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AQUAGENIC URTICARIA: ETIOLOGY, GENETICS, PATHOGENESIS, AND DIAGNOSTICS

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Abstract

Background

Aquagenic urticaria (AU) is a rare form of inducible physical urticaria characterized by the development of pruritic wheals following contact with water, regardless of its temperature or source. Despite its paradoxical nature, the condition remains poorly understood, with limited data on its etiology, genetic basis, and underlying mechanisms.

Objective

This review aims to provide a comprehensive and critical synthesis of current evidence on aquagenic urticaria, focusing on its etiology, genetic predisposition, pathogenesis, and diagnostic approaches, while identifying key gaps in knowledge and directions for future research.

Methods

A structured literature review was conducted using PubMed, Scopus, and Google Scholar, including studies published from 1964 to 2026. Relevant case reports, clinical studies, and review articles were analyzed, with emphasis on clinical presentation, mechanistic insights, and diagnostic strategies.

Results

Available evidence indicates that AU is predominantly sporadic and idiopathic, with occasional familial cases suggesting a potential genetic component. Mast cell activation and histamine release represent the central effector

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mechanisms; however, the upstream trigger remains unidentified. Proposed hypotheses include sebum–water interactions, skin barrier dysfunction, and non-histaminergic pathways involving cytokines and neuropeptides. Diagnosis relies on the water provocation test, supported by clinical history and exclusion of other inducible urticarias.

Conclusions

Aquagenic urticaria remains a poorly understood condition despite decades of clinical observation. Current evidence supports a multifactorial model involving immune, genetic, and barrier-related factors, although definitive mechanisms have not been established. Further research, particularly genomic and mechanistic studies, is required to clarify disease pathways and improve diagnostic and therapeutic strategies.

Keywords

aquagenic urticaria; inducible urticaria; mast cell activation; histamine; skin barrier; diagnosis; rare disease

1. Introduction

Aquagenic urticaria (AU) is among the rarest of the inducible physical urticarias, a heterogeneous group of conditions in which urticarial reactions are provoked by a definable external physical stimulus. Since its original description by Shelley and Rawnsley [1] as a "contact sensitivity reaction to water," AU has attracted sustained clinical and investigative interest disproportionate to its prevalence, largely because of the paradoxical nature of a hypersensitivity response to a universally encountered substance. Although rare, aquagenic urticaria represents a diagnostically challenging condition and is frequently under-recognized in clinical practice, often leading to delayed diagnosis and reduced quality of life.

The condition is clinically characterized by the rapid onset of small (1–3 mm), intensely pruritic wheals surrounded by a prominent erythematous flare, typically appearing within minutes of water contact and resolving spontaneously within 30 to 60 minutes [2, 3]. These lesions preferentially involve the neck, upper trunk, and arms — areas of greatest cutaneous contact with water — though any water-exposed body surface may be affected [4]. Importantly, AU is not temperature-dependent; reactions occur with water of all temperatures, distinguishing it from cholinergic urticaria and aquagenic pruritus [5].

The population affected is predominantly female, with onset most commonly reported in the second or third decade of life, although cases in children, adolescents, and older adults have been described [2, 4]. The clinical burden is

substantial: affected individuals may experience reactions during bathing, swimming, perspiration, rain exposure, and even the consumption of aqueous beverages in severe cases, profoundly limiting daily activities and quality of life [3, 6].

Despite decades of reported cases, the pathophysiology of AU remains incompletely understood. Several mechanistic hypotheses have been proposed — ranging from the generation of a toxic substance from water-soluble follicular antigens to direct mast cell degranulation — but none has been conclusively validated at the molecular level [21, 28]. The genetic basis of the condition is similarly unresolved, with a minority of familial cases suggesting a possible heritable component, yet no causative gene has been identified to date [11–13].

Despite over six decades of clinical observation, the absence of large-scale mechanistic and genetic studies continues to limit a comprehensive understanding of AU. This literature review aims to provide a comprehensive and critical synthesis of current knowledge on AU across four key domains: its etiology, genetic aspects, pathogenesis, and diagnostic methodology. By integrating findings from case reports, systematic reviews, and mechanistic studies, this review seeks to delineate current evidence, highlight existing controversies, and identify key directions for future research.

2. Etiology

The etiology of aquagenic urticaria (AU) is multifactorial and, in the majority of cases, no identifiable precipitating cause or associated systemic condition is found. AU is therefore most often classified as an idiopathic inducible urticaria. However, a range of associated conditions and proposed triggering mechanisms have been described in the literature, although their causal relevance remains uncertain.

2.1 Classification and Subtypes

Rujitharanawong and colleagues [4] categorized AU into distinct subgroups: familial AU, AU associated with systemic or dermatological conditions, and sporadic (idiopathic) AU. This classification is clinically relevant, as it suggests potential heterogeneity in underlying mechanisms. However, the limited number of reported cases and the predominance of case-based evidence restrict the ability to validate these subtypes as biologically distinct entities.

2.2 Associated Conditions

Several reports have described AU occurring in association with other conditions, including HIV infection, hematological malignancies, and co-existing physical urticarias [2, 4, 10]. A notable familial case described by Treudler et al. [8] reported co-occurrence with lactose intolerance, raising the possibility of shared

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metabolic or genetic pathways. Nevertheless, these associations remain largely observational, and no direct causal relationships have been established.

Additional observations, such as AU onset following epilation or sea water exposure, suggest that disruption of the skin barrier may play a contributory role in lowering the threshold for water-induced reactions. Similarly, reports of overlapping cholinergic and histaminergic responses indicate that AU may not represent a single uniform entity but rather a spectrum of inducible urticaria phenotypes.

2.3 Demographic and Epidemiological Features

AU affects individuals across all age groups and ethnicities, with a consistent female predominance reported in the literature [2–4]. Onset typically occurs during adolescence or early adulthood, suggesting a possible role of hormonal or developmental factors, although this remains speculative and insufficiently studied. The true prevalence of AU is unknown but is considered extremely low, which significantly limits large-scale epidemiological investigation.

The rarity of AU contributes to frequent diagnostic delays and under-recognition in clinical practice. This highlights the need for increased clinician awareness and standardized diagnostic approaches.

Table 1. Summary of Key Reported Cases and Studies of Aquagenic Urticaria

Author	Year	Study Type	Key Findings
Walter B. Shelley & Hugh M. Rawnsley	1964	Case report	First description of aquagenic urticaria; proposed sebum interaction hypothesis
R. Rothbaum & J. S. McGee	2016	Review	Highlighted diagnostic challenges and importance of provocation testing
C. Rujitharanawong et al.	2022	Systematic review	Identified subtypes of AU and emphasized clinical heterogeneity
A. C. Kai & C. Flohr	2013	Case report (twins)	Provided evidence supporting genetic predisposition
R. Treudler et al.	2002	Case report	Familial AU associated with lactose intolerance
J. E. Seol et al.	2017	Clinical study	Confirmed mast cell activation via biopsy during WPT
K. Kulthanan et al.	2022	Review	Demonstrated central role of histamine in inducible urticarial
P. Abdi et al.	2024	Case report	Highlighted clinical variability and management challenges

3. Genetics

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The genetic basis of aquagenic urticaria remains poorly understood. While most cases are sporadic, evidence from familial reports and twin studies suggests that heritable factors may contribute to disease susceptibility in a subset of patients.

3.1 Familial Cases

Familial AU cases provide early evidence supporting a genetic component. Reports of parent–child transmission [12, 13] suggest a possible hereditary pattern; however, the absence of genetic analysis in these cases limits interpretation. These observations may reflect shared genetic susceptibility, environmental exposure, or both.

3.2 Twin Studies

The report of monozygotic twins affected by AU [11] represents one of the strongest indications of a genetic contribution. Nevertheless, the interpretation of twin concordance is limited by the inability to fully exclude shared environmental influences. As such, while suggestive, these findings are insufficient to establish a definitive genetic mechanism.

3.3 Genetics of Urticaria — Broader Context

Insights from the broader field of urticaria genetics indicate that variants in immune-related genes, including those involved in histamine signaling and cytokine regulation, may contribute to disease susceptibility [16]. However, no studies have specifically investigated these pathways in AU, representing a significant gap in current knowledge.

3.4 Current Limitations and Future Directions

A major limitation in the field is the absence of genome-wide or targeted genetic studies specifically focused on AU. The rarity of the condition, combined with potential genetic heterogeneity, poses significant challenges for traditional genetic approaches. Future research employing next-generation sequencing in well-characterized familial cases may provide critical insights into underlying mechanisms.

4. Pathogenesis

The pathogenesis of aquagenic urticaria (AU) has been the subject of considerable investigation and debate since the condition's initial description. While mast cell activation with histamine release is widely accepted as a central event, the upstream mechanisms by which water contact triggers this activation remain incompletely defined. Current evidence suggests that AU is not driven by a single mechanism but likely represents a heterogeneous condition involving multiple interacting pathways.

4.1 The Mast Cell Hypothesis

Mast cell degranulation with consequent histamine release is regarded as the primary effector mechanism in most AU cases. Rothbaum and McGee [21] described both histamine-dependent and histamine-independent pathways, noting that while antihistamines are effective in many patients, incomplete responses in others suggest additional non-histaminergic mechanisms.

Histopathological studies demonstrate perivascular and interstitial infiltrates of degranulated mast cells in lesional skin [23, 24], supporting their central role. Seol et al. [23] further confirmed mast cell activation following water provocation testing with concurrent biopsy. These findings establish mast cell activation as a consistent downstream event, although they do not explain the initiating trigger.

4.2 The Shelley Hypothesis: Sebum-Water Interaction

The Shelley hypothesis proposes that water interacts with a water-soluble component of sebum or follicular contents to generate a substance capable of inducing mast cell degranulation [28]. This theory is supported by the localization of lesions in sebum-rich areas and the involvement of the pilosebaceous unit.

However, despite its conceptual appeal, no biochemical mediator has been identified, and the hypothesis remains unproven at the molecular level [24, 28, 29]. This lack of direct evidence limits its explanatory power and suggests that it may represent only one component of a broader pathogenic process.

4.3 Non-Histaminergic and Alternative Mechanisms

The presence of antihistamine-refractory cases indicates that non-histaminergic pathways may contribute to disease expression. Proposed mechanisms include the involvement of cytokines, neuropeptides, and other vasoactive mediators [25, 30].

Clinical heterogeneity in symptom severity and treatment response further supports the possibility of multiple underlying mechanisms. It is plausible that AU represents a spectrum of related conditions rather than a single uniform disease entity.

4.4 Role of the Skin Barrier

An emerging area of interest is the role of skin barrier integrity. Disruption of the stratum corneum may facilitate the penetration of water or water-soluble substances into deeper skin layers, where mast cells reside, thereby lowering the activation threshold.

This hypothesis is supported by observations of AU onset following epilation and parallels with other barrier-related conditions such as atopic dermatitis. However, direct experimental evidence remains limited, and the precise contribution of barrier dysfunction requires further investigation.

4.5 Proposed Integrated Model

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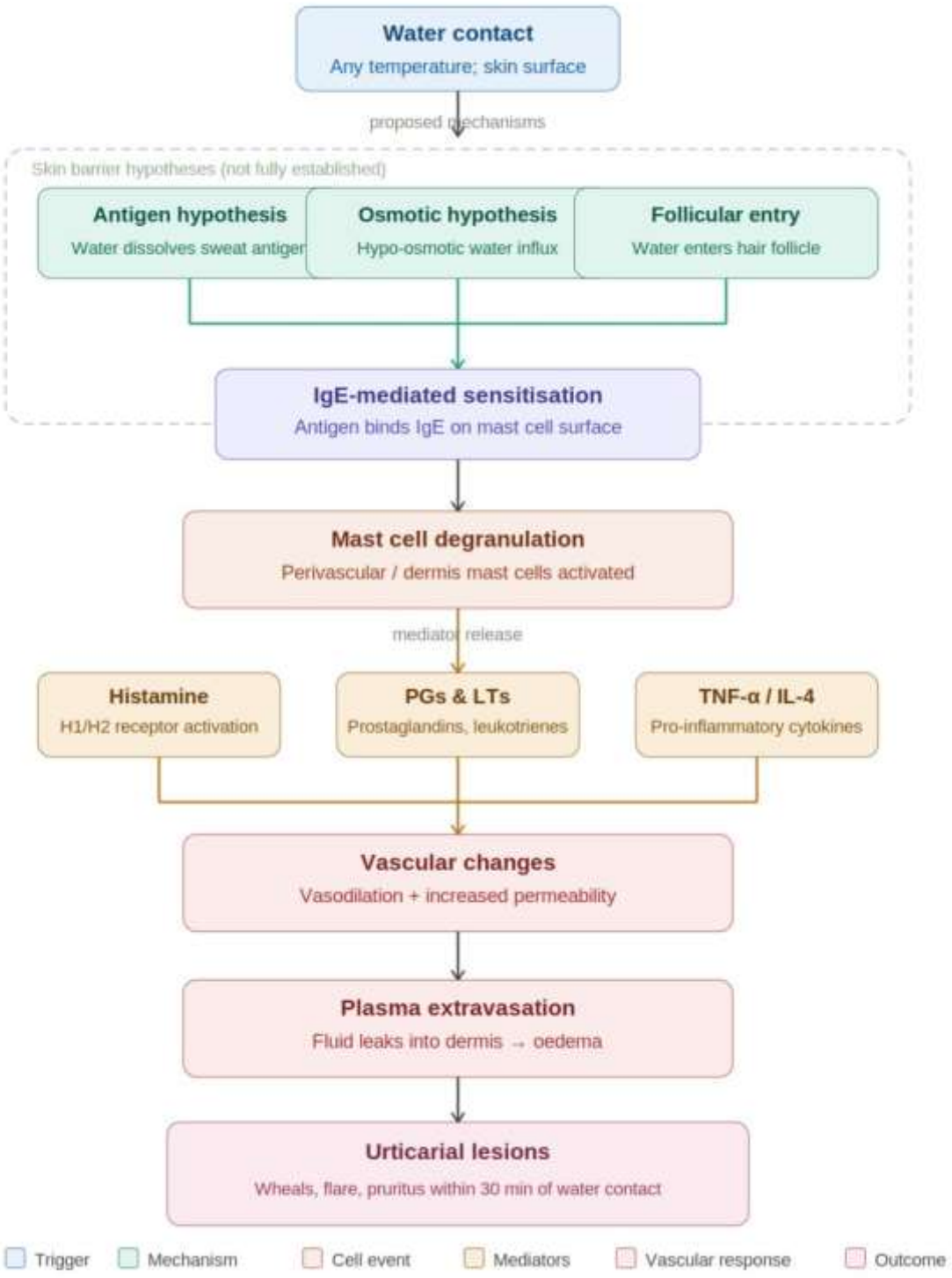
Based on current evidence, we propose that aquagenic urticaria results from a multifactorial interaction between skin barrier dysfunction, local biochemical triggers, and individual mast cell sensitivity. Water exposure may facilitate the penetration or activation of yet unidentified mediators within the skin, leading to mast cell degranulation through both histaminergic and non-histaminergic pathways. This integrated model may explain the observed clinical heterogeneity and variability in treatment response.



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5. Diagnostics (Improved Version)

The diagnosis of aquagenic urticaria (AU) requires an integrated approach combining clinical history, physical examination, standardized provocation testing, and systematic exclusion of differential diagnoses. Given the rarity of the condition and its overlap with other inducible urticarias, a structured and reproducible diagnostic framework is essential.

5.1 Clinical Presentation and History

A detailed clinical history remains the cornerstone of AU diagnosis. The hallmark presentation involves the rapid onset of pruritic wheals (1–3 mm) with surrounding erythema within 20–30 minutes of water exposure, resolving within 30–60 minutes after cessation [1, 2].

Clinicians should assess:

- type and temperature of water exposure
- distribution of lesions
- reproducibility of symptoms
- associated systemic manifestations

A family history should also be obtained to identify potential hereditary patterns [4, 11].

However, reliance on patient history alone is insufficient. Studies have demonstrated discrepancies between self-reported symptoms and objective testing outcomes, emphasizing the need for standardized provocation testing [6].

5.2 The Water Provocation Test

The water provocation test (WPT) is considered the diagnostic gold standard. The standard protocol involves applying a wet compress at approximately 35°C to the upper body for 20–30 minutes, followed by evaluation for wheal-and-flare reactions [2, 7].

A positive result typically appears within 15–20 minutes and is characterized by localized urticarial lesions. The test must be conducted under controlled conditions to avoid confounding factors such as temperature-induced urticarias.

Despite its utility, the WPT has limitations. False-negative results may occur, particularly in patients with intermittent symptoms or variable disease expression. In such cases, repeated testing or protocol modification may be necessary.

5.3 Differential Diagnosis

Accurate diagnosis requires exclusion of other inducible urticarias. Key differential diagnoses include:

- **Cholinergic urticaria** — triggered by heat or exercise
- **Cold urticaria** — temperature-dependent reactions
- **Aquagenic pruritus** — pruritus without wheals

Distinguishing features include trigger specificity, lesion morphology, and response to provocation tests.

The EAACI/GA2LEN/EDF/WAO guidelines provide a standardized framework for classification and diagnosis, ensuring consistency across clinical practice [3].

5.4 Additional Investigations

Additional investigations may support diagnosis and identify associated conditions. Skin biopsy following provocation may demonstrate mast cell degranulation, confirming underlying pathophysiology [23, 7].

Laboratory tests, including serum tryptase or histamine-related markers, may provide supportive evidence in selected cases. Screening for associated systemic conditions should be considered in atypical presentations.

5.5 Diagnostic Synthesis

Diagnosis of AU should not rely on a single test but rather on the integration of clinical history, objective provocation testing, and exclusion of alternative diagnoses. A stepwise diagnostic approach improves accuracy and reduces the risk of misclassification.

6. Discussion

Aquagenic urticaria represents a unique clinical entity at the intersection of dermatology, immunology, and genetics. Its rarity, paradoxical trigger, and incomplete mechanistic understanding contribute to its continued scientific relevance despite decades of study.

From an etiological perspective, AU remains difficult to classify within conventional disease frameworks. While most cases are sporadic and idiopathic, the presence of familial clustering and twin concordance suggests an underlying genetic susceptibility. However, the absence of molecular genetic data highlights a critical gap between clinical observation and mechanistic understanding. Reported associations with systemic conditions may reflect shared immune dysregulation, but current evidence remains insufficient to establish causality.

Pathogenetically, AU is characterized by mast cell activation and histamine release, yet the initiating trigger remains unresolved. The persistence of the Shelley sebum hypothesis underscores the lack of a definitive alternative model, despite its limited biochemical validation. The presence of antihistamine-refractory cases further suggests that AU cannot be explained solely by histaminergic pathways and likely involves additional mediators, including cytokines, neuropeptides, or complement-related mechanisms.

Importantly, the available evidence supports the concept that AU should not be regarded as a single uniform condition, but rather as a heterogeneous disorder with multiple potential pathogenic pathways. This perspective may explain the observed variability in clinical presentation and treatment response.

From a diagnostic standpoint, the water provocation test provides a reliable and standardized method for confirmation. However, the continued under-recognition of AU in clinical practice suggests that diagnostic awareness remains insufficient. Improved clinician education and adherence to established guidelines are essential to reduce diagnostic delays.

The genetic dimension of AU represents the most significant unmet need in current research. The lack of genome-level studies is particularly notable given the suggestive familial evidence. Application of next-generation sequencing technologies may provide critical insights into disease susceptibility and shared pathways with other inducible urticarias.

Finally, this review highlights the need for a more integrated conceptual framework of AU. We propose that the condition arises from the interaction of skin barrier integrity, local biochemical triggers, and individual immune responsiveness, leading to mast cell activation through both histaminergic and non-histaminergic pathways. This integrative perspective may better account for the clinical heterogeneity observed in patients.

7. Conclusion

Aquagenic urticaria is a rare but clinically significant inducible urticaria characterized by water-triggered mast cell activation. Despite over six decades of clinical observation, its etiology, genetic basis, and precise pathogenic mechanisms remain incompletely understood.

Current evidence supports a multifactorial model involving immune, genetic, and barrier-related factors, although definitive molecular pathways have yet to be identified. The absence of targeted genetic studies and the limited availability of mechanistic data represent major gaps in the field.

Advancing understanding of AU will require integrated research approaches, including genomic analysis, mechanistic studies, and improved clinical characterization. Greater awareness among clinicians is essential to ensure timely diagnosis and appropriate management, ultimately improving patient outcomes.

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