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Original Article

Darier's disease: survey of 32 Chinese patients

華人毛囊角化病研究 **32** 例

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A multi-clinic, 20-year, retrospective study had been carried out to review the clinico-pathological features of Chinese patients with Darier's disease (DD) in the Social Hygiene Service. The incidence of DD in Hong Kong was 0.025 per 100,000 per year. The peak age of onset was in the second decade of life with an average of 15. Male to female ratio was around 1:1. Twenty (62%) patients had positive family history. The major symptom experienced was itching. Keratotic papules were invariably present in our patients and mixed pattern with seborrhoeic plus flexural involvement was the commonest phenotypic variation. All of them had acral signs; 38% had oral mucosal lesions. Lesions were most frequently found on face, neck, front chest and ears. There was no full remission. Systemic retinoid was the most effective therapy for our patients although minor side effects were common.

本文對社會衛生科中的華人毛囊角化病的臨床及病理表現進行了一項多診所的二十年回顧性研究。香港毛囊角化病的發病率為每年每十萬人 0.025 宗。發病高峰期為 11 至 20 歲，平均 15 歲。男女比例為 1:1。 20 名(62%)患者有陽性家族史。主要症狀為痕癢。所有病人均有角化性丘疹。最常見的表現型為脂溢區併曲摺區混合型。所有患者皆有肢端體徵；38%有口腔粘膜損傷。皮損最常位於面、頸、前胸和耳。患者均無完全緩解。儘管常見有輕微副作用，口服維甲酸為最有效治療。

Keywords: Chinese, Darier's disease

關鍵詞：華人，毛囊角化病

Introduction

Darier's disease (DD) or keratosis follicularis is a rare cutaneous disease with an autosomal dominant mode of inheritance. It was first described by Darier and White in 1889.[1,2] Greasy papules and plaques arise on the seborrhoeic areas and in the flexures and almost all patients have nail abnormalities. Itch, disfigurement, and malodour are the most common disturbing symptoms. Acantholysis and dyskeratosis are the typical histological findings. Recent studies showed that the underlying defect is a result of mutations in the ATP2A2 gene on chromosome 12q23-24[3] that encodes for a sarco/endoplasmic reticulum calcium ATPase pump (SERCA 2) expressed on human skin and mucosa.[4] Oral retinoid is the

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treatment of choice for severe disease but their adverse effects are troublesome.[5] Topical retinoids, topical corticosteroids, dermabrasion and laser surgery have their advocates but evidence on their efficacy is sparse.[5]

Epidemiological study on Darier's disease were carried out in different parts of the world including the United Kingdom,[6] Denmark,[7] Slovenia.[8] The present study is to review the clinico-pathological features of patients with Darier's disease in our locality.

Methods

The skin biopsy reports of dermatology clinics in the Social Hygiene Service, Department of Health, Hong Kong SAR from 1st January 1983 to 31st March 2003 were screened manually and biopsy results that contained keywords such as 'Darier's disease', 'keratosis follicularis' and 'acantholytic dyskeratosis' were retrieved. Thirty two clinical records were retrieved and thoroughly studied. Four cases were finally excluded from this study. These included three patients with Hailey-Hailey disease confirmed by subsequent skin biopsies and one patient with incompatible clinical features despite skin biopsy suggested DD. Each of the 28 recruited DD patients were invited via phone to attend an interview conducted by one author (YH Chan) and telephone interview was carried out if patient declined invitation. Informed consent was obtained for the interview. A repeat of history taking and physical examination including fundal examination for any retinal anomalies were carried out by the author during the interview. Patients' clinical features were classified as mild, moderate and severe according to the criteria set up by Sakuntabhai et al.[9] First degree relatives of index cases were invited to attend an assessment for any features of Darier's disease. Skin biopsy was performed for suspected lesions to confirm the diagnosis. Four more cases of DD were recruited in this way, making up a total of 32 cases in the cohort altogether. The data were analysed by using SPSS 10.0. Mann-Whitney U test and Kruskal Wallis test were used for comparing continuous variables between groups. Fisher's exact test was used to test significance of sex ratio.

Results

Demographic data

Thirty-two Chinese patients from 22 families were studied. The average incidence of DD from 1983 to 31st July 2003 was 0.025 per 100,000 per year. The age range was 11-86 years with a mean 41.84 years. There were 15 male and 17 female patients with approximately equal sex ratio. Twenty patients (62%) had a positive family history of DD whilst the others were sporadic cases. The mode of inheritance was probably autosomal dominant as there was no skip of generation and equal sex distribution. There was no statistical difference for the mean age of onset between male and female patients. The disease began before 20 years in 25 patients (78%) and the peak age of onset was at 11 to 20. The distribution of age of onset of our patients is shown in Figure 1.

Clinical features

The commonest morphology of lesions found in our patients were greasy hyperkeratotic papules followed by verrucous plaques. Face (78%), neck

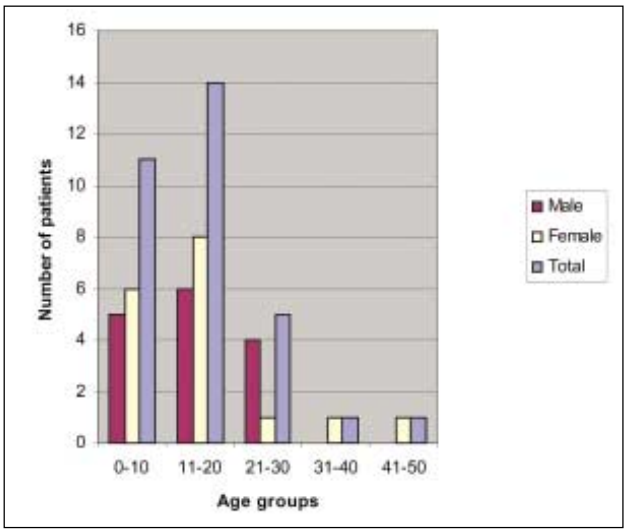

Figure 1. Age of onset of DD according to gender.

(75%), front chest (75%), axilla (66%), scalp (53%) and ears (53%) were the six commonest areas affected whilst buttocks (3%), perineum (3%) and genitalia (6%) were the least frequently involved. Oral mucosal involvement with cobblestone appearance over upper palate or buccal mucosa was found in 38% of our patients. The pattern of disease was recorded according to the distribution of lesions. It was found that 57% of them had a mixed pattern with seborrhoeic, flexural involvement. Pure seborrhoeic form and pure flexural form occurred in 28% and 9% cases respectively. All but one of our patients could recall their site of onset. The disease most commonly started on the face (52%) which was followed by the neck (13%), ears (9%) and hands (9%).

According to the criteria set up by Sakuntabhai et al,[9] thirteen percent (3 men and 1 woman) had mild disease, thirty-eight percent (5 men and 7 women) had moderate disease and forty-nine percent (7 men and 9 women) had severe disease. There was no statistical difference in the clinical severity between male and female patients in this study ($p = 0.505$, Mann-Whitney U test). The presence of family history also did not result in any statistically significant difference in clinical severity.

Symptoms

Seventy-five percent of the patients complained of itch while six percent experienced pain as the major irritating symptom. Twenty-eight percent were bordered by the malodour. Bacterial infection was fairly common in our patients (66%) necessitating topical or systemic antibiotics therapy. Fungal infection and herpes simplex infection were found in 19% and 9% respectively. There were no associated disorders such as salivary gland obstruction, bone cysts, psychiatric illness found in our patients.

Acral involvement

All the patients had hand involvements. Common findings included palmar pits (53%). Finger nail features included V-shaped nicks (47%), longitudinal ridging (38%) and brittle nails (28%). Toenails involvement was found in three (9%) patients only. Only two patients (6%) had the pathognomic nail triad of alternating red and white streaks.

Aggravating factors

Heat, sweating and sunlight were claimed to aggravate their disease in more than ninety percent of patients. Other exacerbating factors included stress (22%), menstruation (22% female patients) and high humidity (16%) had also been mentioned. A history of drug induced exacerbation was not recorded in our patients. Three female patients (Patient 2, 12, 28) claimed improvement of their disease after menopause.

Treatment and response

In our patients, 14 (44%) were on topical therapy whilst 14 (44%) were on systemic therapy with oral retinoid (Figure 2).

Topical therapy which include emollient, steroid, keratolytics, antibiotics and antifungal were prescribed regularly during the course of the disease. Topical steroid had been used in 97% patients and was reported by most patients to be effective in relieving pruritus and erythema associated with DD. In our study, emollient was used on a long term basis in 91% patients and most patients found it useful to decrease "rough

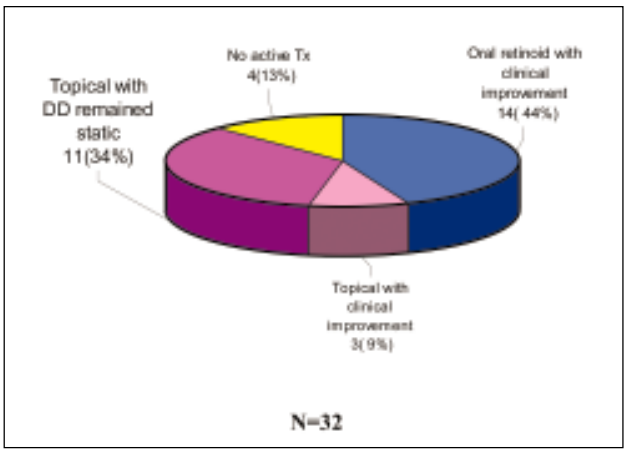

Figure 2. Treatment outcome.

feeling" of their skin. Topical tretinoin had also been tried in 50% patients but stopped subsequently because of either irritating effect on skin or lack of remarkable improvement.

Systemic retinoid that included acitretin or isotretinoin was used. It was prescribed in 14 (44%) out of 32 of our patients at the dose of 0.33-0.5 mg/kg. All of these patients had improvement in flattening of keratotic papules, reduction in skin pruritus and malodour. However, most lesions persisted and in none of our patients a complete remission could be achieved. Side effects of oral retinoid were experienced in a significant number of our patients. Xerosis (92%), hands and feet desquamation (92%), lip dryness and dermatitis were the four most common minor side effects reported. Hyperlipidaemia complicated the treatment in one patient and was managed by low fat diet and lipid lowering agent. None of these 14 cases developed liver dysfunction during the course of retinoid therapy. Despite these undesirable effects, all our patients on systemic retinoid therapy preferred to continue the therapy.

Among our DD cases, 14 (44%) were on topical therapy whilst 14 (44%) were on systemic therapy with oral retinoid (Figure 2). In contrast to many overseas studies, our DD patients on systemic therapy tend to continue such therapy despite its side effects as most of them found oral retinoid improved their skin condition in the sense of flattening of papules and plaques plus reduced erythema. The dose of retinoid used was between 0.33-0.5 mg/kg/day. Initial effect was noted at 4-6 weeks (mean: 4.71 weeks) whilst maximal effect occurred by 8-12 weeks (mean: 9.71 weeks).

Full remission of their skin disease was not achieved in all our patients, a comment of "Wax and wane and never go away completely" was given by most patients during interview. On the other hand, none reported a deterioration of their condition with time. In 15 patients, their skin disease remained static on topical therapies with or without systemic retinoid therapy. In 13 patients, clinical improvement could be achieved (10 of them (77%) were on oral retinoid therapy).

Discussion

Epidemiology

The prevalence of DD is estimated to be 1 in 100,000 in Denmark,[7] 1 in 45,000 in Slovenia,[8] 1 in 55,000 in central England.[6] The prevalence in HK was estimated to be 1 in 220,000 in the present study which was much lower than that in Europe. This can partially be explained by the fact that these European studies involved multiple dermatology centres within their state or country. Except the study by Svendsen and Albrechtsen in Denmark which showed a male to female ratio of 1.6:1,[7] other large-scale epidemiologic studies indicated an equal sex distribution of DD.[6] In the present study, the male to female ratio was around 1:1. The peak age of onset of DD was found to be in the second decade in two epidemiologic studies[6,8] whilst the Denmark series by Svendsen and Albrechtsen indicated an earlier onset in the first decade of life.[7] In our cohort, mean and median age of onset were 14.75 and 13 respectively with peak in the second decade.

Clinical aspects of Darier's disease

DD usually present with multiple greasy, hyperkeratotic, firm skin coloured to brown papules over seborrhoeic areas, flexures, behind the ears, neck and acral areas. But lesions may occur on extensor aspects of limbs. These papules may coalesce into plaques. DD can be classified in the seborrhoeic, flexural, acral or mixed pattern according to the major areas affected.[6] In contrast to the study in England by Burge and Wilkinson where a predominance of seborrhoeic pattern of DD (92%) was noted, our study showed that mixed pattern (seborrhoeic plus flexural) was more common (57%) in Hong Kong.

In the present study, the most common site of onset was the face (56%) while chest, shoulders and back were the most common in UK population.[6] Itch

was the most frequent complaint (75%) followed by body odour and pain. Hands involvement may take the form of palmar pits, punctate papules or plaques over dorsum of hands whilst nail involvement include white or red lines, longitudinal ridges, V-shaped nicks and subungual hyperkeratosis. The combination of a red and white sandwich of streaks associated with a V-shaped notch is the pathognomonic nail sign which was present in only two of our patients. Acral haemorrhagic macules occur less frequently but were found to be associated with missense mutations.[10]

Oral involvement usually appear as fine granular or coarse pebblestone lesions over the palate and less commonly, the tongue and buccal mucosa.[11] Most of these lesions are asymptomatic and require no treatment. Parotid gland swelling due to metaplasia of parotid ductal lining with secondary obstruction had been reported.[11,12] In the present study, 38% patients had oral involvement. This proportion is lower than that reported by Svendsen et al[7] and Macleod et al[11] which were both around 50%. In all of our patients, parotid gland enlargement was not detected.

Malodour, secondary bacterial and fungal infection can cause significant disturbance to the usual daily living of DD patients and lead to social embarrassment.[5] In the present study, bacterial infection was the most common complication encountered by our DD cases (66%) which was followed by malodour (28%), fungal infection (19%) and herpes simplex infection (9%).

Various forms of DD had been recognised including vesicobullous,[13] cornifying,[14] acral,[15] comedonal,[16] linear,[17] haemorrhagic[18] and hypopigmented or depigmented variants.[19] Linear form of DD is localised disease following Blaschko's lines. It represents genetic mosaicism resulting from a post-zygotic mutation in the DD gene.[20] None of the these DD variants were present in the current study.

There are reports suggesting excess of neuropsychiatric disorders such as mental retardation,[6] schizophrenia,[21] bipolar affective disorder[22] and epilepsy in a number of families with DD. In one study, a possible association between DD and retinitis pigmentosa was speculated.[23] In the present study, no association between DD and these disorders can be found.

Reported exacerbating factors for DD include heat and sweating, sunlight, emotional stress, menstruation, pregnancy, drugs such as lithium.[24] More than 90% of our DD cases considered heat, sunlight and sweating as the major exacerbating factors for their skin condition. Some female patients also complained of premenstrual flare.

Treatment of Darier's disease

The main treatment aims for Darier's disease are symptomatic relief and treatment of complications.[5] Cotton clothing, sunblock and sunprotection for those with history of photoaggravation, avoidance of sweaty exercise, use of emollients and soap substitutes should be advised.

Mild or moderately potent topical steroid can be employed to control inflammation, but generally the impact of such therapy is disappointing.[25] Bacterial colonisation can be reduced with antiseptics or topical steroid combined with an antibiotics.[25]

Topical retinoid such as isotretinoin gel, tretinoin cream and tazarotene gel are shown in small studies and case reports to be effective in reducing hyperkeratosis in DD but skin irritation is the main drawback.[26] An alternate day regimen or in combination with topical steroid may overcome this problem.[25] In our study, half of the patients were ever prescribed topical retinoid but stopped for its irritation and poor efficacy. Topical 1% 5-Fluorouracil was reported to be useful in two patients with refractory DD.[27] Complete clearance was achieved within 3 weeks and remission lasted for 2-6 months. However, both of these 2 patients were also taking oral retinoids. Topical calcipotriol

has been proved to be ineffective in DD.[28] None of the 32 DD cases in this study were ever prescribed topical 5-Fluorouracil or topical calcipotriol and thus, no data on their efficacy in our population was available.

Oral retinoid therapy is the single most effective therapy in DD.[6] The dose of 0.33-0.5 mg/kg was prescribed in our patients. Hyperkeratosis improved and flattening of the skin lesions was achieved. Most patients on retinoid therapy will experience improvement in disease severity and extent after 6-8 weeks. Acitretin,[29] isotretinoin and etretinate[30] are all effective at the dose of 0.5-1 mg/kg/day but isotretinoin is recommended for young females because contraception needs to be continued for only 1-2 months after ceasation of therapy. Dose related side effects such as cheilitis, alopecia, pruritus, xerosis, dermatitis, paronychia, mucosal dryness, epistaxis, conjunctivitis are common. Informed consent should be obtained and adequate patient education on such adverse reactions plus emphasis on the use of emollient and fluid intake should be given prior to start of therapy. In a review of 163 DD cases by Burge and Wilkinson, 91% of those prescribed oral retinoid had clinical improvement although 23% of them finally stopped the therapy because of adverse effects.[6] In the present study, 14 DD patients received systemic retinoid therapy at the dose of 0.33-0.5 mg/kg/day. Clinical improvement was noted at 4-6 weeks (mean: 4.71 weeks) and the maximal effect occurred at 6-12 weeks (mean: 9.71 weeks). Only one patient (patient 29) developed hyperlipidaemia after initiation of retinoid therapy and was managed by low fat diet and lipid lowering agent. On the other hand, most of them experienced minor side effects such as xerosis, palm and sole scaling, erythema and skin pruritus. But they preferred to continue retinoid therapy despite of these adverse effects as they all considered retinoid effective in reducing the severity of DD. Systemic antibiotics were needed in case of superimposed bacterial infection. Herpes simplex virus can cause painful exacerbations in DD and should be treated aggressively with systemic acyclovir. Systemic steroid[31] and cyclosporine[32] were reported to be effective in reducing the inflammation in "eczematous" DD but papules and erosions persist.

The role of surgical approaches in the DD had not been supported by any controlled trials or large scale studies. Electrosurgery was reported to be useful in two patients with DD refractory to etretinate therapy.[33] Surgical excision with skin grafting was advocated for hypertrophic DD.[34] Dermabrasion up to the whole thickness of papillary dermis had been reported to be beneficial in five patients with severe DD.[35] Laser therapy such as carbon dioxide laser[36] and Ebrium Nd:YAG laser[37] were found to be effective in isolated cases. Photodynamic therapy using topical 5-aminolaevulinic acid as a photosensitiser was commented as a potential adjuvant therapy to oral retinoid in one small uncontrolled study.[38]

In summary, Darier's disease is a genetically determined chronic keratinisation disorder that is symptomatic. Currently available treatments are merely capable of partially suppressive of clinical symptoms. Continued search for a better treatment armamentarium is warranted.

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