

## Aquagenic Urticaria: A Review of Literature and Case Reports

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### Abstract

**Background:** Hypersensitivity to specific stimulus presenting as pruritic wheals is pathognomonic of urticaria, a common malady worldwide, but such vulnerability to water is a rare and a distressing phenomenon requiring considerable lifestyle modifications. Aquagenic urticaria, a rare subtype of urticaria is most probably an allergic response to water. Though histamine is the most potent mediator of the phenomenon, a few reports implied that acetylcholine and genetic predisposition also plays a crucial role in the pathogenesis. Till date only a limited number of case reports are available worldwide with indefinite etio-pathogenesis and treatment guidelines. Therefore it is of utmost importance to summarize the available theranostics to provide guidance for the management of the condition and explore the future possibilities in light of recent advancements in understanding the pathophysiology of the disease. We attempt to describe the pathogenesis, case reports to the best of our knowledge and available treatment options from the literature.

### Introduction

According to *Gerald W. Volcheck*, "Urticaria represents transient, localized areas of oedema within skin tissue that appear as pruritic, raised erythematous, skin-colored or white, non-pitting, blanching plaques of variable size" [1]. Urticaria term was first used by a Scottish physician *William Cullen* in 1769 [2]. 'Urticaria' word has its origin from a Latin word *urtica*, meaning stinging hair or nettle, as the classical presentation follows the contact with a perennial flowering plant '*Urtica dioica*' [3]. The history of urticaria dates back to 1000-2000BC with its reference as a wind type concealed rash in a book "The Yellow Emperor's Inner Classic" authored by *Huang Di Nei Jing*. *Hippocrates* in 4th century first described urticaria as 'Knidosis' after the Greek word 'Knido' for nettle [4]. The discovery of mast cells by *Paul Ehrlich* in 1879 bro-

ught urticaria and similar conditions under a comprehensive idea of allergic conditions [5].

Aquagenic urticaria or 'water allergy' once known as a rare physical urticaria is reclassified as separate subtype of urticaria [6]. It was first reported by *Walter B Shelley* et al in 1964 [7]. Pruritic hives on contact with water mostly presenting for the first time during puberty in females of reproductive age is seen in aquagenic urticaria. Males are less often affected [8,9,10]. Even if majority cases are sporadic in nature, familial cases are also recorded [8, 11, 12]. Water in all forms such as tap or sea water, swimming pool, sweat, tears, saliva can induce the lesions [13,14,15].

## Clinical Features

It is usually a self-limiting allergic disorder characterised by the appearance of pruritic hives on exposure to the water irrespective of its nature [16, 17]. Lesions usually appear as 2-3 mm sized pin point papules on reddish base [18]. Erythematous lesions are distributed primarily on upper half of body [19, 20, 21, 22]. Few cases presented with associated dermatographism [12]. In most cases, characteristic lesions appear within half an hour of exposure lasting for 30 to 90 minutes [11, 12, 13, 23]. Duration of contact dictates the number, severity and duration of persistence of lesions. Episode of aquagenic urticaria may be followed by a refractory period up to several hours [12]. A few cases demonstrated salinity and high temperature of water as additional invoking factors for lesions to appear [24, 25]. Hives may appear atypically as a localized subtype on sea water exposure [25]. Exercise induced perspiration and humid environment is also reported to invoke lesions in susceptible individuals [12, 14]. In some cases organic solvents do not induce pruritic wheals themselves but augments the subsequent response to water challenge [13]. Oral mucosal swelling, burning sensation in mouth or facial oedema on drinking water is a less common presentation [20, 23]. Lesions are not produced by any pressure or UV exposure [12, 19]. Usually it is not associated with other systemic symptoms but extra-cutaneous manifestations like seasonal allergic rhinitis, migraine and bronchial asthma are also reported [9, 12, 23]. More than one subtype may be present in individual producing overlapping symptoms [26, 27, 28].

Disorders of immune dysregulation like HIV or Hepatitis C infection may have an associated aquagenic urticaria presentation [23]. In a few reports aquagenic urticaria has shown a tendency of familial inheritance [22]. A possible association with familial lactose intolerance has been suggested by appearance of characteristic lesions in cases over 3 generations [11]. Lesions of aquagenic urticaria more intense on saline or hot water exposure were reported in 3 siblings of a family with *Bernard Soulier syndrome* [8]. A few cases of aquagenic urticaria with extra cutaneous manifestations and salt dependency is depicted in (Table 1).

## Pathophysiology of Aquagenic Urticaria

Even though underlying pathophysiology of the aquagenic urticaria is poorly understood, several contrivances have been proposed. *Shelley and Rawnsley* postulated that water when reacts with sebum produces a noxious substance which causes the mast cell degranulation and histamine release causing pruritis, later supported by *Chalamidas et al* [12, 13]. Wheal is due to antidromic sensory nerve vasodilation [12]. Raised blood histamine levels and local mast cell degranulation is usually seen in acute stage [13, 23]. *Tromovitch* concluded the presence of potential water soluble foreign irritants like bacterial antigens that do not occur within the normal epidermis or sebaceous secretions are responsible for the hives [29]. *Sibbald et al* debated against above mentioned postulates since the removal of the stratum corneum or factors enhancing permeation of water through it amplified the hypersensitive response to water [13, 30]. He proposed possibility of water induced activation of the cholinergic pathway leading to the histamine release which is supported by high blood level of histamine in the patients. As per *Czarnetzki et al* water-soluble antigen in the epidermal horny stratum penetrates into the dermis causing the release of histamine from sensitized dermal mast cells [31] This claim is supported by the good response to UV therapy which causes skin thickening and local immune suppression which prevents mast cell degranulation [20, 32].

*Tkach* suggested the passive diffusion of water around the hair follicles changes in osmotic pressure as the mechanism of the urticarial [30]. It's also stated that 5% saline is more effective in provoking wheals when compared to distilled water reflecting the influence of change in salt concentration and osmolality [24]. Association of hydrogenic urticaria with familial syndromes like lactose intolerance and *Bernard-Soulier* depicts the involvement of different gene loci. Raised IgE levels resulting from altered T and B lymphocyte interactions may be related to the appearance of aquagenic urticaria in some immune-compromised patients [23, 33, 34].

**Table 1.** Aquagenic Urticaria with Extra Cutaneous Manifestations

S. no	Year	Age and sex	Clinical presentation	Place	Management	Outcome	Reference
1.	1986	29 Female	Aquagenic Urticaria with polymorphous light eruptions  Complain of pruritic hives following shower and skin eruptions with joint swelling and swelling following sun exposure	UK	Psoralen +UVA (PUVA) therapy	Disease condition improved	28
2.	1997	40 Male	A forty year aged male who is positive for HIV and hepatitis C and intra venous drug abuse consulted with a complaint of emergence of pruritic hives on the body within 5-10 minutes after swimming and vanished within 30-40 minutes. Similar complaints occurred on exposure to water. Swelling and burning sensation in mouth, shortness of breath.	Spain	1) H1 and H2 receptor antagonist like hydroxyzine, chlorpheniramine and cimetidine.  2.Stanozol 10mg/day	Antihistamines had no therapeutic effect. Stanozol successfully controlled the symptoms.	23
3.	2004	11 Male	Boy aged 11 years with pruritic hives on exposure to water regardless of its physical properties and source. Erythematous lesions of size 2-3 mm appeared more on trunk, predominantly in hairy areas than extremities and lasted for 20-40 minutes. History of one or two incidents of bronchospasm allied to sweating.	USA	Antihistamine Hydroxyzine 25mg twice daily	Patient is asymptomatic after one month follow up	20
4.	2005	20 Female	Aquagenic urticaria with migraine  Women aged 20 year having atopic rhinitis and asthma consulted with a complaint of multiple events of pruritic hives on exposure to water since last 3 years. Lesions were of size 1-4 cm, developed within 5 minutes regardless the nature of the water and existed for about 20 minutes.	Spain	1) Initially on Doxepin 25mg and cetirizine 10mg daily.  2)Cyproheptadine 4mg twice daily and scopolamine 1.5mg patch for 10 days  3) Scopolamine was replaced with methylscopolamine bromide 2.5mg orally.  4) Migraine was dealt with sertraline 25mg daily	Regime one was unable to control hives and headache  Regime two successfully controlled symptoms  Anticholinergic side effects were effectively reduced by regime three  Migraine was controlled within 2 weeks of medication	9
5.	2006	30 Female	Aquagenic urticaria with Bernard Soulier in a thirty year old female. Wheals developed on exposure to salt and normal water, more on trunk than extremities. Mother and two female siblings of the patient of age 26 and 24 years had Bernard soulier syndrome.	Brazil	Antihistamines  Patient was on cetirizine 5 mg and hydroxyzine 25mg daily prior to contact with water. Siblings were managed with cetirizine 5mg daily	Partial improvement in patients and disappearance of lesions in siblings.	8
6.	2013	Female	6 young women with pruritic hives localized on face & neck on sea water exposure	Italy	Antihistamines	Poor response	25

We can conclude that even if mechanism of urticaria is not clearly understood, evidence from the case reports suggests it as a histamine mediated one [13, 23]. This is supported by the partial or complete refraction from the symptoms by antihistamines [18]. Reported cases and investigations also suggest other etiologic mechanisms of urticaria like antigen-antibody complexes, cryoglobulins, and cold agglutinins [19]. Acetylcholine or methacholine is projected as the mediator of the histamine release whose role is not clearly drawn [13, 19]. This justifies the further need of study in this field.

### Diagnosis & Work Up

Coexistence of various subtypes of urticaria may pose a diagnostic challenge & warrants the prudent usage of clinical skill and diagnostic tools. Wide spectrum of eliciting factors demands meticulous history, physical examination and laboratory investigations. History should have comprehensive details regarding the lesions and associated symptoms. It includes onset of lesions, size and distribution, triggering factors, frequency and duration of symptoms and associated any pruritus or pain. Personal history of allergy, drug intake, life style and work environment should be asked for. Family history of similar complaints, autoimmune and allergic disorders is to be enquired [12, 35]. Appropriate questions should be asked to rule out bleeding disorders, immunocompromised state and lactose intolerance in the patient and family [8, 11, 23].

In most of the cases physical examination is normal without any evidence of skin disorder [19, 20, 29]. Test for dermatographism should be included. Immunocompromised patients presenting with aquagenic urticaria should be carefully examined for coexisting cutaneous disorder like drug allergy, lichen planus, vasculitis, porphyria cutanea tarda, mixed essential cryoglobulinaemia [23, 36].

Investigations include specific laboratory test for specific associated systemic diseases and specific test for triggers. Complete blood count, coagulation profile, metabolic profile, complement, antinuclear and anticytoplasmic antibodies, rheumatoid factor, cryoglobu-

lins, c1 esterase inhibitor, immunoglobulin, lesional skin biopsy, allergen tests are few of the investigations required as per the clinical assessment [6, 8, 11, 23]. Degree of basophilic degranulation and release of histamine can be estimated by Fluorescence-activated cell sorting of blood sample [20]. Radical screening is not recommended [6].

Specific provocation tests helps to differentiate subtypes and triggering factors example Cold provocation test (cold urticaria), Pressure test (delayed pressure urticaria), Heat provocation & threshold test (heat contact urticaria), Exercise test (cholinergic urticaria), Patch test (contact urticaria) and Water challenge test (aquagenic urticaria). Water challenge test involving application of 35°C wet compress to upper part of body for 30 minutes producing pruritic pin point hives is highly suggestive of aquagenic urticaria [10, 16, 37]. Prior application of topical atropine at the site of water challenge test can help to differentiate the symptoms arising from associated cholinergic urticaria in selected cases [18, 38].

### Management

The more poignant part of this disorder is the lack of desensitization for water as allergen even on repeated exposure [20]. Avoidance of allergen as a general principle in any allergic disorder necessitates the evasion of water exposure. Topical application of antihistamines like 1% diphenhydramine before water exposure is reported to reduce the hives [24]. Oil in water emulsion creams, petrolatum as barrier agents for water can be used prior to shower or bath with good control of symptoms [13, 39]. Therapeutic effectiveness of various classes of drugs differs from case to case. Antihistamines were used successfully in most of the case [10, 18, 20]. First generation antihistamines like chlorpheniramine maleate, cyproheptadine and hydroxyzine were commonly used in earlier cases. Sedation was the main drawback [12, 13, 27]. In recent years newer generation antihistamines with better patient compliance like Cetirizine, Desloratidine, Rupatidine, Ketotifen are used [7, 17, 21]. Anticholinergic drugs like methscopolamine

may be required in addition to Antihistamines for adequate control [9].

A case with incomplete response to antihistamines alone has shown complete resolution with no lesions on water exposure with concomitant escalating doses of PUVA therapy for 2 weeks [32]. However another similar case reported to have only partial improvement by UVB therapy. The photochemotherapy (PUVA) has also shown complete resolution of symptoms in aquagenic urticaria complicated with polymorphous light eruptions in a case [28]. Migraine as extra-cutaneous symptom in one of the cases is reported to be controlled by low dose Sertraline [9]. SSRI's has shown promising results in controlling chronic urticaria associated with panic disorder suggesting the probable similarity of mediators in pathogenesis of Panic disorder, Migraine and urticarial [9, 40]. Effective use of Stanozolol in hereditary angioedema and familial cold urticaria and Danazol in cholinergic urticaria conceived the idea of using of Stanozolol in resistant cases of aquagenic urticarial [39, 41, 42]. Stanozolol in low daily dose is reported to completely control the symptoms in a HIV positive patient resistant to conventional treatment [23].

## Conclusion

Recent progress in dermatology has explored many postulated theories behind the pathogenesis of this rare urticaria. Aquagenic urticaria even if rare, severely affects the quality of life by its agonizing symptoms, protracted course and unpredictability. Different treatment regimens have been tried with limited success, theranostic approach should be considered for personalized treatment. More studies with a holistic view is required for better understanding of cellular and molecular mechanism, possible gene loci association for familial cases and treatment options for this chronic urticaria.

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