Pediatric Allergic Contact Dermatitis
Prevalence, culprit allergens and regulatory issues

Acne Keloidalis Nuchae Treatment
Pachyonchia Congenita Overview
Eczema Review
Pachyonychia congenita (PC) is a rare skin disorder caused by mutations affecting a group of keratins found in specific regions of the epidermis. Although originally classified as a nail dystrophy, its major impact on adult patients is from painful plantar keratoderma. Other manifestations also commonly occur. This article reviews the clinical presentation, genetic diagnosis, pathogenesis and current and future treatment options for PC.

CLINICAL PRESENTATION

Data gathered by the International PC Research Registry (IPCRR) on more than 600 individuals with genetically confirmed PC show that PC always includes at least 1 other feature along with nail dystrophy.1

The most debilitating condition for those with PC is exquisitely painful plantar keratoderma. In some cases, this is the predominant clinical presentation with little or no nail dystrophy.2,3 Other common manifestations of PC are extensive cysts including sebaceous cysts, leukokeratosis, follicular hyperkeratosis and palmar keratoderma (Figures 1-7).1 However, only thickened nails may be evident in neonates and infants with PC.4 Natal teeth may also be present at birth, predominantly in one PC subtype. Leukokeratosis is another finding for PC infants and is often misdiagnosed and treated as thrush. Although florid leukokeratosis has often been incriminated as the cause of difficulty in feeding during infancy, especially with laryngeal involvement, an alternative underlying cause is a painful “first bite syndrome” experienced by some PC children. This is being assessed in a series of unpublished cases in the IPCRR. In each of these patients, a change to soft nipples with large holes immediately resolved the feeding problem.

Blisters or callus on the feet usually begin when a child with PC first begins to walk and the age of onset of plantar keratoderma is a function of the extent of weight on the feet. The pain is usually constant by age 10.4 Many adults with PC rely on canes, crutches or wheelchairs or even resort to crawling on their knees to avoid increased plantar pain by walking. Utilizing ultrasound images, researchers have recently captured images of the

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Pachyonychia congenita (PC) is a rare skin disorder caused by mutations affecting a group of keratins found in specific regions of the epidermis. Although originally classified as a nail dystrophy, its major impact on adult patients is from painful plantar keratoderma. Other manifestations also commonly occur. This article reviews the clinical presentation, genetic diagnosis, pathogenesis and current and future treatment options for PC.

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From age 4 to 14 years, children with PC may experience extensive follicular hyperkeratosis especially in areas of friction around the waist, knees and elbows. In some types of PC, cysts are the dominant feature, characterized by milia in infancy and childhood and extensive body cysts at puberty continuing throughout adult life.

**PATHOGENESIS**

Keratins are structural proteins that promote the integrity of epithelial cells. As a result mutations in the genes encoding keratins lead to cell fragility. The skin expresses the largest number of keratin genes of any organ. Widely distributed lesions in keratin disorders, as occurs in epidermolysis bullosa simplex, result from mutations in genes expressed throughout the epidermis. PC is caused by mutations in 5 keratin genes KRT6a, KRT6b, KRT16, KRT17 and KRT17, which are expressed only in palmoplantar skin, the nail bed, pilosebaceous unit and oral mucosa, leading to selective involvement of these sites in PC.

**GENETIC DIAGNOSIS**

PC is an autosomal-dominant disorder, which has been reported worldwide with approximately equal prevalence in males and females. More than 45% of cases appear spontaneously with no family history of PC. The overlapping clinical presentation with other genetic disorders, only genetic testing can confirm the PC diagnosis.

With nearly 100 distinct PC mutations now identified, correlating the signs of PC with specific mutations and genes has led to a new classification system of PC. While in the past, PC has been classified according to phenotypic features into PC-I and PC-2, the disorder is now classified into 5 subgroups corresponding to the underlying genetic defects: PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17.

As treatment development is focused on specific genes and mutations, free genetic testing is available.

**PACHYONYCHIA CONGENITA OVERVIEW**

The inherited nail dystrophy is associated with painful plantar keratoderma.

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**Figures 1-7.** Typical characteristics of pachyonychia congenita include (a) facial cysts (b and c) palmar keratoderma (d) leukokeratosis (e) follicular hyperkeratosis (f) segmental alopecia (g) localized hypohidrosis.
In a clinical trial, injection into plantar skin of a small interfering RNA (siRNA) that specifically suppressed mutant KRT6a reduced the keratoderma at the injection site. However, the pain of treatment highlighted the need for alternative delivery methods particularly because such treatment requires regular application to sustain the clinical result.

A clinical trial of KRT6a siRNA, delivered by microneedles, is undergoing regulatory approval. Rapamycin has been shown to inhibit the translation of K6a mRNA but has significant toxicity in its oral formulation. A trial of topicaly-applied rapamycin for the plantar keratoderma is under way.

CONCLUSION
PC is a rare genetic disorder for which there are very few therapeutic options. By building a patient community through the IPCRR, and a physician and researcher community through the IPCC, PC Project is moving research forward to better understand the condition and to develop effective treatments.

Working alone, a single patient or physician cannot solve the questions of a rare disease. Similarly experimental trials on individual patients will not yield the data required to set standards of practice to provide effective treatment to all PC patients. Only by working together can we make a difference. We invite all patients, researchers and dermatologists to join with us in a cooperative effort to make progress in finding effective treatments for this painful condition.

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References

Currently there is no specific therapy for PC so the main aim of treatment is to alleviate the pain caused by the plantar keratoderma. Mechanical methods to remove the callus are most effective. The "not too thick, not too thin" motto is essential in caring for keratoderma. Bleach baths can reduce the onset of infections.

TREATMENT
Currently there is no specific therapy for PC so the main aim of treatment is to alleviate the pain caused by the plantar keratoderma. Mechanical methods to remove the callus are most effective.9 The "not too thick, not too thin" motto is essential in caring for keratoderma. Bleach baths can reduce the onset of infections.

Many common treatments recommended by dermatologists (such as urea or salicylic acid-based emollients) are not useful in managing the PC keratoderma and are inferior to at least weekly trimming in most types of PC. Retinoid treatments, effective for some of the other keratin disorders, are also ineffective for PC plantar keratoderma and may increase pain.10 Mechanical treatment for nails is also favored and surgical removal of cysts is often required.9

An important aspect of patient care is recognizing the feeling of isolation associated with this rare and highly visible skin disorder. Encouraging patients to become part of the IPCRR can provide tremendous emotional support because it connects them with others who understand the pain of PC and the functional and psychological affect of the disorder.11 This can be especially important for patients who have no other affected family members.

More effective treatments are under investigation in preclinical and clinical trials. Physician members of the International PC Consortium (IPCC) have access to the latest PC research results and will be invaluable partners for PC patients as therapies are emerging and clinical trials results become available.