Aquagenic palmoplantar keratoderma therapeutic response to topical glycopyrronium

Emily J. Medhus, BS, Ansley C. DeVore, BS, and Karen DeVore, MD
Spartanburg and Charleston, South Carolina

Key words: aquagenic acrokeratoderma; aquagenic palmoplantar keratoderma; aquagenic syringeal acrokeratoderma; aquagenic wrinkling of the palms; cystic fibrosis; glycopyrronium.

INTRODUCTION

The pathogenesis of aquagenic palmoplantar keratoderma (APK) is not well understood. Typically, it occurs in those with cystic fibrosis, but idiopathic and drug-induced cases have been reported. Medications associated with APK include aspirin, nonsteroidal anti-inflammatory drugs, celecoxib, and clarithromycin. We describe the case of a young female with idiopathic APK who responded to therapeutic intervention with topical glycopyrronium.

CASE REPORT

A 30-year-old female presented with palm wrinkling and associated burning sensation occurring after about thirty seconds of water exposure of any temperature. These symptoms began when she was about 8 years old and worsened as she got older. She attempted using waterproof gloves for prevention, which only exacerbated the condition due to increased sweating. This appeared to be a large contributing factor, as sweating alone could trigger her symptoms. Notably, salt water did not affect the problem. Past medical, family, and surgical history were noncontributory. The patient denied recent changes to medications or use of nonsteroidal anti-inflammatory drugs, aspirin, or celecoxib.

Physical examination of dry hands before water submersion revealed symmetric, small, whitish papules with some confluence bilaterally (Fig 1). After submerging the hands in lukewarm water for less than 1 minute, whitish papules and plaques enlarged significantly, appearing macerated and edematous (Fig 2) with prominent dilated punctae (Fig 3). This response allowed for the clinical diagnosis of APK to be made.

Various topical and oral medications were tried. Among these, topical triamcinolone cream, which was applied after water submersion, appeared to lessen the discomfort but did not help with symptom prevention. After taking oral glycopyrrolate 0.2 mg daily for 2 weeks, the patient reported a mild reduction in palmar and axillary sweating but no improvement in hand appearance or discomfort. The patient was then initiated on daily topical 20% aluminum chloride hexahydrate solution, which provided some clinical improvement but without complete resolution after 2 weeks of use. Finally, topical glycopyrronium cloth 2.4% completely stopped the palmar perspiration, eruption, and discomfort when used once per day (Fig 4). Patient education regarding the risk of pupillary mydriasis was provided. She was instructed to avoid any contact between her hands and her face and eyes after applying the medication. OnabotulinumtoxinA palmar injections were not tried.

DISCUSSION

Aquagenic palmoplantar keratoderma is a rare dermatologic disorder usually associated with cystic fibrosis. It has been reported that 40%-84% of patients with cystic fibrosis have concomitant APK. While the exact pathophysiology remains...
unclear, several mechanisms and associations have been proposed.

Increased sodium retention in the stratum corneum resulting in increased water uptake capacity is a commonly described mechanism that could explain APK.\textsuperscript{3,5} Other theories include stratum corneum barrier dysfunction, possible involvement of transient vanilloid receptor type 1, and increased skin aquaporin expression.\textsuperscript{6} One additional hypothesis associates APK with increased sympathetic activity\textsuperscript{7} and the involvement of eccrine sweat glands which are innervated by the sympathetic nervous system.\textsuperscript{7} This theory is supported by the fact that various anticholinergic medications have been effective in treating APK.

Currently, there is no consensus on APK treatment, and a variety of modalities have been tried. Many treatment options have been described in the literature, including 20% aluminum chloride hexahydrate solution, topical aluminum chlorohydrate

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Palms before submersion in water. Whitish papules with some confluence distributed symmetrically on otherwise normal appearing palms.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Palms after submersion in water for approximately 60 seconds. Prominent whitish, flat-topped, papules and plaques with a macerated and edematous appearance distributed symmetrically across bilateral palms.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Closer look at the left palm after submersion in water for approximately 60 seconds. Whitish, flat-topped, papules and plaques with prominent dilated punctae.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Palms after submersion in water for 60 seconds after using topical glycopyrronium for 4 consecutive days. Improvement in hand appearance compared with Fig 2. Whitish papules are present but significantly less prominent.}
\end{figure}
emulsion, corticosteroids, topical keratolytics, oral antihistamines, oral anticholinergics, botulinum toxin injection, and iontophoresis.8

To our knowledge, the treatment of APK with topical glycopyrronium has not been previously described. Our patient’s improvement with glycopyrronium supports the hypothesis that sympathetic over-activity and eccrine duct involvement is responsible for the development of APK. Additionally, glycopyrronium may serve as an effective treatment option for patients who do not respond to other modalities. Due to the risk of pharmacologic pupillary mydriasis, patient education and counseling is particularly important.

Interestingly, our patient had a better response to topical glycopyrronium cloths compared with oral glycopyrrolate 0.2 mg. This may be due to drug pharmacokinetics and bioavailability associated with differing routes of administration. It is also possible that the dose of oral glycopyrrolate was not high enough for our patient to reach a therapeutic response.

Ultimately, additional research is still needed to determine the exact pathophysiology of APK, which will then help to identify an effective treatment. Until then, we hope this case will help to support the proposed theory, while also offering a novel treatment option.

**Conflicts of interest**
None disclosed.

**REFERENCES**

1. Elliott RB. Letter: wrinkling of skin in cystic fibrosis. *Lancet*. 1974;2(7872):108.
2. Khuu PT, Duncan KO, Kwan A, Hoyme HE, Bruckner AL. Unilateral aquagenic wrinkling of the palms associated with aspirin intake. *Arch Dermatol*. 2006;142(12):1661-1662.
3. Okwundu N, Snyder-Howerte S, Young J, Lear BW. Idiopathic aquagenic syringeal acrokeratoderma. *J Dermatol Dermatol Surg*. 2019;23(1):46-48.
4. Cabrol C, Bienvenu T, Ruaud L, et al. Aquagenic palmoplantar keratoderma as a CFTR-related disorder. *Acta Derm Venereol*. 2016;96(6):848-849.
5. Uyar B. Aquagenic syringeal acrokeratoderma. *Indian J Derma- tol*. 2014;59(6):632.
6. Tchernev G, Semkova K, Cardoso JC, Ananiev JJ, Willina U. Aquagenic keratoderma. Two new case reports and a new hypothesis. *Indian Dermatol Online J*. 2014;5(1):30-33.
7. MacCormack MA, Wiss K, Malhotra R. Aquagenic syringeal acrokeratoderma: report of two teenage cases. *J Am Acad Dermatol*. 2001;45(1):124-126.
8. Liu X, Liu Z, Zhang S. Aquagenic acrokeratoderma: a case report and review of the literature. *Int J Clin Exp Pathol*. 2020;13(6):1426-1430.