

# Aquagenic Urticaria: A Perplexing Physical Phenomenon

Cindy Wassef<sup>1</sup>, Anacristina Laureano<sup>2</sup>, Robert A. Schwartz<sup>2</sup>

<sup>1</sup>Dermatology, Stony Brook University, Stony Brook, New York, USA; <sup>2</sup>Dermatology, Rutgers University New Jersey Medical School, Newark, New Jersey, USA

## Corresponding author:

Professor Robert A Schwartz MD,  
MPH, DSc (Hon), FRCP Edin  
Dermatology  
Rutgers New Jersey Medical School  
185 South Orange Avenue H-576  
Newark  
New Jersey 07103  
[roschwar@cal.berkeley.edu](mailto:roschwar@cal.berkeley.edu)

**ABSTRACT** Aquagenic urticaria (AQ) is a rare physical urticaria induced by contact with water. It may be distinctive clinically, evident as 1-2 mm folliculopapular urticaria, a pattern also characteristic of cholinergic urticaria. AQ has a truncal and upper extremity distribution within 20-30 minutes after contact with water, regardless of its temperature or source. AQ is usually symptomatic with mild to severe pruritus and a burning sensation. The mechanism by which water produces mast cell degranulation and histamine release remains unclear. We review its clinical presentation, diagnostic parameters, differential diagnosis, and treatment.

**Key words:** aquagenic urticaria, physical urticaria

Received: March 7, 2017

Accepted: July 21, 2017

## INTRODUCTION

Aquagenic urticaria is a type of physical urticaria produced by contact with water. It was first described in 1964 as a reaction to a toxic component of water, leading to mast cell degranulation and urticaria (1). Further hypotheses regarding the cause of this urticaria include acetylcholine propagated histamine release and mast cell degranulation secondary to epidermal antigen diffusion into the dermis upon contact with water (2,3). However, when histamine levels are measured before and after water challenge with aquagenic urticaria, histamine levels may remain within normal limits and symptoms may not be prevented with the use of antihistamines or anticholinergics (4). In this review of aquagenic urticaria, we will describe its various clinical presentations, diagnostic assessments, differential diagnoses, and treatments.

## CLINICAL PRESENTATION AND DIAGNOSIS

Aquagenic urticaria is produced when water comes into contact with the epidermis. Urticaria is produced irrespective of water temperature, pH, or

psychogenic factors (5,6). Incidence is slightly greater in women than in men; onset is usually on or around puberty. Approximately 100 cases have been reported in the literature (6). In general, wheals are seen within 20-30 minutes of aqueous contact and subside 30-60 minutes after water is removed. Alcohol or other organic solutions do not cause an urticarial reaction, but can propagate the effect of water by enhancing its permeability through skin (6). Shelley and Rawnsley (1) first described this entity as primarily 1-2 mm folliculopapular urticaria with a truncal and upper extremity distribution, associated with mild to severe pruritus and burning (Figure 1).

Clinical criteria that needed for this diagnosis include elimination of other physical urticarias as a cause of symptomatology and a positive response to a water provocation test (6). The standard water provocation test is a 30-minute application of water compresses at 35 degrees Celsius; however, local application of water to other areas following negative compress testing can also be done (4,6-8). While ur-

**Table 1.** The differential diagnoses to be considered when evaluating a patient for aquagenic urticaria

Differential diagnosis	History and physical exam findings
Cholinergic urticaria	<u>Induced</u> by exercise, sweat, heat, emotion  Sweat-induced: perform exercise that induces sweating and observe for urticaria formation Localized heat-induced: compress test with compress soaked in hot water
Delayed pressure-induced urticaria	Apply a weight of 0.2-15 kg/cm <sup>2</sup> to a localized area for 20 minutes and after its removal observe for any urticaria
Solar urticaria	Expose skin to varying wavelengths of ultraviolet and visible light and observe for urticaria
Dermatographic urticaria	Perform maneuvers that induce dermatographism and observe for urticaria
Cold-induced urticaria	Apply an ice pack to a localized area for 20 minutes and observe for any hive or wheal formation
Contact-induced urticaria	Perform a prick test and then document for wheal formation over a 20 minute period
Aquagenic pruritus	Elicit pruritus upon exposure to water but no hive formation

ticaria can be induced by water of any temperature, maintaining the water at room temperature aids in differentiating aquagenic urticaria from cold-induced or local heat urticaria (9). In addition, the compress test is often done on the upper body as opposed to the extremities because the extremities are less frequently affected by aquagenic urticaria (6). This test is considered positive if pruritic hives are noted in the tested area. Familial associations have been noted, with one case of monozygotic twins both having aquagenic urticaria; however, no specific gene locus has been identified and most reported cases are sporadic (6,10). One cases series described the association of aquagenic urticaria and lactose intolerance over three generations as a possible gene loci association (11). A family history of atopy has occasionally but not consistently been reported among those affected (6). Other symptoms sometimes noted in association with physical urticaria upon contact with water include headache, wheezing, shortness of breath,



**Figure 1.** Multiple folliculopapular wheals on the back of a 25-year-old woman affected by aquagenic urticaria. Lesions are extremely pruritic and appeared following a luke-warm shower.

and dizziness (4,11). Routine laboratory values including erythrocyte sedimentation rate, complete blood count, total eosinophil count, glucose, electrolytes, liver and kidney function tests, and immunoglobulins including IgE, anti-nuclear antibodies, cryoglobulins, VDRL, cold agglutinins, and complement levels are usually all within normal range (7,12).

### DIFFERENTIAL DIAGNOSIS

Aquagenic urticaria must be differentiated from other physical urticarias, particularly from cholinergic urticaria and aquagenic pruritus. A thorough history and physical examination with a focus on factors that trigger urticaria and specialized in-office procedures help to eliminate other causes on the differential diagnosis list. Aquagenic and cholinergic urticaria are identical clinically; differentiation of the two is based upon inciting factors. Cholinergic urticaria can be induced by exercise, sweating, heat, and emotion while aquagenic urticaria is limited to water-induced lesions only (6). Various physical exam findings can also help differentiate aquagenic urticaria from other physical urticarias. To differentiate from delayed pressure-induced urticaria, one can apply a weight of 0.2-1.5 kg/cm<sup>2</sup> to a localized area for 20 minutes and observe for any wheals after its removal (9). Solar urticaria can be tested for by exposing skin to varying wavelengths of ultraviolet and visible light; dermatographic urticaria can be elicited simply by performing maneuvers that induce dermatographism, such as a stroke test. Contact urticaria can be identified by performing a prick test and then observing for wheal formation over a 20-minute period (9). Cold-induced urticaria can be tested for by applying an ice pack to a localized area

for 20 minutes and observing for any wheal formation (9,10). Having the patient perform activities that induce sweating and then observing them for a period of time can aid in differentiating aquagenic from sweat-induced urticaria (6). Cholinergic urticaria is traditionally tested via exercise, but it can also be evaluated by intradermally injecting either 0.05 mL of 0.002% carbamylcholine chloride (carbachol) or 0.05 mL of 0.02% (0.01 mg) methacholine and observing for any wheals, which are usually seen in 51% of subjects (15). Aquagenic pruritus is characterized by pruritus upon exposure to water, but lacks the characteristic hive formation seen in aquagenic urticaria (6) (Table 1).

### TREATMENT

Pre-exposure non-sedating, second-generation H1 antihistamines are a first-line treatment and have had effects varying from complete symptom control to no response (6,7,10,14). Dosing amounts vary; doses up to four times the amount of the standard daily dose have been administered (10). A minority of cases are resistant to anti-histamines and other anecdotal therapies. PUVA and UVB may control symptoms in patients resistant to antihistamines (15-18). Ultraviolet light may alleviate symptoms of aquagenic urticaria by thickening the epidermis and thus prevent the penetration of water (15). Combination PUVA and antihistamines have also been used. In one instance, PUVA therapy was begun in an antihistamine resistant case with methoxsalen 0.6 mg/kg four times a week with a starting UVA level of 3 J/cm<sup>2</sup>, which was gradually increased by 1 J/cm<sup>2</sup> until a maximum dose of 12 J/cm<sup>2</sup> was reached. After two weeks, new wheal formation had ceased; however, the patient was still pruritic with water contact, which was confirmed by a water provocation test. After 20 sessions, the patient started receiving PUVA only once weekly, and two weeks later new lesions were noted. Astemizole 10 mg/day was then added to her regimen and all symptoms cleared (16). PUVA may theoretically offer benefits through epidermal thickening. In one case of antihistamine-resistant aquagenic urticaria in a patient with HIV, stanazolol 10 mg/day treatment was successful in resolving the symptomatology (19). Barrier creams have also been used as treatment for aquagenic urticaria. These topical agents prevent water contact with the skin by creating a barrier with a hydrophobic agent such as petrolatum (15). Barrier creams have varying efficacy, providing complete avoidance of symptoms in some cases while only allowing for prolonged exposure to water before the development of hives in others (2,15,20). Omalizumab, a recombinant anti-IgE antibody, may be used in selected patients (21).

### CONCLUSION

With only 100 cases reported in the literature, aquagenic urticaria is a rare yet potentially debilitating form of physical urticaria (6). While the complete pathogenesis of this entity has not been fully elucidated, the role of histamine appears to be central. Accordingly, non-sedating, second-generation H1 antihistamines have emerged as the gold standard of treatment (6,7,10,14). In the antihistamine-resistant patient, barrier creams and stanazolol may show efficacy, as may the recombinant humanized monoclonal anti-IgE antibody omalizumab (2,15-21). The presence of these resistant cases indicates that another underlying factor is contributing to aquagenic urticaria. Further research into this factor will help in generating better clinical treatments.

### References:

1. Shelley WB, Rawnsley HM. Aquagenic urticaria. contact sensitivity reaction to water. *JAMA* 1964;189:895-8.
2. Sibbald RG, Black AK, Eady RA, James M, Greaves MW. Aquagenic urticaria: evidence of cholinergic and histaminergic basis. *Br J Dermatol* 1981;105:297-302.
3. Czarnetzki BM, Bretholt KH, Traupe H. Evidence that water acts as a carrier for an epidermal antigen in aquagenic urticaria. *J Am Acad Dermatol* 1986;15:623-7.
4. Luong KV, Nguyen LT. Aquagenic urticaria: report of a case and review of the literature. *Ann Allergy Asthma Immunol* 1998;80:483-5.
5. Seol JE, Kim DH, Park SH, Kang JN, Sung HS, Kim H. Aquagenic Urticaria Diagnosed by the Water Provocation Test and the Results of Histopathologic Examination. *Ann Dermatol*. 2017;29:341-5.
6. Dice JP. Physical urticaria. *Immunol Allergy Clin North Am* 2004;24:225-46, vi.
7. Rothbaum R, McGee JS. Aquagenic urticaria: diagnostic and management challenges. *J Asthma Allergy*. 2016; 29:209-13..
8. Bonnetblanc JM, Andrieu-Pfahl F, Meraud JP, Roux J. Familial aquagenic urticaria. *Dermatologica* 1979;158:468-70.
9. Arıkan-Ayyıldız Z, Işık S, Çağlayan-Sözmen S, Karaman O, Uzuner N. Cold, cholinergic and aquagenic urticaria in children: presentation of three cases and review of the literature. *Turk J Pediatr* 2013;55:94-8.
10. Park H, Kim HS, Yoo DS, Kim JW, Kim CW, Kim SS, et

- al.* Aquagenic urticaria: a report of two cases. *Ann Dermatol* 2011;23:S371-4.
11. Kai AC, Flohr C. Aquagenic urticaria in twins. *World Allergy Organ J* 2013;6:2.
  12. Treudler R, Tebbe B, Steinhoff M, Orfanos CE. Familial aquagenic urticaria associated with familial lactose intolerance. *J Am Acad Dermatol* 2002;47:611-3.
  13. Mathelier-Fusade P, Aissaoui M, Chabane MH, Mounedji N, Leynadier F. Association of cold urticaria and aquagenic urticaria. *Allergy* 1997;52:678-9.
  14. Schwartz RA. Cholinergic urticaria. *eMedicine from WebMD*. Updated 2017. Available at: <http://emedicine.medscape.com/article/1049978-overview>
  15. McGee JS, Kirkorian AY, Pappert AS, Milgraum SS. An Adolescent Boy with Urticaria to Water: Review of Current Treatments for Aquagenic Urticaria. *Pediatr Dermatol* 2014;31:116-7.
  16. Martínez-Escribano JA, Quecedo E, De la Cuadra J, Frías J, Sánchez-Pedreño P, Aliaga A. Treatment of aquagenic urticaria with PUVA and astemizole. *J Am Acad Dermatol* 1997;36:118-9.
  17. Juhlin L, Malmros-Enander I. Familial polymorphous light eruption with aquagenic urticaria: successful treatment with PUVA. *Photodermatology* 1986;3:346-9.
  18. Parker RK, Crowe MJ, Guin JD. Aquagenic urticaria. *Cutis* 1992;50:283-4.
  19. Fearfield LA, Gazzard B, Bunker CB. Aquagenic urticaria and human immunodeficiency virus infection: treatment with stanozolol. *Br J Dermatol* 1997;137:620-2.
  20. Bayle P, Gadroy A, Messer L, Bazex J. Localized aquagenic urticaria: efficacy of a barrier cream. *Contact Dermatitis* 2003;49:160-1.
  21. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, Pfoehler C, Staubach P, Treudler R, Wedi B, Magerl M. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. *J Allergy Clin Immunol*. 2017 Jul 24. [Epub ahead of print].

