Aquagenic keratoderma. Two new case reports and a new hypothesis

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ABSTRACT

Aquagenic keratoderma has been described as a transient condition affecting predominantly young females and defined clinically by the appearance of palmar hyper-wrinkling accentuated after immersion in water. We present two new cases with aquagenic palmoplantar acrokeratoderma – a child and a young male. A significant clinical improvement was achieved after topical treatment with aluminum salts. Aquagenic palmar keratoderma may be a clue to cystic fibrosis in adolescents and young adults. We developed a new hypothesis on its pathogenesis.

Key words: Aquagenic keratoderma, cystic fibrosis, gene association, sympathetic small fibres, treatment

INTRODUCTION

Aquagenic keratoderma (AK) is a rare skin disorder also known as acquired aquagenic palmoplantar keratoderma, transient reactive papulotranslucent acrokeratoderma, aquagenic wrinkling of the palms or aquagenic syringeal acrokeratoderma.The disorder was first described by English and McCollough in 1996.[1]

Its main characteristic is skin wrinkling with edema of palms/soles, whitish papules, pruritus, burning, and pain after contact with water.[2] Most patients are females. Prolongation of water exposure and temperature of the water affect the rate and intensity of lesion development. However, pathogenesis of AK is poorly understood.[3-5]

We report two new cases and provide an overview about clinical presentation, histopathology and genetics, and therapy.

CASE REPORTS

Case 1

A 12-year old girl presented with three months history of burning of palms and loss of skin dermatoglyphics after exposure to water [Figure 1]. Symptoms were temporary; changes faded away within 20 min. The patient did not have concomitant diseases and was not on any medication. Clinical examination revealed hyper-wrinkling of the palms after immersion in water without any other skin and/or mucous changes. Routine laboratory examination was unremarkable.

Therapy was initiated with 20% alcohol solution of aluminum chloride hexahydrate once daily at night. The treatment resulted in significant clinical improvement with reduction of the frequency and duration of AK episodes.

Case 2

The second patient was a 27-year-old male suffering from cystic fibrosis (CF) and focal palmar hyperhidrosis. He was tested positive for homozygosity for the ΔF508 mutation of the CF transmembrane conductance regulator (CFTR) gene. His medication consisted of macrolide antibiotic prophylaxis and inhaled corticosteroids. Without immersion in the water, he showed whitish translucent papules and increased wrinkling of the palms [Figure 2]. Symptoms worsened after water immersion. He did not report pruritus or pain sensation.

We treated him twice daily with a topical aluminum chlorohydrate emulsion (Ansudor N, Galderma). Palmar symptoms improved markedly.

DISCUSSION

AK is a rare symmetrical condition of palms and occasionally soles. AK is an acquired dermatosis with a predilection for adolescents and women.

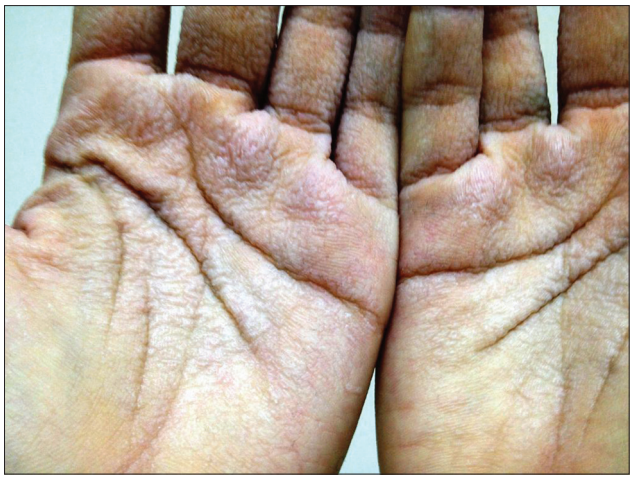

Figure 1: Aquagenic keratoderma of the palms after water immersion in a 12 year-old girl

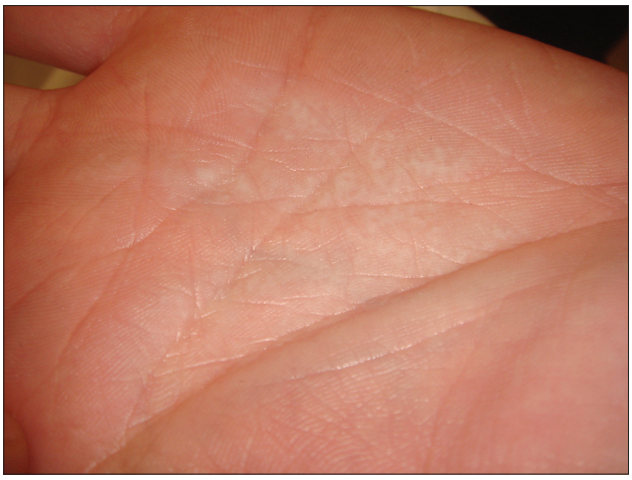

Figure 2: Aquagenic keratoderma of the palms in a 27 year-old male with palmar hyperhidrosis and cystic fibrosis. In the presentation without water immersion a milder clinical appearance of whitish translucent papules is obvious

Most cases are sporadic, but familial involvement has also been reported in the literature.[6-9]

Clinically, it is characterized by whitish papules, edema and hyper-wrinkling with or without desquamation of the palms and/or soles. Erythema is uncommon.[3] The morphological changes develop after contact with water, with gradual improvement within 2-20 min.[3] This accentuation of skin lesions after water immersion is known as the "hand-in-the-bucket" sign and is considered diagnostic.[9]

Several unusual presentations have been reported in the literature, including a localized form on the heel[7] and involvement of the dorsum of fingers,[10] sparing of the palms,[11] and a unilateral type.[12,13]

In histopathology, most characteristic findings are spongiotic changes in the stratum corneum, orthohyperkeratosis with acanthosis, and, in the majority of cases, dilation of eccrine acrosyringia, and crenulated appearance of the luminal cells of the secretory eccrine coils. Increased capillary proliferation adjacent to the former could also be found.[14,15] The biopsy should be taken after exposure to water as no abnormalities are seen in tissue specimens after drying the skin.

AK continues to be also a focus of research as to its genetic predisposition and association with other diseases including CF, focal hyperhidrosis, and Raynaud phenomenon.[16,17]

Regarding CF, it is estimated that between 44% and 80% of patients with CF have AK.[2,16] That is why, this disease served as a model to study the genetic association and the underlying pathogenic mechanisms of AK. In fact, the cause of development of these associated disorders is a homo-or heterozygous mutation for ΔF508, which was first discovered in the CFTR gene in CF.[18,19] CFTR is involved in the regulation of electrolyte transport, and the mutation leads to the reduction of electrolyte reabsorption in eccrine ducts; thus, increasing the levels of salt in the sweat.[20] The latter explains the pathogenic formulation and development of AK as the increased electrolyte composition results in increased diffusion of liquids in palmar skin. Higher concentrations of salts in the sweat increase the specific thermal capacity what might contribute to subjective sensory symptoms.

Similar pathogenic mechanism has been proposed for the development of AK associated with various medications such as celecoxib and rofecoxib. These drugs lead to inhibition of the enzyme cyclooxygenase-2, contributing to the concentration of electrolytes in sweat.[13,17,21,22]

AK is limited to those areas, which are positive in Minor's iodine starch test for focal hyperhidrosis.[23] The autonomous nerve system seems to be involved in AK. Water immersion test is used to assess small sympathetic nerve function. It has been demonstrated that fingertip skin wrinkling is related to digit pulp vasoconstriction.[24]

The high sweat salt concentrations as in CF-associated AK contributes to an increased water holding capacity of the horny layer.[25] An increase of natural moisturizing factor (NMF) would result in higher water holding capacity of human epidermis, but would require time for synthesis and transport.

Concerning the rapid, but temporary effect of water immersion, we suggest an overactivity of certain aquaporins (AQPs). Indeed, an aberrant expression of AQP5 was detected in secretory clear cells of eccrine sweat glands in the involved palmar area in contrast to healthy skin where only dark cells express AQP5.[23] On the other hand, clear cells are considered the source of focal hyperhidrosis.[26]

Water immersion may be the major exogenous factor of higher stratum corneum water binding. Furthermore, swelling

of the stratum corneum could lead to sweat retention in the whole epidermis. The stratum corneum water binding capacity is directly related to the external osmotic pressure. Human keratinocytes express the transient vanilloid receptor type-1 (TVRT-1).[27] TVRT-1 is an osmosensitive receptor. Its sensitivity is further enhanced by temperature and protons.[28] From clinical experience higher temperature during water immersion exerts a stronger AK response. Higher salt concentrations in sweat increase thermosensitivity of the receptor. Hyperosmolarity of sweat and increased water temperature leads to increased $Ca2^{+}$ influx and swelling of cells.[28]

AQPs may also be involved since they regulate various functions of the skin. AQP3 is expressed by keratinocytes from the basal epidermal layer up to the spinous layer in human skin. AQP 10 is a water transporting AQP first localized in intestinal glycocalyx.[29] It is also expressed in human skin.[30] Because of its capability to open water channels rapidly in addition to carrier-mediated transport, AQP 10 more than AQP3 would be a possible candidate for the abnormal reaction of palmar skin to water immersion. When expression of AQP3 is increased by all-trans retinoic acid, none of the features of AK develop.[31] AK therefore seems to represent the product of sympathetic over-activity and rapid changes of water holding capacity by AQPs.

AK can be associated with CF and it is extremely important to exclude pauci-symptomatic or heterozygous CF with the use of the appropriate ancillary studies.[2,32]

A variety of topical treatments have been published. Based upon available data, pathogenesis and own experience, we suggest avoidance of water immersion, the use of aluminum salts or iontophoresis.[33-35]

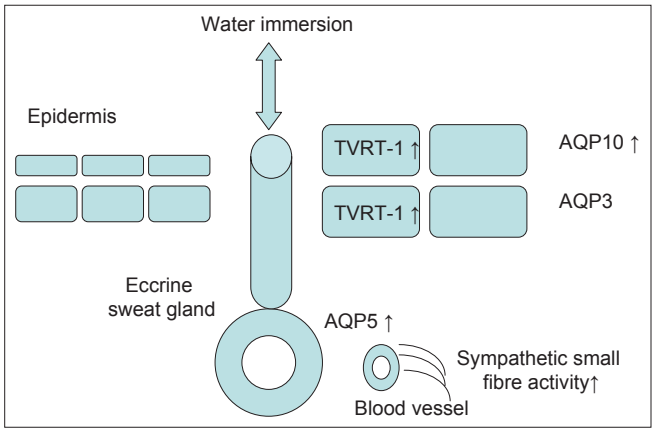

Figure 3: Aquagenic keratoderma (AK) pathogenesis. Normal epidermis (left), AK skinafter water immersions (right). The secretory coil in AK shows an increased expression of aquaporin (AQP) 5. Water immersions and secretion of hyperosmotic sweat activates osmosensitive transient vanilloid receptor type-1, increasing the $Ca2^{+}$-influx, and AQP 10. Skin wrinkling is further attenuated by small sympathetic fiber activity

Botulinum toxin A (BoNT-A) is effective in hyperhidrosis and it affects preganglionic sympathetic and parasympathetic nerves and postganglionic parasympathetic nerves. Some authors obtained good results with intracutaneous injections of BoNT-A in AK.[36,37] We recommend BoNT-A for cases not responding to topical treatment, as second line therapy.

In conclusion, AK is an exogenous skin disease based upon increased sympathetic activity, possible involvement of TVRT-1, and increased expression of selected AQPs in involved skin [Figure 3].

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