Darier's disease in Slovenia

J. Miljkovič, N. Kecelj, V. Balkovec, M. Penko and A. Kansky

Abstract

Background. Dyskeratosis follicularis (Darier-White, morbus Darier, MD) is an autosomal dominant skin disorder characterized by warty papules and plaques primarily in seborrheic areas, palmo-plantar pits and nail abnormalities. Our purpose was to collect the information on the prevalence of patients affected with MD in Slovenia.

Materials and methods. Records from Departments of dermatology in Slovenia were studied and new cases were registered. Clinical symptoms and other relevant data from 27 patients who had followed our invitation for a re-examination were collected in special questionnaires.

Results. Altogether 44 patients were recorded, 20 were males and 24 females. Taking into account that the Slovenian population amounts to roughly 2 million, this would give a prevalence of 2.2/100 000. Altogether 27 patients followed the invitation for a re-examination. Greasy papules were expressed in all the patients, nail involvement ranked second with 89%. Trunk and limbs were involved in 89% of patients and the face in 89%. The onset of the disease was in the majority of cases in the second decade of life, in all patients the symptoms appeared before the age of forty.

Conclusion. The prevalence of this condition is similar to that in England, Denmark and Croatia.

KEY WORDS

dyskeratosis follicularis, mb Darier, prevalence, Slovenia, genetics, symptoms, pathogenesis

Introduction

Dyskeratosis follocularis (Darier-White disease, morbus Darier, MD) is an autosomal dominant skin disorder characterized by warty papules and plaques primarily in seborrheic areas, palmo-plantar pits and nail abnormalities. The prevalence of the disease has been estimated at 1.8/100 000 inhabitants from Central England (1), 2.8/100 000 from Northeast England (2), 1/100 000 from Denmark (3), 1.3/100 000 from Croatia (4).

We know from previous studies, that certain genodermatoses are quite frequent in Slovenia: e.g. palmoplantar keratoderma (5,6,7), epidermolysis bullosa hereditaria, erythropoetic protoporphyria and others.

Our purpose was to collect the information on the prevalence of patients affected with MD in Slovenia.

Table 1. Darier's disease in Slovenia: symptoms investigated in 27 patients.

symptoms	no. of patients	%
follicular and extrafollicular greasy, keratotic papules	27	100
hypertrophic plaques	12	44
erosions	8	30
leukoderma	4	15
scales on the scalp	11	41
punktiform keratoses on the palms and soles	3	11
broken papillary lines	3	11
plane papules on the back of the hands and feet	12	45
white "cobblestone" papules of the mucous membranes in the oral cavity	3	11
white longitudinal bands on the nail plate	17	63
red longitudinal bands on the nail plate	9	33
v-shaped nick at the free margin of the nail	6	22
subungual keratoses	6	22
fragility of the nails	14	52

Material and methods

In order to obtain the data on MD patients in Slovenia records were studied in the Departments of Dermatovenereology in Ljubljana, Maribor, Celje and Novo Mesto. New cases were also registered; thus a 30-years-period was covered. The diagnosis was established by clinical observation and patients' histories, in 24 cases a skin biopsy was performed. For families with two or more affected members pedigrees were prepared. Symptoms and other relevant data from 27 patients who had followed our invitation for a re-examination were collected in specially prepared questionnaires and analyzed.

Results

Altogether 44 patients were recorded, 20 males and 24 females. Taking into account that the Slovenian population amounts to roughly 2 million, this would give a prevalence of 2.2/100 000.

The 27 personally observed patients were from 15 to 72 years old and belonged to 21 families, 10 of them were isolated cases. There were four Slovene families with two cases, three families with three cases, one family with four cases and two families with five cases of MD (Fig. 1).

All examined patients had typical clinical symptoms: follicular and extrafollicular greasy, keratotic papules, half of them also hypertrophic plaques. Other symptoms observed were: scales on the scalp; plane papules on the back of the hands and feet; white or red longitudinal bands of the nail plate with V shaped notches at the free edge, indicating a fragility of the nails. Only a minority of patients observed had white »cobblestone« papules of the mucous membranes in the oral cavity. The symptoms recorded in the 27 patients who followed our invitation for a re-examination are presented in Table 1. Predilection sites were the neck, trunk, nails, face, limbs, scalp and scalp margins and back of hands (Table 2). Almost half of patients complained of itching and deterioration, if exposed to sunshine.

The onset of MD in our patients occurred before the fourth decade. In the half of the patients skin symptoms appeared in the second decade of life. Only in two patients the onset of MD was during the first year of life, in one in the 5th year, in two in the 9th year,

Table 2. Darier's disease in Slovenia: predilection sites investigated in 27 patients.

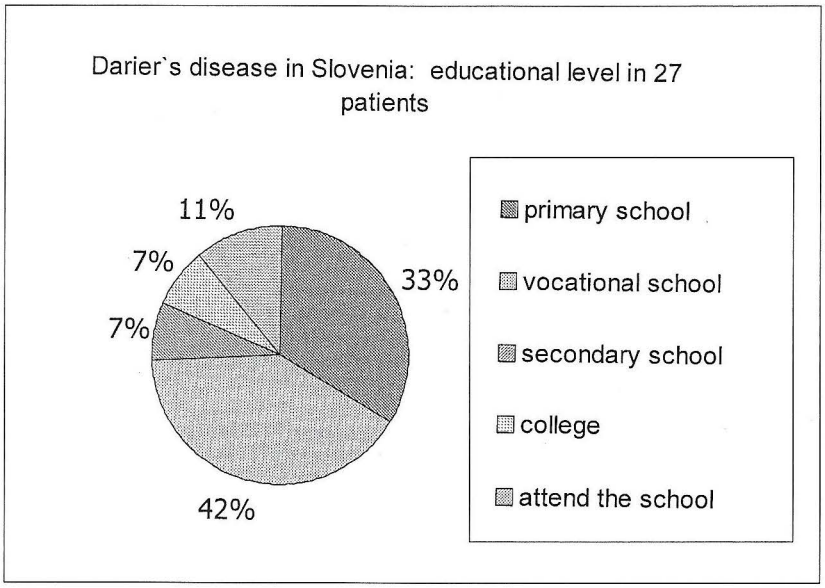
predilection sites	no. of patients	%
face	17	63
neck	24	89
trunk	24	89
limbs	14	52
axillae	7	26
groins	3	11
anogenital region	3	11
scalp and scalp margins	16	59
palms	9	33
soles	4	15
back of the hands	13	48
back of the feet	7	26
buccal mucosa	4	15
nails	24	89
clavicular region	6	22

while in two of them the disease developed after 40 years.

We also tried to evaluate the education level of our patients; 20 of them (75%) finished only the primary school or a vocational school, 2 of them (7%) graduated from a secondary school, 2 of them (7%) finished college of further education, while three are still attending the school: one a primary school, the second one a secondary school and the third one a college of further education (Graph 1).

We also observed an impairment of memory and concentration with the majority of our patients, though in two of them serious symptoms were expressed: one of them had epilepsy and a second paresthesia.

Involvement of the skin was relatively mild in 18 patients (66%), severe in 8 patients (30%) and very severe in one (4%). Approximately 37% of all observed patients, mostly with a severe form of the disease, were treated with synthetic retinoids orally.



Graph 1. Darier's disease in Slovenia: educational level in 27 patients.

Discussion

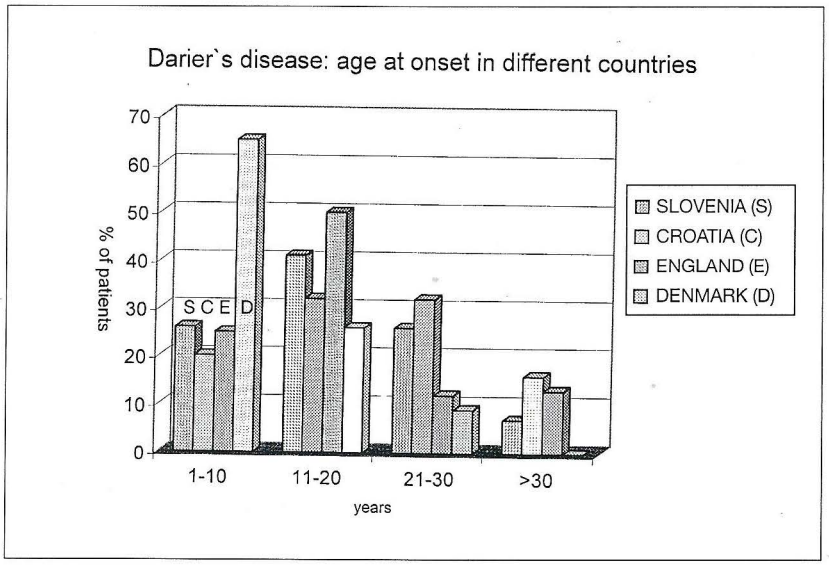
Our results show a relatively high prevalence of MD in Slovenia. Compared with data on occurrence of MD in Croatia, Denmark and England, the prevalence was higher only in Northeastern England (1-4).

MD is inherited as an autosomal dominant trait with variable penetrance and expressivity (8). We examined eleven families with more than two affected members. 10 sporadic cases, whose parents are normal, probably represent new mutations, but other possibilities must also be considered: penetrance might be incomplete, not recognized very mild symptoms in parents as well as non-paternity (9).

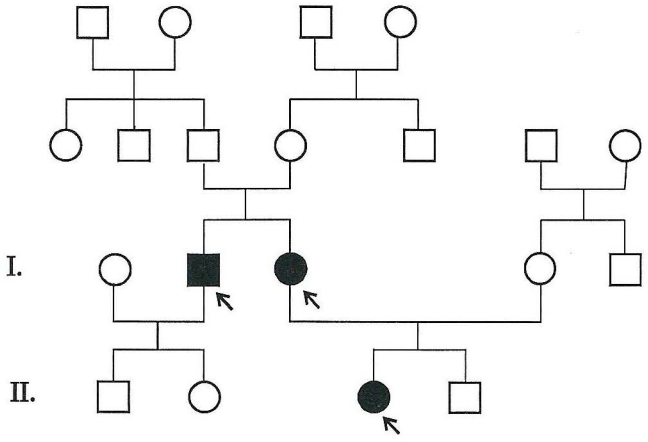
Various groups of researchers tried to detect the genetic defect in MD; desmoglein, desmocollin, desmoplakin and other components of the desmosome were incriminated (10-13). An abnormality in the desmosome -keratin filament interaction appears to be responsible for the breakdown of cell adhesion. The histopathological characteristics of MD are suprabasal clefting (lacunae) in-between suprabasal epidermal cells (acantholysis) and abnormal keratinization (dyskeratosis) with round dyskeratotic cells (corps ronds). Inside the lacunae there are single as well as small groups of epidermal cells (acantholytic cells) (8,14,15). The intercellular spaces between the prickle cells adjacent to lacunae are widened and the number of desmosomes is reduced. Electron microscopy also revealed loss of desmosomal attachments, perinuclear aggregations of keratin filaments and cytoplasmic vacuolisation (16-18). This data suggest that molecules, which mediate adhesion between keratinocytes might be involved in the loss of cell-cell adhesion in the epidermis. Desmosomes are the prime cell-cell adhesion junctions in the epidermis and are composed of various components, e.g.: desmosomal transmembrane proteins (desmogleins and desmocollins), desmosomal plaque proteins (desmoplakin, envoplakin and plakoglobulin) and plaque-associated proteins such as plakophilin I (19-21). Desmosomes interfere with the keratin intermediate filaments network in cytosol. In 1993 two British group excluded linkage of MD to any of the desmosomal genes mapped on chromosome 18 and to the type II keratin cluster at the chromosomal region 12q11-q13 (22,23). The defective gene probably regulates the expression of certain adhesion molecule.

New data concerning the pathogenesis were publi-

Graph 2. Darier's disease: age at onset in different countries.



Family 1.



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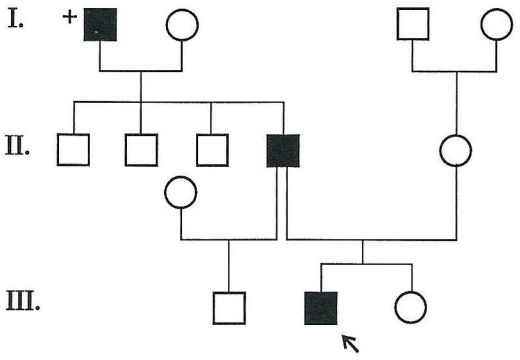

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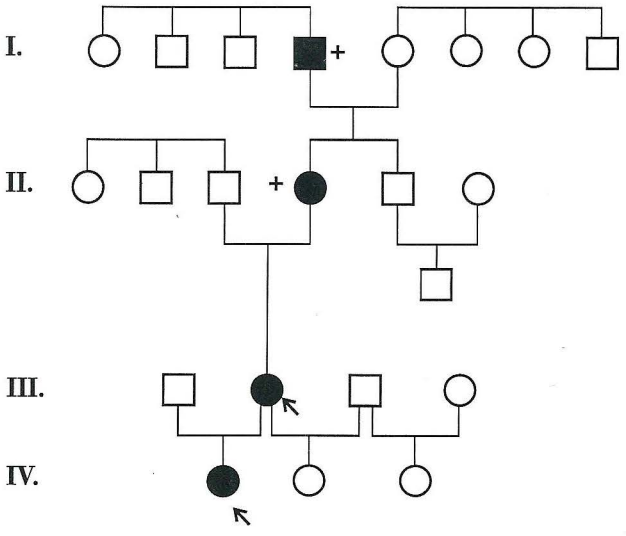

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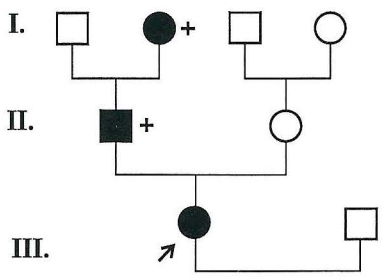
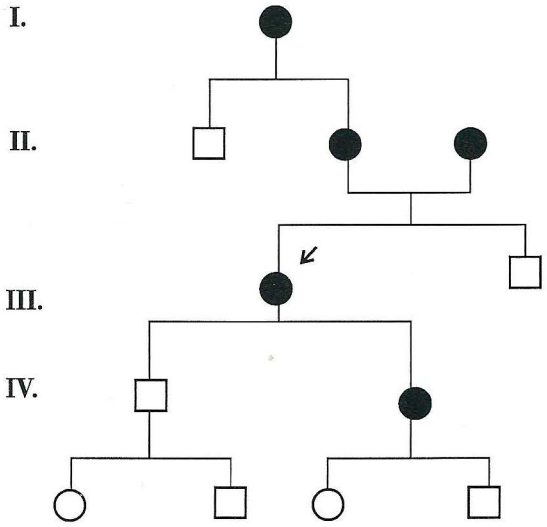


Family 5.



Family 6.

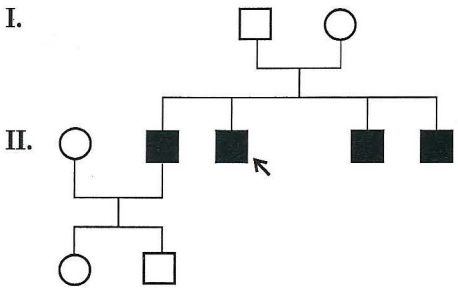


Figure 1. Pedigrees of six families with morbus Darier including three or more involved persons.

shed by Sakuntabhai et al. who identified mutations in the ATP2A2 gene, which encodes the sarco/endoplasmic reticulum Ca^{2+}-ATPase isoform 2 (SERCA2) and is highly notable in keratinocytes (24). ATP2A2 gene is located on chromosome 12q23-24.1. SERCA2 is a Ca^{2+} pump that has a pivotal role in intracellular Ca^{2+} signalling and maintaining low cytosolic Ca^{2+} concentration. ATP2A2 gene mutation could be responsible for MD because cytosolic Ca^{2+} is known to have a role in the development of epithelial junctions and in regulating cell differentiation. Mutation in ATP2A2 gene disrupts important domains of the molecule and is likely to result in complete or partial loss of function of the SERCA2 mutated pumps.

Clinical symptoms of MD vary, they may be minimal or severe with widespread itchy malodorous crusted plaques, painful erosions, blistering and mucosal lesions (25). The majority of patients have rather mild clinical symptoms. We found some similar reports in literature: according to Burge and Wilkinson (25) the chest, the back, the forehead and the supraclavicular fossae were involved in more than 80% of cases under observation. The nail involvement was observed in over 90% of English and in 71% of Croatian patients (24). Lesions of oral mucosa and neuropsychiatric abnormalities were relatively rare in our patients and also in other studies: according to Burge and Wilkinson in 15% of patients and in Croatian patients in 18 %. Many of our patients complained about disturbance of concentration and of an impaired memory. The majority of them finished only the primary school or a professional school. All these data suggest that in the majority of patients with MD a mild mental retardation exist. Munro (2) believes that the observation of a frequent mental subnormality in patients with MD in Denmark could indicate that additional genes are involved in cases observed in that country.

Sunlight, heat, sweating and poor personal hygiene exacerbated the disease in the majority of our patients, whereas on the contrary psychic stress, various infections, operations and pregnancy usually did not affect their condition. Sunlight has been mentioned as an exacerbating factor in 58% by British and in 89% by Croatian patients (25).

At the onset of the disease the age in our patients was under forty, while in half of the cases clinical symptoms appeared in the second decade. There are similar reports from other countries (Graph 2). Burge and Wilkinson (26) mentioned that in their study the peak of onset of MD occurred between the ages of 11 and 15. Sokol and Kansky (4) reported in their 28 cases two peaks of onset, namely in the age group 5 to 9 and in 20 to 24 years.

We still do not have an ideal method for treatment of MD (24). First of all, the patient should eliminate all the triggering factors and maintain a regular personal hygiene. For mild forms of MD simple emollients are usually sufficient. Cryotherapy with liquid nitrogen, topical application of tretinoin gel, calcipotriol or 5-fluorouracil can be used successfully on non-irritated skin. Corticosteroid creams and ointments are necessary during periods of irritated skin. For the patients with a severe form of the disease systemic retinoids are recommended. The patients with severe form of disease in our study were treated with synthetic retinoids orally, at least for the first couple of months. One patient with a very severe form of disease who is being treated with synthetic retinoids for over 10 years does not exhibit serious side effects.

It is interesting that in certain genodermatoses the symptoms become notable only at a later stage of the disease. This is also a reason to search for a sensitive and specific diagnostic method for an early diagnosis of MD. The replacement of mutated genes that are responsible for MD, may be a solution of this problem in the future.

Acknowledgement

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REFERENCES

1. Wilkinson JD, Marsen RA, Dawber RPR. Review of Darier's disease in the Oxford region. Br J Dermatol 1977; Suppl 15: 13.

2. Munro CS. The phenotype of Darier's disease: penetrance and expressivity in adults and children. Br J Dermatol 1992; 127: 126-30.

3. Svendsen LB, Albrechtsen B. The prevalence of dyskeratosis follicularis (Darier's disease) in Denmark. Acta Derm Venereol (Stockh) 1939; 39: 256-69.

4. Sokol J, Kansky A. Follicularis dyskeratosis (mb Darier) in Croatia. Acta derm Iug 1991; 18: 57-66.

5. Košiček M, Perkovič T, Lunder T, Penko M, Kansky A. Keratodermia palmoplantaris papulosa, Acta Dermatoven APA 1998; 7: 24-8.

6. Kansky A, Arzenšek J, Rode M, Strojan J. Keratodermia palmoplantaris of the Unna- Thost Type in Slovenia. Acta Derm Venerol (Stockh) 1984; 64: 140-3.

7. Arzenšek J, Kansky A. Palmoplantarna keratodermia tipa Unna-Thost. Acta derm Iug 1977; 4: 129-52.

8. Griffiths WAD, Leigh IM, Marks R. Disorders of Keratinization. In Rook et al: Textbook of Dermatology, 5th ed., Blackwell, Oxford 1992; p 1362-6.

9. Munro CS. The phenotype of Darier's disease: penetrance and expressivity in adults and children. Br J Dermatol 1992; 127: 126-30.

10. Sotoyama M, Hashimoto K, Tashiro M. Immunolocalization of desmoglein I on acantholytic cells in pemphigus vulgaris, Darier's disease and Hailey - Hailey disease. J Dermatol 1991; 18: 500-5.

11. Sotoyama M, Choi KC, Hashimoto K et al. Desmoplakin I and II in acantholytic dermatoses: preservation in pemphigus vulgaris and erythematosus, and dissolution in Hailey-Hailey disease and Darier's disease, J Dermatol 1991; 2(1): 9-17.

12. Burge SM, Garrod DR. An immunological study of Darier's disease and Hailey-Hailey disease. Br J Dermatol 1991; 124(3): 242-51.

13. Hashimoto K, Fujiwara K, Harada M et al. Junctional proteins of keratinocytes in Grover's disease, in Hailey-Haileys disease and Darier's disease. J Dermatol 1995; 23(3): 159-70.

14. Lever WF, Schaumburg-Lever G. Histopathology of the skin. 7th ed, Lippincott, Philadelphia 1990.

15. Pinkus H, Mehregan AH. A guide to Dermatohistopathology, 2nd ed. Appleton, New York, 1976; 399-400.

16. Caulfield JB, Wilgram MD. An electron microscopic study of dyskeratosis and acantholysis in Darier's disease. J Invest Dermatol 1963; 41: 47-65.

17. Biagini G, Costa AM, Laschi R. An electron microscopic study of Darier's disease. J Cut Pathol 1975; 2: 47-49.

18. Mann JB, Haye KR. An electron microscopic study on the acantholytic and dyskeratotic process in Darier's disease. Br J Dermatol 1970; 82: 561-6.

19. Burge S. Cohesion in the epidermis. Br J Dermatol. 1994; 131: 153-159.

20. Garrod DR, Chidgey MAJ, North AJ. Desmosomes: differentiation, development, dynamics and disease. Curr Opin Cell Biol 1994; 8: 670-678.

21. Burdett IDJ. Aspects of the structure and assembly of desmosomes. Micron 1998; 29: 309-328.

22. Bashir R, Munro CS, Manson S et al. Localization of a gene for Darier's disease. Hum Molec Genet 1993; 2: 1973-9.

23. Craddock N, Dawson E, Burge S et al. The gene for Darier's disease maps to chromosome 12q23-q24. Hum Molec Genet 1993; 2: 1941-3.

24. Sakuhtabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S. et al. Mutations in ATP2A2, encoding a Ca^{2+} pump, cause Darier disease 1999; 21: 271-276.

25. Miljkovič J, Kansky A, Korge B. Darier's disease (dyskeratosis follicularis). Acta Dermatoven APA. 1997; 6: 136-43.

26. Burge SM, Wilkinson JD, Darier. White disease: A review of the clinical features in 163 patients. J Amer Acad Dermatol 1992; 27: 40-50.

AUTHORS' ADDRESSES

Jovan Miljkovič MD, Dpt. Dermatovenereology, Maribor Teaching Hospital, Ljubljanska 5, 2000 Maribor, Slovenia
Nada Kecelj MD, Dpt. Dermatovenereology, University Clinical Centre, Zaloška 2, 1525 Ljubljana, Slovenia
Valerija Balkovec MD, Dpt. Dermatovenereology, General Hospital, Šmihelska 1, 8000 Novo mesto
Marta Penko MD, Director Dpt. Dermatovenereology, University Clinical Centre, Zaloška 2, 1525 Ljubljana, Slovenia
Aleksey Kansky MD, PhD, professor of dermatovenereology, corresponding author, same address