Treatment of Pachyonychia Congenita

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There are currently no specific treatments for pachyonychia congenita (PC). Available treatments generally are directed at specific manifestations of the disorder, and an effective treatment plan must recognize that different patients are more or less troubled by different manifestations of the disease. Treatment for all aspects of PC has been less than completely satisfactory. Very few studies have compared different approaches to treatment, and fewer still have given longitudinal follow-up of efficacy and patient acceptance. This review is essentially a compilation of anecdotes. It was collected from physicians’ reports in the literature, from direct communication with physicians currently following patients with PC and from patients who answered a questionnaire on the Pachyonychia Congenita Project web page (http://www.pachyonychia.org/Registry.html).

Key words: epidermis/keratin/nail


The goals of treatment for patients with pachyonychia congenita (PC) are designed to address the four major manifestations of the disease: (1) excess keratin accumulation in the nail unit, the skin or the mucous membranes; (2) blisters; (3) the pain that is associated with blisters in some, but not in all, of the hyperkeratotic areas; (4) the keratin cysts in the dermis. In considering therapies, it is useful to remember that the keratins associated with PC are normally and constitutively expressed in hair follicles and nails and ridged skin of adults (Swensson et al, 1998; McGowan and Coulombe, 2000); those keratins are not thought to be normally expressed in interfollicular epidermis, but can be induced in those locations by friction, trauma, or other acquired insult. It remains an open question as to whether expression of those keratins occurs in neonatal palm or sole or in palm or sole of adults at bed rest. This implies that identification and reduction or removal of the trauma or “insult” should be part of the therapeutic regimen for palmoplantar and interfollicular manifestations of the disease, but might be of less help for the hypertrophic nails and cysts. We discuss below, general categories of treatment that have been used in PC and then focus on treatment for specific manifestation of the disease.

Results and Discussion

Treatment options fall into four broad categories: non-invasive (mechanical), invasive (surgical), chemical, and pharmacological. In every case, these approaches to therapy of PC are non-specific in the sense that the same therapies can and are used or recommended for many hyperkeratotic problems including callosities, psoriasis, or ichthyosis. Likewise, strategies that reduce friction, such as those recommended to patients with other mechanobullous diseases, such as epidermolysis bullosa, are useful for many PC patients, especially those with frequent blisters.

Mechanical removal of keratin in thick nails or keratoses has been achieved using a remarkable array of implements. Almost all patients use some form of hand tool, such as pumice stones, emery boards, paring knives, razor blades, clippers, curettes, rasps, and files. Some use electrical tools, such as table mounted or hand-held grinders, polishers, and sanders. The importance of weight, friction, and pressure as a co-factor in producing signs of PC is emphasized by the many anecdotes of symptomatic improvement following bed rest, casting for fractures and even weight loss. The old literature has many examples of patients’ soles improving on prolonged bed rest (Garb, 1950). Efforts to distribute weight, pressure, and friction using specially constructed shoes, orthotics, insoles, or simply socks and gloves are mechanical approaches that many patients find useful. For patients with significant pain, crutches or a wheelchair become important adjuncts to therapy.

Application of various chemicals to hyperkeratotic areas has been used as monotherapy or as a preliminary step to facilitate mechanical removal. Empirical observations have shown that water, humectants such as urea or propylene glycol, and weak organic acids such as salicylic and α-hydroxy acids all serve to facilitate removal of the outer keratin layers. Periodic soaks in dilute bleach to reduce microbial colonization make sense, but its usefulness has never been proven.
Surgical approaches, including electrofulguration, deep curettage, and excision followed by grafting of autologous skin from an unaffected site, have been applied more successfully to nails than to palms or soles. Keratoses recur in transplanted skin on the soles; we could find no examples of successful surgery for the soles.

Separate pharmacological approaches address specific physical manifestations of PC. Systemic retinoids, including natural vitamin A (Kelly and Pinkus, 1958), isoretinoin (Thomas et al., 1984), and etretinate (Dupre et al., 1981; Lucker and Steijlen, 1995), have been used to reduce hyperkeratosis. Most patients and physicians find that retinoids are effective in reducing hyperkeratosis, but that they also can increase tenderness and blistering. It is a fact that most patients who try retinoids do not stay on them forever. It is not known whether acceptance could be improved by empirically tailoring dosage and schedule to individual patients. At the time when phenytoin was thought to be useful for dystrophic epidermolysis bullosa, it was also tried in PC patients who were troubled by blisters (Blank, 1982). Few believe that it still has a place in the therapy of PC, although one respondent to the PC Project questionnaire reports continued success in reducing blisters and follicular hyperkeratosis using phenytoin. Levothyroxin has been reported to help reduce blisters and hyperkeratosis in one patient (Chowdhury and Banerjee, 1967). Secondary infection of blister fluid, hyperkeratotic masses, or the nail unit is an ever present danger. Culture and treatment with appropriate anti-mycotic or anti-bacterial agents is a periodic feature of the treatment regimen for many patients. Despite apparent response to empiric antibiotic treatment, the nature of such infections, and whether they represent true infection or inflammatory reaction, remains to be determined. Finally, many patients require non-narcotic (especially non-steroidal anti-inflammatory drugs) or, occasionally, narcotic analgesics for pain control; some use topical anesthetics for painful blisters and fissures.

Certain treatments for specific manifestations of PC warrant special comment.

**Nails** Nail care in PC is probably as varied as the number of patients with the disease. Pastes of 20%–40% urea or 15%–20% salicylic acid, often applied overnight under occlusion, seem to be favorite methods to soften the nails. Appreciation that the different genes which cause PC have slightly different patterns of expression (De Berker et al., 2000; McGowan and Coulombe, 2000) should give pause to recommendation of a one-therapy-fits-all approach. Keratins 6 and 16 appear to be constitutively expressed in suprabasal cells of the ventral surface of the proximal nail fold, in the nail bed and in the digit pulp, but not in the nail matrix. By contrast, keratin 17 is expressed throughout the nail bed epithelium and in the nail matrix, starting in the basal layer (McGowan and Coulombe, 2000). This distribution of keratins may explain why some surgeons have obtained satisfactory results from ablation of the nail matrix (Thomsen et al., 1982) whereas others have not (Cosman et al., 1964). Perhaps Thomsen’s patient, who responded well to matrix ablation, had a keratin 17 mutation whereas Cosman’s patient, who required nail bed ablation, had a keratin 6 or 16 mutation. The older literature describes even more aggressive and drastic surgery. Distal digital amputation was felt by one individual, reporting after a 20-y follow-up, to have provided an overall satisfactory result (Wright, 1956).

**Palms and soles** Blistering, hyperkeratosis with fissuring, and pain on the palms and soles are the main difficulties for many patients with PC. Combinations of many of the general classes of treatments mentioned above are used by most patients. Many patients report hyperhidrosis as a particularly troubling manifestation of their disease. One report indicates that treatment of the hyperhidrosis with aluminum chloride is effective in reducing blistering (Tidman and Wells, 1988), and this observation goes along with the frequent report that patients are worse in summer than winter. Plantar injections of botulinum toxin have reduced the pain and hyperkeratosis in three patients with PC (Swartling and Vahlquist, unpublished data). Excision and grafting of plantar skin for PC was abandoned years ago. Although aggressive surgical intervention may be helpful for some inherited plantar keratodermas (Pupo and Farina, 1953), this approach fails in PC because of reappearance of the hyperkeratosis (Garb, 1950). A favorable response of the plantar pain to hypnotherapy has been reported in a paper that is equally interesting for its chronology of treatments recommended for PC between 1929 and 1950 (Mullins et al., 1955).

**Keratoses and itching** Itching is not usually considered to be a direct manifestation of PC, yet many patients report that their hands and feet itch or that they itch elsewhere on their body, for example see (Connors et al., 2001). Our understanding of the induction of the PC keratins by trauma would suggest that this symptom should be treated, whatever its cause. It remains to be seen whether this symptom will be best addressed by the use of oral antihistamines or by topical anesthetics or steroids.

**Mucous membranes** Angular cheilitis and fissures are a common complaint, usually treated with heavy emollients. Some patients reported that brushing their tongue has a beneficial effect on oral leukoplakia, but this has not been studied systematically. Although it is not uncommon to identify *Candida* species in leukoplakia lesions, the usual experience is that anti-fungal agents have no effect on the leukoplakia. By contrast, one patient reported that oral tetracycline had a beneficial effect on her oral leukoplakia. Difficulty with suckling has been observed in the transgenic mice that have absent or mutant PC-associated keratins (Wojcik et al., 1999; Wong et al., 2000). This can be a troublesome manifestation of PC in human neonates, which, once recognized, can be managed in the neonatal period using bottles that have free-flowing nipples and/or topical anesthetics.

**Cysts** There are no reports that cysts should be treated by any method other than those usually used for cysts: excision, incision, and drainage, hyfrecation or diathermy.

**Conclusions**

As we choose therapies to try in our patients, we should be cognizant of the pathophysiological implications of a dom-
inant-negative keratin defect. First, friction plays an important role in all the keratin disorders. In PC, friction can be expected to contribute to cell fragility and induce new synthesis of dominant-negative keratins in cells that would not normally express them. Therefore, it would be prudent to avoid therapies that rely mainly on friction. Second, treatments that reduce stratum corneum cohesivity should be beneficial, as they should reduce the friction needed to remove excess stratum corneum. Finally, we must not underestimate the severity of the disability for some affected individuals. Frequent tales of family planning that includes decisions to have no children or to undergo prenatal or preimplantation genetic testing are clear testimony to patients’ distress from their disease. As with all patients who have chronic disabling, painful or disfiguring problems, adequate attention to pain and depression are essential parts of an overall treatment plan.

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References
