to the cleavage of the epidermal cells.

The reason why patients with HHD in general do not have extracutaneous manifestations is unknown. Also, the predominant involvement of flexures and the exacerbation of symptoms by infection, ultraviolet radiation, sweating, friction, and heat remain poorly understood.

Many of the HHD patients in the local study were found to have mutations in the *ATP2C1* gene.[1] Out of the seventeen patients coming from thirteen families, a total of ten different mutations were

identified in the patients. Seven novel mutations were identified in ten patients and the remaining three mutations were known ones. This study revealed a high allelic heterogeneity and the absence of clustering of *ATP2C1* gene mutations in Hong Kong Chinese, in keeping with the studies in other localities. There was no definite genotype-phenotype correlation.

Clinical features

In the UK series,[2] the peak age of onset was in the third decade. The mean age of onset in the Chinese series of 69 Chinese patients was 29 years.[3] The mean age of onset in the local study was 36.59 years.

There is usually a delay in making the diagnosis. The delay might be due to mild disease, late presentation to a dermatologist, low index of suspicion among medical practitioners and a passive attitude of patients towards the disease. As pointed out by Burge, the morphology of the lesions was immensely varied and misdiagnosis was common even in patients with a family history of skin problem.[2]

The clinical manifestations include erythema, vesicles, macerated or crusted erosions in the flexural areas which heal without scarring leaving post-inflammatory hyperpigmentation. Painful fissures is a common feature. The eruption may be widespread but not necessarily severe. In the local study, the initial lesion usually involved the groin or the neck. In the Chinese series, it was found that the genital area, neck and axillae were common sites of initial involvement. However, in the UK series, the site of initial involvement was mostly on the neck. All flexures might be affected by the disease. In female patients, the inframammary area was often involved. Nail changes might be present and it was reported that multiple asymptomatic longitudinal white bands were present in 70% of the patients in the UK series.[2] However, none of the cases in the local series had nail changes.

Many patients complain of itchiness and pain in the skin lesions resulting in social handicap and limitation of physical activities, especially when the groins are involved. Seasonal variation in disease severity is usually observed. Since the condition is worsened by heat, sweating and friction, most patients suffer from exacerbation in summer.

Some patients might have skin infection caused by bacteria, herpes and fungus. Most organisms isolated from active HHD lesions were thought to represent secondary colonisation rather than primary infection. Biopsy proven HHD has been demonstrated following the application of Staphylococcus aureus and Candida albicans to the skin.[14,15] The frequent response of HHD to antimicrobial preparations also supports a contributory role for infective agents. Widespread skin involvement by herpes simplex virus in patients with underlying HHD has been reported.[16-19] However, it is unclear that whether the virus actually induces lesions of HHD.

Rarely, HHD patients may develop extensive lesions, usually following insults such as drug eruptions or scabies.[20] A patient with extensive histologically proven HHD whose initial clinical presentation was suggestive of erythema multiforme or toxic epidermal necrolysis had been described.[21]

The occurrence of malignant neoplasms in HHD is rare. A basal cell carcinoma developed in an irradiated site nine years after radiation therapy for skin lesions of HHD.[22] Squamous cell carcinoma was found in a lesion at the penoscrotal junction in a patient who was treated with arsphenamine early in the disease.[23] Recently, another case of squamous cell carcinoma was reported to arise de novo in a skin lesion of HHD.[24]

Gisondi studied the impact of HHD on the quality of life of 22 patients.[25] They were asked to complete two self-administered validated questionnaires: the Skindex-29 and the 12-item General Health Questionnaires. Substantial poor quality of life scores in the three domains of

symptoms, emotions and social scores and significant psychological stress were found. It should be noted that hospitalised patients, presumably in a more severe period of their disease in terms of physical and psychological stress, were recruited in Gisondi's study. Harris et al studied handicap in 66 patients with HHD.[26] The patients were interviewed at home using a mailed Dermatology Life Quality Index Questionnaires and asked to consider their condition over the previous week. Highest mean scores were obtained for questions relating to symptoms and feelings. Domains relating to personal relationship and work obtained low mean scores even in severe disease. Most patients could maintain good social relationship at work and at home. The DLQI scores showed no correlation with physician's assessment of clinical severity. It was also shown that in the local study that the impact of HHD on the quality of life was not significant.

Pathology

Criteria for diagnosis of fully developed lesions of HHD are as follows:[27] (a) acantholytic cells throughout at least half the thickness of the epidermis in some foci; (b) acantholytic, dyskeratotic (prematurely cornified) cells within the epidermis; (c) epidermal hyperplasia; and (d) suprabasal separations. Partial acantholysis throughout the epidermis gives rise to a dilapidated brick wall appearance.

Differential diagnosis

The condition is not infrequently misdiagnosed. This might be due to a low index of suspicion and limited clinical experience on this rare disease. Many a time, the disease is mistaken for intertrigo and fungal disease. The lesions of intertrigo are usually not well demarcated. In fungal diseases, active margin and satellite pustules may be present. Skin scrapings for microscopic examination and culture will be helpful. HHD might also be mistaken for acanthosis nigricans. However, in acanthosis nigricans, the skin is hyperpigmented, roughened, warty and velvety and there is usually no maceration or erosion. Pemphigus vegetans is another diagnosis that may cause confusion. Crusted vegetations and pustules and oral erosions may be present in pemphigus vegetans. Darier's disease is a disease that may have similar clinical features as HHD. However, they have a different pattern of distribution. Moreover, Darier's disease usually presents earlier. V-shaped notches of edge of nail plate and palmar pits may be present in Darier's disease. Another easily confused condition is inverse psoriasis. However, inverse psoriasis has sharper borders, fewer erosions and less crusting. Nail pitting may also be found in inverse psoriasis.

Treatment

In the management of HHD patients, general measures should not be overlooked. These include wearing light weight clothes and treatment of any possible infections. A variety of medical and surgical therapies exist for HHD. However, as HHD is a rare disease, the literature consists of case reports rather than well controlled studies. Thus, most of the data on treatment response are based on a small number of patients. First-line agents include topical antibiotics, topical steroids, topical antifungals and oral antibiotics. Systemic steroids, oral retinoids, methotrexate, dapsone, cyclosporin, and thalidomide are also reported to be effective. Surgical approaches include surgical excision with healing by secondary intention, primary closure, grafting, dermabrasion, CO_2 laser vaporisation, Er:YAG laser ablation.

Topical tacrolimus was found to be effective in the treatment of HHD.[28] Moreover, it is relatively safe and noninvasive.[29] Partial clearing was seen in HHD after treatment with topical and oral cyclosporine and tacrolimus. This might due not to immunologic mechanisms, but instead to the ability of the drugs to inhibit calcineurin. Cyclosporine-induced calcineurin inhibition induces tolerance to high extracellular Ca^{2+}.[30]

Reports have documented the efficacy of systemic calcitriol on HHD at the daily dosage of 0.25 mg. This might be due to the inhibitory effect of calcitriol on T cells and on some inflammatory mediators.[31] Topical application of tacalcitol, another vitamin D3 derivative, twice a day for one month cleared the lesion. It might affect the calcium gradient in differentiating keratinocytes and could regulate and preserve the desmosome assembly and integrity.[32] Nasca et al[33] reported that a relatively short-course treatment with oral erythromycin 600 mg tds for three to four weeks induced a long-lasting remission for eight months. Bacteriological investigations excluded local infection in all of these patients.

Patients with axillary HHD treated with botulinum toxin type A showed good response.[34] More aggressive approaches like dermabrasion or laser ablation may also be effective in severe HHD. However, they may need a longer period of post-operative care and may be inconvenient. Wide excision and grafting can also be used.[35] These have all provided sustained remission of the disease. Since 1959, the use of Grenz-rays, very low-energy X-rays, has been found to offer temporary relief. However, there is little evidence that it alters the natural history of this disease.[36] Recently, it was reported that photodynamic therapy[37] and etanercept, a soluble TNF-α receptor that inhibits the activity of TNF-α,[38] were effective in the treatment of HHD.

In the local series, all patients under treatment received topical steroid often in combination with antifungal and/or antibiotics.[1] 21.4% of the patients receiving treatment needed additional systemic therapy to control the disease activity. These patients received long-term antibiotics and dapsone (DDS).

In the UK series of 58 HHD patients,[2] 50 patients (86%) found topical steroid/antibiotics helpful, 25 patients (43%) had been given courses of oral antibiotics which had been helpful. Some patients were given long-term low dose erythromycin or penicillin. Two patients were given prednisolone 3-5 mg/day. Two patients took oral retinoids and only one of them showed some improvement. Four out of five patients receiving Grenz ray found it helpful and the remaining patient deteriorated. One patient received cryosurgery with unsuccessful results.

In the Chinese series of 69 patients,[3] none of the patients responded to topical therapy alone and many patients received systemic therapy. The agents used included dapsone, prednisone, Leigongteng (雷公藤, Tripterygium wilfordii 6-8 tablets/d) and antibiotics (tetracycline 0.25 g qid, erythromycin 0.25 g qid or TMP 0.1 g bid). The results are summarised in Table 1.

Table 1. Treatment for the patients in the Chinese series of HHD patients[3]

Treatment	No. of patient (%)	No. of patient with improvement (%)
Dapsone 50 mg bd	12 (17)	6 (50)
Prednisone (20-25 mg/d)	5 (7)	4 (80)
Dapsone + prednisone	7 (10)	6 (85.7)
Dapsone + prednisone + antibiotics + Leigongteng (Tripterygium wilfordii)	22 (32)	19 (86.4)
Dapsone + prednisone + thalidomide	4 (5.8)	2 (50)
Grenz ray (for patient not responded to oral/topical treatment)	8 (12)	8 (100)
Topical therapy		None responded to topical therapy alone

(N.B. *leigongteng* (from *T. wilfordii*) was described in some of the ancient Chinese medical texts, where it is indicated mainly for treatment of swellings, breast abscesses, and skin diseases. It is widely used in China because of its remarkable effectiveness for so many diseases that are not readily treated by modern medicine, e.g. it is used in the treatment of autoimmune diseases and used as a substitute for steroid.)

In the UK series, topical treatment was helpful in 86% of patients and only a few patients were put on systemic therapy. None of the patients in the Chinese series responded to topical therapy alone and 58 patients (84%) had been given systemic therapy. In the local series, the results seem to be intermediate between these two large series.

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