

Aquagenic Wrinkling of the Palms in Patients With Cystic Fibrosis Homozygous for the $\Delta F508$ *CFTR* Mutation

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Background: Aquagenic wrinkling of the palms (AWP) is a rare condition characterized by the rapid and transient formation of edematous whitish plaques on the palms on exposure to water (the so-called hand-in-the-bucket sign). The changes may be asymptomatic or accompanied by pruritic or burning sensations. First described in 1974 in patients with cystic fibrosis—and still primarily reported in these patients—this condition has been previously described only in females. Specific mutations in *CFTR*, the gene responsible for cystic fibrosis, have not been reported previously in patients with AWP.

Observations: We describe 2 patients with AWP, both of whom are homozygous for the $\Delta F508$ mutation in

CFTR: a 17-year-old boy—the first male reported to have this condition—who has had AWP for 3 years and a 13-year-old girl who has had AWP for 6 months.

Conclusions: Cystic fibrosis should be considered in patients with AWP, and patients with cystic fibrosis should be asked about symptoms of this condition. Although the etiology of AWP is unknown, the association with cystic fibrosis, and with marasmus and cyclooxygenase-2 inhibitors, suggests that exposure of the skin to abnormally high concentrations of salt may play a role in its pathogenesis.

Arch Dermatol. 2005;141:621-624

FIRST NOTED BY ELLIOTT¹ IN 1974 in a 1-paragraph letter to *The Lancet* entitled “Wrinkling of Skin in Cystic Fibrosis,” aquagenic wrinkling of the palms (AWP) is characterized by the transient development of edematous whitish plaques on the palms on exposure to water (the so-called “hand-in-the-bucket” sign).² The soles are involved in some patients. Some patients have reported this reaction to tap water but not to saltwater,^{3,4} whereas others have responded in like manner to both.³ There may be associated hyperhidrosis and pruritus, burning, tingling, or discomfort. The reaction resolves within hours. Histologically, dilated eccrine ostia and hyperkeratosis have been described.^{5,6} The etiology and pathogenesis of the condition are not known.

We describe herein 2 patients with AWP, including the first male reported to have the disease. Both patients were homozygous for the $\Delta F508$ mutation in *CFTR*, the gene that is solely responsible for causing cystic fibrosis (CF).⁷ This represents the first time that specific *CFTR* gene mutations have been reported in patients with CF who have AWP, based on our search of the English-language, MEDLINE-indexed literature. We

also review hypotheses regarding the pathogenesis of AWP and treatments used in patients with this condition. Statistical analysis was performed using a software program (Stata 6.0; StataCorp, College Station, Tex).

REPORT OF CASES

PATIENT 1

A 17-year-old boy with CF (homozygous for the $\Delta F508$ *CFTR* mutation, with a sweat chloride level of 106 mEq/L [reference range, <40 mEq/L]), palmar hyperhidrosis, primary Raynaud disease, and asthma reported a 3-year history of an asymptomatic eruption on his palms that occurred within 2 minutes of exposure to water. The eruption consisted of ill-defined, pitted, white papules and plaques on the palms (**Figure 1**). Within 2 hours of exposure to water, the palms would return to their baseline appearance. The soles did not react. The patient was reportedly less symptomatic during the summer of 2003, when there was abnormally low precipitation in the patient’s hometown.⁸

At the onset of the eruption, the patient was undergoing treatment with

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Financial Disclosure: Dr Katz has optioned intellectual property to Cutix Pharmaceuticals, Inc.

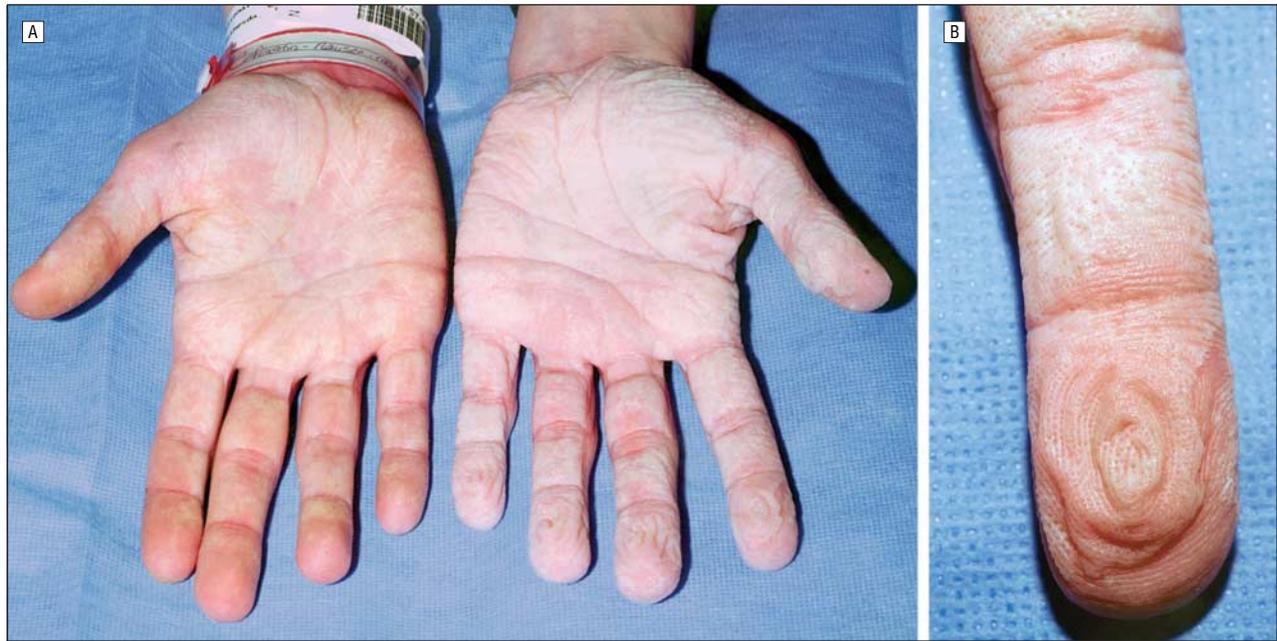


Figure 1. The palmar surfaces of the hands of patient 1. A, The left hand is shown 2 minutes after immersion in tap water. The right hand was not exposed to water. B, Close-up of the palmar surface of 1 of the digits on the left hand 2 minutes after immersion in tap water.

amikacin sulfate and meropenem for a *Mycobacteria abscessus* lung infection. He was also taking pancrelipase, beta carotene (vitamin A), cholecalciferol (vitamin D), vitamin E, phytonadione (vitamin K), and, for the previous 4 years, acetaminophen and ibuprofen several times weekly for headaches. Daily treatment with 20% aluminum chloride hexahydrate solution (Glades Pharmaceuticals, Suwanee, Ga) for 2 weeks was not effective.

PATIENT 2

A 13-year-old girl with CF (homozygous for the $\Delta F508$ *CFTR* mutation), mild palmar hyperhidrosis, acne vulgaris, keratosis pilaris, and ichthyosis vulgaris had a 6-month history of palmar rash. The rash manifested as pale white thickening of the palms (sparing the soles) with punctate depressions and was unsuccessfully treated as pitted keratolysis with topical erythromycin. As the eruption evolved, the patient noted that activities related to water (eg, washing her hair or hands) or prolonged immersion of her hands in water resulted in an uncomfortable burning sensation and worsening of the rash on her hands. A trial of 20% aluminum chloride hexahydrate solution (Drysol; Person & Covey Inc, Glendale, Calif) 3 times daily for 1 week and then 2 to 3 times per week resulted in moderate improvement, but she complained about excessive drying of the hands. She does not take any nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors.

Immersion of the patient's right hand in tap water resulted in burning and discomfort and thickening of the palmar skin within 1 to 3 minutes, whereas simultaneous immersion of the left hand in hypertonic saline solution (23%) did not produce any changes (**Figure 2**). After a remission of 3 months, the condition recurred.

COMMENT

The 17-year-old boy represents the first case of AWP described in a male. This boy and the 13-year-old girl described herein are the 29th and 30th cases reported overall.^{2-6,9-15} These patients are part of a cohort of other cases of AWP associated with CF, 15 of whom have been described previously.^{4,5,9,10}

Aquagenic wrinkling of the palms has also been termed *transient reactive papulotranslucent acrokeratoderma*,^{5,12} *aquagenic palmoplantar keratoderma*,² *aquagenic syringeal acrokeratoderma*,^{3,4,6} *aquagenic keratoderma*,¹¹ and, simply, *wrinkling of skin*.¹ Because the disorder is likely to be the result of abnormal electrolyte fluxes rather than hyperkeratosis—the hallmark of other keratodermas—we prefer the term *aquagenic wrinkling of the palms* for this disorder rather than terms that include *keratoderma*.

Aquagenic wrinkling of the palms is distinct from hereditary papulotranslucent acrokeratoderma, an autosomal dominant disorder that manifests during puberty with persistent asymptomatic yellow-white translucent papules and plaques on the margins of the palms and soles.¹⁶ The first patient described as having hereditary papulotranslucent acrokeratoderma indicated excessive wrinkling of the palmar skin after immersion in water when the hereditary papulotranslucent acrokeratoderma-associated papules were first appearing. This reaction abated with time.¹⁶

All 15 of the previously described patients with AWP whose sex was reported were female (age range, 9-33 years). Eight patients, including ours, have been treated topically with aluminum chloride, with at least some improvement.^{2,4,11} Other reported treatments have included iontophoresis,⁵ antihistamines,³ and acetic acid.¹⁷



Figure 2. The palmar surfaces of the hands of patient 2 before immersion (A) and 3 minutes after immersion of the left hand in tap water and the right hand in 23% hypertonic saline solution (B). Note the more dramatic response in the palm exposed to tap water.

Temporary spontaneous remissions have been described in 6 patients,^{2,3,6} including ours.

Including our patients, 17 of 30 reported patients with AWP have documented CF (56.7%; 95% confidence interval, 37.4%-74.5%).^{4,5,9,10} Other patients with CF have been mentioned, but specific numbers were not given.¹⁷ Specific mutations in *CFTR*, the gene responsible for CF, and sweat chloride concentrations in other patients with AWP have not been previously reported in the English-language, MEDLINE-indexed literature. Although more than 1000 mutations and polymorphisms in the *CFTR* have been reported, the $\Delta F508$ mutation is by far the most common, accounting for 70% of CF cases in northern European white patients; the next 4 most common mutations each occur in approximately 1% of patients.⁷ The fact that both of our patients with CF were homozygous for $\Delta F508$ *CFTR* mutations suggests that this particular mutation may be a predisposing factor for the development of AWP, and it warrants further study.

Cystic fibrosis is an autosomal recessive disease, and *CFTR* resides on the long arm of chromosome 7.⁷ It has been hypothesized that AWP is an autosomal recessive trait.¹² That the sister of 1 patient with AWP, without CF, also had AWP supports this hypothesis. The pathogenesis of AWP is thought to involve an increase in the water-binding capacity of keratins, mediated by increased salt concentrations in the epidermis.¹⁸ Genes that encode keratins reside on chromosomes 12 and 17,¹⁹ so that it is highly unlikely that a keratin gene, by linkage to the *CFTR* gene on chromosome 7, is responsible for AWP. The sweat of patients with CF has relatively high concentrations of salt, which may vary depending on the patient's CF mutation(s).²⁰ Increased sweat chloride concentrations may, in fact, be the sole manifestation of mutations in the *CFTR* gene.²¹ Infants with marasmus, a form of protein-energy malnutrition, also may have elevated sweat chloride concentrations²² and have been observed to have excessive skin wrinkling similar to that seen in patients with CF.¹

A role for increased epidermal salt concentrations was also suggested by the recent report of an 18-year-old woman who developed AWP 1 month after starting treatment with rofecoxib.¹³ The reaction resolved almost completely 3 weeks after use of the drug was discontinued. Rofecoxib is a cyclooxygenase-2 inhibitor that was hy-

pothesized to increase sodium concentrations in the skin, similar to its effect on the kidney.²³

Aquagenic wrinkling of the palms in patients with CF may be mediated by abnormal *CFTR* regulation of cell membrane water channels such as aquaporin 3,²⁴ which is involved in the regulation of transepidermal water loss.²⁵ Alternative hypotheses for the pathogenesis of AWP have implicated a defective barrier function of the stratum corneum,^{3,11} occlusion of eccrine duct ostia,⁶ weaknesses of the eccrine duct wall,⁵ and influx of water across an osmotic gradient into eccrine ducts.⁴

The association between AWP and CF deserves further study, including measurement of sweat chloride concentrations in patients with AWP and investigation of possible *CFTR* mutations in patients with and without CF. Such studies may provide insights into the pathogenesis of both diseases.

Accepted for Publication: November 2, 2004.

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Funding/Support: Dr Katz is supported by a Kirschstein National Research Service Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Md.

Acknowledgment: We thank Steven M. Holland of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health for referring us one of the patients.

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