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Nail Abnormalities In Genodermatose

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ABSTRACT

Introduction
Nail abnormalities may serve as early indicators of various genodermatoses, either presenting in isolation or alongside systemic features. These abnormalities, though sometimes cosmetic, often hold significant diagnostic value, especially in inherited ectodermal disorders. Understanding the anatomy and embryology of the nail unit is crucial for identifying the origin and nature of such defects.

Method
This literature review was conducted by analyzing selected journal articles, case reports, and textbooks focusing on genodermatoses with distinct nail involvement. The analysis centered on the classification of nail abnormalities based on their anatomical origin: nail matrix, nail bed, or combined mesodermal-ectodermal defects.

Results
Findings revealed that nail abnormalities are prominent in several genodermatoses. Nail matrix defects are observed in congenital dyskeratosis, marked by nail dystrophy, leukoplakia, and mucocutaneous pigmentation. Nail bed defects, as seen in congenital pachyonychia and hydrotic ectodermal dysplasia, lead to thickened, dystrophic nails and associated skin changes. Combined mesodermal-ectodermal disorders, such as nail-patella syndrome, present with absent or hypoplastic nails alongside skeletal, renal, and ocular abnormalities. Each condition displayed specific nail manifestations that can aid early diagnosis.

Discussion:
The review emphasizes the importance of integrating knowledge of nail anatomy and development to differentiate between types of nail abnormalities. Identifying the anatomical origin aids in narrowing the differential diagnosis and can provide early clues to systemic genodermatoses, even before other clinical signs emerge.

Conclusion:
Nail abnormalities are important diagnostic markers in genodermatoses. Routine nail examination should be an integral part of dermatological assessments to facilitate early recognition and diagnosis of underlying genetic disorders.

Keywords: congenital dyskeratosis, ectodermal dysplasia, genodermatoses

Introduction

Nail abnormalities may be either congenital or acquired, and can present in isolation or alongside systemic conditions.[1] Nail abnormalities are frequently among the first and most consistent clinical findings in both inherited and congenital ectodermal disorders. While these

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abnormalities may at times be limited to cosmetic issues, they can also provide important diagnostic indicators, indicating both current and past disease processes.[2]

Telfer proposed a straightforward classification of congenital and hereditary nail disorder, grounded in the pathophysiological and embryological aspects of nail development. This classification considers abnormalities in the nail matrix, nail field, nail bed, as well as a defectrs in mesodermal or ectodermal tissues. Understanding the anatomical structure and embryological development of the nail is essential for diagnosing nail abnormalities, particulary in genodermatoses.[3]

Approximately 10% of patients consulting dermatologist and venerologist present with nail-related complaints. Although a wide range of genodermatoses exhibit nail involvement, this review does not aim to provide an exhaustive overview of all such conditions.[3] Rather, it highloghts selected disorders in which nail abnormalities represent a predominant and diagnostically significant feature of the syndrome.[2]

Nail abnormalities can be associated with skeletal abnormalities, such as in nail- patella syndrome.[4] There are also genodermatoses accompanied by characteristic nail abnormalities, such as congenital pachyonychia and congenital dyskeratosis. [5,6]

This literature review discusses nail abnormalities found in several genodermatoses with characteristic clinical presentations. It is hoped that this article will enhance knowledge and diagnostic capabilities for cases involving nail abnormalities.

Nail Anatomy

Nail appartus includes the nail plate, lanula, matrix, nail bed, lateral and proximal nail folds with cuticle, and hyponychium. The distal phalanx's dermis at the nail bed and periosteum link it to the nail unit. As a result, abnormalities of the nail are frequntly associatedwith underlying bone abnormalties.

The nail plate constitutes a keratinized structure that grows indefinitely. The nail plate develops through the maturation as well as keratinization within the nail matrix epithelium. It has been attached to a portion of the nail bed structure. Nail growth is determined by the individual's age, vascular as well as nerve supply, nutrition, along with physical function. Nails develop 0.5-1.2 mm every seven days on fingers when 0.2-0.5 mm on toes. [7] Fingernail replacement takes 6 months, and toenail replacement takes 12-18 months.[1] During maturation, nail plate thickness increases. The middle, distal, and free outermost lunulas increase nail thickness. Thin nails suggest nail matrix disorders, whereas thick nails indicate nail bed disorders.[7,9] The distal lunula is the area where the proximal nail bed is located; in this area, the nail matrix ends. Because the matrix is located here, where the nail plate is produced, damage to the matrix will also damage the nail plate.[9] The nail plate has three parts: dorsal, intermediate, as well ventral. This proximal as well as lateral nail plates are surrounded by nail folds. The cuticle protects the nail plate and proximal nail fold.[7,9] The dermis on the proximal nail fold is made up of a variety of capillaries that are plainly apparent under a microscope.

Arterial and venous capillaries are placed parallel. The nail plate above the lunula is made up of only the dorsal and intermediate parts. The hyponychium separates the nail plate tip from the rest.[7]

Two lateral digital arteries feed blood to the well-vascularized nail bed. Epithelium and dermal connective tissue form longitudinal ridges and grooves in the nail bed from the lunula to the hyponychium.(1) The nail bed is loaded with glomus bodies, which are neurovascular structures made up of arteriovenous anastomoses and nerve terminals that regulate temperature.7,12 Nail matrix and bed lack melanin. Melanocytes activated by proximal nail fold trauma may form transient longitudinal bands, particularly in darker skin.

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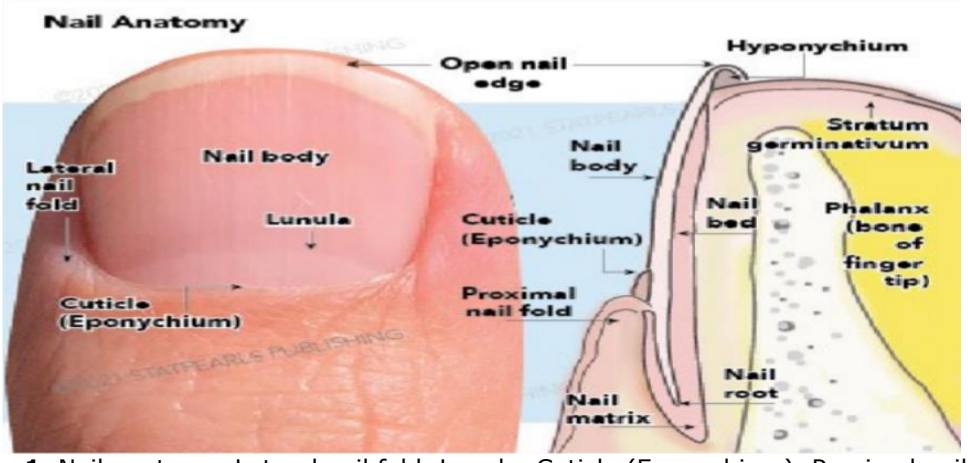

Figure 1. Nail anatomy, Lateral nail fold, Lunula, Cuticle (Eponychium), Proximal nail fold, Hyponychium, Stratum germinativum, Phalanx (bone of finger tip), Nail matrix, Nail root

Nail Embryology

The nail structure starts developing at 9 weeks of gestation and reaches full maturation by 20 weeks of pregnancy. Congenital nail anomalies that occur during this timeframe are termed embryopathies, whereasirregularities that develop after 20 weeks of gestation are referred to as fetopathies. [7,12]

By the tenth week, the nail plate, a rectangular region encompassing the dorsal tip of the fingers, forms the nail structure. A germinative epithelium in the dermis creates the nail matrix proximally from the nail plate. Lateral and proximal nail folds form in week 11. The nail bed is formed by uniting the distal ridge, lateral nail folds, and matrix. Keratinization of the nail bed starts at the distal ridge.[7,12]

By week 14, the nail bed is completely granular. Flat keratinocytes form the nail plate from the proximal nail fold outward. The granular nail bed layer progressively disappears, and the nail bed keratinocytes unite to form the nail plate basis.[7,9,12]

Nail Abnormalities In Genodermatoses

Genodermatoses are genetically inherited skin disorders with various inheritance patterns, most commonly through single-gene inheritance, but may involve point mutations, deletions, or chromosomal abnormalities. Genodermatoses present with various skin manifestations and are generally ectodermal syndromes, involving abnormalities in the nervous system, eyes, central nervous system, skin, and its appendages, including the nails. [2,8,9]

Nails can be a sign of various genodermatoses, sometimes only nails are found as the initial abnormality of a genodermatoses. Telfer divides hereditary nail abnormalities into abnormalities of the nail bed, abnormalities of the nail plate, abnormalities of the matrix, and combinations of ectodermal and mesodermal abnormalities. [1,3,7,12] Abnormalities in the nail matrix, for example, are found in congenital dyskeratosis, [9,13] abnormalities in the nail cross-section are found in ectodermal dysplasia, [2,3,13] abnormalities in the nail bed, for example, are found in congenital pachyonychia, [5,6] and abnormalities in the combination of mesodermal and ectodermal are found in patella and nail syndrome. [6,10]

Nail Matrix Defects

Congenital dyskeratosis (defect in matrix function)

Congenital dyskeratosis (CD), also known as Zinsser-Cole-Engman syndrome, is a rare genodermatosis, inherited in an X-linked recessive manner.[9,13] CD is characterized by mucocutaneous, ocular, and hematological abnormalities. The three clinical hallmarks of CD

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are: (1) nail dystrophy, (2) leukokeratosis of the oral and anal mucosa, sometimes with ulcers in the oral and gastrointestinal mucosa, and (3) *net-like* skin pigmentation resembling *poikiloderma atropicans vasculare.* Most DK patients experience pancytopenia or hypoplastic anemia. Abnormalities are also found in the teeth, neurological system, and immune system. Death is usually caused by pancytopenia or malignant transformation of mucocutaneous lesions.[9,10]

Mucocutaneous symptoms, alterations in nails, andleukoplakia typically arise first, occ urringbetween the ages of 5 and 10 years. Reticular pigmentation appears on the upper back, neck, shoulders, and thighs. Featuring typical telangiectasia andgrayish degeneration. Some of the skin characteristics include hyperkeratosis, hyperhidrosis, and blisters on the palms and soles caused by trauma. Nail alterations may advance from pitting, ridging, thinning, splitting, and pterygium to total nail deformities resulting from the nail's inability to develop a nail plate. [9,12] Occasionally, diffuse non-scarring alopecia with thin and pale eyelashes is observed. Leukoplakia occurs in 78% of instances on the oral mucosa but can also appearon the genitals, urethra, anal mucosa, and conjungtiva. Leukoplakia may progress into invasive squamous cell carcinoma. [9,10] Congenital dyskeratosis is genetically characterized as autosomal dominant (OMIM 127550), autosomal recessive (OMIM 224230), or X-linked (OMIM 305000). The X-linked and autosomal dominant genes involved in this condition include DKC1 and hTERG, a dyskerin gene product that regulates telomerase RNA. It is currently thought that DK is caused by *defective telomerase maintenance,* resulting in limited hematopoietic and epithelial cell proliferative capacity.[8,13]

Figure 2. Clinical appearance of Dyskeratosis Congenita. (a) Ridging and splitting of nails affecting all fingernails with varying severity. (b) Brown lacy reticular network of pigmentation on the neck and V area of the chest. (c) Leukokeratotic lesions over a background of hyperpigmentation on the dorsal aspect of the tongue. (d) Thickening of palmar skin with dyspigmentation

Nail Plate Defects

The nail matrix is an area on the dorsal digitalis of the fetus, formed by primitive grooves, and it is in this area that the entire nail apparatus will form, including the nail matrix and nail bed. [7,12]

Hydrothic ectodermal dysplasia

Ectodermal dysplasia encompasses 150 clinical presentations of various combinations of growth abnormalities in the skin, hair, teeth, nails, and sweat glands. These defects may be associated by other deformities including intellectual disabilities, syndactyly, hearing impairment, cleft lip/palate, ptosis, as well as auricular duct anomalies.[2,3]

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Anhidrotic/hypohidrotic and hydrotic diseases are two of the most common. Hydrotic ectodermal dysplasia (HED) is characterized by unique and severe nail abnormalities.[3,13]

Hydrostatic ectodermal dysplasia (HED), frequently referred to as Clouston syndrome (OMIM 129500), is an autosomal dominant genetic condition marked by nail dystrophy, hair abnormalities (hypotrichosis, alopecia), and palmoplantar keratoderma. Individuals experiencing HED exhibit normal sweating and sebaceous glands. The main abnormality in this syndrome is nail dystrophy, which can sometimes be the only manifestation in one-third of cases.[2,13]

The nail plate in HED is small. The nail apparatus is normal, except for shrinkage of the nail unit. The distal edge attached to the nail plate is more proximal than in normal nails. [3,2,13]

According to Stratigos, the nails are thicker, striated, and discolored. They grow slowly and can induce paronychia infections that destroy the nail matrix. The skin under the distal nail, nail joints, between the knees, and joints often thickens. Palmoplantar keratoderma develops and may extend to the dorsal areas of the hands and feet. [9,10,13]

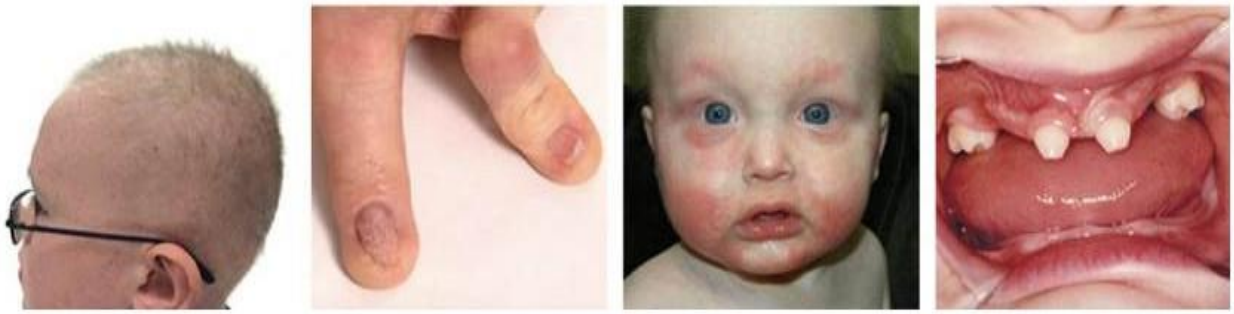

Figure 3. Typical of Hydrothic ectodermal dysplasia

Nail Bed Defects

The natural nail bed epithelium is made up of only a few corneocytes in the nail bed's lowest layer. Nail bed proliferation leads to hypertrophy and thickness of the nail. [7,9]

Congenital pachyonychia

Congenital pachyonychia (CP) is a collection of autosomal dominant ectodermal illnesses distinguished by hypertrophic nail dystrophy. The most prevalent kinds of PK are PK-1 and PK-2 (15). Nails in PK-1 (Jadassohn-Lewandowsky, MIM 167200) may be normal at time of birth, but within a few months thicken and darken, with increased transverse curvature and subungual hyperkeratosis (*pincer nail effect*)[5,6] Other characteristic features often observed include symmetrical focal palmoplantar keratoderma accompanied by or not with hyperhidrosis, angular cheilitis, follicular hyperkeratosis, hoarseness, as well as oral leukokeratosis.[6,8,12] Compared to the PK-1 phenotype, nail thickening in PK-2 is milder, oral involvement is minimal, and keratoderma is mild. What distinguishes it is the presence of multiple steatocystomas, *tortuous hair*, and in some cases, eruption of teeth at birth. [5,8]

Omicodystrophy is a clinical feature almost always present (98%), although the severity varies between patients. Typically, all twenty nails are affected, becoming hard, thickened, and discolored. Nail abnormalities are an early manifestation of PK and are present at birth. Dominant thickening of the nail plate, with progressive distal elevation, forms a pincer or omega pattern.5,6 Hyperplasia occurs at the distal base of the nail, or hyponychium, resulting in an abundance of subungual keratin. This allows the nail plate to rise and curve, resulting in a free edge like a horseshoe. 9

PK-1 syndrome is caused by mutations in keratin K6a or K16, while mutations in keratin K6b or K17 cause PK-2. 8,13

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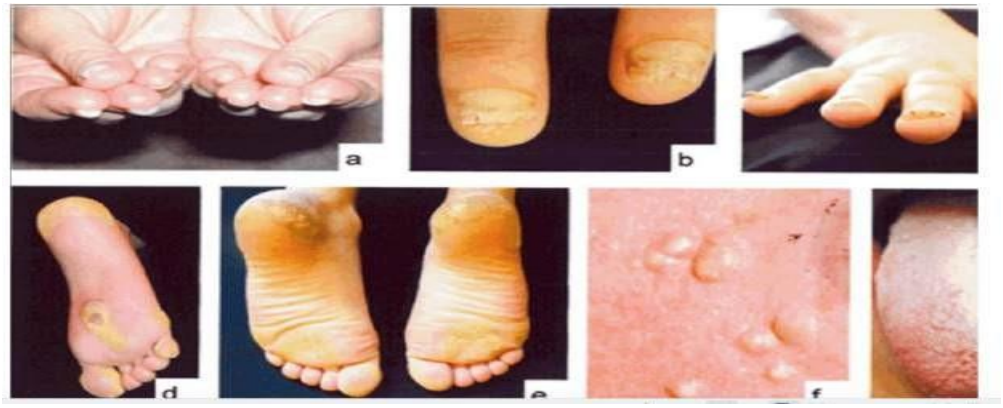

Figure 4. Common findings of pachyonychia congenita include: thickened and dystrophic nails (both fingernails and toenails) (a-c); bullae (usually on the pressure points of the heels and soles); hyperkeratosis (d-e); cysts (f); and oral leukokeratosis (g).

Mesodermal And Ectodermal Defects

The nail unit is inextricably linked to the distal phalanx; anonychia arises when the distal phalanx does not develop or is aberrant. This relationship can extend to the middle phalanx, where anonychia has been observed when the middle phalanx fails to develop. Loss of the nail matrix occurs in syndromes with digital errors or broad mesodermal abnormalities. The nail matrix may be destroyed even if the underlying digit bones remain undamaged, as in nail-patella syndrome. [4,9,12]

Nail-patella syndrome

In nail-patella syndrome (*hereditary osteoonychodystrophy*) (OMIM 161200), nail dysplasia is accompanied by skeletal, renal, and ocular abnormalities. In typical cases, nails fail to grow, or grow shorter and rarely develop to the nail tip. A characteristic feature is the presence of a triangular lunula. Nail abnormalities may be an early sign suggesting this diagnosis.[4,10] The first finger of the hand is almost always affected, and the severity decreases from the index finger to the little finger.[14] The toenails are rarely involved. Nails may be abnormal from birth. In 98% of patients, nails may be absent, hypoplastic, brittle, spoon-shaped, longitudinally ridged, or split.[4,10]

The patella is tiny than average as well as inadequate, resulting in knee fragility. One-third of patients suffer from chronic glomerulonephritis, which includes proteinuria and fibrillar collagen deposition. Radiological examination reveals the existence of a posterior iliac horn, as well as Lester iris (irregular hyperpigmentation at the pupil's edge.[4,10,12] The gene that causes this condition is found on the long arm of chromosome 9 (9q34.1).[4,13]

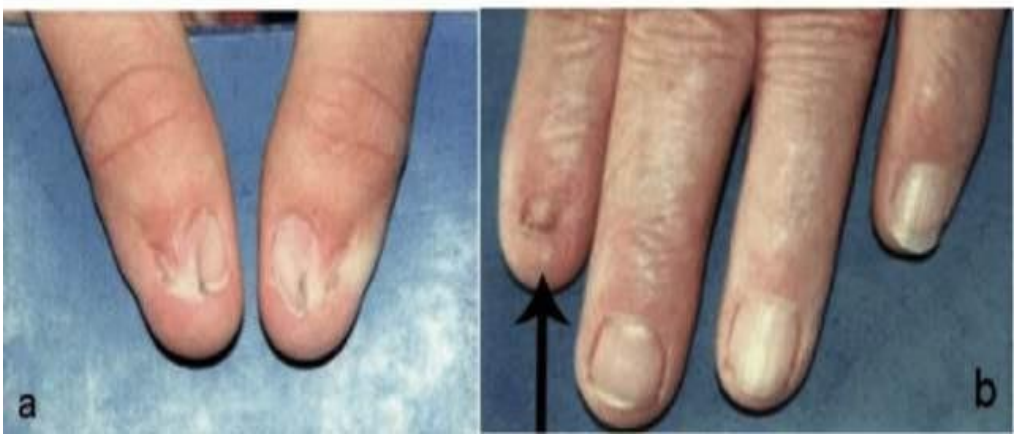

Figure5. Typical presentation of thumb nails (a) and finger nails (b) in nail-patella syndrome.

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Conclusion

Nail abnormalities should not be overlooked in determining the diagnosis of a disease. Almost all genodermatoses have nail abnormalities, and knowledge of nail anatomy and embryology can help clinicians estimate where the nail defect occurred. In some cases, nail abnormalities are not the primary reason patients seek consultation but are rather incidental findings. Therefore, examination of the nails of the hands and feet should be included as part of the dermatological clinical examination.

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