

Review Article

Aquagenic Pruritus: A Review of the Pathophysiology – Beyond Histamine

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Abstract: Aquagenic pruritus is a common dermatological problem with prevalence as high as 26.5% in some locations of the world. Pruritus is the major symptom manifesting as prick-like, burning or biting sensation after contact with water. Histamine from mast cells has been the main culprit responsible for the itching associated with this problem and some patients are relieved by anti-histamines when given. However, anti-histamines do not relieve symptoms of aquagenic pruritus when given to some other groups of patients; implying that other risk factors or chemical mediators outside histamine may be responsible for this problem. Recently, other associated risk factors have been enumerated from various scientific researches to be responsible for this health problem. This article reviews these other risk factors that are linked up to the pathophysiology of aquagenic pruritus and the possible pharmacological intervention adopted by various authors and researchers globally.

Keywords: Aquagenic, Pruritus, Dermatological, Antihistamine, Histamine, Water

1. Introduction

Aquagenic pruritus is a dermatological condition that is characterized by severe itching or prick-like sensation associated with water contact at any temperature and yet without any obvious skin lesion [1, 2]. It is a diagnosis of exclusion when other causes of pruritus have been excluded [1, 2]. Various sources of water have been implicated. The water involved may be cold, hot or tepid water. It affects both sexes with male to female ratio of 1.7:1 [3]. The pruritus is usually almost immediately or several hours later following contact of skin with water. This varies in individuals. The duration of itch may be ranging from minutes to hours. Mean age of manifestation is 25 ± 3.8 years [4]. The peak age of development of this condition is during infancy, adolescent or early childhood [3].

Aquagenic pruritus is a global dermatological problem and is common. The diagnosis is usually missed because many physicians are not aware of this condition. Some physicians have attributed this to a psychiatric-like problem [5]. The exact prevalence of aquagenic pruritus is not exactly known and some of the facts/figures obtained about prevalence are

environment-based [4]. Salami *et al*, conducted a study at south western Nigeria and they reported a prevalence of 23.5 % [4]. Again Olumide and Oresanya confirmed a prevalence of 21% in another study done at Lagos, Nigeria [5]. Though Potassman *et al* has reported a prevalence of 4.5% in another study done in Israel [6].

2. Clinical Features

Commonly affected parts of the body include the arms, chest, back, and the abdominal wall; while areas like soles, palms, mucosal surfaces are rarely affected. Also, the head, face, and neck are rarely affected. It occurs in trunk, proximal extremities, with tingling, itching or burning sensation [7, 8].

3. Predisposing Factors/Risk Factors

Aquagenic pruritus has been linked to number of disease conditions such as polycythemia vera [9], lymphoblastic leukemia [10], T-cell non-Hodgkins lymphoma [11], metastatic cancer [12], hepatitis [13], lactose intolerance [7], and certain medications such as chloroquine, and bupropion.

Also there are certain individuals who seem to have hereditary link to manifesting aquagenic pruritus [3]. These groups of people have a genetic origin of this problem [3]. Aquagenic pruritus is found to commonly occur in patients with polycythemia vera [7]. Sometimes, it may precede a diagnosis of polycythemia by several years or more; also it may be one symptom of polycythemia vera. Lactose intolerance has also been noticed to be a contributing factor in about 25% of individuals with aquagenic pruritus [7]. It is seen as a possible co-factor. Dermographism has also been commonly reported as a finding in certain infants with aquagenic pruritus [3].

Aquagenic pruritus may be idiopathic in some cases.

4. Pathophysiology of Aquagenic Pruritus

4.1. Role of Histamine

The exact pathophysiology of aquagenic pruritus is still under research. It is not fully known [8]. However, various researchers have come up with different possibilities. Top on the list is increased mast cell degranulation with subsequent release of histamine into circulation. Histamine is usually produced by the basophils and mast cells and is involved in the inflammatory response and has a central role as a mediator of pruritus [14]. The fact that histamine has been implicated as a mediator of pruritus has been supported by increased level of circulating histamine in aquagenic pruritus, and effectiveness of anti-histamines in relieving symptoms of aquagenic pruritus when given to affected patients. Anti-histamines significantly reduced the symptoms of aquagenic pruritus. This is not so for all patients presenting with symptoms of aquagenic pruritus as they are not all reported. Combining histamine blockers viz: Loratadine (H₁ blocker) and Cimetidine (H₂ blocker) blocks the activity of histamine and reduces pruritus significantly [15]. Similarly, Steinman *et al* reported symptomatic relief with anti-histamines in about 47% of patients with aquagenic pruritus [2]. Antihistamines act via the four subclasses of histamine receptors to carry out their actions.

A possible mechanism of histamine involves temperature – induced mast cells degranulation. After exposure of skin to water, and the cooling down of the skin by the water, there is a release of adenosine diphosphate from red blood cells, and catecholamines from adrenergic vaso-constrictor nerves resulting in blood vessel contraction and activation of platelets. Platelets may release pluritogenic factors such as prostaglandins E₂ (PG E₂) and serotonin. Mast cell, by release of histamine, is another source of pluritogens in aquagenic pruritus. Jackson *et al* found that pruritus patients have higher levels of mast cells (by inference, histamine) than the general population. Histamine blockers have been known to improve symptoms [16]. Histamine is also shown in a study by Davis RS *et al* to be elevated in aquagenic pruritus into systemic circulation following a 41°C bath. Injected PG E₂ and serotonin have also been known to cause pruritus [17].

However, many patients presenting with aquagenic pruritus have been given anti-histamines for treatment of symptoms of

pruritus, all to no avail. This emphasizes that histamine, alone cannot be the only factor responsible for the pruritus in these groups of patients.

Some other attributed factors implicated in the aetio-pathogenesis of aquagenic pruritus include: Increased skin fibrinolytic activity [18], release of acetylcholine [14], release of neuropeptides like substance P [18], inappropriate activity of sympathetic neurons system, amongst others [19, 20].

4.2. Acetylcholine Release

Studies have shown that acetylcholine plays a role in aquagenic pruritus, as there have been symptomatic relieve by topical hyoscine (an acetylcholine antagonist) [14] Bircher *et al* studied the aetio-pathology of aquagenic pruritus by taking punch biopsy specimen before and after contact with water. The sample was prepared and histochemical studies done for acetylcholinesterase (ACHE) activity. Their finding indicated that acetylcholine activation might support clinical diagnosis of aquagenic pruritus [21].

4.3. Neuropeptides Release

Neuropeptides like substance P have also been implicated in the pathogenesis of aquagenic pruritus. Certain researchers reported the excellent results achieved by the use of capsaicin cream in relieving symptoms of aquagenic pruritus when applied before and after contact with water [18]. Capsaicin is thought to enhance the release of neuropeptides such as substance P which helps in treating pruritus. More researches are still on-going in this regard [18].

4.4. Increased Cutaneous Fibrinolytic Activity

Certain researchers, have noted that cutaneous fibrinolytic activity is elevated prior to, and after contact with water. This increased fibrinolytic activity is thought to be mediated by acetylcholine or histamines. It is also noted that increased cutaneous fibrinolytic activity both before and after contact with water is said to explain the lack of wheal formation in aquagenic pruritus [18].

4.5. Inappropriate Activity of Sympathetic Nervous System

Propanol and Atenolol (both of which are anti-sympathetic) are used to relieve symptoms of aquagenic pruritus. Cao T *et al* found that when skin comes in contact with water, certain mediators are released which cause stimulation of dysfunctional and hyper-innervated c-fibers which may have resulted from a sodium channel defect. Atenolol exerts its effect by blocking over-activated neuronal sodium channels [19, 20].

5. Diagnosis of Aquagenic Pruritus

Laboratory investigations to make a diagnosis of aquagenic pruritus do not seem to exist. It is usually a diagnosis of exclusion, when possible diseases that can result in pruritus of the affected patient have been ruled out. These include effects of medication such as bupropion, chloroquine, and

clomipramine [21]; systemic diseases such as polycythemia vera, and urticaria [9]. Aquagenic pruritus diagnosis satisfies certain clinical conditions [7, 34]:

1. Severe itching which may be burning, prick-like, stinging on exposure to water
2. Absence of visible skin diseases such as effect of medication
3. Pruritic reaction may take minutes after exposure
4. Exclusion of all other physical urticarias.

6. Treatment of Aquagenic Pruritus

Over the years various therapeutic agents have been employed in the treatment of aquagenic pruritus with some level of success. Below is a summary of various agents of treatment that have been used over time.

Table 1. Overview of research findings on treatment of aquagenic pruritus

Therapeutic Agent of Measure	Researchers
Sodium Bicarbonate emollients	Wolf R <i>et al</i> [2]
Ultraviolet B phototherapy and oral antihistamines	Steinman/Greaves [2]
Baking Soda Bath	Bayoumi <i>et al</i> [23]
Capsaicin cream	Lotti T <i>et al</i> [18]
Naltrexone (Endogenous opiates)	Ingber S <i>et al</i> [24]
PUVA and Astemizole	Martinez-Escribano <i>et al</i> [25]
Atenolol	Cao T <i>et al</i> [20]
Ultraviolet A/narrow band /UV B therapy	Koh/Chong [26]
Tight fitting clotting	Spelman/Dicker [27]
Repeated PUVA	Goodkin B [28]
PUVA and Capsaicin	Smith RA <i>et al</i> [29]
Alcohol	Norris JF [30]
Propanolol	Thomsen K [31]
Psoralen Photochemotherapy	Menage HD <i>et al</i> [32]

7. Complications of Aquagenic Pruritus

Aquagenic pruritus is a serious dermatologic problem and may lead to the following complications:

1. Severe itching, hindering normal activities [3]
2. Lichen simplex chronicus [33]
3. Prurigo nodules and excoriations [33]
4. Psychological disturbance from insomnia [33].
5. Generalized itching with disturbance of normal activities [3]
6. Suppressing the urge to bath [3].

8. Conclusion

Aquagenic pruritus is a common dermatological problem all over the world including the tropical countries like Nigeria. Its major symptom, pruritus is worrisome and discomforting as it can suppress day to day normal activities. Besides histamine, other aetiologies have been linked to aquagenic pruritus. This knowledge will enhance more pharmacological approach to patient management. A good differential diagnosis of aquagenic pruritus is polycythemia vera. All patients suspected to have aquagenic pruritus should be investigated for the presence of polycythemia vera as well.

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