

Localized salt-dependent aquagenic urticaria: a subtype of aquagenic urticaria?

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Summary

Aquagenic urticaria is a rare form of inducible urticaria characterized by wealing at the site of contact of the skin with water, regardless of its temperature, within minutes of exposure. We describe six young women who reported urticarial rashes, triggered mostly by sea bathing, characteristically localized on the inferior facial contours and neck. In four of the six patients, this was the only localization. All six reacted with erythema and wealing to challenge tests with hypertonic saline (3.5% NaCl) applied to the submandibular area and/or neck. Two patients reacted also to tap water or to normal saline, but less intensely. Challenge tests with different hypertonic water solutions, performed in one patient, showed that both salinity and hypertonicity may be pathogenically relevant. Response to antihistamines was poor in three patients. Our experience suggests the existence of a distinct salt-dependent subtype of aquagenic urticaria (SDAU) that affects young women, with a characteristic localization on the inferior facial contours and neck. SDAU is possibly under-recognized and under-reported.

Aquagenic urticaria (AU) was first described by Shelley and Rawnsley in 1964,¹ and about 50 cases have subsequently been reported. In 2001, we described a case of localized AU apparently dependent on the ionic concentration and/or osmolarity of water.² The patient was a young woman whose urticarial rashes were restricted to the lower facial contours, and were more intense on contact with sea water and hypertonic saline than with tap water. We report six further cases with similar characteristics.

Report

Six women (mean $\pm$ SD age 29.6 ± 10.63 years, range 19–47 years) presented to us over a period of time, with each reporting that sea bathing induced fleeting, highly pruritic urticarial rashes on their face

(periauricular, mandibular and/or submandibular regions) and neck. None had a family history of similar symptoms. Three reported that the reaction sometimes involved the upper chest and shoulders as well. The reaction cleared within 30 min after showering with tap water, except in one patient who experienced similar, although attenuated, symptoms from contact with tap water as well. Another patient reported problems with both sea and swimming-pool bathing, but not with tap water. Application of a water-in-oil (W/O) barrier cream before sea bathing attenuated the rash in most of the patients, whereas antihistamines at standard dosage were effective only in three of them. The patients' clinical characteristics, investigations and results are summarized in Table 1.

All patients were challenged with tap water and with a hypertonic NaCl water solution (3.5%, iso-osmolar with sea water) at room temperature, by means of soaked compresses applied for 20 min to their mandibular region or neck, and also to the antecubital flexures as control areas. Additional challenges were performed in individual patients, depending on their willingness to undergo further

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Table 1 Summary of clinical characteristics and challenge test results.

Clinical characteristics				Water-challenge tests*						
Patient	Gender/age, years	AU duration, years	Trigger(s)	Involved body areas	Other conditions	Response to anti H1†	Tap water	3.5% NaCl	Other solutions	Additional information
1	F/19	4	Sea water	Periauricular(sub) mandibular	No	Yes	NR	++	ND	ND
2	F/37	18	Sea water (also sweat, sporadically)	Facial contours	Allergic rhinitis	No	NR	++	5.3% NaHCO ₃ (++), 3.5% KCl (++), distilled water (NR), glucose 20% (NR)	Up to four times the standard 5 mg dose of desloratadine was necessary to inhibit wealing from the 3.5% NaCl challenge. Topical capsaicine before the 3.5% NaCl challenge inhibited pruritus but did not inhibit the weal and flare reaction
3	F/29	> 10	Sea water	Periauricular(sub) mandibular neck, trunk	Allergic rhinitis, food allergy	Yes	NR	++	ND	—
4	F/47	> 10	Sea water	Periauricular(sub) mandibular	Allergic rhinitis	Yes	NR	+	ND	The reaction was limited to sites where, owing to gravity, water accumulated during the test
5	F/21	1	Sea water, swimming-pool water, tap water	Periauricular(sub) mandibular neck, upper chest	No	Partial	+	++	Distilled water (NR)	ND
6	F/25	3	Sea water, swimming-pool water (also sweat, sporadically)	(sub)mandibular neck, décolleté	No	No	±	++	Normal saline (+)	ND

Anti-H1, antihistamine 1; ND, not done; NR, no reaction. ±, Patches of faint itchy erythema. +, Pruritus with few tiny weals and patchy erythema; ++, pruritus with diffuse erythema and numerous weals. All patients underwent serum electrophoresis, and tests for anti-nuclear antibody, anti-thyroid antibodies, rheumatoid factor, and C3-C4. *Water-challenge tests with hypertonic saline (3.5% NaCl) applied on the submandibular region of 20 control subjects elicited no reaction; †at standard dose.

tests. In particular, one patient was challenged with different aqueous solutions iso-osmotic with 3.5% NaCl, namely 3.5% KCl, 5.3% NaHCO₃ and 20% glucose (the glucose to verify the effect of a hypertonic non-ionic trigger). She was also tested with 3.5% NaCl, 5 h after receiving increasing doses (5, 10, 15, 20 mg) of desloratadine and 30 min after pretreatment of the tested area with capsaicin 0.1% aqueous solution for 1 min (sufficient to cause a transient burning sensation without erythema).

AU is a rare disease that affects both genders, but has a female predominance. Familial cases have been reported.^{1–4} The usual clinical presentation consists of small, intensely pruritic weals, reminiscent of cholinergic urticaria, most commonly localized to the neck, upper trunk and arms. They develop within 5–20 min of contact with water, regardless of its temperature, and resolve within 30–60 min. The most commonly reported trigger is tap water, followed by sea water, but swimming-pool water, rain, snow and even sweat, tears and saliva have sometimes been implicated.^{2–7} Association with other forms of inducible urticaria and, exceptionally, with systemic symptoms, has been reported.^{3,8}

The diagnosis is based on the clinical history and on water-challenge tests, usually consisting of compresses soaked with tap water at room temperature and applied to the upper body for 30 min. Different water/aqueous solutions and different body areas can be tested, depending on the patient's history. AU must be differentiated from aquagenic pruritus and from other forms of inducible urticaria that may develop after water exposure, in particular cold urticaria.

The pathogenesis of AU is obscure. A cholinergic mechanism has been suggested but never confirmed.⁹ It was also suggested that water may act as a solvent and vehicle of some toxic sebum component¹ or of some stratum corneum-derived antigen, which would then diffuse into the dermis, causing histamine release from mast cells.⁴ However, aquagenic wealing was shown to be worsened, rather than prevented, by complete removal of the stratum corneum.⁹

A peculiar feature of our six patients is that they all reported sea bathing to be a trigger of their urticaria and they all reacted to a challenge test with 3.5% NaCl (Fig. 1). Furthermore, when patient 2 was challenged with different water solutions that were iso-osmotic with sea water, she reacted intensely to all solutions containing salts (3.5% NaCl, 3.5% KCl and 5.3% NaHCO₃), whereas she did not react to a similar osmotic load with hypertonic glucose, or to distilled and tap water. Therefore, both salinity and hypertonicity seem to be pathogenically relevant, at least in some patients.

Two other patients reacted also to tap water or normal saline, although less intensely than to hypertonic saline (Fig. 2), which is in accordance with our previous report,² and suggests the existence of a subtype of AU that is dependent on salt concentration, and is part of a spectrum of severity, with milder forms triggered only by hypertonic salty solutions. The literature reports only one patient who developed hives from contact with hypotonic aqueous triggers, such as tap water and snow, but not with sea water. However, this was not confirmed by specific challenge tests.⁷

We hypothesize that the transient receptor potential 1 vanilloid subtype (TRPV1) channel may play a role in salt-dependent aquagenic wealing. In fact, this non-selective sodium permeable channel can act as a 'cellular sensor' of osmotic concentration.¹⁰ Treatment



Figure 1 Positive challenge test with hypertonic saline in a typical localization of salt-dependent aquagenic urticaria.



Figure 2 Strong reaction to hypertonic saline (left side of the neck) compared with the faint reaction to normal saline (right side of the neck) in patient 6.

with topical capsaicin, a well-known activator/desensitizer of TRPV1, was therefore attempted in patient 2. Application of capsaicin before a hypertonic NaCl challenge in this patient suppressed the itch but was unable to prevent the erythema and wealing. The hypothesis that some salt/osmotic-sensitive receptor may be involved in the pathogenesis of AU remains intriguing nonetheless.

Treatment of SDAU includes reducing contact with water and the application of W/O lotions before sea bathing. Anti-histamines may be helpful, but some patients are refractory or respond only to high doses. SDAU is possibly under-recognized and under-reported, as two of our patients reported their sea bathing-induced urticaria incidentally during a referral for patch testing. Other patients may fail to properly describe wealing and report only itchy erythema. This, in turn, may be misinterpreted as a generic sign of reactive/sensitive skin, particularly in patients with atopy.

In conclusion, SDAU may represent a distinct AU subtype affecting young woman with a peculiar, sometimes exclusive, localization at the lower facial contours and neck. This feature is so characteristic that, in our opinion, SDAU should be suspected and investigated in any young woman who reports fleeting pruritic rashes in this location.

Learning points

- AU is characterized by wealing at the site of contact of the skin with water, regardless of its temperature, within minutes of exposure.
- The most commonly reported trigger is tap water.
- A salt-dependent subtype of aquagenic urticaria (SDAU) is triggered mostly by sea bathing, and affects young women, with a characteristic localization on the inferior facial contours and neck.
- SDAU should be suspected and investigated in any young woman who reports fleeting pruritic rashes in this location.
- SDAU can be confirmed by applying a gauze pad soaked with a hypertonic NaCl water solution (3.5 g%), at room temperature, to the mandibular regions or neck for 20 min. Tap water

should be tested on the opposite side of the face/neck.

- Treatment of SDAU consists of reducing the time of contact with water and in the application of W/O lotions before sea bathing. Anti-histamines are sometimes helpful, but high doses may be required in refractory cases.

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CPD questions

Question 1

What is salt-dependent aquagenic urticaria?

- a) A form of allergic contact urticaria.

- b) A form of cholinergic urticaria occurring only in female patients.
 - c) An itchy condition mainly triggered by salty water that occurs mainly during sea bathing.
 - d) A generalized form of aquagenic urticaria sparing the face.
 - e) A condition usually associated with serum auto-immune markers (anti-thyroid and anti-nuclear antibodies).
- e) Application of gauze pads soaked with hypertonic salty water to the lower facial contours, neck, or upper chest.

Question 2

The clinical suspicion of salt-dependent aquagenic urticaria can be confirmed by which of the following?

- a) Prick testing with hypertonic salt water.
- b) Intradermal tests with salt water.
- c) Application of gauze pads soaked with salty water to the antecubital flexures for 20 min.
- d) Application of gauze pads soaked with a 30% glucose solution for at least 20 min.

Instructions for answering questions

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