Clinical and Genetic Studies of 3 Large, Consanguineous, Algerian Families With Mal de Meleda

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Background: Mal de Meleda (MIM 248300), also referred to as keratosis palmoplantaris transgrediens of Siemens, is a rare autosomal recessive skin disorder with a prevalence in the general population of 1 in 100,000. The main clinical characteristics are transgressive palmoplantar keratoderma, hyperhidrosis, and perioral erythema, but there are also associated features such as brachydactyly, nail abnormalities, and lichenoid plaques.

Observations: We studied the clinical and genetic characteristics of 3 large, consanguineous, Algerian families, including 14 affected individuals. Homozygosity mapping of the third family confirmed localization of the responsible gene to 8qter in all 3 families.

Conclusions: Although some differences in phenotypic expression among subjects were noted, genetic analysis of the 3 families who shared a common ethnic background indicated that a single gene is responsible for mal de Meleda in this population.

Arch Dermatol. 2000;136:1247-1252

MAL DE Meleda (MdM) (MIM 248300), also referred to as keratosis palmoplantaris transgrediens of Siemens, is a rare genodermatosis with autosomal recessive transmission. Mal de Meleda was first observed by L. Stulli in 1826 on the island of Meleda in Dalmatia, Yugoslavia, where it was relatively common, whereas the prevalence in the general population is estimated to be 1 in 100,000. It was mistaken for leprosy until 1897, when Hovorka and Ehlers1 realized that it was a noninfectious palmoplantar keratoderma and used the term mal de Meleda. Neumann was the first to report this disorder in 5 families from the island of Meleda in 1898,2 and the autosomal recessive mode of inheritance was described in 1938.3 The diagnostic criteria were established by Schnyder et al4 in 1969 in a report of 10 cases. Linkage of the disorder to the 8qter locus in 2 large, consanguineous, Algerian families was reported in 1998 by Fischer et al.5

Clonically, MdM is characterized by symmetric palmoplantar keratoderma (PPK) and transgressive pachyderma, which involves the palms and soles and the back of the hands and feet (glove-and-stocking distribution). Brachydactyly with short cone-shaped fingers and nail abnormalities, such as koilonychia or pachyonychia, are frequently associated features. Hyperhidrosis, perioral erythema, and lichenoid plaques are also noted.6-8 The evolution of this disorder often exhibits a progressive character.

Histological features include marked acanthosis, pseudospongiosis, and small papilar bodies. A greatly thickened corneal layer, increased stratum lucidum, mild apparent dysplasia of the basal layer, and an expanded granular layer are also typical of the disorder. The sweat glands are often twice the normal size, and there is usually a prominent perivascular, lymphocytic, and histiocytic infiltrate.

We reviewed the clinical characteristics of 14 affected patients from 3 large, consanguineous families from Algeria and undertook genetic analysis using the method of homozygosity mapping.9

RESULTS

CLINICAL DATA

Clinical characteristics of all patients appear in Table 1. The disorder appeared within the first 2 years of life in our pa-
PATIENTS AND METHODS

PATIENTS

We studied 3 large, consanguineous families from Algeria (Figure 1 and Figure 2), comprising 40 individuals. All the family members were examined and clinical data documented (Table 1). There were 14 affected patients and 26 nonaffected individuals. For family A, 3 families who had the same family name were independently identified, and their clinical data collected. A common ancestor in the fifth generation was subsequently identified, and a common pedigree was constructed. In families A (sibships A1 and A2), B, and C, the parents are first cousins, whereas in sibship A3 of family A, no consanguineous relationship between the parents was known. In all 3 families, none of the parents were affected.

HISTOPATHOLOGICAL EXAMINATION

Skin biopsies were performed in 5 patients from families A and B (Table 2). Specimens were taken from the margins of the extending lesions of wrists, feet, and ankles.

TREATMENT

Salicylic acid ointments had been used by all patients, but the ointments merely caused peeling, with no improvement in the condition. Except for the youngest (AA1, AC2, AC3, B1, B2, C10, C11), all patients received several courses of acitretin (Soriatane) at initial doses of 0.5 to 1 mg/kg daily for 3 to 6 months, which was reduced depending on the response and adverse effects. The following symptoms were studied: erythema, contractures of the hands, and hyperkeratosis. Adverse effects were studied at each follow-up examination. Blood tests, including complete blood cell counts and serum bilirubin, alkaline phosphatase, transaminases, creatine, and urea levels, were performed before and during therapy.

GENETIC STUDIES

Blood samples for DNA extraction were collected from 40 members of the 3 families. Standard procedures for DNA extraction from whole blood were used. Fluorescent and nonfluorescent genotyping was carried out as described by Fischer et al.10 Linkage analysis was performed using the LINKAGE 5.1 program,11 assuming autosomal recessive inheritance, full penetrance, and a disease frequency of 1 per 100000 population. Two-point lod scores were calculated with the MLINK program, and consanguineous loops were incorporated into the pedigree files. The allele frequencies used were based on the 40 individuals from the 3 Algerian families. Genetic data from families A and B, which were reported previously in the initial gene localization study, were pooled with newly collected genotyping data from family C.

tients, usually before 5 months of age. Erythema of the palms and soles was the first manifestation, followed rapidly by roughening and thickening of the skin. The clinical picture varied from massive, transparent, yellowish or grayish hyperkeratosis with many fissures (patients AB1, AB2, AB3, AC1, AC2, B1, C2) to less marked hyperkeratosis (AA1, C10) (Figure 3) or slightly red skin (C11). There was a sharply outlined brownish red and scaly border between the palms and the normal skin. Trichophyton rubrum was cultured in 8 cases, and periodic acid–Schiff–positive spores were seen in sections of the stratum corneum in 2 patients. Microscopic examination of skin scrapings revealed no dermatophytes in all cases, however. Hyperkeratosis extended to the sides and the dorsa of the feet and hands (Figure 4) in all patients except the youngest (AA1, C10, C11) and sometimes involved the ankles (AC2, AC3, B1) and the wrists in a glove-and-stocking distribution (AB2). It was delineated by a bluish red border of desquamation about 1 to 2 cm wide.

Transgressive pachyderma was noted between 1 and 3 years of age except in patients C10 and C11. Two patients presented slightly erythematous keratotic plaques with circinate borders on the elbows (AB2 and AB3), which had appeared at 2 and 3 years of age. A brachydactyly corresponding to a shortening of the fingers and especially the fifth finger was observed in 5 patients (AB1, AC1, AC2, AC3, and B1). Conical distal phalanges were noted unilaterally in 3 patients (AB1, AC1, AC2) and on both hands in 1 patient (AC3), all in the same family. This feature was absent in the 2 other families. Contractures of the hand and fingers due to hyperkeratosis were present in 6 patients; they were severe in 1 patient (AB2) (Figure 5), involved all the fingers in 2 patients (AB1, AC3), and involved only the fifth finger in 3 patients (AC1, AC2, C2). A pseudoainhum resulting from constricting fibrous bands of the digits was noted on the fingers of one or both hands in 4 patients (AB1, AB2, AB3, AC1). All the patients except the 3 youngest have palmoplantar hyperhidrosis with fetid odor, especially between the toes.

Nail abnormalities were also observed in most of the patients and consisted of hyperconvexity and/or dystrophy, but in 5 of the patients only the toenails were affected. More than one third of the patients had pachyonychia and koilonychia of all the nails (Figure 5).

An angular cheilitis was noted in 7 patients at the corner of the mouth (AA1, AB2, AB3, AC2, AC3, B1, C2). The progressive character of the lesions became obvious between 1 and 8 years of age in most patients, although in 3 patients this did not become evident until 17 to 20 years of age. Except for these symptoms, all the patients were in good health, and there were no physical deformities, including tooth abnormalities. None of the patients were mentally retarded.

HISTOPATHOLOGICAL FINDINGS

Biopsy specimens revealed hyperkeratosis with areas of orthokeratosis and parakeratosis, hypergranulosis, acanthosis, and moderate perivascular inflammatory infiltration (Table 2).
In all patients, acitretine treatment led to improvement in hyperkeratosis and reduction of contractures of the hands; however, there was little effect on erythema. Relapses were frequently observed when the dose was reduced or acitretine was not available. Dryness of the skin was the main adverse effect. Laboratory findings remained within normal limits.

**LINKAGE AND HAPLOTYPE ANALYSIS**

Linkage analysis performed in families A and B led to the first localization of the MdM gene in an interval of at least 3 cM on 8qter as previously reported5 (Figure 1). A homozygous region at 8qter was also observed in family C, and data from this family were combined with data from

**TREATMENT**

Figure 1. Pedigrees and haplotypes of families A and B. The disease-associated haplotype is surrounded. Affected individuals are indicated by black symbols and nonaffected individuals by open symbols.

Figure 2. Pedigree and haplotypes of family C. The disease-associated haplotype is surrounded. Affected individuals are indicated by black symbols and nonaffected family members by open symbols.
families A and B to reinforce this finding. Haplotypes of the individuals in family C are shown in Figure 2. This caused an increase in the maximum pairwise lod score value from 8.21 at \( \theta = 0 \) for marker D8S1751 to 9.73 at \( \theta = 0 \) for the neighboring marker D8S1836. The smallest cosegregating region at 8qter remained the same, but the haplotype in the region for family C was different from that of the other 2 families, indicating that there was probably no recent common ancestor shared by all 3 families.

**COMMENT**

Our patients showed the main clinical features of MdM according to the criteria of Schnyder et al: diffuse PPK appearing before 5 months of age (7-150 days), transgressive pachyderma with onset usually before 2 years of age (1-3 years), and hyperhidrosis localized on the palms and mainly on the soles. Other features of the disorder were seen with variable frequency: brachydactyly, chiefly of the fifth finger; contractures of the fingers; conical distal phalanges; pseudoainhum, mainly in older patients; nail abnormalities; keratotic plaques on the elbows and perioral erythema; and angular cheilitis at the corner of the mouth in a few patients.

Progressivity of the lesions was seen in all our patients except the youngest; this has been reported previously in a series of patients from Tunisia and the United Arab Emirates, where an age-related progression in the extension of the lesions was mentioned.

Keratotic plaques on the elbows were noted in 2 patients. One of these 2 patients has the characteristic glove-and-stocking–like keratoderma. This probably reflects individual variation in the presentation of the disease. The main histological findings in our patients with MdM were marked orthokeratosis or parakeratosis and hypergranulosis.

Mal de Meleda must be differentiated from other inherited palmar and plantar keratodermas for which the nomenclature and classification are still in a state of fluctuation. Papillon-Lefèvre syndrome (MIM 245000), which was localized to chromosome 11q10 is an autosomal recessive PPK that is typically associated with periodontal lesions and premature loss of teeth; \( \text{cathepsin C} \) was recently identified as the gene responsible for this disorder. Mal de Naxos (MIM 601214) is also an autosomal recessive PPK characterized by additional cardiac symptoms such as cardiomegaly and ventricular tachycardia. However, most of the known diffuse palmoplan-

### Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AA1</th>
<th>AB1</th>
<th>AB2</th>
<th>AB3</th>
<th>AC1</th>
<th>AC2</th>
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<td>7</td>
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<td>15</td>
<td>10</td>
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<td>2</td>
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<tr>
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<td>20</td>
<td>8</td>
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<td>Characteristics of transgressiveness</td>
<td>...</td>
<td>Dorsa of hands and feet</td>
<td>Glove and stocking</td>
<td>Dorsa of hands, malleoli</td>
<td>Dorsa of hands</td>
<td>Dorsa of DIP, ankles</td>
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<td>Brachytelephalangia</td>
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<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
<td>Right hand</td>
<td>Left hand</td>
<td>Fifth finger</td>
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<tr>
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<td>Hyperconvexity</td>
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<td>+</td>
<td>Hands, feet</td>
<td>Feet</td>
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<td></td>
<td>Dystrophy</td>
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<td>+</td>
<td>...</td>
<td>Hands, feet</td>
<td>Feet</td>
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<td></td>
<td>Pachyonychia</td>
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<td></td>
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<td>Contractures of fingers</td>
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<td>Hands</td>
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<tr>
<td></td>
<td>Pseudoinainhum</td>
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<td>Fourth, fifth</td>
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<td>Right hand</td>
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<tr>
<td></td>
<td>Angular cheilitis</td>
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<td>+</td>
<td>+</td>
<td>...</td>
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</tbody>
</table>

* DIP indicates distal phalanges; plus sign, patient positive for characteristic; double plus signs, pronounced effect; and ellipses, characteristic does not pertain to the patient.

### Table 2. Histopathological Characteristics in 5 Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AA1</th>
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<th>AB3</th>
<th>B1</th>
<th>B3</th>
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</thead>
<tbody>
<tr>
<td>Site of biopsy</td>
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<td>Palm</td>
<td>Wrist</td>
<td>Ankle</td>
<td>Feet</td>
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<tr>
<td>Hyperkeratosis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Orthokeratosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parakeratosis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Hypergranulosis</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Acanthosis</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Perivascular inflammatory infiltration</td>
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<td>+</td>
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</table>

* Plus sign indicates patient positive for characteristic; ellipses, does not pertain to the patient.
tar keratodermas are inherited as autosomal dominant traits. Diffuse epidermolytic palmoplantar keratoderma of Vorner and the nonepidermolytic form (Thost-Unna type) (both listed under MIM 144200) share clinically identical features, and mutations have been found in both keratin 9 and keratin 1. These PPKs do not progress to the glove-and-stocking distribution. Vohwinkel syndrome is a diffuse mutilating keratoderma, characterized by ainhum, which leads to mutilations and exhibits some other associated features, such as deafness. Mutations for the classic form of Vohwinkel syndrome (MIM 124500) have been identified in connexin gene \(GJB3\) whereas a molecular defect in loricrin is considered to be responsible for the Vohwinkel keratoderma variant with ichthyosis (MIM 604117). Sometimes MdM may be confused with these 2 forms of erythrokeratoderma in which PPK may be present. In symmetric progressive erythrokeratoderma (MIM 602036), mutations in loricrin were identified, whereas in erythrokeratoderma variabilis of Mendes da Costa (MIM 133200), mutations in connexin gene \(GJB3\) are considered to be responsible. Hereditary palmoplantar keratosis of the Gamborg Nielsen type was reported as a possible subtle variant form of MdM in 1990.

### Table 1: Clinical Manifestations in MdM Families

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th></th>
<th>C2</th>
<th>C5</th>
<th>C10</th>
<th>C11</th>
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<tbody>
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</table>

Figure 3. A, Pronounced, transparent, yellowish hyperkeratosis with red border of desquamation delimiting the hyperkeratotic region in a 7-year-old girl with mal de Meleda. B, Less pronounced hyperkeratosis in a 2-year-old girl.
Since the first description of the disorder in 1826 in the islands off the coast of Dalmatia, other cases have been reported from Europe,23-28 Africa,7 Asia,6,8,29,30 and America.31 This report adds 14 cases from Algeria. This disorder appears to have a broad geographic distribution.

Genetic analysis of 3 families affected by MdM that shared the same ethnic background showed linkage to the $8qter$ locus. In this population, we conclude that a single gene is responsible for the disorder.

Since MdM is resistant to local treatment, oral retinoids have been used in several patients.27,31,32 In our patients, treatment with these drugs improved keratinization significantly but had no effect on erythema.

Accepted for publication March 16, 2000.

This study was supported by the Association Francaise Contre les Myopathies, Evry, France.

We thank the family members for their participation.

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