

SHORT REPORT

Therapeutic effects of cyclosporine on Hailey-Hailey disease

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Running title: Effects of cyclosporine on Hailey-Hailey disease

ABSTRACT

Hailey-Hailey disease is an autosomal dominant hereditary skin disease. Severe cases are often difficult to treat. We report a recent case that was successfully treated using cyclosporine. The case is described from the aspects of treatment and gene mutation.

Keywords: Hailey-Hailey disease; cyclosporine; *ATP2C1*; treatment

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Introduction

Hailey-Hailey disease (HHD) is an autosomal dominant hereditary skin disease associated with vesicles, erosions and crusts on the intertriginous after middle-age. The lesions usually heal without scarring. Sunlight, heat, sweating and friction often aggravate the disorder. Recent studies revealed many types of gene mutations. The responsible gene for HHD is *ATP2C1*, which encodes human secretory pathway $\text{Ca}^{2+}/\text{Mn}^{2+}$ -ATPase protein 1 (SPCA1), a Ca^{2+} pump expressed in the Golgi apparatus^[1]. We also reported the case of 50-year-old Japanese male who had a novel heterozygous c.1627G>T transition on exon 18 of *ATP2C1*, causing premature termination (PT) at amino acid 543 (p.Gly543X)^[2]. Over 150 pathological mutations have been identified throughout *ATP2C1*^[3].

Regarding treatment, severe cases are often difficult to treat. We recently successfully treated a case using cyclosporine. The case is described from the aspects of treatment and gene mutation.

Case Presentation

A 70s-year-old Japanese female had a history of recurrent erythematous lesions with erosions on the axillae and genital region, especially in summer. Approximately 30 years ago, she had been diagnosed with HHD by a dermatologist. Her mother had similar skin lesions, but the details were unclear. Her two daughters have no such skin lesions. Although topical steroids, etretinate (40 mg/d) and/or prednisolone (10 mg/d) were prescribed, she developed difficulty in walking due to painful inguinal erosions and was admitted to our department. Her skin lesions included erosions with pustular discharge and erythematous lesions with vesicles on the inguinal area (**Figure 1**).

Her blood examination results were almost within normal limits. Histopathological examination of vesicular erythema on the back revealed the separation of keratinocytes (acantholysis) at the suprabasal

layers of the epidermis, which resembled a “dilapidated brick wall” (**Figure 2**).



Figure 1. Pustular discharge and erythematous lesions.

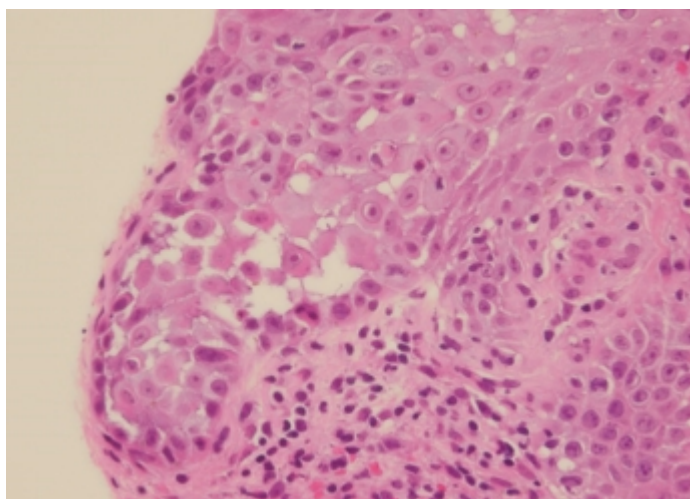


Figure 2. Acantholysis at the suprabasal layers of the epidermis.

Direct immunofluorescence staining was negative. By genetic analysis of the peripheral blood, a novel heterozygous mutation c.2305delG (p.S769Afs*3) on exon 24 of *ATP2C1* was identified and the diagnosis of HHD was confirmed.

After hospitalization, she was administered cyclosporine (3 mg/kg/d) and minocycline (100 mg/d) for 8 days. The lesions gradually improved and fully epithelialized 15 days after the start of treatment (**Figure 3**).



Figure 3. Skin lesion 15 days after the start of treatment.

At the outpatient clinic, a topical steroid was effective for a small erosion on the genital area, and a small amount of cyclosporine was able to control the skin lesions when symptoms worsened.

Discussion

The standard treatments for HHD are directed toward the specific symptoms of each patient. Specific therapies depend upon several factors, includ-

ing the extent and severity of the disease, and patients' age. It is essential to avoid triggers such as sunburn, sweating and friction. Topical corticosteroid and topical antibiotics may be effective for mild cases, whereas more serious cases may require systemic antibiotics or stronger topical corticosteroid, although some of them may cause severe side effects. The treatments for 43 cases reported in Japan between 2002 and 2019 are summarized in **Table 1**.

Treatment	Cases
Topical corticosteroid	31
Topical Vitamin D3	9
Systemic corticosteroid	8
Etretinate	5
Topical tacrolimus	3
CO ₂ laser	2
Split skin grafting	1
Surface skin grafting	1
Cyclosporine	1

Table 1. Summary of main treatments for 43 cases reported in Japan between 2002 and 2019. Secondary or more treatments for infection were excluded from this table

As investigational therapies, botulinum toxin^[4], oral glycopyrrolate and several others have been reported to reduce the effects of sweat glands. For refractory HHD, additional medications have been tried, including vitamin A derivatives (retinoids), such as acitretin and etretinate, and drugs that suppress the immune system such as alefacept^[5] or tacrolimus. Further studies are necessary to clarify

the long-term safety and effectiveness of such drugs.

Very recently, Ichikawa reported a case of HHD with a novel missense/in-frame deletion mutation in *ATP2C1* successfully treated using cyclosporine^[6]. In the practical treatment for intractable inflammatory diseases as well as autoimmune diseases, cyclosporine is often used for initial therapy and/or

maintenance therapy^[7-9]. As cyclosporine may block the calcineurin/NFAT/interleukin-6-mediated suppression of *ATP2C1* transcription^[10,11], it effective for refractory conditions

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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