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Salt dependent aquagenic urticaria: nine new cases and proposal for a diagnostic work-up

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To the Editor,

AquaU is an uncommon form of Chronic Inducible Urticaria (CIndU) characterized by whealing at the site of contact of the skin with water, regardless of its temperature, within minutes of exposure (1). A salt-dependent subtype of aquagenic urticaria (SDAU) has been described that could represent either a distinct variant or part of a severity spectrum of AquaU (2). We herein present nine new patients whose characteristics are consistent with SDAU and we suggest a standardized diagnostic workup for AquaU. We retrospectively reviewed the data of nine female patients (mean age $\pm$ SD, 26.78 $\pm$ 12.36 years) diagnosed with SDAU in our dermatology department from 2016 to 2022. Only one had a family history of similar symptoms and 7/9 had an atopic background. These patients reported highly pruritic urticarial rashes triggered by sea bathing; some of them also reported different degrees of

reactivity to tap water, swimming-pool water and sweat. They underwent the diagnostic workup shown in **figure 1**. The results are summarized in **table I**.

AquaU is considered rare, but its true prevalence is unknown, and it has been suggested that mild cases might be frequent and underestimated (2). It is predominant in young female patients and most cases are sporadic, although a classification into familial AquaU and acquired AquaU has been proposed (3). In addition to fresh and sea water, other rarely reported aqueous triggers include rain, snow, tears and saliva. Wheals commonly occur in localized body areas (mainly trunk and lower face/neck) even in case of exposure of the whole body to water (3, 4). They develop within minutes of water contact and rapidly resolve after its cessation. The pathogenesis of AquaU is a mystery. The different hypothesis so far suggested include the generation of either a toxic substance or of an auto-allergen derived from water-soluble components present in

Table 1 – Clinical characteristics, type of water triggers, results of water challenge tests and treatment in nine patients with SDAU.

Gender/ age (yr)	Atopic back- ground	Total IgE (normal range 0.0- 100.00 KU/l)	Triggers			Timing		Localiza- tion	Water challenge tests			Response to treatment					
			Sea wa- ter (sea bathing)	Tap water	Swim- ming pool water	Sweat or oth- er aqueous triggers (e.g. rain)	Latency of wheals		Duration of wheals	Body areas affected	3.5% NaCl: soaked pads on specific areas		Tap water: soaked pads on specific areas	Tap water: full body	AntiH1 stan- dard dose	Other drugs	
F/30	Allergic rhinitis	31.6	No	No	4	Yes	Yes***	Yes	Sporadically sweat	10'	30-60'	Mandibular area, neck, chest	+	Neg	10' bath ++	Partial response	None
F/24	Allergic rhinitis	130.0	No	No	5	Yes	Yes**	No	Sporadically sweat	10'	60'	Mandibular area, neck, chest, upper back, shoulders	+	Neg	15' shower ++	Good response	None
F/17	Allergic asthma	89.0	No	No	3	Yes	Yes*	No	No	15'	10'	Neck, décolleté, upper back	+++	++	Not per- formed	Poor response	None
F/57	No	47.8	No	Cold u.	2	Yes	No	Yes	No	15'	30'	Widespread	++	+/-	Not per- formed	Partial response	None
F/17	Allergic asthma	300.0	No	No	1	Yes	Yes***	No	Sporadically sweat	15'	30'	Mandibular area, neck, upper trunk	++	+	Not per- formed	Good response	None
F/19	Allergic rhinitis	150.0	No	No	3-4	Yes	Yes*	Yes	Sweat	10'	60'	Neck, décolleté, shoulders	+++	+	Not per- formed	Partial response	None
F/27	Allergic rhinitis and asthma	70.9	No	No	10	Yes	Yes*	Yes	No	10'	60'	Trunk and arms	++	+	Not per- formed	Poor response	None
F/29	No	45.6	Yes, mother	No	20	Yes	Yes***	Yes	No	10'	30-60'	Face, neck, décolleté, shoulders	+/-	Neg	15' shower ++	No treat- ment	None
F/21	Previous atopic derma- titis and allergic rhinitis	176.0	No	Dermo- graphic urticaria	10	Yes	Yes*	Yes	No	10'	30'	Face, neck, décolleté, shoulders, lower limbs	+/-	Neg	10' shower ++	Partial response	Con- trolled by omalizumab

Triggers: *shower, **bath, ***face washing; U: Urticaria; Anti-HI: anti-histamines; none of the patients had systemic symptoms; all patients underwent full blood count, C-reactive protein, tests for anti-nuclear antibodies, C3-C4 and anti-thyroid antibodies with unremarkable results; all patients underwent an ice cube test for cold urticaria as described in the EAACI/ GA2LEN/EDF/ WAO consensus recommendations for ClnDU; all patients underwent water challenge tests with tap water and with a 3.5% NaCl water solution (iso-osmolar with the Mediterranean Sea water) at room temperature, by means of soaked compresses applied for 20' to the body areas that they reported as more intensely affected by AquaU; four patients who reported urticaria from contact with both sea water and tap water but reacted positive to the local challenge with salty water only, underwent a full body tap water challenge test at home (bath or shower without any concomitant use of shower/bath products); the consequent skin reactions were documented by neat pictures taken by patients with their smartphones; intensity of positive reactions to water challenge tests: +/- patches of faint itchy erythema, + pruritus with few (1-4) tiny wheals surrounded by erythema, ++ pruritus with 5 to 10 wheals surrounded by erythema, +++ intense pruritus with diffuse erythema scattered with more than 10 wheals.

Figure 1 - Diagnostic workup of patients presenting with a history suggestive of aquagenic urticaria.

the sebum (5) or in the stratum corneum (6), respectively. The recently reported effectiveness of omalizumab in some patients suggests a role for circulating IgE (2, 7). Sudden changes in osmotic pressure around hair-follicles have also been advocated (3, 4, 8) and may account for SDAU. With the inclusion of the nine cases here described, the number of patients reported to react to salty water (42/118) accounts for 35.6% of total AquaU published cases (2-4, 7-10).

Based on our experience and on the characteristics described by other authors (8-10), many SDAU patients have an atopic background (16/27, 59%) and whealing frequently involves their lower face and neck (20/27, 74%). These associations are difficult to interpret. An altered skin barrier function in atopic patients and a high concentration of hair follicles in the mandibular area might play a role. Basically, the diagnosis of AquaU depends on a suggestive clinical history combined with a provocation test, the common method for which is to apply a cloth dampened with water at room temperature to the skin for 20 minutes, with an urticarial reaction indicating a positive test. We suggest that all patients with suspected AquaU should undergo local challenge tests with both tap water and salty water (NaCl 3.5%, iso-osmolar with sea water), as salty water may be more sensitive, and it may lower the threshold of response. If this observation of ours were confirmed, it would support the hypothesis that salinity is a relevant parameter for AquaU in general. Other water challenges, tailored on the patient's history, are sometimes necessary to clarify the diagnosis (4) (**figure 1**).

In conclusion, we propose a standardized diagnostic work-up (**figure 1**) to be applied in all suspected cases of AquaU to harmonize future reports of the disease.

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Contributions

RG: conceptualization, data investigation, methodology, project administration, supervision, validation, visualization, writing - original draft, writing - review & editing. IT: data curation, methodology, project administration, software, visualization, writing - original draft, writing - review & editing. GG: meth-

odology, software, validation, visualization, writing - original draft, writing - review & editing. RC: software, validation, visualization, writing - review & editing. GM: data curation, investigation, methodology, visualization, writing - review & editing. AP, EC: supervision, validation, visualization, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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