



Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

Original Investigation

Pachyonychia Congenita in Pediatric Patients

Natural History, Features, and Impact

Sonal Shah, MD; Monica Boen, MD; Brandi Kenner-Bell, MD; Mary Schwartz, PhD; Alfred Rademaker, PhD; Amy S. Paller, MD

IMPORTANCE Nail dystrophy in early childhood often suggests a diagnosis of pachyonychia congenita (PC). No previous investigation has focused on the early signs of PC and the natural course of the disease.

OBJECTIVES To determine the course of pediatric PC, correlate the disease course with the clinical appearance and specific gene mutations, and assess the effect of pediatric PC on quality of life.

DESIGN, SETTING, AND PARTICIPANTS One hundred one patients or families with genetically confirmed PC from the International Pachyonychia Congenita Research Registry who completed a survey on the general clinical features of PC and an auxiliary questionnaire on the clinical presentation and quality-of-life issues related to pediatric PC.


EXPOSURE Individuals with pachyonychia congenita.

MAIN OUTCOMES AND MEASURES Completion of both surveys.

RESULTS At birth, toenail changes were present in 47.5% of patients; fingernail changes in 40.6%; and plantar keratoderma in 6.9%. By 5 years of age, these 3 key manifestations were found in 81.2%, 74.2%, and 75.3%, respectively, of individuals with genotype-confirmed PC. The correct diagnosis was made during the first year of life in 26.7% of patients despite the presence of toenail dystrophy in more than 65.3%. Clinical differences that distinguished PC subtypes included (1) later onset and less frequent occurrence of nail dystrophy and keratoderma in PC-K6b, PC-K6c, and PC-K16; (2) concurrent fingernail and toenail thickening in PC-K6a and PC-K17; (3) more palmar keratoderma in PC-K16; (4) cysts primarily in PC-K17 and follicular hyperkeratoses primarily in PC-K6a; (5) hoarseness and/or oral leukokeratoses in the first year of life most often in PC-K6a; and (6) natal teeth exclusively in PC-K17. Among pediatric patients, PC affected the social interactions and function of adolescents most profoundly.

CONCLUSIONS AND RELEVANCE Among patients with a detectable mutation, PC manifests with nail thickening and plantar keratoderma before school age in more than three-quarters of affected children, allowing early diagnosis. The highly visible nail changes and painful plantar thickening exert a psychosocial effect on most affected adolescents. Phenotype-genotype correlations in children with PC validate the new classification based on the affected gene.

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Author Affiliations: Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah, Boen, Kenner-Bell, Paller); Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Kenner-Bell, Paller); Pachyonychia Congenita Project, Salt Lake City, Utah (Schwartz); Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Rademaker).

Corresponding Author: Amy S. Paller, MD, Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 N St Clair, Ste 1600, Chicago, IL 60611 (apaller@northwestern.edu).

Pachyonychia congenita (PC) constitutes a group of almost exclusively autosomal dominant disorders of paired keratins of the nails and skin. Since PC was initially reported in 1906 by Jadassohn and Lewandowsky,¹ more than 500 cases have been registered or otherwise described. Pachyonychia congenita manifests as nail dystrophy, painful focal palmoplantar keratoderma, follicular keratoses, mucosal leukokeratoses, hoarse voice, cystic lesions, and, rarely, natal teeth.^{2,3}

Underlying keratin gene mutations have been described in the 5 keratin genes, *KRT6A* (OMIM 148041), *KRT6B* (OMIM 148042), *KRT6C* (OMIM 612315), *KRT16* (OMIM 148067), and *KRT17* (OMIM 148069), which alter keratins 6a, 6b, 6c, 16, and 17, respectively.⁴⁻⁹ These genes are expressed in the nail bed, palmoplantar epidermis, and mucosa. Keratins play a key role in epidermal cell integrity and mechanical strength. Mutations in these 5 keratin genes cause epidermolysis and compensatory hyperkeratosis at these sites. Historically, 2 major subtypes were based on clinical characteristics. The Jadassohn-Lewandowsky PC type 1 (PC-1) often showed associated oral leukokeratoses,¹ and the Jackson-Lawler PC type 2 (PC-2) often showed cysts and occasionally natal teeth.^{3,10} Pachyonychia congenita type 1 was originally linked to mutations in the type II keratin gene *KRT6A* and its type I expression partner *KRT16* and PC-2 with mutations in *KRT6B* and *KRT17*.^{3,4,6,8,11}

Pachyonychia congenita has been genotyped at no cost in individuals who enroll in an international registry, enabling comprehensive genotype-phenotype analysis.¹²⁻¹⁶ Phenotypic overlap among PC genotypes has now made obsolete the designations of PC-1 and PC-2. Instead, a new classification based on mutations in the keratin-encoding genes *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17* divides PC into subtypes PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17, respectively.¹⁶

Features of PC usually manifest during the first 3 years of life,¹² allowing the diagnosis to be considered. However, little attention has been paid to the disease course, early diagnostic features, and effect on quality of life of PC in children. To facilitate early diagnosis and increase our understanding about the impact of PC in children, affected families and patients were polled about pediatric-specific issues.

Methods

Two questionnaires were administered to families participating in the International Pachyonychia Congenita Research Registry (IPCRR) through the Pachyonychia Congenita Project (www.pachyonychia.org). The study and questionnaires were approved by Western Institutional Review Board (WIRB Study number 1057496; protocol number 20040468). The first questionnaire asked general questions about PC features, their effect on daily life, and interventions after registry enrollment¹² (Supplement [eAppendix]). The diagnosis of PC was confirmed by dermatologists from the Pachyonychia Congenita Project medical and scientific advisory board through assessing family-provided questionnaire data, photographs of skin and nail changes, and a 1-hour patient/family telephone consultation.

An auxiliary 48-question survey (approved by the IRB at Ann and Robert H. Lurie Children's Hospital of Chicago) was sent by the Pachyonychia Congenita Project to 254 registry families with genotype-confirmed PC (Supplement [Appendix]) and addressed pediatric-specific issues, early signs, and the natural history of PC. Parents completed the survey for preteenaged patients with input from children as appropriate; patients of all ages were encouraged to consult with their parents to answer questions related to the disorder early in life. Informed consent was obtained from all participants. The results of both questionnaires were sent to the Pachyonychia Congenita Project, which sorted data by keratin mutation and provided de-identified data for compilation and statistical analysis at Northwestern University. We performed Fisher exact testing to determine statistical significance (defined as $P < .05$) in comparing clinical features with underlying keratin gene mutations. All statistical analyses were performed with commercially available software (SPSS, version 15.0 [SPSS Inc], and Stata, version 10.0 [StataCorp]). Because PC-K6c was first termed PC after the auxiliary questionnaire was introduced (2012), only data from the first questionnaire were available from patients with this subtype. Given its mild clinical features, PC-K6c was excluded in statistical analyses to distinguish among PC subtypes. Data from individuals with mutations in the *GJB6* gene (OMIM 604418), also known as connexin 30, were derived from the original questionnaire.

Results

Of 254 patients enrolled in the IPCRR who completed the original questionnaire and had genetically confirmed PC, 101 responded to the addendum questionnaire (response rate, 39.8%). The demographic features of these 101 PC patients and the 8 PC-K6c patients who responded to the original questionnaire are described in **Table 1**. Of the returned questionnaires, 78.0% were completed by adult patients who were able to report the onset of features and impact of PC throughout the first 18 years of life, whereas 22.0% of the returned questionnaires reflected the experience to date of affected individuals currently in their first 2 decades of life. Among the respondents, 42.2% had mutations in *KRT6A* (PC-K6a), and an additional 28.4% had mutations in *KRT16* (PC-K16). Almost 60% in the registry had a family history of PC, reflecting the high rate of spontaneous mutation in keratin genes. The diagnosis of PC by a physician was made before 1 year of age in 27 patients (26.7%, of whom 12 [44.4%] had a known family history) despite the presence of toenail and fingernail dystrophy in approximately 60% of the affected infants (see below). By 5 years of age, the correct diagnosis was made in 43 patients (42.6%, of whom 18 [41.9%] had a known family history) despite toenail dystrophy in 81% (82 of 101), fingernail dystrophy in 74% (75 of 101), and plantar keratoderma in 75% (76 of 101).

Toenail Dystrophy

The earliest and most common clinical characteristic of PC was toenail dystrophy (**Figure 1A**), noted to involve at least 2 digits in 98.2% of patients by the time of reporting; the only ex-

Table 1. Demographics of Registry Patients and Distinguishing Clinical Features Among PC Subtypes^a

Feature	All (N = 109 [100.0%]) ^b	PC Subtype					P Value ^c
		PC-K6a (n = 46 [42.2%])	PC-K6b (n = 10 [9.2%])	PC-K6c (n = 8 [7.3%])	PC-K16 (n = 31 [28.4%])	PC-K17 (n = 14 [12.8%])	
Demographic							
Current age, y							
Mean (SD)	36.0 (19.9)	32.4	36.1	37.6	43.6	30.1	>.05
Median (range)	35.5 (0-81)	33	41	44	43	27	
Age group, y							
		(0-63 y)	(9-54 y)	(6-72 y)	(1-81 y)	(3-68 y)	
0-5	9 (8.3)	5 (10.9)	0	0	1 (3.2)	3 (21.4)	
6-10	8 (7.3)	4 (8.7)	1 (10.0)	2 (25.0)	0	1 (7.1)	
11-17	7 (6.4)	2 (4.3)	1 (10.0)	0	3 (9.7)	1 (7.1)	
≥18	85 (78.0)	35 (76.1)	8 (80.0)	6 (75.0)	27 (87.1)	9 (64.3)	
Sex							
Female	61 (56.0)	26 (56.5)	2 (20.0)	5 (62.5)	17 (54.8)	11 (78.6)	>.05
Male	48 (44.0)	20 (43.5)	8 (80.0)	3 (37.5)	14 (45.2)	3 (21.4)	
Family history positive for PC	65 (59.6)	21 (45.7)	8 (80.0)	8 (100.0)	20 (64.5)	8 (57.1)	>.05
Keratin gene mutation		<i>KRT6A</i>	<i>KRT6B</i>	<i>KRT6C</i>	<i>KRT16</i>	<i>KRT17</i>	>.05
Clinical							
Dystrophy							
Toenail	107 (98.2)	46 (100.0)	10 (100.0)	6 (75.0)	31 (100.0)	14 (100.0)	>.05
Fingernail	84 (77.1)	46 (100.0)	4 (40.0)	0	21 (67.7)	13 (92.9)	<.001
Keratoderma							
Plantar	107 (98.2)	45 (97.8)	10 (100.0)	8 (100.0)	31 (100.0)	13 (92.9)	>.05
Palmar	47 (43.1)	17 (37.0)	4 (40.0)	0	21 (67.7)	5 (35.7)	<.05
Pain ^d							
Plantar	100 (91.7)	43 (93.5)	10 (100.0)	8 (100.0)	30 (96.8)	9 (64.3)	<.05
Palmar	23 (21.1)	11 (23.9)	1 (10.0)	0	9 (29.0)	2 (14.3)	<.05
Oral leukokeratosis	81 (74.3)	45 (97.8)	4 (40.0)	0	17 (54.8)	5 (35.7)	<.001
Cyst	71 (65.1)	41 (89.1)	7 (70.0)	1 (12.5)	9 (29.0)	13 (92.9)	<.001
Follicular hyperkeratosis	54 (49.5)	37 (80.4)	6 (60.0)	0	4 (12.9)	7 (50.0)	<.001
Natal teeth	14 (12.8)	2 (4.3)	0	0	0	12 (85.7)	<.001
Hoarseness	17 (15.6)	14 (30.4)	0	0	1 (3.2)	2 (14.3)	<.05

Abbreviation: PC, pachyonychia congenita.

^a Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

^b Includes the 101 patients who responded to both questionnaires and the 8 PC-K6c patients who responded to the original questionnaire only.

^c Statistical analysis compares subtypes PC-K6a, PC-K6b, PC-K16, and PC-K17. *P* < .05 indicates statistical significance.

^d Indicates percentages with pain among patients with plantar or palmar keratoderma.

ception was absence of toenail dystrophy in 2 of the 8 PC-K6c patients (25.0%) (Table 1). Of the patients with toenail involvement, all 10 toenails were affected in 74.3%, 98.0% had involvement of toenails of the fifth digit, and 98.0% had changes of the hallucal nails by the time of reporting. Toenail abnormalities were present at birth in 39.0% of respondents overall, although they appeared most often in neonates with PC-K6a and PC-K17 (*P* < .001) (Supplement [eFigure, A]). By 1 and 5 years of age, nail dystrophy was noted in 65.3% and 80.2% of all respondents, respectively. By 5 years of age, all 46 children with PC-K6a, the most common subset, showed toenail changes. In contrast, toenail changes did not appear in children with PC-K6b until at least 1 year of age and progressively increased in occurrence thereafter. In 99.0% of patients with toenail dystrophy, more than 1 nail became dystrophic concurrently, and 70.3% had all 10 nails become dystrophic at the

same time; patients with PC-K6a were more likely to have all 10 toenails affected at onset than were patients with PC-K16 or PC-K6b (*P* < .001). The hallucal nail was the most common of the toenails to first become affected (89.1% of PC patients with toenail dystrophy). The most common initial toenail change was thickening (77.2% of all patients), and 65.3% also showed toenail discoloration at onset. Toenail thickening progressed throughout the first decade of life in most of the patients. The nail dystrophy occurred before 6 years of age in 5 of the 6 PC-K6c patients with this feature (83.3%), but the dystrophy was mild, affecting only 1 toenail bilaterally (usually the fifth toenail) or, in 1 case, multiple toenails unilaterally. The 2 PC-K6c patients without nail involvement were adults.

Fingernail changes occurred overall in 76.1% of patients and, as with toenail changes, were most severe in PC-K6a. Overall, 40.6% of patients had fingernail changes at birth. Finger-

Figure 1. Representative Images of Clinical Features of Pachyonychia Congenita and Genotype in Affected Children



A. Subungual hyperkeratosis and V-shaped thickening of the toenails in a toddler with a *KRT17* M88K mutation. B. Discolored and thickened distal aspect of all fingernails owing to a *KRT16* R127P mutation. C. Severe plantar keratoderma in a child with a *KRT16* S130del mutation. D. Mild plantar keratoderma in a child with a *KRT6C* E472K mutation. E. Oral leukokeratosis of the tongue in an infant with a *KRT6A* L468P mutation. Leukokeratosis was misdiagnosed initially as a candidal infection. F. Oral leukokeratosis of the tongue in an adolescent with a *KRT6A* N172del mutation. G. Follicular keratoses on the knee owing to a *KRT6A* N172del mutation.

nail involvement occurred in most of the neonates with PC-K6a and PC-K17 but infrequently in neonates with PC-K16 and never in neonates with PC-K6b ($P < .001$) (Supplement [eFigure, B]). Fingernail changes never developed in 5 patients with PC-K6b (50.0%), 11 patients with PC-K16 (35.5%), 1 patient with PC-K17 (7.1%), and the 8 patients with PC-K6c (100.0%). By 5 years of age, all children with PC-K6a and 13 children with PC-K17 (92.9%) showed fingernail dystrophy, in addition to toenail dystrophy. Fingernail dystrophy developed simultaneously in all 10 nails in 68.7% of PC patients; only 6.0% reported involvement in only 1 nail, with no consistency as to the involved digit. The initial change in fingernails was nail thickening in 65 of the 86 patients with nail changes (75.6%), usually in combination with changes in color (41 [63.1%]). All

patients with fingernail dystrophy, regardless of PC subtype, had toenail involvement. However, patients with PC-K6a and PC-K17 were more likely to develop dystrophy of their fingernails and toenails concurrently, whereas patients with PC-K6b and PC-K16 were more likely than other subtypes to develop toenail dystrophy first ($P < .001$).

The toenails and fingernail dystrophy varied in appearance from thickened, shortened, friable nails to nails with marked subungual thickening and a typical pinched, V-shaped curvature (Figure 1A and B). We found no correlation between the appearance of the nails and the PC subtype.

Periungual infections occurred in 76.6% of PC patients overall but more often in those with PC-K6a (43 of 46 [93.5%]) than those with other subtypes ($P < .05$). Most patients with

nail infections (52 of 73 [71.2%]) never sought treatment by a physician. Most of these patients treated nails by soaking them (38 of 61 [62.3%]), lancing purulent areas or trimming the nails (35 of 61 [57.4%]), or using topical medication (28 of 61 [45.9%]). Nail infection or its clearance did not lead to a change in appearance of the dystrophic nail.

Painful Plantar Keratoderma

The feature of PC that has the most profound effect on quality of life is painful plantar keratoderma (Figure 1C and D).¹² Although present at birth in fewer than 10% of individuals with PC, 24.8% of PC patients overall noted plantar keratoderma by 1 year of age, 75.3% by 5 years of age, and 89.1% within the first decade of life (Supplement [eFigure, C]). Of the 27 patients diagnosed with PC before 1 year of age, 12 (44.4%) had plantar keratoderma by the time of diagnosis. In patients with PC-K6a, PC-K16, and PC-K17, the onset of plantar keratoderma usually occurred before age 5 years, whereas in patients with PC-K6b and PC-K6c, onset was usually after age 5 years. The most common initial locations of the plantar keratoderma were at pressure points on the heel (66 of 98 [67.3%]) and ball (63 of 98 [64.3%]) of the foot. During the first decade of life, 70 of the 73 patients with keratoderma (95.9%) had plantar pain, which compromised their function; pain occurred later in children with PC-K6b than the other subtypes ($P < .05$). Most patients with plantar keratoderma also had local skin infections (47 of 99 [47.5%]).

Palmar keratoderma occurred in only 45.5% of patients overall by the time of the response to the questionnaire. Of those who developed palmar keratoderma, 24 of 47 (51.1%) saw changes by 5 years of age, and 32 of 47 (68.1%) by 10 years (Supplement [eFigure, D]). Palmar keratoderma was more often reported in PC-K16 than in any other subtype (67.7%; $P < .05$) and was often complicated by painful erosions, bullae, or fissures of the palms, usually before 5 years of age.

Other Clinical Manifestations

Although PC-K6b and PC-K6c were often distinguishable from other forms because of their more limited manifestations, features other than nail dystrophy and keratoderma were helpful in differentiating among the PC-K6a, PC-16, and PC-17 subtypes in children. In particular, oral leukoplakia, cysts, and keratoses varied by PC subtype.

Oral Leukokeratoses

The oral leukokeratoses occurred in 70.3% of PC patients and were more strongly associated with PC-K6a than with any other subtype ($P < .001$). Of those affected, the median age at onset was 3 weeks, and 26 of 71 (36.6%) experienced a first occurrence during the first year of life. Oral leukokeratoses were often mistaken for thrush (Figure 1E) but failed to respond to anticandidal therapy. Oral leukokeratoses were most commonly noted on the tongue (Figure 1E and F) (68 of 71 [95.8%]). Hoarseness was noted in 12.9% of patients overall, and PC-K6a patients were more likely to develop hoarseness than PC-K6b and PC-K16 patients ($P < .05$) but not PC-K17 patients. The onset of hoarseness was variable but always present before 3 years of age in the affected patients. Of the PC patients who

developed hoarseness, 16 (93.3%) concurrently showed oral leukokeratoses. Natal teeth virtually clinched the diagnosis of PC-K17 (86.0% [$P < .001$]) but were noted in 2 of 46 infants (4.3%) of infants with PC-K6a. The teeth were described as soft or crumbly and were rapidly lost or were described as normal in appearance and persistent until the deciduous teeth erupted.

Cysts

Cysts were noted overall in 69.3% of patients with PC. Most patients who developed cysts had PC-K6a, PC-K6b, or PC-K17, without a statistically significant difference in the risk for developing cysts among these subgroups. Patients with the PC-K16 subtype were the least likely to develop cysts ($P < .05$), and cysts did not develop in PC-K6c patients. The onset of cysts occurred most often from 6 to 10 (31.6%) and 11 to 20 (36.8%) years of age. Patients primarily treated their cysts by lancing them (37 of 54 [68.5%]) or applying topical antibiotic ointment (26 of 54 [48.1%]).

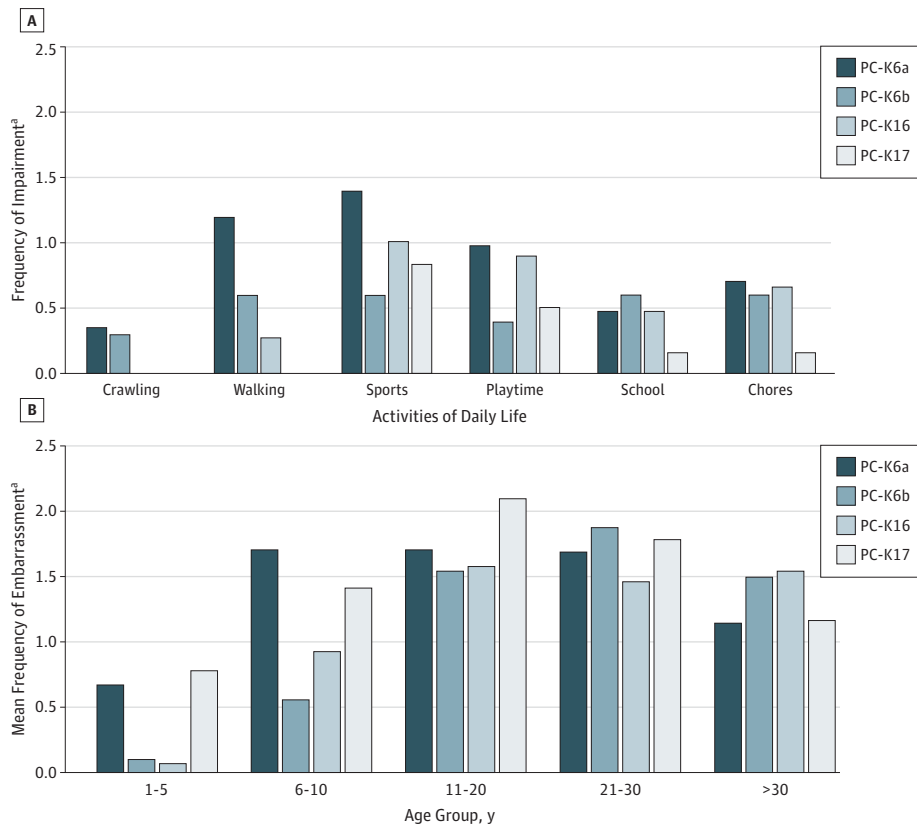
Follicular Hyperkeratoses and Hyperhidrosis

Follicular hyperkeratoses were described in more than half of the PC patients, although only in 26 (25.7%) by preschool age (Figure 1G). They occurred most often in PC-K6a (80.4%) and PC-K6b (42.9%) and least commonly in PC-K16 (12.9%; $P < .001$ compared with PC-K6a). In patients with PC-K6a, 14 of 37 (37.8%) developed cysts at 1 to 5 years of age and 23 of 37 (62.1%) showed follicular hyperkeratoses by the second decade of life (Supplement [eFigure, E]). Only 1 PC-K16 patient developed follicular hyperkeratoses during childhood, and 27 of 31 patients with PC-K16 (87.1%) never developed follicular hyperkeratoses by the time of reporting. Hyperhidrosis was described in 51.5% of respondents of all ages, but in only 5 of 22 children (22.7%). Alopecia was not an issue in children with PC in the first decade of life, and its association with PC is questionable. In the original survey of 254 PC patients, 15 patients ranging in age from 15 to 81 years had hair loss. Of these patients, 10 were male and most had no other hair abnormality, raising the question of androgenic alopecia as the cause. All but 1 of these individuals had PC-K6a or PC-K16.

Effect on Quality of Life in Adolescents

Plantar keratoderma in PC was characteristically painful by the second decade of life and led to the greatest effect on quality of life. More than 50% of children found that the plantar keratoderma affected walking and playtime; however, less than half of patients also found impediment with crawling, schoolwork, and chores (Figure 2A). The effect on function more often began after 5 years of age, peaked during adolescence, and occurred most often with PC-K6a. Pachyonychia congenita affected the social life of virtually all patients of school age or older. Most experienced limitations related to wearing clothes and playing sports (Figure 2A), experienced teasing, and were embarrassed by their nails, especially during adolescence (Figure 2B and Table 2). Of the 84 PC patients with fingernail involvement, 66 (78.6%) concealed their nails, especially by keeping the fingers curled (50 [59.5%]) or crossing the arms (46 [54.8%]). Other techniques included keeping hands in the pocket

Figure 2. Functional Impairment and Extent of Embarrassment by Pachyonychia Congenita (PC) Subtype



A, Effects of plantar or palmar keratoderma on activities of daily life. B, Age at embarrassment about the appearance of nails. Given its mild clinical features, the PC-K6c subtype was excluded from the analysis. ^aPatients or families graded frequency on a 4-point scale, where 0 indicates never; 1, little effect; 2, moderate effect; and 3, always/worst burden.

Table 2. Effects of PC on Social Life of School-aged Children

Effect	All, No. (%) (n = 92)	PC Subtype, No. (%) Reporting an Adverse Effect on Social Life ^a				P Value ^b
		PC-K6a (n = 41)	PC-K6b (n = 10)	PC-K16 (n = 30)	PC-K17 (n = 14)	
Teasing	69 (75.0)	37 (90.2)	4 (40.0)	20 (66.7)	8 (72.7)	<.01
Difficulty wearing certain clothes/accessories	79 (85.9)	36 (87.8)	5 (50.0)	29 (96.7)	9 (81.8)	<.01
Difficulty participating in recreational activities	63 (68.5)	36 (87.8)	6 (60.0)	26 (86.7)	8 (72.7)	.13
Dating problems	40 (43.5)	22 (52.6)	3 (33.3)	12 (40.0)	5 (45.5)	.68

Abbreviation: PC, pachyonychia congenita.

^a None of the patients with PC-K6c reported an adverse effect on their social life.

^b Statistical analysis compares subtypes. *P* < .05 indicates statistical significance.

ets (31 [36.9%]), using nail polish (25 [29.8%]), using artificial nails (9 [10.7%]) and wearing gloves (7 [8.3%]).

PC-Like Early Nail Dystrophy and Connexin 30 Mutations

Only patients with gene-confirmed PC subsets completed the pediatric-specific questionnaire. However, among patients in the original registry questionnaire, 7 with nail dystrophy and clinically presumed PC had mutations in the connexin 30 gene (*GJB6*) (Table 3). Of these, 5 (71.4%) had abnormalities of the toenails and fingernails at birth, with the other 2 developing dystrophy of the fingernails and toenails concurrently at 2 and 4 years of age. Two additional features found commonly with

connexin 30 mutations, but not PC, were hearing loss and alopecic patches or sparseness, with hair that was described as thin and sometimes brittle.

Discussion

Pachyonychia congenita constitutes a group of primarily autosomal dominant inherited disorders caused by mutations in paired keratins. Genotyping has been provided since 2004 as a service for families enrolled in the IPCRR and has yielded a wealth of information about PC characteristics and genotype-

Table 3. Demographics and PC-Like Clinical Characteristics of 7 Participants With Mutations in the Connexin 30 Gene^a

Feature	Data
Demographic	
Current age, y	
Mean (SD)	48.3 (30.5)
Median (range)	37 (6-92)
Age group, y	
0-5	0
6-10	1 (14.3)
11-17	0
≥18	6 (85.7)
Sex	
Female	3 (42.9)
Male	4 (57.1)
Family history positive for PC	7 (100.0)
Clinical	
Dystrophy	
Toenail	7 (100.0)
Fingernail	7 (100.0)
Keratoderma	
Plantar	3 (42.9)
Palmar	3 (42.9)
Pain	
Plantar	2 (28.6)
Palmar	2 (28.6)
Hearing loss	3 (42.9)
Abnormal hair	4 (57.1)
Oral leukokeratoses	1 (14.3)
Cysts	1 (14.3)
Hyperhidrosis	2 (28.6)
Hypohidrosis	2 (28.6)
Learning disabilities	1 (14.3)

Abbreviation: PC, pachyonychia congenita.

^a Unless otherwise indicated, data are expressed as number (percentage) of patients.

phenotype correlations. By pooling data collected through the IPCRR questionnaire and an auxiliary questionnaire, we were able to address the early features of PC in an effort to aid early diagnosis and bring attention to the profound effect this genodermatosis has on the quality of life of affected children and adolescents.

Our data confirm the frequent misdiagnosis of PC in pediatric patients, showing that most children manifest the key features in the first year of life, but the diagnosis is made in only about 25%. This delay in diagnosis may lead to inappropriate management (eg, topical or oral antifungals for presumed fungal infection, potent topical corticosteroids for presumed psoriasis) or incorrect information about prognosis and inheritance (eg, mistaking hidrotic ectodermal dysplasia with connexin 30 mutations for PC). The unifying feature of PC is nail dystrophy,¹⁷ although the clinical appearance of nails can be variable, even within families, and does not always show the classic V-shaped thickening. During the first year of life, dystrophy of the fingernails and toenails occurs in most of the

affected infants, providing an initial clue. By 5 years of age, plantar keratoderma is seen in 75.3% of children in addition to the nail dystrophy and is often painful. Thus, the diagnosis of PC should easily be suspected before kindergarten. Although genotyping should be performed through the registry to subclassify the disease, the combination of data about age at onset, concurrent dystrophy of fingernails and toenails, palmar keratoderma, and the presence of oral leukokeratosis and/or hoarseness, cysts, follicular keratoses, and natal teeth helps the practitioner to suspect a specific PC subtype and counsel families, even before genotyping is completed. For example, the presence of nail dystrophy at birth, especially involving all nails, predicts PC-K6a or PC-K17 ($P < .001$); the concomitant development of oral leukokeratosis and often hoarseness during the first year of life suggest the diagnosis of PC-K6a ($P < .001$); and the concurrence of natal teeth indicates PC-K17 ($P < .001$). In contrast, the development during childhood of palmar keratoderma, especially with later onset of other features, may signal PC-K16. The presence of an isolated dystrophic fingernail or toenail is quite uncommon in PC (77 patients with fingernail involvement overall and 6 [5.5%] with only 1 fingernail involved; 106 with toenail involvement and 1 with only 1 toenail involved [0.9%]); the exception is PC-K6c, in which localized nail involvement is common.^{18,19}

These features, although helping to differentiate among the PC subtypes, also allow us to reject the old classifications of PC-1 and PC-2 in pediatric PC. For example, cysts and natal teeth are most common in PC-K17 (formerly classified as PC-2) but were both described in individuals with PC-K6a (formerly PC-1) in our pediatric cohort and other published series.^{12,13} Hair disorders, at one time attributed to PC-2 *KRT6B* and *KRT17* mutations, do not seem to be associated with autosomal dominant PC more often than in the general population. Alopecia has recently been described in association with severe PC manifestations in a patient with homozygous dominant missense mutations (from each affected parent) in keratin 17.²⁰ These data support restructuring of the classification of PC from 2 different subtypes to a system that categorizes the disease based on specific keratin mutations.^{12,16,21}

As a keratinopathy, PC is associated with increased cellular fragility and compensatory epidermal thickening at the sites of gene expression (particularly plantar keratoderma and nail dystrophy). The greater dystrophy of toenails vs fingernails and of the hallucal and fifth toenails likely reflect the propensity toward more pathological features with trauma. Natal teeth, which occurred in 13.9% of patients with PC overall and 86% of patients with PC-K17, have similarly been described in epidermolysis bullosa simplex, which results from mutations in keratins 5 or 14.²² The role of keratin abnormalities in tooth formation is poorly understood.

The genetic disorder that is most commonly confused with PC is hidrotic ectodermal dysplasia (Clouston syndrome), which results from mutations in connexin 30. Five of the 7 individuals from 2 families with Clouston syndrome who were enrolled in the PC registry for genotyping also showed multiple toenails and fingernails affected at birth, and several individuals developed painful plantar kerato-

derma. However, the presence in hidrotic ectodermal dysplasia of hearing loss (a common feature of connexin gene defects) and thin, sparse hair during childhood is not typical of PC. Another genetic disorder with which PC could be confused results from mutation of *FZD6*. The *FZD6* gene encodes frizzled 6, a Wnt-signaling pathway receptor that is localized to the nail matrix; autosomal recessive mutations in *FZD6* lead to hypertrophic nail dystrophy from birth without plantar or palmar keratoderma.^{23,24}

Our study emphasizes the negative effect of the nail and skin changes of PC in preteenaged and adolescent patients. Most patients reported embarrassment, teasing, an effect on dating, and limitations in participation in physical activities with classmates. Early diagnosis and discussion allow proactive management of psychosocial issues, including how a child can comfortably inform peers about the disorder or how a teen-

ager can improve the appearance of nails and keratoderma, thus improving patient coping.

This study was limited by its retrospective nature, leading to the risk of recall bias, particularly when inquiring about disease characteristics at onset during the pediatric years given that most of the patients were well into their adult years when they responded to the questionnaire. Nevertheless, the data in this registry database show that PC can be diagnosed during early childhood based on the constellation of clinical features and genotyping. Genotyping is currently performed at no cost on a research basis (ie, not by a Clinical Laboratory Improvement Amendment–approved laboratory) by registering with the IPCRR (www.pachyonychia.org). The many genotype-phenotype and subtype-phenotype correlations allow for early classification, prediction of clinical features and their age at onset, and optimal management.

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REFERENCES

- Jadassohn J, Lewandowsky P. Pachyonychia congenita: keratosis disseminata circumscripta (follicularis): tylomata: leukokeratosis linguae. *Ikonographia Dermatol*. 1906;29:31.
- Irvine AD, McLean WH. Human keratin diseases. *Br J Dermatol*. 1999;140(5):815-828.

- Leachman SA, Kaspar RL, Fleckman P, et al. Clinical and pathological features of pachyonychia congenita. *J Invest Dermatol Symp Proc*. 2005;10(1):3-17.
- Bowden PE, Haley JL, Kansky A, Rothnagel JA, Jones DO, Turner RJ. Mutation of a type II keratin gene (K6a) in pachyonychia congenita. *Nat Genet*. 1995;10(3):363-365.
- Cogulu O, Onay H, Aykut A, et al. Pachyonychia congenita type 2, N92S mutation of keratin 17 gene. *Eur J Pediatr*. 2009;168(10):1269-1272.
- Covello SP, Smith FJ, Sillevs Smitt JH, et al. Keratin 17 mutations cause either steatocystoma multiplex or pachyonychia congenita type 2. *Br J Dermatol*. 1998;139(3):475-480.
- McLean WH, Rugg EL, Lunny DP, et al. Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet*. 1995;9(3):273-278.
- Smith FJ, Jonkman MF, van Goor H, et al. A mutation in human keratin K6b produces a phenocopy of the K17 disorder pachyonychia congenita type 2. *Hum Mol Genet*. 1998;7(7):1143-1148.
- Smith FJ, Liao H, Cassidy AJ, et al. The genetic basis of pachyonychia congenita. *J Invest Dermatol Symp Proc*. 2005;10(1):21-30.
- Clementi M, Cardin de Stefani E, Dei Rossi C, Avventi V, Tenconi R. Pachyonychia congenita Jackson-Lawler type. *Br J Dermatol*. 1986;114(3):367-370.
- Munro CS. Pachyonychia congenita. *Br J Dermatol*. 2001;144(5):929-930.
- Eliason MJ, Leachman SA, Feng BJ, Schwartz ME, Hansen CD. A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. *J Am Acad Dermatol*. 2012;67(4):680-686.
- Fu T, Leachman SA, Wilson NJ, Smith FJ, Schwartz ME, Tang JY. Genotype-phenotype correlations among pachyonychia congenita patients with K16 mutations. *J Invest Dermatol*. 2011;131(5):1025-1028.
- McLean WH, Hansen CD, Eliason MJ, Smith FJ. The phenotypic and molecular genetic features of pachyonychia congenita. *J Invest Dermatol*. 2011;131(5):1015-1017.
- McLean WH, Smith FJ, Cassidy AJ. Insights into genotype-phenotype correlation in pachyonychia congenita from the human intermediate filament mutation database. *J Invest Dermatol Symp Proc*. 2005;10(1):31-36.
- Wilson NJ, Leachman SA, Hansen CD, et al. A large mutational study in pachyonychia congenita. *J Invest Dermatol*. 2011;131(5):1018-1024.
- Ward KM, Cook-Bolden FE, Christiano AM, Celebi JT. Identification of a recurrent mutation in keratin 6a in a patient with overlapping clinical features of pachyonychia congenita types 1 and 2. *Clin Exp Dermatol*. 2003;28(4):434-436.
- Wilson NJ, Messenger AG, Leachman SA, et al. Keratin K6c mutations cause focal palmoplantar keratoderma. *J Invest Dermatol*. 2010;130(2):425-429.
- Akasaka E, Nakano H, Nakano A, et al. Diffuse and focal palmoplantar keratoderma can be caused by a keratin 6c mutation. *Br J Dermatol*. 2011;165(6):1290-1292.
- Wilson NJ, Pérez ML, Vahlquist A, et al. Homozygous dominant missense mutation in keratin 17 leads to alopecia in addition to severe pachyonychia congenita. *J Invest Dermatol*. 2012;132(7):1921-1924.
- Spaunhurst KM, Hogendorf AM, Smith FJ, et al. Pachyonychia congenita patients with mutations in *KRT6A* have more extensive disease compared with patients who have mutations in *KRT16*. *Br J Dermatol*. 2012;166(4):875-878.
- Liu HH, Chen CJ, Miles DA. Epidermolysis bullosa simplex. *ASDC J Dent Child*. 1998;65(5):349-353.
- Naz G, Pasternack SM, Perrin C, et al. *FZD6* encoding the Wnt receptor frizzled 6 is mutated in autosomal-recessive nail dysplasia. *Br J Dermatol*. 2012;166(5):1088-1094.
- Perrin C, Langbein L, Schweizer J. Expression of hair keratins in the adult nail unit. *Br J Dermatol*. 2004;151(2):362-371.