
Aquagenic urticaria: report of a case and review of the literature

Khanh vinh quoc Luong, MD, FACP and Lan Thi Hoang Nguyen, MD

Objective: To present a case of aquagenic urticaria and to review the literature regarding this very rare physical urticaria.

Method: We described the clinical history of a patient with aquagenic urticaria. A water challenge test was performed, with plasma histamine levels measured before and after the challenge.

Result: Our patient presented with a history of severe itching and wheals within five minutes of contact with water, regardless of its temperature or source (sea or tap water). A water challenge produced hives but serum histamine levels did not change. Prophylaxis with antihistamine or anticholinergic medications was not effective.

Conclusion: Exposure to water can cause urticaria in susceptible patients and antihistamine and anticholinergic medication may not prevent the reaction. The mechanism of this phenomenon remains poorly understood.

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INTRODUCTION

Water is an essential constituent of the human body. Contact of the skin with water is an unavoidable condition. This contact is considered harmless and often pleasurable. It is difficult to realize that some people may react adversely to contact with water. For a small number of patients, contact with water at any temperature may be associated with cutaneous discomfort, such as pruritus and urticaria.^{1,2} In the present paper, we report a case of aquagenic urticaria (AU).

CASE PRESENTATION

A 20-year-old Vietnamese male had suffered headache, respiratory distress, severe itching, and wheals within five minutes of contact with water. These symptoms would occur regardless of temperature or source (sea or tap water) of water. The urticaria usually lasted for approximately 15 to 20 minutes. The lesions occurred on almost all parts of the body except for the palms and soles; however, he was able

to drink water without problem. The problem had been present persistently for over the last 10 years. Some doctors told him that he had a “psychogenic problem” when he sought medical advice about his illness. There was no personal or family history of atopy. A general physical examination yielded no abnormal findings, except for dermatographism. Laboratory studies including serum chemistry and electrolytes, blood counts and thyroid function tests were normal or unrevealing. The serologic studies were negative for rheumatoid factor and syphilis.

A water challenge test was applied by washing patient’s face with cool tap water at room temperature. His face developed small punctuate wheals (1 to 2 mm in diameter) on an erythematous base in the area of contact with water within five minutes. He had associated headache and shortness of breath with bilateral wheezing on auscultation. The urticaria spontaneously resolved without residue after 20 minutes. Plasma histamine was collected with result as follows: before water challenge, 74 ng/mL (normal, 25–175) and during urticaria, 88 ng/mL.

The patient failed to respond to prophylaxis with antihistamines (terfena-

dine and hydroxyzine) and anticholinergic agents (scopolamine patch). He avoided swimming and learned to bath rapidly and to dry himself quickly.

DISCUSSION

Aquagenic urticaria is a rare form of physical urticaria in which contact with any source of water (for example, sea or tap water) evokes hives. The condition must be differentiated from aquagenic pruritus, first described by Greaves et al,¹ in which contact with water induces itching without cutaneous lesions. In AU, tap and distilled water appear to be equally effective in evoking wheals^{2–5}; while direct contact with ice for 15 to 300 seconds or application of ice cubes in a thin plastic film produced no urticarial response.^{2,6,7} There was one reported patient who had no urticaria when swimming in the ocean.⁸ Urticarial reaction did not occur with either acetone or absolute acetone when these substances were applied locally for 5 minutes^{2–6}; this observation indicated that organic solvents did not evoke the reaction as the water did. These same experiments showed that pretreatment of the skin with organic solvents enhanced the subsequent urticarial response to challenge with water. A solution of lanolin, mineral oil, and a nonionic emulsifier in bath water greatly reduced the number of hives.⁶ Intradermal injection of triamcinolone acetonide also prevented the development of wheals after contact with water.⁹ Approximately 25 cases have been reported in the medical literature (Table 1). Familial AU was noted in some patients.^{2,5,6,7,10} Serum IgE and complement C1-esterase inhibitor levels were normal. Females were affected more often than males (Table 1).

Of interest, dermatographism may be present, especially in male patients

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Table 1. Summary of Some Characteristic of Aquagenic Urticaria Reported in the Literature

Number	References	Age	Sex	Dermographism	Associated condition
1	2	27	Female		None
2	2	?	Male		?
3	2	24	Female		None
4	3	49	Male	Absence	None
5	4	30	Female		None
6	4	14	Female		None
7	5	29	Female	Absence	None
8	5	?	Female		?
9	5	?	Female		?
10	5	17	Female		None
11	6	15	Female	Absence	None
12	6	17	Female	Absence	Achlorhydria
13	6	?	Male	Presence	?
14	6	20	Male	Presence	Asthma
15	7	30	Female	Presence	None
16	7	40	Female		None
17	8	30	Female	Absence	None
18	9	55	Male	Presence	Wheezing with drinking water
19	10	33	Female	Absence	Polymorphous light eruption
20	10	?	Male		Lung cancer
21	11	3	Male		None
22	12	21	Female		None
23	13	7	Male	Presence	Asthma
24	20	11	Female		Cholinergic urticaria
25	21	29	Male	Absence	None
26	*	20	Male	Presence	Wheezing with water challenge

* Our patient.

with a history of asthma.^{6,9,13} Further, systemic reactions were not reported in AU. Our patient, however, experienced a systemic symptom, such as wheezing, during the water challenge. These findings suggested an association between cutaneous and bronchial hyperreactivity. Henz et al¹⁴ reported that patients with urticarial dermatographism had an increase in airway resistance and a decrease in specific airway conductance. The reflex erythema surrounding urticarial wheals is currently thought to be mediated by an axon reflex and by release of substance P from free nerve endings in the skin¹⁵; high levels of substance P have been demonstrated in urticarial lesions.¹⁶ Substance P is of special interest in immediate allergic reaction since it also causes bronchial edema and bronchoconstriction¹⁷; increased cutaneous reactivity to substance P has been reported in patients with asthma.¹⁸

The pathogenesis of AU is not completely understood, but several mechanisms have been proposed. In 1964,

Shelley and Rawnsley⁶ first described three cases of AU. They suggested that water reacts with component in or on the stratum corneum, sebum, forming a toxic compound that is absorbed and released histamine from the perifollicular mast cells. Chalamidas and Charles³ further supported this hypothesis. They performed patch testing with a patient's own sweat, which produced erythema and pruritus without urticaria, while patch testing with both the patient's own sweat and sebum produced marked perifollicular hives and erythema. Later, Sibbald et al⁴ found that the removal of the stratum corneum exaggerated the ability of the skin to respond to challenge with water. They suggested that whatever the nature of the stimulus-response coupling mechanism, it requires a close association between water and components in the epidermis or dermis. Furthermore, Czarnetzki et al.⁵ suggested that patients with AU react to a water-soluble antigen in the epidermal horny layer that diffuses into the dermis to

cause histamine release from sensitized dermal mast cells. Injected aqueous extracts of human callus intracutaneously resulted in burning sensations in the patients' skin but not in control skin. Injection of buffer alone or of supernatants of stimulated epidermal cell suspension induced no abnormal reactions in patients' skin or control skin. Callus extracts also caused in vitro basophilic histamine release from patients' peripheral blood basophils but not from cells of a healthy volunteer.

Acetylcholine is believed to be the chemical mediator that initiates sweating and it may produce degranulation of mast cells around the sweat glands, thus releasing histamine and producing hives.^{3,4,6} This phenomenon can usually be initiated in affected individuals by the subcutaneous injection of methacholine chloride only in sweat areas. Methacholine chloride injected intradermally in the same subject, however, did not evoke any response.⁶ The involvement of acetylcholine in the pathogenesis of AU is suggested by

the ability of the specific acetylcholine antagonist scopolamine to suppress the whealing response to water application.⁴ Histamine appears to be another chemical mediator in this phenomenon. This was demonstrated by a marked urticarial reaction to intradermal injection or topical massage of histamine liberator substance (48/80) in AU.^{3,6}; however, there was no urticarial response in normal subject injected with substance 48/80.³ False negative responses can occur when the exhaustion of the histamine supply has occurred. Chalamidas and Charles³ demonstrated an exhaustibility of the phenomenon by repeating showers in AU patient. They noticed the only faint perifollicular erythema without any pruritus or hives at the end of the fifth shower. Aquagenic urticaria is also associated with elevated blood histamine levels and degranulation of mast cells in the water-challenged skin. Before bathing, the baseline venous blood histamine concentration was less than 1 ng/mL. After challenge with water, it rose to a maximum of 6.5 ng/mL.⁴ That activity was attributed to histamine because the response of the smooth muscle preparation to the venous blood samples was blocked by a specific histamine antagonist mepyramine. High proportions of degranulated mast cells were presented in affected skin.^{6,9} In addition, oral antihistamines before exposure to water can suppress the clinical reaction in AU.^{4-6,8,11} Our patient, however, had a normal histamine level with water challenge and he failed to respond to prophylaxis to antihistamine and anticholinergic agents; these findings did not support the roles of acetylcholine and histamine in our patient. Such observations also were noted in other reports.^{4,9} Sibbald et al⁴ reported that one of their patients had a normal histamine level after challenge with water. Anticholinergic agents did not prevent the urticarial reaction in another AU patient.⁹ In addition, tissue specimens from urticarial lesions revealed no perifollicular mast cells.^{3,4}

Antihistamines have been used in the treatment of AU. Ultraviolet (UV)

therapy may be considered as an alternative treatment if antihistamines fail to prevent the urticarial reaction. Psoralen/ultraviolet A (PUVA) therapy was effective in one patient,¹⁰ but only partially improved in other report.¹² Parker et al,¹³ reported the effect of a combination of ultraviolet B (UVB) and hydroxyzine in controlling UA symptoms. The effect of PUVA could be an immunosuppression or decreased mast cell response.¹⁹ A thickening of the epidermis after UV treatment may also contribute to the improvement of this disorder by inhibiting the penetration of water.

In conclusion, our patient presented with AU. His serum histamine levels did not change with a positive water challenge and he failed to respond to prophylaxis with antihistamine and anticholinergic medications. These findings do not support the roles of histamine and acetylcholine in our patient, leaving the mechanism of his AU unexplained.

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Request for reprints should be addressed to:
Khanh V Q Luong, MD
9188 Bolsa Ave
Westminster, CA 92683