Review

DARIER'S DISEASE (DYSKERATOSIS FOLLICULARIS)

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SUMMARY

The existing data indicate the prevalence of morbus Darier (MD) from 1.0 to 2.8 per 100 000 inhabitants. The majority of authors agree that MD is an autosomal dominant disease. The symptoms are not present at birth; they usually appear during the first 10 years of life or even later. The major symptoms are brown, greasy papules located predominantly in seborrhoic areas, inguinal or perineal flexures and further areas may be involved too. Sunlight and poor personal hygiene are substantial triggering factors. There is good evidence that the main pathogenic factors are not due to a defect in keratin molecules, but rather to anomalies in the structure of the desmosomes.

KEY WORDS

dyskeratosis follicularis, mb Darier, prevalence, genetics, symptoms, micromorphology, pathogenesis, treatment

INTRODUCTION

Darier-White disease (dyskeratosis follicularis, morbus Darier, MD) is a relatively rare disease characterized by papular skin lesions, predominantly in seborrhoic areas. Skin appendages may also be involved. In most instances it is inherited. Darier and White described it independently in 1889.

PREVALENCE

Data on the occurrence of MD were reported from certain countries. As they are based on reports from clinical departments (mostly dermatologic) they might not be correct in a statistical sense; still they represent a valuable information. A prevalence of 1.8/100 000 was reported from central England (1) and even 2.8 from northeast England (2), 1.0 from Denmark (3), 1.3 from Croatia (4). In Slovenia such an investigation is in progress, preliminary data show that it will be more than 2.2. Table 1.

GENETICS

The disease is considered to be determined by an autosomal dominant gene with variable penetrance (5,6). Burge and Wilkinson mentioned however that among their 163 patients in 46 no family history could be detected (7). Contrary to this Munro (4)

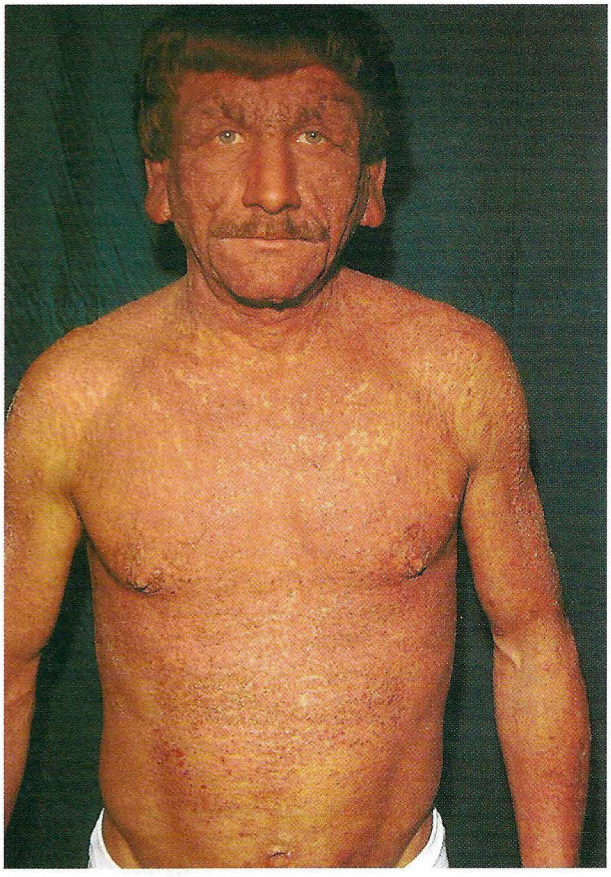

Fig. 1. Darier's disease: severe, generalized form.

reported that in 9 families 66 out of 136 adult members (with one affected parent) displayed symptoms of MD, thus indicating complete penetrance of an autosomal dominant gene. 18 individuals gave no family history, but 7 of these were members of affected kindred's. New cases whose parents are normal probably represent new mutations or non-paternity rather than incomplete penetrance.

Efforts are being made by various groups of researchers to detect the genetic defect in MD. An abnormality in the desmosome-keratin filament interaction appears to be responsible for the breakdown of cell adhesion, and therefore candidates are genes encoding desmosomal and cytoskeletal proteins.

In 1993 two British groups carried out linkage analysis studies (8,9). They excluded linkage of the disease to any of the desmosomal genes mapped on chromosome 18 as well as to the type II keratins clustered at the chromosomal region 12q11-q13 in the families investigated. They were however able to localize a gene responsible for MD to the chromosome 12q22-q24. Munro and cow obtained similar results.

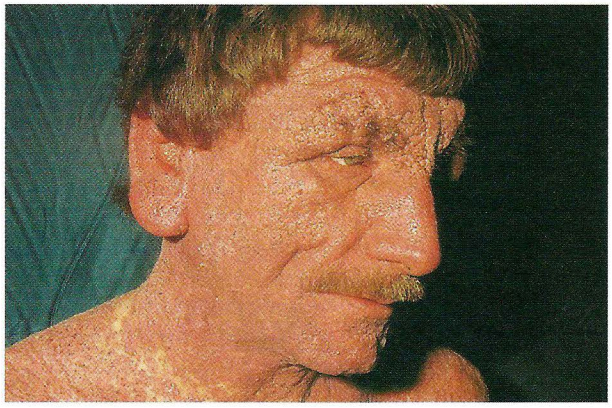

Fig. 2. Darier's disease: face and neck of the same patient.

(10), who used the microsatelite DNA polymorphism to examine linkage to the locus of the disease.

During the following two years further confirmatory results have been reported from Britain (11), United States and Canada (12,13,14). Table 2.

CLINICAL SYMPTOMS

In most cases skin symptoms do not appear at birth or soon afterwards, but usually start in childhood, in adolescence or even later. Burge and Wilkinson (7) mentioned that in 110 out of 163 patients the lesions became apparent between the ages of 6 and 20 years, with a peak between ages of 11 and 15 years. The disease may start later in life e.g. between 41 and 50 or 51 and 60 years. Sokol and Kansky (3) reported in their 28 cases two peaks of onset: the age group 5 to 9 years (21.4%) and 20 to 24

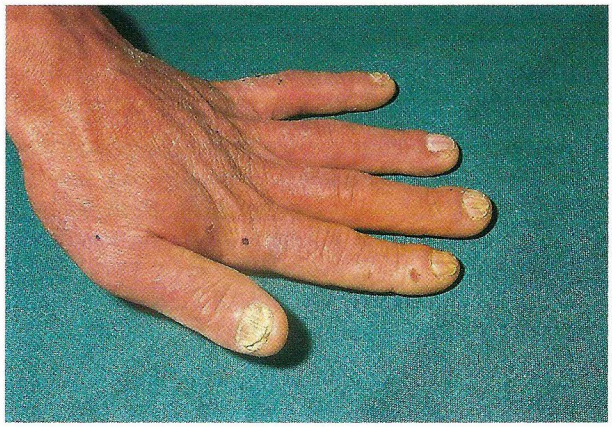

Fig. 3. Darier's disease: nail dystrophy and sububgual hyperkeratoses.

Table 1. Data on the incidence of morbus Darier (dyskeratosis follicularis are available only from a few countries

Country	Incidence	Author	Publication
Denmark	1.0/100 000	Svendsen LB Albrechtsen B	Acta Derm Ven (Stock) 1939; 39: 256
Central England	1.8/100 000	Wilkinson JD et al	Br J Dermatol 1977; Suppl 15: 13
North-East England	2.8/100 000	Munro CS	Br J Dermatol 1992; 127: 126
Croatia	1.3/100 000	Sokol J, Kansky A	Acta derm Iug 1991; 18: 57
Slovenia	≤ 2.2/100 000	study in progress	

years. Only in one male patient the disease developed after the age of 35 years.

The disease is characterized by firm rather greasy keratotic papules of a yellow-brown, dark brown color. The predilection sites are seborrhoic areas of the trunk and face, the lateral parts of the neck and the supraclavicular regions (Fig. 1-5). In certain patients the flexures notably the groins, and the anogenital region are involved. The papules may coalesce to form wart-like, vegetating and often malodorous plaques. According to Burge and Wilkinson (7) the center of the chest was involved in 87%, the back in 85%, the forehead in 84% and the supraclavicular fossae in 82% of cases under observation.

On the back of the hands and feet flat yellow papules resembling lesions in akrodermatitis verruciformis may be present. The frequency of these symptoms is given in Table....

On the palms and tips of the fingers punctiform keratoses and minute pits are rather frequently observed: in 84% of English and in 53.5 of Croatian patients. Similar findings are present on the soles.

A further observation are the specific dermatoglyphic patterns (discontinued lines), especially on the tips of the fingers and on the palms (15). In contrast to such earlier report in a recent study no significant quantitative or qualitative differences were found between dermatoglyphic features of 11 Jewish patients with MD and those of a healthy population (16).

Nails are frequently involved, characteristic are the longitudinal red and/or white lines extending from the base of the nail across the lunula to the free margin. Both of them may be expressed in the same nail. Longitudinal ridging may be expressed as well. V- shaped notches at the free edge of the nail are a pretty constant feature. Painful splits and subungual hyperkeratoses are additional symptoms (17). Usually only a few nails are affected, but in some patients all the nails can be involved. In the English patients the nail involvement was observed in over 90% and in Croatian in 71.4%. Toe nails can also be involved.

Although the typical hyperkeratotic papules are as a rule hyperpigmented, depigmented macules or even papules may be occasionally observed (18,19). Both brown papules and leukoderma showed typical histological features in one case (20).

Lesions of the oral mucosa were observed in 15% of patients by Burge and Wilkinson (7) and in 17.8% in the Croatian patients' (3). They consist of fine whitish papular lesions, sometime of cobblestone appearance, on the hard palate, tongue, and alveolar ridges or on buccal mucosa. Pharynx, larynx, vulva and anal mucosa may also be involved. Lately affection of the vulva were mentioned again in the literature (21).

Symptoms of obstructive sialadenitis have been occasionally reported as a feature of MD. Parotid sialograms in 3 patients with MD revealed dilatation's with periodic strictures and indentations affecting the main ducts (22), thus indicating a probably more frequent affection.

FACTORS TRIGGERING SKIN SYMPTOMS

Sunlight has been mentioned as an exacerbating factor in 58% by British and in 89.3% by Croatian patients. Heat and sweating as well as dirty working conditions or poor personal hygiene have a similar

effect. Wool and synthetic fibers may also have a deleterious effect on the course of MD.

Psychic stress was mentioned as impairing the condition by 43% of British patients. Only a minority of female patients reports premenstrual exacerbations. Pregnancy seems to improve the conditions in certain women while worsening in others.

There are two reports on exacerbation of MD by lithium carbonate treatment for psychiatric disorders (23). In a further case the disease appeared after the initiation of lithium carbonate treatment (24).

INVOLVEMENT OF OTHER ORGANS

An opinion exists among dermatologists that various affections of the central nervous system may coexist with MD (3). Burge and Wilkinson reported that 8/163 patients were mentally retarded and 7 had a history of epilepsy (7), which is more frequent, compared to the incidence in general population.

A simultaneous occurrence of a major affective disorder and MD was reported in 5 members of a family (25). In an other study linkage between manic depressive illness and MD was excluded (26). All the mentioned observations may represent a casual association between MD and mental disorders in a certain families.

Munro (2) believes that the observation of a frequent mental subnormality in patients with MD in Denmark could indicate that different genes are coinvolved in cases observed in that country.

LIGHT AND ELECTRON MICROSCOPY

The dominant light-microscopic characteristic of MD is acantholytic dyskeratosis of the epidermis. The appearance of clefts (fissures) above the basal layer (lacunae) is a prominent pathohistologic feature

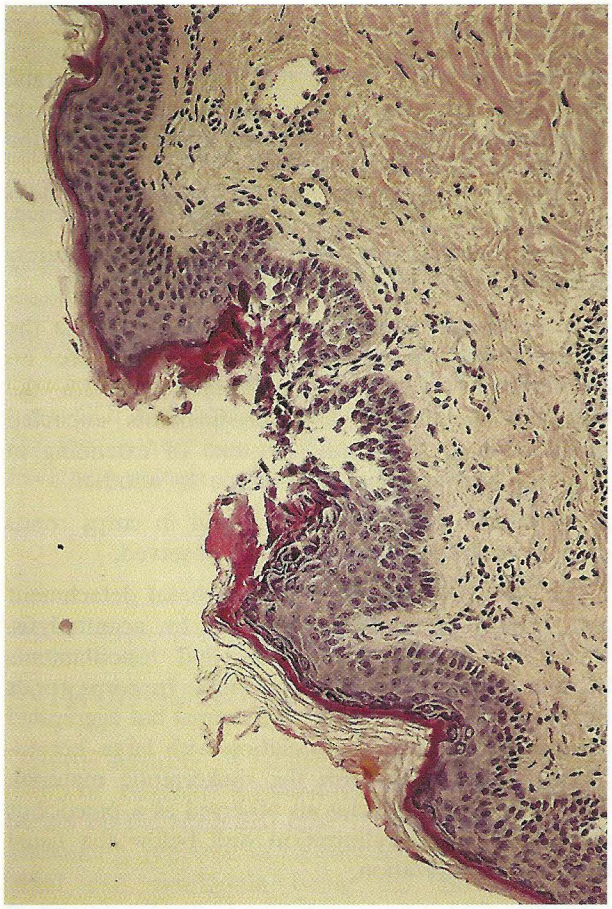

Fig. 4. Darier's disease. Histopathology: focal acantholytic dyskeratosis

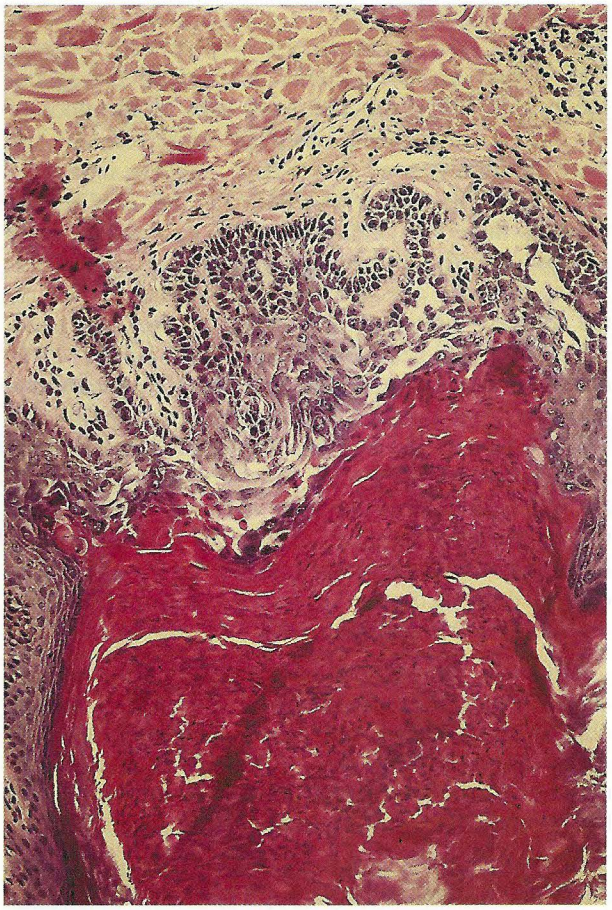

Fig. 5. Darier's disease. Histopathology: verruciform hyperkeratosis, acantholysis, lacunae

Table 2. Recent data on the location of the defective gene in patrients with morbus Darier (dyskeratosis follicularis)

Author	Publication		Gene location	Markers
Bashir R et al	Hum Mol Genet	1993	12q14-q24.1	D12S78-D12S79
Craddock N et al	Hum Mol genet	1993	12q23-q24.1	D12S76
Parfitt E et al	Hum Mol Genet	1994	12q23-q24.1 12 cM apart	D12S78, D12S79
Ikeda S et al	J Invest Dermatol	1994	12q23-q24.1 5 cM apart	
Kennedy JL et al	Amer J Med Genet	1995		D12S56-D12S4
Richard G et al	J Invest Dermatol	1994	12q23-q24.1	D12S84-D12S129
Carter SA et al	Genomics	1994	12q23-q24	D12S105-D12S129
Keratin II gene cluster			12q11-q13	

(Fig. 4 and 5). The lacunae may extend throughout the prickle cell layer. The basal cells at the floor of the lacunae are usually distinctly separated. An upward proliferation of the dermal papillae into lacunae (villi) is often observed (27,28). Inside the lacunae there are individual cells as well as small groups of cells (acantholytic cells). The intercellular spaces between the prickle cells adjacent to lacunae are widened and the number of desmosomes is reduced. A number of cells display a large, usually dark-staining nucleus surrounded by clear cytoplasm and a glistening ring simulating a membrane (Corps ronds). These cells undergo a premature partial keratinization. Further upwards, small cells with shrunken, eosinophilic cytoplasm, which may contain remnants of the nuclei are to be seen (grains). A variable degree of focal hyperkeratosis, parakeratosis and/or acanthosis may be expressed. Sometimes a hypertrophic, verrucous form of MD may be observed (29).

Although the described histologic features are characteristic, they are not specific as certain similar observations can be made in a few other acantholytic dermatoses e.g. transient or persistent acantholytic dermatosis, acantholytic dyskeratotic nevus or chronic benign familial pemphigus (Hailey-Hailey).

Caulfield and Wilgram who have already in 1963 described the ultrastructural aspects of MD mentioned the following observation (30):

1. In basal cells near to a lacuna the desmosomes at the base of a cell facing the basement membrane were normal in number and appearance, however on all remaining surfaces there was a decrease in the number of desmosomes.

2. The spaces between adjacent cells were widened.

3. The tonofilaments were aggregated and rarely extended to the attachment plaque.

4. In basal cells forming the floor of the lacuna the changes were more pronounced: there were no desmosomes except on the surface opposite the basement membrane. The tonofilaments encircled the nucleus in thick bands instead of extending in thin strands from one cell surface to another.

5. In prickle cells near lacunae and in corps ronds even more intense changes were observed.

The authors concluded that suprabasal detachment and lacunae formation was due to acantholysis, which was caused by the fact that tonofilaments became separated from desmosomes. In corps ronds the individual tonofilaments were normal but aggregated around the nucleus in association with large keratohyaline granules to form the dyskeratotic material. They defined the dyskeratosis observed as a precocious and incomplete keratinization well below the usual zone of keratinization.

Similar observations were made by Biagini et al (31). Man and Haye on the basis of their studies put forward the opinion that the acantholytic process

Table 4. Morbus Darier (dyskeratosis follicularis). Recent data on pathogenesis

Author	Publication	Location of defect	Defective material organelle
Setoyama M et al	J Dermatol 1991	acantholytic cells diffusely in cytoplasm lost peripheral dotted pattern	desmoglein I (glycoprotein)
Setoyama M et al	J Dermatol Sc 1991	plaque component of desmosome	desmoplakin I, II
Burge S et al	Br J Dermatol 1995	acantholytic cells intracellular distribution	desmoplakin desmoglein desmocollin
Steijlen et al	Br J Dermatol	extracellular matrix component (dermis)	tenascin increased
Harada M et al	J Dermatol	diffusely in cytoplasm lost peripheral dotted pattern	desmoplakin I,II
Hashimoto K et a	J Dermatol 1995	dissolution attachment plaque	desmoplakin

starts rather in the desmosome and not in the tonofilaments (32).

PATHOGENESIS

The exact mechanism responsible for the development of skin lesions in MD remains unknown, but many interesting new data are available. As mentioned already the keratins do not seem to be primarily involved, for this reason the investigators concentrated their efforts on desmosomes. Table 4.

It was postulated that desmoglein I, one of the major transmembrane glycoproteins of the desmosome under normal conditions adheres to the attachment plaque inside the cell. Sotoyama et al investigated desmoglein I with specific antibodies and mentioned that the normally observed dotted or rim-like pattern at the cell periphery was lost already in early acantholysis in MD and that the immunoreactive desmoglein protein was observed diffusely in the cytoplasm (33). They expressed the opinion that primary abnormalities of desmosomes may be involved in MD.

The similar observations were made when investigating the plaque components of the desmosome, the desmoplakin I and II (34). The authors concluded that primary or secondary abnormalities of desmosomes might be involved in the pathogenesis of MD. Burge and Garrod studied the distribution of desmoplakin, desmoglein and desmocollin, Indicating that acantholysis in MD preceded the abnormal cytoplasmatic distribution of desmosomal components (35).

This observation was confirmed in a recent study published by Hashimoto et al (36). In contrast to such observations the surface glycoprotein CD 44 was well preserved even on cell membranes of acantholytic cells. They concluded that the dissolution of desmosomal attachment plaque is the primary event in acantholysis in MD as well as in Hailey-Hailey and Grover's disease.

According to a further report the extracellular matrix component tenascin is grossly increased in MD and in epidermolytic hyperkeratosis (37).

TREATMENT

A survey of literature shows that a variety of regimens have been applied, but there is no ideal method of treatment. First of all attempts should be made to eliminate all the triggering factors and a meticulous personal hygiene should be observed. Patients with a mild form of the disease require no special treatment except for simple emollients. Cryotherapy with liquid nitrogen, topical application of tretinoin gel, calcipotriol or 5-fluorouracil can be

used successfully, when applied to non-irritated skin (38,39). Dermabrasion has resulted in some cases in longer periods of remission (40).

During periods of irritated skin corticosteroid creams and ointments are necessary or even systemic application of corticosteroids. One has however to bear in mind all the possible side effects.

For patients with a severe form of the disease, at least in periods of exacerbation, synthetic retinoids orally are recommended in doses of 0.5 to 1.0 mg/kg body weight during 2 - 5 weeks. This treatment should be followed by a longer period on a maintenance dose of 20 to 50 mg etretinate daily (41). The side effects like cheilitis, dryness of mucous membranes, hair loss and thinning of the skin are usually well tolerated; many patients are however refusing reintroduction of such therapy. It seems that treatment with cyclosporine was not so efficient as it was expected (42).

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