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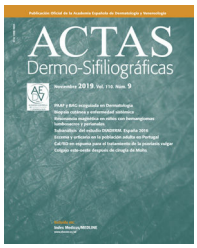

REVIEW

[Translated article] Aquagenic Keratoderma: Treatment Update

M. Carbonell Pradas, R. Grimalt Santacana*

Facultat de Medicina i Ciències de la Salut, UIC-Barcelona, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Barcelona, Spain

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Abstract Aquagenic keratoderma is an uncommon acquired dermatosis characterized by edema and whitish-translucent papules triggered by immersion or contact with water. Cases have been described in association with certain medications, hyperhidrosis, and cystic fibrosis. The aim of this review is to evaluate the effectiveness of different treatments for aquagenic keratoderma. We reviewed the literature and analyzed treatments for aquagenic keratoderma described in case series and reports. Aquagenic keratoderma associated with hyperhidrosis can be treated effectively. Tap water iontophoresis, endoscopic thoracic sympathectomy, botulinum toxin injections, and oxybutynin are effective against refractory forms. Topical salicylic acid and aluminum salts are effective, but of little value as maintenance therapy. Oral oxybutynin 5 mg/d is probably the best option for treating aquagenic keratoderma. The reported pathophysiological effects of nonsteroidal anti inflammatory drugs in this setting suggest that the use of prostaglandins might be justified. Additional studies are needed to investigate these hypotheses and resolve other questions.

PALABRAS CLAVE
Queratodermia acuagénica;
Toxina botulínica;
Anti-colinérgicos;
Hiperhidrosis

La queratodermia acuagénica: actualización terapéutica

Resumen La queratodermia acuagénica (QA) es una afectación dermatológica adquirida poco frecuente que se caracteriza por la aparición de edema y pápulas blanquecinas-translúcidas desencadenado por la inmersión o contacto con el agua. Se han descrito casos asociados a fármacos, hiperhidrosis y a fibrosis quística. Los objetivos del estudio son evaluar la efectividad de los distintos tratamientos existentes para la QA. Realizamos una revisión de la literatura existente al respecto hasta el momento, incluyendo series de casos y reportes de caso. El tratamiento de la QA es efectivo en las formas asociadas a hiperhidrosis. La iontoforesis del

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* Corresponding author.
E-mail address: rgrimalt@uic.es (R. Grimalt Santacana).

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agua del grifo, la simpatectomía torácica endoscópica, las inyecciones de toxina botulínica y la oxibutinina son efectivas en las formas refractarias. La aplicación tópica de ácido salicílico o sales de aluminio es efectiva, pero resulta poco eficaz como tratamiento de mantenimiento. Probablemente la mejor alternativa para el tratamiento de la QA sea la oxibutinina 5 mg/día vo. Se ha observado que los efectos fisiopatológicos de los antiinflamatorios no esteroideos en la QA podrían justificar el uso de las prostaglandinas como un tratamiento dirigido de la enfermedad. Se necesitan estudios adicionales para fortalecer estas deducciones y abordar las incertidumbres restantes.

Introduction

Aquagenic keratoderma (AK) is an uncommon skin disease marked by the rapid appearance of edema, confluent whitish-translucent papules, and the accentuation of dermatoglyphics; signs are triggered by immersing the palms or soles in water for a few minutes.[1] Pruritus and discomfort or pain will sometimes also be present. Symptoms are generally transient, disappearing in less than an hour, usually within 2–20 min after drying.[2,3]

The prevalence of AK is difficult to establish, but it is believed to be uncommon. Its pathogenesis is unknown. Hypotheses that have been put forward are abnormal or failing sweat glands and functional defects in the stratum corneum.[4,5] Abnormal electrolyte flow has also been suggested to cause sodium retention by epidermal keratinocytes and cell volume expansion due to a rise in osmolarity, leading to the formation of the characteristic edematous papules on the palms.

Even though the etiology of AK is unknown, several studies report its presence in patients with cystic fibrosis or carriers of the gene responsible for that disease (Table 1).[4–10] In these individuals, it is believed that sweat hypertonicity due to loss of function of the *CFTR* gene (cystic fibrosis transmembrane conductance regulator) could lead to a higher ratio of flux from eccrine glands in the palms.[11–17] The CFTR protein, which has 1480 amino acids, is found in the cell membranes of the sweat glands, the pancreas, the intestines, and the kidneys. A *CFTR* mutation that codes the CFTR protein causes sodium chloride concentrations to rise in the secretions of patients with cystic fibrosis.

Another theory that might explain the origin of forms of AK that are unrelated to cystic fibrosis involves the dysregulation of aquaporins 3 and 5. These cell membrane proteins are responsible for channeling water, and their dysregulation could be responsible for changes in the palmoplantar stratum corneum.[18,19]

Some studies have found that certain drugs, such as nonsteroidal antiinflammatory drugs[13] among others, can trigger AK, but most cases of this disease are reported as idiopathic.[7–9]

When the literature was reviewed for a case report published in 2016 by Megna et al.,[11] most cases of AK were found to be classified as either idiopathic or associated with cystic fibrosis (Table 1). However, as neither gene sequencing nor sweat tests were undertaken in any of the cases cited, associations with cystic fibrosis cannot be definitively ruled out. Idiopathic cases may be fewer than reported, and cases in patients with cystic fibrosis or carriers of the *CFTR* mutation may be more numerous than realized (Table 2).

Certain substances and drugs have been described as triggering AK.[20–40] Examples are aspirin[6]:celecoxib; rofecoxib[12]; paracetamol; ibuprofen; indomethacin; sulfasalazine; spironolactone[22]; the association of indomethacin, caffeine, and prochlorperazine dimaleate; gabapentin[21]; tobramycin prescribed for cystic fibrosis[38]; and vitamin C taken with clarithromycin.[11]

Although AK usually affects both palms, cases involving a single palm, the dorsal surface of digits, heels, or soles have also been described. Palmar involvement was found to be more frequent in young women (mean age, 22.3 years), but ages ranged from 3 to 65 years according to one group's review of the literature.[11] Familial AK has been described, although most cases are acquired.

AK is diagnosed clinically. The appearance of reproducible signs after 5 min of immersion in water confirms the diagnosis.

The purposes of treatment are to eliminate lesions, ameliorate discomfort, and prevent recurrence. The choice of treatment depends on location, the size of the affected area, the number and type of papules, the patient's age, and the degree of cooperation. The physician's experience with one treatment or another also plays a large role.

AK is self-limiting over time in many cases, something to take into account when considering certain invasive or aggressive therapies among those compared below.

Studies that have evaluated treatments have been relatively inconclusive. This review provides an updated list of the therapeutic alternatives available to manage AK.

Table 1 Etiology of AK.

Cause	%
Cystic fibrosis	67.9
Idiopathic	25.1
Carrier of cystic fibrosis gene	4.4
Drugs	2.6

Abbreviation: AK, Aquagenic keratoderma.

Table 2 Treatments for AK according to levels of evidence.

Reference	Treatment	Study design	Findings	No. of patients	Evidence level[a]
MacCormack et al., 2001[14]	Topical ammonium lactate, 12%; petroleum jelly; gloves	Case series	Case 1, no effect Case 2, gradual remission without treatment	2	3
Itin & Lautenschlager, 2002[15]	Antihistamines	Case series	Spontaneous remission at 2 y	2	3
Uyar, 2014[22]	Botulinum toxin; aluminum chloride, 20%; salicylic acid, 5%; petroleum jelly; urea, 20%, cream; and salicylic acid, 5%; and mometasone furoate.	Case series	No improvement	1	3
Ertürk-Özdemir et al., 2015[25]	Urea cream 10% + salicylic acid 10% + hydroxychloride aluminum 19% ointment	Case series	Improvement in 60% of patients	10	3
Diba et al., 2005[26]	Botulinum toxin	Case report	Recurrence at 5 mo, need to repeat injections	1	3
Niharika et al., 2018[27]	Oral oxybutynin 5 mg Maintenance with topical oxybutynin and salicylic acid, 12%	Case report	Improvement at 3 wk	1	3
Yan et al., 2001[28]	Aluminum chloride, 20%	Case series	Case 1, complete resolution of symptoms after 3 mo of intermittent use Case 2, improvement for several weeks and fewer exacerbations Case 3, symptoms controlled with maintenance therapy	3	3
Syed et al., 2010[29]	Aluminum chloride, 15%	Case series	Partial improvement and greater tolerance	2	3
Berna Aksoy et al., 2010[31]	Oral acitretin vs application of topical salicylic acid and urea, 10%	Case series	No recurrence for 6 mo on follow-up; topical salicylic acid and a urea, 10% preparation were effective but did not prevent recurrences.	2	3
Capella et al., 2004[32]	Oral acitretin vs topical mometasone	Case series	Acitretin was significantly better ($P < .0001$) and the improvement maintained 5 mo after stopping treatment	42	3
Thestrup-Pedersen et al., 2001[33]	Oral acitretin	Case series	50% reduction in symptoms ($P < .01$) vs 9% reduction in the placebo group ($P > 0.05$)	29	3
Lowes et al., 2000[34]	Iontophoresis	Case report	No response	1	3
Errichetti & Piccirillo et al., 2015[35]	Iontophoresis (no response after previous application of aluminum chloride, 20%)	Case report	Significant response	1	3
Zekayi et al., 2015[36]	Urea, 10% ointment; aluminum chloride, 19% cream; botulinum toxin	Case report	No response	1	3
Sezer et al., 2015[39]	Endoscopic thoracic sympathectomy	Case report	No recurrence after 1 year	1	3
Żychowska et al., 2017[41]	Aluminum chloride, 20%	Case report	Improvement without recurrences for 6 mo	1	3
Cemil et al., 2018[42]	Aluminum chloride, 20% cream	Case report	Recurrence after treatment stopped	1	3
Angra et al., 2016[45]	Aluminum chloride, 20%	Case report	Improvement in the extension, frequency, and duration of episodes	1	3

Abbreviation: AK, Aquagenic keratoderma.

[a] The categories of the Scottish Intercollegiate Guidelines Network (SIGN) were used to assess evidence quality.

Methods

Search strategy

We searched the literature between 1996 and 2018 in 5 databases (PubMed, Trip, UpToDate, Scopus, and Science Direct) using the following search terms: *aquagenic keratoderma*, *syringeal acrokeratoderma*, and *aquagenic wrinkling*. After excluding repeated titles, we read the full texts of articles retrieved, excluding articles whose objectives did not coincide with the focus of our review.

Inclusion and exclusion criteria

Given that AK is a rare condition, or at least an underdiagnosed one according to some authors, the inclusion criteria were broad. We mainly sought articles focused on treating AK, prioritizing case series over individual case reports or letters to the editor. Since we found no case-control, cohort, or randomized controlled trials, nearly all the articles reviewed gave evidence classified as level 3 (case reports and series) or 4 (expert opinion reviews).

Data extraction

Titles were retrieved by a single investigator from the aforementioned databases. The following information was recorded for each article: the first author's surname, the year of publication, the time period covered, and the country in which the study took place or in which the case originated. For case series or expert opinion reviews, we also recorded the number of patients discussed.

Analysis of study quality

A single investigator assessed the quality of evidence according to the grading system of the Scottish Intercollegiate Guidelines Network,[20] based on the type of research design. As noted above, all the studies included were case reports, case series, or expert opinion articles and thus provided level 3 or 4 evidence.

Treatments for AK

The rates of successful treatment of AK are highly variable.[22,23,36] Diverse preparations and therapeutic options have been proposed: topical treatments based on aluminum chloride, 20%[4,22,23]; a lotion containing ammonium lactate, 12%[24]; a topical corticosteroid (mometasone furoate)[22,24]; and a topical preparation of urate, 20%, with salicylic acid, 5%.[25,30,31] Retinoids such as acitretin proved effective in patients with defective keratinization,[32,33] a scenario that seems to play a key role in the etiology and pathogenesis of AK. Other therapies tried were iontophoresis,[24] botulinum toxin injections,[22,26] oral oxybutynin chloride,[27] and drugs prescribed to treat hyperhidrosis, given that the 2 conditions may share pathogenic mechanisms.

Topical salicylic acid

Salicylic acid, 5%, is keratinolytic agent that thins the stratum corneum. It has proved effective when combined with urea, 20%.[25,30,31] The main drawback to salicylic acid cream is that the active ingredient is absorbed through the skin, potentially causing burning, metabolic acidosis, tinnitus, nausea, and vomiting. The risk of adverse effects is greater in children, in whom this cream should be used on no more than 10% of the body.

Topical ammonium lactate

Topical ammonium lactate is a moisturizer with mild keratinolytic activity. A 12% topical preparation was ineffective in only 2 cases,[14] whether used alone or in combination with petroleum jelly.

Topical aluminum chloride

Topical aluminum chloride is a first-line treatment for hyperhidrosis. A 20% lotion was effective in treating AK in a series of 3 cases, producing rapid improvement of symptoms,[28] and in a 13-year-old boy.[41] However, some patients are unable to tolerate the irritant properties of this treatment. In the event of intolerance, lowering the dose of the active ingredient to 15% can be tried, according to the literature review accompanying a case report.[29] Some patients who do tolerate the 20% formulation, however, experience recurrence of symptoms when treatment stops.[42] Recurrence can also occur after discontinuation of oral oxybutynin treatment, but at least in that case there is no added discomfort from the application of topical preparations.

Oral oxybutynin

Oral oxybutynin at high doses (>15 mg/d) is an anticholinergic therapy for urge incontinence. Because a side effect of such treatment is reduced sweating, oxybutynin now forms a part of therapy for hyperhidrosis.[43] AK is treated at a lower dose (<10 mg/d), which has an acceptable safety profile and avoids unwanted systemic effects while attenuating symptoms. Brazilian researchers presented an atypical case of AK on the unusual locations of the anterior wrist and dorsal surface of the hand.[27] Three weeks after starting treatment with 5 mg of oxybutynin daily, the patient had experienced substantial improvement even on immersion in water. The patient continued treatment with oxybutynin, and the clinical response improved further with application of a topical keratinolytic cream (salicylic acid, 12%).

Combination therapies

In a series of 10 cases published in 2015 by Ertürk-Özdemir et al.,[25] treatment with a combination of topical urea, 10%, and salicylic acid, 10%, along with an aluminum hydroxychloride, 19%, ointment was successful in 6 of the patients. Clinical signs improved in these 6 patients and they could tolerate water for longer periods. The remaining 4 patients had a partial response.

Oral retinoids

Retinoids, such as acitretin were shown to be effective in treating defective keratinization,[32,33] a condition that seems to play a fundamental role in the etiology and pathogenesis of AK. It was recently suggested to be a cause of AK.[46]

Iontophoresis

Iontophoresis consists of passing a low-voltage electrical current through the skin. The precise mechanism of action is unknown, but the procedure is believed to act selectively by means of local electrochemical coagulation of proteins in eccrine glands, where the levels of electrolytes are high. Another theory is that iontophoresis alters the ionic gradient, thereby inhibiting normal secretion of sweat, making it a possible treatment for hyperhidrosis. The exact means by which iontophoresis acts in AK is unknown, but it remains a possible treatment in patients who do not respond to topical preparations of aluminum chloride, 12%. Only 2 reports of iontophoresis treatment of AK have been published,[34,35] and one of the reports did not specify the outcome.[34] Errichetti & Piccirillo,[35] however, described significant improvement of AK with this treatment, along with reduced sweating. Such positive results suggest that iontophoresis might be particularly useful when AK fails to respond to topical treatment. Accidental heat or chemical burns are the main adverse effects of this modality.

Botulinum toxin

The success of iontophoresis, which modifies sweating, suggests that eccrine glands play a role in the pathogenesis of AK. The efficacy of other treatments for excessive sweating, such as botulinum toxin injections, which offer a disease-free period of up to 5 months, supports this link.[26]

Endoscopic thoracic sympathectomy

Surgery is the most aggressive treatment option for AK. Hyperhidrosis is the main indication for this procedure, in which the sympathetic nerves are clipped in the thoracic region. Surgery is the only treatment that gives permanent results. A case letter describing a 31-year-old man who underwent this procedure for palmar hyperhidrosis refractory to treatment with topical aluminum chloride and iontophoresis noted that the patient also had lesions consistent with palmar AK. Most lesions were seen to have resolved at the 1-month follow-up visit, although lesions in the thenar region of the palm had not cleared completely. No recurrence was reported during the year of follow-up. The authors therefore suggested that endoscopic thoracic sympathectomy could offer a definitive treatment of AK, especially when it is associated with severe palmar hyperhidrosis.

Discussion

The literature we reviewed revealed a narrow range of effective therapies for AK.[40–43] The most effective treatments to date are those that address both hyperhidrosis and AK: oral oxybutynin, botulinum toxin injections, iontophoresis, and thoracic sympathectomy. Sympathectomy is an aggressive and possibly disproportionate choice and could therefore be reserved for cases of AK in a context of debilitating hyperhidrosis. Botulinum toxin injections, which are also invasive, are expensive as they are repeated 4 or 5 times a year to provide a sustained effect. Finally, iontophoresis in general gives inferior results and is troublesome for patients.

Given the available therapies, we believe that oral oxybutynin at a dose of 5 mg/d offers a good balance of safety and efficacy and is probably the treatment of choice. Although oxybutynin is an anticholinergic agent, adverse effects are scarce at low doses and its efficacy parallels a reduction in the hyperhidrosis associated with AK. Oxybutynin was neither a first nor a second-choice treatment for hyperhidrosis in the recent review of Nawrocki et al.,[44] however. Still, we suggest it should nevertheless be taken into consideration. Our reasoning is that AK becomes a more debilitating and bothersome disease when there is a high degree of hyperhidrosis. Moreover, the majority of patients have poor tolerance for aluminum salts, considered the first line of treatment for AK, whereas oxybutynin is both more effective and easier for the patient to take. Thus, the findings of this review lead us to feel justified in suggesting that oral oxybutynin be counted among first-line treatments.

Limitations

Idiopathic AK accounts for 25% of cases, and the nearly 3% induced by drugs do not respond to treatment. A therapeutic alternative is needed for patients whose AK is resistant to all the treatment modalities we found in the literature.[36] In addition, our review of therapies does not deal with all existing forms of this condition.

Moreover, all the results we describe were obtained in observational studies (case reports and series), which are subject to biases, and provide only level 3 evidence. The lack of other study designs is attributable mainly to the low incidence of AK or underdiagnosis.

Future possibilities

Our review of the literature revealed a common denominator in drug-induced cases of AK, namely elevated sodium retention by epidermal keratinocytes, leading to greater water uptake in the stratum corneum.[44–47] These effects are secondary to the inhibition of cyclooxygenase, which undoubtedly plays a large role in the pathogenesis of AK related to the widespread use and abuse of nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, indomethacin, celecoxib, and salicylates. These drugs, which are prescribed often and may even be self-prescribed, have been reported to trigger AK. In fact, drugs are the only potentially avoidable cause of AK. Our review therefore leads us to hypothesize that prostaglandins could reverse the effects of NSAID-induced AK.

Prostaglandins have many medical applications, such as in the treatment of glaucoma. Topical application of prostaglandins has been said to increase the rate of growth of eyelashes and even to increase their density. For this reason these drugs have been put forth as a treatment for

alopecia areata of eyelashes. The effects of NSAIDs and the counter effects of prostaglandins have also been seen in the management of persistent ductus arteriosus patency or premature closure. Thus, just as prostaglandins are used in congenital heart disease to prevent closure of the ductus arteriosus and NSAIDs to inhibit to inhibit prostaglandins and counter their effects, prostaglandins might be of use in treating idiopathic AK, refractory AK, or AK related to NSAIDs, celecoxib, and salicylates. Cyclooxygenase would then no longer be inhibited and sodium retention in epidermal cells, and associated palmoplantar symptoms would be attenuated.

Topical formulations would be prescribed to avoid major systemic toxicity, and the frequency would have to be every 6–8 h given that the effect is short-lived. An occlusive dressing might facilitate the absorption of topical prostaglandins into the stratum corneum of the soles and palms. A nanotechnology approach, using liposomal formulations, could possibly provide the vehicular means to deliver the drugs. Oral intake, with all the systemic repercussions that result, would thereby be avoided.

Conclusions

Although AK is a rare condition, cases that may have been triggered by frequent handwashing during the COVID-19 pandemic have recently been reported.[47] Physicians should take this possibility into account in order to avoid underdiagnosing AK or categorizing a case as idiopathic whenever the condition is not associated with cystic fibrosis.

The management of AK is currently problematic given the absence of consensus-based recommendations in dermatology. Treatment is often frustrating for both patient and physician because there is no established optimal treatment with a balanced combination of a low rate of recurrence, high efficacy, and fewer side effects. Recent years have seen studies suggesting that anticholinergic agents could increase the risk of dementia in adults.[48] Given that AK is transient and of limited seriousness, milder forms need not be treated, at least not continuously.

This narrative review offers an up-to-date account of AK and new evidence that has come to light.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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