Pachyonychia congenita

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Summary
Pachyonychia congenita (PC) is a rare genodermatosis affecting the nails and other ectodermal tissues. It is mainly characterized by gross thickening of all finger and toe nails. Different additional clinical features are observed; they fit into two major types: the Jadassohn-Lewandowsky and the Jackson-Lawler syndrome. The condition is usually transmitted as an autosomal dominant trait, though recessive forms have been described. A purely clinical classification does not correlate satisfactorily with the observed phenotypic expression in most reported cases. Actually it has been recognized that molecular genetic analysis helps the clinical distinction in subtypes. PC type I is due to mutations in the KRT16 gene encoding keratins K6a and K16, type II is caused by mutations in the KRT17 gene encoding keratin 17. The only effective treatment for nail lesions is surgery with radical excision of the nail, nail bed, and nail matrix and skin implantation at the site of the removed nail. The most recent literature refers to descriptions of about 250 cases up until 1993.

Keywords: onychodystrophy, hyperkeratosis, steatocystoma multiplex

Name of the disease and synonyms

- Pachyonychia congenita (PC)
- Congenital dyskeratosis
- Pachyonychia ichthyosiformis

Definition

PC is a rare hereditary disorder characterized by gross thickening of all finger and toe nails [1]. This condition is usually transmitted as an autosomal dominant trait, but recessive forms have also been described [2]. Mutations in the genes encoding keratins K6a, K16 and K17 cause fragility of mucosal epithelia, follicular keratinocytes, palmo-plantar epidermis or pilosebaceous units for the formation of abnormal tonofilaments, resulting in different phenotypes of PC [3-5].

Diagnostic criteria

The most striking features for the diagnosis of PC are symmetrically thickened dysmorphic nails and hyperkeratotic skin lesions.

Differential diagnosis

PC should be differentiated from traumatic thickening of nails and from congenital onychogryphosis that, however, are easy to recognize because they do not involve all nails and are not associated with dyskeratotic skin lesions. PC should be also distinguished from the curly hair-acral keratoderma-caries

syndrome, recently described and characterized by premature loss of curly, brittle hair, premature loss of teeth due to caries, nail dystrophy and acral keratoderma [6].

Prevalence

The most recent literature refers to descriptions of about 250 PC cases up until 1993 [2]. Fifteen cases with onset in the second-third decade, known as PC tarda ones, have been reported [7].

Clinical manifestations

In addition to onychodystrophy of all finger and toe nails, dyskeratosis of skin and mucous membranes can be associated, as well as palmar and plantar hyperhydrosis, natal or neonatal teeth and hair anomalies.

Nail dystrophy usually appears in the first or second year of life, followed by thickening of circumscribed areas of the palms and soles [8]. Cases with onset in the second or third decade have been described as PC tarda [9].

Among concomitant diseases, the most common is steatocystoma multiplex but cataracts, laryngeal lesions, hoarseness and mental retardation often coexist. The association of these peculiar clinical symptoms with nail hypertrophy identifies different types of this disorder. However, PC affecting the nails only is also described [10].

According to the classification of Feinstein *et al.*[1], four types of PC have been delineated even though two types are mostly reported (Table 1).

Table 1. Classification of pachyonychia congenita proposed by Feinstein *et al.*[1]

Type	Basic clinical findings	Additional clinical findings	P
I Jadasson-Lewandowsky syndrome	Nail hypertrophy and dystrophy, palmoplantar keratosis, follicular keratosis, oral leukokeratosis		56.2%
II Jackson-Lawler syndrome	Clinical findings of type I (oral lesions or significant keratoderma are rare)	Bullae of palms and soles, hyperhidrosis of palms and sols, natal or neonatal teeth, steatocystoma multiplex	24.9%
III	Clinical findings of type II	Angular cheilosis, corneal dyskeratosis, cataracts	11.7%
IV (rarely described)	Consists of signs and symptoms of signs and symptoms of types I, II, III	Laryngeal lesions, hoarseness, mental retardation, hair anomalies, alopecia	7.2%

P: relative prevalence

Congenital teeth are usually not normal in structure and fall out within 1 year while neonatal teeth, that appear a short time after birth, are normal in structure and fall out at about 5 years of age.

Laryngeal involvement can represent a life-threatening complication. Actually, airway obstruction, due to leukokeratosis, can lead to severe respiratory distress [11].

In addition to the Feinstein's classification, several subdivisions of PC have been previously suggested [1, 12, 13].

Useful diagnostic criteria have been recently established for types I and II relying on both phenotype and genotype data:

- mutations in the *KRT16* gene encoding keratins K6a and K16 trigger the PC type I phenotype, whereas *KRT17* mutations cause type II;
- the presence of pilosebaceous cysts following puberty is the best indicator of PC type II;
- PC in prepubescent patients is more difficult to classify due to the lack of cysts;
- natal teeth are indicative of PC type II, although their absence does not preclude the PC type II phenotype [14].

New types of PC have been sporadically reported in the literature: symptoms consisting of thickening of all nails in association with severe generalized hypotrichosis in absence of keratins mutations have been discovered in two patients [15].

Nail dystrophy of PC is histologically characterized by changes in the nail bed [16]. A longitudinal lesion, filled with granular tissue, is

evident in the keratinized substance located between the nail and the nail bed [17].

Diagnostic methods

The rapid unraveling of molecular defects in this disabling inherited disease makes it possible a more precise and earlier prenatal diagnosis in the future, creates new options for suitable therapeutic regimens, and even offers the hope of curing such type of skin disease by means of somatic cell gene therapy [24].

Etiology

The pattern of pachyonychia correlates well with the keratin gene mutation. Actually, mutations in the *KRT16* gene encoding keratins K6a and K16 produce the PC type I phenotype, whereas mutations in the *KRT17* gene cause type II. Keratins K6 and K16 are expressed in mucosal epithelia, follicular keratinocytes and palmo-plantar epidermis [18]. By contrast, K17 is constitutively expressed in the pilosebaceous unit and basal appendage keratinocytes, with some basal expression in palmoplantar skin [19].

Management-treatment

Emollients and keratolytics as well as topical retinoids are usually prescribed for palmo-plantar hyperkeratosis [20]. Oral retinoic acid has been also demonstrated to improve the hyperkeratotic skin lesions [21]. Concerning treatment, 2% glutaraldehyde solution has been demonstrated to determine marked improvement of the hyperkeratotic plantar lesions. Topical glutaraldehyde has in fact been used over the years for plantar hyperhidrosis for its antiperspirant effect as well as for hyperkeratotic diseases [22,23].

The only effective treatment for nail lesions is surgery with radical excision of the nail, nail bed, and nail matrix and skin implantation at the site of the removed nail.

Surgical treatment is also important in case of oral lesions with hoarseness or respiratory problems. Airway obstruction, due to leukokeratosis, can in fact lead to severe respiratory distress.

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