Aquagenic Wrinkling of the Palms in Cystic Fibrosis

Comparison With Controls and Genotype-Phenotype Correlations

David R. Berk, MD; Heather M. Ciliberto, MD; Stuart C. Sweet, MD; Thomas W. Ferkol, MD; Susan J. Bayliss, MD

Objective: To determine the prevalence of aquagenic wrinkling of the palms (AWP) in patients with cystic fibrosis (CF) compared with control patients, and evaluate for genotype-phenotype correlations. Since its first description over 30 years ago, AWP has frequently been anecdotally associated with CF, but this association has not been confirmed in a rigorous prospective case-control study.

Design: Blinded comparison.

Setting: The CF and dermatology clinics at St Louis Children's Hospital.

Participants: Forty-four individuals with CF from a CF clinic and 26 controls from a dermatology clinic.

Intervention: Participants were tested for AWP using 3 minutes of water immersion with room-temperature tap water.

Main Outcome Measure: The degree of AWP was scored from 0 (no wrinkling) to 4 (severe wrinkling) by 3 blinded physicians. For genotype-phenotype correlations, patients with CF were divided into those homozygous for the ΔF508 mutation and those with other genotypes.

Results: The mean AWP score of the CF group was significantly higher than the mean score of the control group (1.5 vs 0.6; P < .001). Patients with CF who were homozygous for the ΔF508 mutation (n = 27) had significantly higher scores than patients with CF who were not homozygous for the ΔF508 mutation (n = 17) (1.7 vs 1.1; P = .02). The 17 patients with CF who were not homozygous for the ΔF508 mutation still had higher scores than the control group (1.1 vs 0.6; P = .03). There was no correlation between sweat chloride concentrations measured at the time of diagnosis and AWP score.

Conclusions: Our results confirm the association between AWP and CF. Among patients with CF, greater AWP occurs in those who are homozygous for the ΔF508 mutation.


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reported a “long series” of children with CF and control children tested for AWP, but this article focused on photographic techniques without describing the methodology used, sample size, or presenting data for systematic analysis. Since these early publications, only rare case reports have followed. Of all reported cases of AWP, slightly over half were described in patients with CF, 1 most of whom were female, and the authors often hypothesized that AWP is significantly underreported in CF. 15,16 Although AWP is included as having a known association with CF on patient education Web sites and in a recent review of the cutaneous manifestations of CF, 2 to our knowledge, this association has not been confirmed in a larger, rigorous, prospective case-control study, and many questions remain unanswered. We sought to determine the prevalence and quantify the degree of AWP in patients with CF compared with controls. In addition, we systematically examined the relationship between AWP and both genotype and sweat chloride concentrations obtained at the time of diagnosis.

METHODS

After institutional review board approval, 44 patients were recruited from the CF clinic at St Louis Children’s Hospital (Table). Twenty-six controls matched for age, sex, and ethnicity were recruited from dermatology clinics at St Louis Children’s Hospital. All patients with CF were diagnosed based on characteristic clinical features (ie, chronic sinopulmonary disease, pancreatic insufficiency, recurrent pancreatitis, meconium ileus, or a history of CF in the immediate family) and 2 elevated sweat chloride measurements or identification of 2 mutant CF transmembrane conductance regulator (CFTR) alleles. Sweat chloride concentrations at diagnosis were available for 40 of the 44 patients with CF and were measured using pilocarpine electrophoresis (median age at testing, 7 months). Every patient with CF underwent genetic testing to define CFTR mutations. Exclusion criteria for both those with CF and controls included atopic dermatitis or recent isotretinoin therapy because of potentially altered skin barrier properties.

After informed consent, participants placed one hand in room-temperature tap water for 3 minutes (all testing was performed by D.R.B. or H.M.C.). All patients began with dry hands with no evidence of wrinkling. One hand was immersed (patients’ choice of which hand), and the other hand was used for comparison. After 3 minutes, the participants briefly dried their hands, and the palmar surfaces of both hands were photographed. Individuals were questioned about symptoms associated with the immersion, personal history of palmoplantar hyperhidrosis, and family history of AWP. After complete enrollment, photographs were randomized. Three dermatologists (S.J.B. and 2 third-year dermatology residents in their last month of residency) who were blinded to patient history (CF vs control) and interview responses graded the degree of AWP in photographs on a scale of 0 to 4: 0 = no wrinkling, 1 = minimal wrinkling, 2 = mild wrinkling, 3 = moderate wrinkling, and 4 = severe wrinkling. For each patient, the mean of the 3 scores was used as the final AWP score.

Statistical analysis was performed using the free, downloadable “R” software program (http://www.r-project.org/). An unpaired t test was used to compare AWP scores of patients with CF with those of control participants. This analysis was confirmed using the Wilcoxon rank-sum test. Linear regression was used to compare AWP scores of patients with CF who were homozygous for the ΔF508 mutation with scores of patients with CF who were nonhomozygous for the ΔF508 mutation. Linear regression was also used to compare AWP scores of patients with CF who were homozygous for the ΔF508 mutation with those of controls, and to compare AWP scores of patients with CF who were nonhomozygous for the ΔF508 mutation with those of controls.

RESULTS

The Table shows patient demographics. The CF and control groups had similar sex distributions (23 of 44 females vs 12 of 26 females, respectively) and mean ages (11.5 years vs 9.3 years, respectively). The AWP scores were not associated with sex or age.

The mean (SD) AWP score for patients with CF was 1.5 (0.98) (median, 1.3) vs 0.6 (0.53) (median, 0.7) for controls (P < .001; unchanged after adjusting for age and sex) (Figure 1 and Figure 2). Four of 44 patients with CF reported symptoms (mild discomfort, tightness, and tingling) with water immersion, in comparison with none of the controls. Two patients with CF reported a history of hyperhidrosis, whereas none of the controls had this complaint. Two patients with CF reported a family history of AWP. The 8 patients with CF with symptoms, hyperhidrosis, or a positive family history did not differ from other patients with CF in AWP score (mean score, 1.4).

We investigated whether CF genotype was associated with AWP score. We compared patients with CF who were homozygous for the ΔF508 mutation (n=27) and those who were hemizygous for the ΔF508 mutant allele or had other mutations (n=17). Patients with CF who were homozygous for the ΔF508 mutation had a mean AWP score of 1.7 (median 1.7; P < .001 vs control patients, adjusting for age and sex). Patients with CF who were not homozygous for the ΔF508 mutation had a mean AWP score of 1.1 (median, 0.7; P=.03 vs controls, adjusting for age and sex). Among patients with CF, those who were homozygous for the ΔF508 mutation had higher mean AWP scores (1.7 vs 1.1; P=.02, adjusting for age and sex).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group</th>
<th>Patients With CF, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>44</td>
</tr>
<tr>
<td>Females, No. (%)</td>
<td>12 (46)</td>
<td>23 (52)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>9.3</td>
<td>11.5</td>
</tr>
<tr>
<td>CFTR genotype</td>
<td>F508/F508</td>
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</tr>
<tr>
<td>ΔF508/R553X</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>ΔF508/1998 + 1G → A</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ΔF508/5452X</td>
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<td>1</td>
</tr>
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<td>ΔF508/5510D</td>
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<td>ΔF508/W1282X</td>
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<tr>
<td>ΔF508/1717 + 1G → A</td>
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<tr>
<td>2184insA/4357 2A→G</td>
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</table>

Abbreviations: CF, cystic fibrosis; NA, not applicable.

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Because increased salt content in the skin of individuals with CF could lead to greater water absorption, we examined the association between sweat chloride concentration and AWP score. We hypothesized that higher AWP scores would correlate with sweat chloride concentrations in patients with CF. The mean sweat chloride concentration for the patients with CF was 96.2 mmol/L (median, 98 mmol/L). The mean (SD) sweat chloride level measured for patients who were homozygous for the ΔF508 mutation was 95.7 mmol/L (12.3 mmol/L) compared with 97.1 mmol/L (10.3 mmol/L) for other patients with CF. There was no relationship between sweat chloride concentration and AWP score (r = −0.05).

To assess the reproducibility of the wrinkling assay, intraclass correlation coefficients between the assessments of the 3 examiners were calculated based on a 2-way analysis of variance with patients and raters considered as random effects. The values were 0.59 (95% confidence interval [CI], 0.40-0.74) for patients with CF and 0.28 for normal controls (95% CI, 0.06-0.53).

**COMMENT**

In this article, we present the largest cohorts of patients with CF and controls thus far tested for AWP, to our knowledge. Although the mean AWP score was relatively low (1.7, indicating mild to moderate wrinkling) for the CF group, our study confirms previous anecdotal observations that AWP is associated with CF and contradicts reports that females are disproportionately affected with AWP. In addition, our results in controls offer insight into the normal degree of palmar wrinkling following brief water immersion. Finally, we found that patients homozygous for the ΔF508 mutation had greater AWP than those with other CFTR genotypes. Few reports of AWP in patients with CF have included CFTR genotype. Katz et al recently reported 2 patients with CF who were homozygous for the ΔF508 CF mutation, but because the ΔF508 mutation is very common, it was unclear if this association was real.

Determining the prevalence of AWP in patients with CF is important for several reasons. Clarifying the link between AWP and CF may advance our understanding of the pathogenesis of both conditions. Furthermore, identifying patients with AWP is important because, anecdotally, effective therapies exist for AWP (and associated symptoms), including aluminum chloride, antihistamines, botulinum toxin injections, and iontophoresis. Some cases spontaneously remit. Several hypotheses exist regarding the pathogenesis for AWP. Increased cutaneous salt content in CF may enhance water absorption by keratins, but our failure to find an association between sweat chloride concentration and AWP score argues against this hypothesis. Alternatively, eccrine gland or nerve dysfunction, or altered cell volume regulation may be critical. Hyperhidrosis, in particular, may mediate AWP.

The lack of a well-validated tool to measure AWP represents an important limitation for our study. Choosing the exact parameters (eg, duration of immersion, water temperature) to test for AWP was challenging. Unfortunately, to our knowledge, there are no standard testing parameters, such as duration of water immersion or water temperature, in the literature, nor are there descriptions of what degree of AWP to expect for controls without CF. Aquagenic wrinkling of the palms has been reported at durations of water immersion ranging from several seconds to 15 minutes. We chose 3 minutes because we felt 10 minutes would lead to considerable AWP in controls and because of previous observations.©2009 American Medical Association. All rights reserved.
that “in all cases of cystic fibrosis that show marked wrinkling after 10 minutes, a degree of wrinkling is present after 2 minutes.” We declined to test participants at multiple time points (eg, at 3 minutes and at 10 minutes) to avoid interrupting the period of water immersion and to increase enrollment by minimizing the time required for participation. However, it is possible that testing at multiple time points may have allowed us to plot the rate of wrinkling against time. Immersing both hands in water with removal of one hand at 3 minutes and the other at 10 minutes would have represented another study design. It is possible that a longer duration of water immersion may facilitate detection of larger differences between the groups and development of more symptoms among the CF group.

Most case reports describe AWP as an all-or-none or threshold phenomenon (one either has or does not have AWP). Our results support conceptualizing AWP as occurring along a spectrum. Interestingly, although grading AWP allowed us to detect a difference between patients with CF and controls, none of our participants demonstrated AWP to the degree of patients documented in most case reports.

Our study has several other limitations. We did not control for exposure to nonsteroidal anti-inflammatory agents (NSAIDs) and antibiotics, although cases of rofecoxib-induced, aspirin-induced, and tobramycin-induced AWP have rarely been reported. Furthermore, we did not account for hand edness or recent hand washing (ie, soapiness or elevated skin pH), both of which have anecdotally been described as modifying factors. Also, the study was not powered to identify specific phenotype-genotype correlations.

Many questions remain about AWP, including whether patients without CF who present with AWP should be tested for CF carrier status, whether AWP is truly associated with conditions like marasmus, whether AWP is associated with nutrition, how commonly NSAIDs contribute to AWP, whether anecdotally modifying factors (hand edness, handwashing, and water salt content, pH, and temperature) are important, and whether differences detected after 3 minutes would change at 10 minutes. Finally, some have suggested that understanding the mechanism of AWP may provide insight into novel treatments for xerosis and eczema, such as moisturizers containing cyclooxygenase inhibitors or aldosterone antagonists.

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Author Contributions: Drs Berk and Ciliberto had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Berk, Sweet, and Bayliss. Acquisition of data: Berk, Ciliberto, Ferkol, and Bayliss. Analysis and interpretation of data: Berk, Ciliberto, and Ferkol. Drafting of the manuscript: Berk, Ciliberto, and Ferkol.

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