
Familial aquagenic urticaria associated with familial lactose intolerance

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Aquagenic urticaria is a rare disorder characterized by the occurrence of pruritus and wheals after temporary contact with water. The familial occurrence of aquagenic urticaria over 3 generations is reported here in association with familial lactose intolerance, a condition in which the enzyme lactase encoded on chromosome 2, is deficient. In two patients, a young man and his mother, we verified the appearance of pruritic hives 5 to 10 minutes after contact with water of any temperature. Other types of physical urticaria were absent, and mastocytosis was excluded by extensive laboratory investigations; lactose intolerance was confirmed in both patients by H₂-exhalation test. In these patients the clinical symptoms did not respond to antihistamines or UV-radiation therapy. Four other members of the family had wheals from water contact, two of whom had lactose intolerance. Two other members had lactose intolerance only. Although the association of aquagenic urticaria with lactose intolerance may be coincidental, attention is drawn to the fact that the 2 conditions, known to be familial, may coexist in the same family, possibly based on an association of gene loci. (*J Am Acad Dermatol* 2002;47:611-3.)

Aquagenic urticaria is a rare disorder in which contact of the skin with water of any temperature leads to pruritus and the appearance of wheals, as described first by Shelley and Rawnsley¹ in 1964. Angioedema or wheezing when drinking water was reported occasionally; further systemic reactions were not found.¹⁻⁹ Fewer than 50 patients with this disease have been described in the medical literature, and in a few cases the symptoms also were present in other family members.^{3,10} Here, we report for the first time the occurrence of aquagenic urticaria in several members of a family. This family also had familial intolerance to lactose, but not all members of the family had both sensitivities.

CASE REPORT

A 19-year-old white man presented with history of pruritic wheals appearing after contact of his skin with water of any temperature in a time period of 5 to 20 minutes. These lesions appeared when taking a bath or a shower, in the rain, in a swimming pool, in the ocean, and after sweating that was the result of heat or exercise. The lesions did not appear after

contact with his own tears or when drinking water. Symptoms had started in early adolescence with worsening during the last months. In 2 episodes dizziness occurred after having taken a shower. Treatment with oral cetirizine, taken 30 minutes before water contact, only initially alleviated the symptoms. In the history, the patient reported diarrhea after milk ingestion since his early childhood, and seasonal allergic asthma treated with an inhaled bronchodilator. He was presented at the Berlin Department to judge his symptoms and his capability for army recruitment.

Four other members of the family, all females, suffered from the same symptoms after contact with water. In the mother and grandmother, the symptoms had first appeared in early age and had become worse over the years. In one aunt and in a cousin, 48 and 24 years old, respectively, the symptoms were reported to be less prominent, requiring long water contact for arising urticarial lesions. In the mother, neither antihistamines nor UV radiation over 6 weeks relieved the symptoms. In a recent consultation she reported that the symptoms had become worse, even appearing after application of a body lotion. Consequently, all affected members of the family reduced water contacts in frequency and duration.

Diarrhea after ingestion of milk products also occurred in the mother, the grandmother, one sister, and an uncle (Fig 1). In all these family members milk intolerance had been noticed in childhood or early adolescence; none of them had inflammatory

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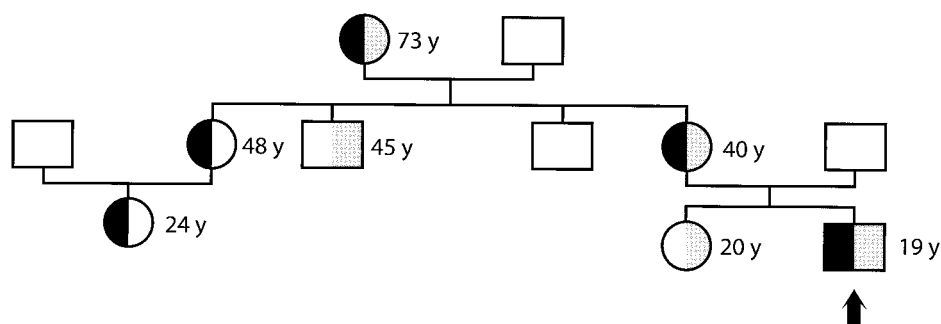


Fig 1. Aquagenic urticaria (black) and lactose (gray) intolerance in a family: pedigree of 3 generations. Females (circles) were affected more often than men (rectangles). Both diseases were present either in combination with or independent from each other. Presenting patient is identified by arrow; ages of patients are given in years (y).

bowel disease. Therefore, they all avoided fresh milk or products containing high amounts of milk in their diet.

RESULTS

In the young man, application of wet dressings, a shower, a bath, and exercise-induced sweat led to the appearance of pruritus and hives of 2 to 3 mm in diameter after 5 to 10 minutes, mainly on the trunk, upper arms, thighs, and feet; the palms and soles remained free of lesions. Symptoms were independent of the water's temperature. Examinations for other types of physical urticaria (cold, heat, pressure) as well as dermatographism were negative. Histologic examination of a biopsy specimen taken from a wheal showed edema of the papillary dermis, no increased amounts of mast cells, and no eosinophils. Electron microscopy also showed intercellular edema without any other alterations.

All routine blood tests performed were within the normal range. Repeated determinations of serum tryptase (Pharmacia, Germany) were taken before and 5, 30, and 60 minutes after the patient had taken a shower and disseminated hives had occurred; stable values between 4 and 5 ng/ml (normal values <13.5) were found.

Prick testing showed positive reactions to grass pollen, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*, and was negative for distilled water. Total IgE was normal, 42.5 kU/L, specific IgE was not detectable against casein, lactoglobulin, or lactalbumin by means of an enzyme immunoassay test (CAP-FEIA, Pharmacia).

Lactose intolerance was diagnosed by measurements of breath hydrogen: the H₂-exhalation test, based on the hydrogen value released from unabsorbed lactose, showed a breath hydrogen excretion of 92 ppm H₂ after 120 minutes (normal value: 50 ppm).

Exposure of the mother of the patient to tap water under supervision in the hospital confirmed local appearance of pruritus and numerous hives measuring 2 to 3 mm in diameter. Clinical and laboratory examinations of the mother for other types of physical urticaria and cutaneous/systemic mastocytosis were negative, whereas type 1 sensitization to birch pollen was found and the H₂-exhalation test was positive, indicating the presence of lactose intolerance. Other members of the family were not available for physical examination.

DISCUSSION

In aquagenic urticaria, wheals usually appear after contact with water, irrespectively of the source or temperature, and clear within 30 to 60 minutes.¹⁻¹⁰ Only 1 patient has been reported to react exclusively to cold water.¹¹ The condition has to be differentiated from aquagenic pruritus, in which contact with water induces itching without visible lesions, and from cholinergic urticaria, in which lesions occur with heat, sweating, exertion, or emotional stress.¹² Cholinergic and aquagenic types of urticaria may, however, be associated.¹³

The patients presented here had a typical history of aquagenic urticaria with regard to the development, location, and size of the wheals, independent of type and temperature of the water. There were no signs that other physical factors or mastocytosis were involved in producing the clinical symptoms.

The pathogenesis of aquagenic urticaria is still not fully understood. Initially, a toxic substance has been assumed to be formed by water acting on sebum or the sebaceous gland.¹ Such substances may cause perifollicular mast cells to degranulate, releasing histamine and resulting in hives. Also other mediators such as acetylcholine, serotonin, and bradykinin have been discussed as possibly relevant.¹⁴ On the other hand, water-soluble antigens in the

epidermal horny layer may diffuse into the dermis to cause a histamine-controlled allergic reaction.¹⁵

For treatment of aquagenic urticaria, antihistamines have been used (ie, hydroxyzine, cyproheptadine, terfenadine, cetirizine, promethazine) with various responses.^{3,16} The effect of a combination of UVB with hydroxyzine in controlling the symptoms was reported.⁹ In our patients, no prolonged therapeutic effect was achieved by either antihistamines or by UVB radiation. PUVA therapy was reported to be effective in 1 patient, but it only partially improved the symptoms in another report.^{16,17} The effect of UV radiation may result in thickening of the epidermis with subsequent reduced penetration of water, interaction with dendritic cells, and immunosuppression or decreased mast cell response.^{3,15} In one HIV-positive patient, aquagenic urticaria responded to stanazolol treatment.¹⁸

In a few cases, aquagenic urticaria was reported to be familial.^{1,3,10,15} Women seem to be more often affected than men; our patient was the only affected male in his family. Association of aquagenic urticaria with other diseases, some of them being genetically determined, has been described, ie, atopy, polymorphous light eruption, cholinergic urticaria, HIV infection, and cancer of the lung.^{3,14,17,18} In the family described here, the association of familial aquagenic urticaria with familial lactose intolerance over 3 generations is reported.

In lactose intolerance individuals have a deficiency in the enzyme lactase, which hydrolyzes lactose into glucose and galactose. Nonhydrolyzed lactose leads to shifts of fluid into the intestinal tract with diarrhea as the main clinical symptom. The condition may be either hereditary or acquired (ie, in sprue, enteritis, or infections of the intestinal tract). The hereditary form is present in most tropical and in all subtropical countries as well as in East Asian populations, with high prevalences in African Americans and Asian Americans; in whites the prevalence is lower.¹⁹ Chromosome 2q21 was identified to carry the responsible gene regulating the manufacturing of the enzyme lactase.²⁰ The age of manifestation may differ: The adult-type lactase deficiency is the most frequent, usually starting in childhood or adolescence. Although the exact underlying defect is not known, an autosomal recessive trait is discussed. In two other types, the symptoms start in neonates (congenital lactase deficiency, autosomal recessive trait) or in early childhood (congenital lactose intolerance, autosomal dominant trait suspected).¹⁹⁻²² In our patients, the clinical absence of infectious signs or inflammatory bowel disease together with the familial occurrence is pointing out a hereditary form, possibly the adult-type lactase deficiency.

Although the reported association of aquagenic urticaria with lactose intolerance may be regarded as coincidental, we wish to draw attention to the fact that the 2 conditions known to be occasionally familial may coexist over several generations, possibly based on an association of gene loci.

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