Isolated Congenital Nail Dysplasia

A New Autosomal Dominant Condition

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Objective: Developmental nail abnormalities are extremely heterogeneous, with hereditary isolated conditions being a small and rare subgroup. An unusual congenital nail dysplasia observed in a large South German kindred was characterized clinically to review the question of uniqueness.

Design: Case series of affected family members.

Setting: University department of dermatology and houses of patients.

Patients: The history and clinical features in 22 affected family members (13 females and 9 males, aged 5 to 74 years) were recorded and documented by photographs. Nail biopsy samples were taken from 2 patients.

Interventions: None.

Results: The pedigree spanning 5 consecutive generations was best compatible with autosomal dominant inheritance with complete penetrance. Nail alterations were mostly present since birth and soon reached an individually variable degree of severity. Affected persons showed longitudinal streaks and thinning of nail plates, mostly of all fingernails and toenails, with some accentuation of the thumbnail and big toenails, longitudinal angular ridges of individual nail plates occasionally starting proximally from a reddish prominence, pteryonychia and koilonychia of individual nails often overgrowing the lateral folds, and notches and fissures of the free margins. Histological abnormalities included a prominent granular layer of the nail matrix and epithelial strands and buds extending from the nail bed. There were no associated anomalies. Other nail dystrophies were excluded by differences in clinical and histological features.

Conclusion: The nail abnormality observed in our family represents a new autosomal dominant disorder for which we propose the term isolated congenital nail dysplasia.

Arch Dermatol. 2000;136:1239-1243

DEVELOPMENTAL abnormalities of the nails constitute a large and extremely heterogeneous group of disorders. They range from slight, hardly noticeable changes to complete absence of nails; they may be present at birth or occur considerably later; they may be inherited or acquired in fetal life; and they may appear as an isolated anomaly or, as a minor feature, forming part of a complex syndrome. All conditions in question are rare.

Recently, we had the opportunity to observe a large kindred with a hereditary congenital nail disease lacking further associations. As the features are not consistent with any other known congenital nail dysplasia, we assume we are dealing with a new condition.

REPORT OF CASES

A 13-year-old boy was admitted to the Department of Dermatology, University of Würzburg, Würzburg, Germany, with impetigo contagiosa. In addition, all of his nails showed unusual alterations that were reported to have been present since birth. His mother, who was also affected, helped to draw up an extensive pedigree of the family (Figure 1).

In the following months, we examined 22 affected and 11 healthy family members. Most of them were living in a village of the Main-Tauber district in South Germany about 30 km from Würzburg. When visiting them, clinical findings were recorded meticulously and photographs of all nails of each individual assessed to be affected were taken. Notes and photographs served for later evaluation and application of severity scoring.

PEDIGREE ANALYSIS

The nail disease could be traced back across 5 consecutive generations. Of the 45 family members shown in the pedigree (Figure 1), 33 individuals and 8 husbands of affected adults were available for examination. Six were deceased, and the remaining 6 were living remotely or refused examination by us. Twenty-two of the 33 members (13 female and 9 male) examined were classified as involved. The youngest patient was 5...
years of age; the oldest, 74. In a few instances only, it was difficult to differentiate between uninvolved and very mildly affected. Adding available information about the family members who were not examined personally, 13 of 21 male and 14 of 23 female descendants of the great-great-grandmother (I:1) were affected by the nail disease. The method of transmission was best compatible with autosomal dominant inheritance with complete penetrance.

HISTORY

In most family members, nail alterations were reported to be present since the first day of life and, soon after that, to reach an individually variable degree of severity with little change afterward. Apart from cosmetic disability, affected persons complained about increased vulnerability of the free nail margins, especially in longer nails. Therefore, they used to cut nails short and avoid filing. The speed of nail growth was reported to be unimpaired.

Two patients (IV:4 and IV:5) were reported to have had ingrown big toenails. An 11-year-old girl (V:6) was reported to have had unruly scalp hair in infancy that had returned to normal.

CLINICAL FEATURES

The nail changes and their relative frequency observed in 22 affected members of the kindred are listed in the Table. In nearly all patients, all fingernails and toenails were symmetrically involved, with some accentuation of the thumbnail and big toenails (Figure 2 and Figure 3). Longitudinal streaks and thinning of the nail plates were the most consistent findings (Figures 2 and 3, Figure 4, and Figure 5). In most patients, the lunulae were poorly developed or absent (Figures 2-5). Some nail plates, especially of the first digits, seemed to broaden distally by escaping the guideway of the lateral nail fold and overgrowing it (Figures 2 and 4). This sign was sometimes combined with a flattening or spoon-shaped deformation of the nail plate in terms of platonychia or koilonychia (Figures 2 and 4). In most patients, longitudinal angular ridges of individual nail plates could be observed (Figures 2, 4, and 5). Occasionally, they started from a conspicuous reddish dome-shaped prominence of the proximal nail plate (Figures 2, 4, and 5). This latter feature may be regarded as the most characteristic finding of the condition but was present in only about half of the patients. Partly due to increased vulnerability and partly to marked longitudinal ridging, individual nails showed fissures and notches of the free nail margin in about half of the patients (Figures 2, 4, and 5).

SEVERITY OF INVOLVEMENT

Based on the 12 features mentioned in the Table, a scoring system was used to evaluate the individual severity of involvement. Male patients proved to be, on average, more severely affected than female patients (median score, 10 vs 7), which is explained at least in part by the less intensive
and less regular nail care performed by the male patients.

Children younger than 12 years had slightly more severe nail changes than adolescents and adults (median scores, 10, 9, and 9, respectively). The interindividual severity was considerably variable, even in first-degree relatives.

HISTOLOGICAL FEATURES

Two men (IV:3 and IV:4) agreed to undergo longitudinal biopsy of papular convexities of the proximal nail plate after written informed consent. The specimens were routinely processed, and the slides were stained with hematoxylin-eosin and periodic acid–Schiff reagent. Histological examination of the dorsal and ventral surfaces of the proximal nail fold did not reveal pathologic changes. Unlike healthy nails,1,2 the epithelium of the nail matrix showed a prominent granular layer (Figure 6). The nail bed adjacent to the matrix region appeared normal, being flat and keratinized without a granular layer. More distally, in a circumscribed area of the nail bed, irregularly arranged epithelial strands and buds extended from the nail bed epithelium (Figure 7). Here, the nail bed collagen fiber network appeared somewhat condensed. Inflammatory cells were completely absent.

FURTHER FINDINGS

In the index patient (V:23), results of routine laboratory tests were all within the normal range. Mycological cultures of nail scrapings yielded negative findings. Skeletal abnormalities of the phalanges of the hands and feet and of the patellae were ruled out by radiographs.

In 4 patients (III:4, IV:5, IV:9, and V:22), a diastema between the upper medial incisors was present. Two patients (III:3 and III:4) had onychomycosis of several toenails in addition to congenital nail abnormalities; in another 2 (V:13 and V:26), scoliosis was diagnosed. One patient each suffered from congenital hip dysplasia (IV:7), cleft lip and palate (V:2), and partial syndactyly of the second and third toes (IV:4), respectively. Except for impetigo contagiosa in the index patient and chronic dermatitis of the fingertips in a man (IV:6), there were no abnormalities of the skin and mucous membranes in the affected individuals. Hair growth, dentition, and the function of sweat glands and sense organs were not impaired.

COMMENT

We herein present the clinical features of a congenital nail disease in a large kindred across 5 generations. Most changes observed in 22 affected family members constitute a dysplasia of the nails resulting in thin, striated, occasionally deformed nail plates with increased vulnerability. Longitudinal streaks of all fingernails and toenails were the most consistent finding present in nearly all patients. The most
conspicuous but still inconstant feature of the condition was longitudinal angular ridges of individual nails, which sometimes started at a reddish convexity adjacent to the proximal nail fold. In other nails, especially of the thumbs and big toes, platonychia or koilonychia was noted with the nail plates overgrowing the lateral nail folds. General characteristics include autosomal dominant transmission with complete penetrance and variable expressivity, congenital manifestation, and absence of associated defects of ectodermal structures, bones, and other organs.

Longitudinal nail biopsy specimens showed an abnormal keratinization of the matrix epithelium with a broad granular layer. Although keratohyalin granules are absent in the keratogenous zone of healthy nails, focal hypergranulosis is a common pathologic feature in inflammatory and compressive insults to the nail matrix. However, the diffuse hypergranulosis in the condition described herein likely represents an inborn error of keratinization of the nail matrix cells. Epithelial outgrowths from the nail bed, the other conspicuous histopathological finding, probably account for the papular convexities of the proximal nail plate.

The differential diagnosis of congenital nail abnormalities includes a wealth of hereditary conditions and less numerous malformations acquired in fetal life. As a minor feature, nails are involved frequently in many complex syndromes and in several chromosomal anomalies. Nail dysplasias of various forms and severity occur in combination with disturbances of hair growth, dentition, and/or sweating within the large group of ectodermal dysplasias, in association with deafness, and as a result of skeletal abnormalities, such as in nail-patella syndrome and Iso and Kikuchi syndrome. The onychopathy in this family clearly differs from these conditions by the type of nail deformity and the absence of extracutaneous findings.

Furthermore, a number of genodermatoses primarily involving the skin and mucosa are associated with more or less characteristic nail changes. Epidermolysis bullosa, especially junctional and dystrophic types; X-linked dyskeratosis congenita; pachyonychia congenita; and Darier disease are the best-known examples. In rare cases, pachyonychia congenita and Darier disease may be limited to the nails. Darier disease typically presents with red and/or white longitudinal streaks, often terminating in a V-shaped notch, and thus shares some features with the nail disease described herein. However, nail involvement in Darier disease develops later in life, tends to be progressive, and is almost always associated with cutaneous signs. In our family, only the nail changes vaguely resembled Darier disease, and none of the affected members had skin changes consistent with this genodermatosis. Histopathological criteria typical of Darier disease, such as suprabasal clefts containing acantholytic cells in the dorsal portion of the proximal nail fold and the nail matrix and multinucleate epithelial giant cells in the cornified cells of the nail bed and nail plate, were not detectable in the biopsy specimens of our patients.

Some nail features in our family resemble those in lichen planus. This condition may be limited to the nails, in childhood in rare cases, and has been observed quite often in families. However, more than 2 family members are affected only rarely. Genetic susceptibility in terms of polygenic inheritance is suggested to account for familial cases rather than a monogenic trait, although the association with specific HLA antigens is disputed. Clinically, familial lichen planus differs from sporadic cases by an earlier age of onset; a tendency to more severe, widespread, and atypical forms; a longer duration; and a higher likelihood of recurrence of the disease. However, no significant differences in the frequency of nail lesions could be observed. Lichen planus of the nail does not usually begin before adulthood and is self-limiting or promptly regresses with treatment in most cases. Permanent damage to the nail matrix occurs only in a small subset of patients. Histological findings correspond to those in cutaneous lichen planus and include hyperkeratosis, hypergranulosis, “saw-tooth” acanthosis of the nail matrix and bed epithelium, and a bandlike lymphocytic infiltrate in the superficial dermis. Thus, they differ considerably from the noninflammatory histological features in the biopsy specimens of the present family series.

Among the hereditary conditions exclusively involving the nails, congenital malalignment of the great toenails appears to be the most frequent disorder. In exceptional cases, absence (anonychia) or severe hypoplasia (onychoatrophia, micronychia, hyponychia) of 1 or more nails follow dominant and recessive patterns of inheritance. Furthermore, koilonychia, trachyo-
nychia,\textsuperscript{26} leukonychia,\textsuperscript{28} brachyonychia,\textsuperscript{30} clubbing,\textsuperscript{30} periodic shedding,\textsuperscript{31} partial onycholysis,\textsuperscript{32} onychogryposis,\textsuperscript{33} overcurvature of the nails,\textsuperscript{34} pterygium inversum unguis,\textsuperscript{35} and circumferential toenails\textsuperscript{56} have been observed as hereditary variants. Although of genetic origin, most developmental abnormalities affect only certain nails.

A congenital anomaly of all fingernails and toenails was described by Prandi and Caccilanza\textsuperscript{37} under the term soft nail disease and is probably identical to the condition described by Friederich in 1950.\textsuperscript{38} Nail plates were normally curved but thin and short, and the lunulae were absent. However, the nails lacked many further characteristics of the nail disease observed in our family; they did not grow and never needed cutting; and both cases were sporadic. Two other conditions affecting most or all nails and inherited as an autosomal dominant trait were reported by Pavone et al\textsuperscript{39} and Arias et al.\textsuperscript{40} Hereditary 20-nail dystrophy observed in a Sicilian family\textsuperscript{41} is not identical to the nail disease we observed because of the slowly progressive nail involvement with final nail loss at 10 to 20 years of age. Thin, rough, and opalescent nails with ridges, pterygia, and longitudinal splitting in individual nails characterize the disorder reported under the term familial severe 20-nail dystrophy by Arias et al.\textsuperscript{42} However, additional mild distal onycholysis and subungual hyperkeratosis, occasional sparing of fingernails, and frequently associated malocclusion of teeth were not noted in our patients, whereas several nail features of our patients, such as platonychia and koilonychia with overgrowth of the lateral nail folds and signs of increased fragility of the free nail margins, are not mentioned in the report by Arias et al. Moreover, epithelial strands and buds of the nail bed epithelium, probably accounting for the prominences of the proximal nail plate in our patients, were absent in the longitudinal nail biopsy performed in the index patient by Arias et al. We therefore assume that the 2 conditions are similar but not identical.

\textbf{CONCLUSIONS}

All conditions in which nail changes are associated with other cutaneous or extracutaneous manifestations easily can be excluded to account for the nail disease described herein. It also differs considerably from most other congenital conditions mentioned that involve the nails only. To our knowledge, there is no identical nail disease on record in the literature. We therefore conclude that we are dealing with a new entity for which we propose the descriptive term isolated congenital nail dysplasia. We hope that further studies will elucidate the genetic defect, since genetic linkage analyses are in progress. As other structures of ectodermal origin are not affected and the abnormality seems to be confined to the epithelium of nail matrix and nail bed, it is tempting to assume a hereditary defect of a structural protein exclusively produced by the keratinocytes of the nail organ.

We thank all examined family members for their kind cooperation.

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\textbf{REFERENCES}