Aquagenic pruritus

Howard K. Steinman, M.D., and Malcolm W. Greaves, M.D., Ph.D.
London, England

The clinical characteristics of aquagenic pruritus (AP) based on a series of thirty-six patients are presented. AP is characterized by the development of severe, prickling-like skin discomfort that is without observable skin lesions and that is evoked by contact with water at any temperature. Other causes of pruritus associated with water contact must be excluded. In the thirty-six patients, skin discomfort developed within minutes of water contact in approximately half. In others, discomfort began 2 to 15 minutes after water exposure had ceased. The pruritus was usually generalized, lasting from 10 to 120 minutes (average, 40.6 minutes), and in 55% was associated with symptoms of acute emotional lability. There was no increased prevalence of atopy. Thirty-three percent reported a family history of water-related itching. Of fourteen patients treated with ultraviolet B phototherapy, eight (57%) noted significant relief. Of thirty-four patients, sixteen (47%) noted partial relief with oral antihistamine therapy. Patients with polycythemia rubra vera (PRV) may present with symptoms similar to those of AP, and all patients with symptoms consistent with AP should be investigated for the presence of PRV. (J AM ACAD DERMATOL **13**:91-96, 1985.)

Contact of the skin with water is an essential everyday occurrence that is taken for granted as being harmless and often pleasurable. For a small percentage of the population, however, contact with water may be accompanied by distressing skin discomfort. In many of these individuals, discomfort occurs only after certain types of water contact, and the water per se is not the cause. In cold urticaria, for example, cold water contact may induce cutaneous symptoms and signs, but the water itself is not the incitant. Likewise, in cholinergic urticaria and heat urticaria, symptoms and signs can be provoked by contact with warm water, and in symptomatic dermatographism, the force of the jet of water during showering or vigorous toweling after bathing may induce pruritus and wheals. Aquagenic urticaria, the rarest form of physical urticaria, results directly from water contact by an unknown mechanism. All of these conditions are accompanied by clinically observable skin changes, typically wheals. In this article we wish to describe an additional type of water-mediated reaction that develops after all forms of water contact, causes intense, sometimes incapacitating skin discomfort, but is not associated with observable skin changes. We shall term this reaction "aquagenic pruritus" (AP). Greaves et al[1] first described AP as a distinct clinical entity in a report of three patients in 1981. Since then we have seen a total of thirty-six patients, indicating that this condition is not exotic. The clinical characteristics of AP, based on the findings in these thirty-six patients, are presented.

From the Institute of Dermatology and St. John's Hospital for Diseases of the Skin.

Accepted for publication March 7, 1985.

Reprint requests to: Dr. Howard K. Steinman, Chief, Dermatology Section, Veterans Administration Medical Center, 3350 La Jolla Village Dr., San Diego, CA 92161.

MATERIALS AND METHODS

The diagnosis of AP was based on the following general criteria (Table I): (1) skin discomfort characterized as an itching, prickling, or burning sensation developed after contact with water, irrespective of the water temperature, (2) intense discomfort that began within minutes of water contact, (3) no visible skin

Table I. Criteria for the diagnosis of aquagenic pruritus

1. Severe pruritus occurs after water contact, regardless of water temperature.
2. Pruritus develops within minutes after water contact.
3. No visible skin changes occur.
4. No chronic skin disease or internal disorder is present that could explain the discomfort, nor can drugs be implicated.
5. Cold, vibratory, pressure, aquagenic, cholinergic, and heat urticaria and symptomatic dermatographism are excluded.
6. PRV is excluded.

changes associated with the skin discomfort, (4) no chronic cutaneous disease or internal disorder that could explain the water-induced skin discomfort, nor could drugs be incriminated, (5) absence of cold, vibratory, pressure, aquagenic, cholinergic, or heat urticaria, as well as absence of symptomatic dermatographism, and (6) no evidence of primary polycythemia rubra vera (PRV).

Thirty-six patients fulfilling these criteria were seen at St. John's Hospital for Diseases of the Skin between June, 1979, and April, 1984. The patients' medical records were reviewed, and each patient was sent a questionnaire requesting additional information regarding other family members with symptoms of AP, other stimuli (besides water) that caused the same type of skin discomfort, and their response to therapy. Of the thirty-six patients, thirty-four completed the questionnaire. Additional information, when necessary, was obtained by personal interview. The data obtained from the medical records, personal interviews, and questionnaires are the basis of this report.

RESULTS

A total of thirty-six patients, sixteen women and twenty men, were diagnosed as having AP. They ranged in age from 17 to 81 years of age (Table II). The average age was 41.9 ± 12.6 years (SD) for the women, 43.1 ± 16.2 years for the men, and 42.6 ± 14.6 years for the entire group. The average age of onset was 29.4 ± 13.4 years for the women, 34.5 ± 20.0 for the men, and 32.7 ± 17.1 years for the total group. The average duration of symptoms prior to diagnosis was 11.8 ± 8.3 years for the women, 7.9 ± 9.3 years for the men, and 9.7 ± 8.9 years for the group overall. No cases of spontaneous remission of AP were noted. Of the thirty-six patients, five (14%)

Table II. Average age, age of onset, and duration prior to presentation

	Female	Male	Total
Age (yr)	41.9 (19-63)	43.1 (17-81)	42.6 (17-81)
Age of onset (yr)	29.4 (10-52)	34.5 (8-78)	32.7 (8-78)
Duration prior to presentation (yr)	11.8 (2-30)	7.9 (5/12-30)	9.7 (5/12-30)

had a personal history of atopy (defined as the presence of asthma, eczema, or hay fever) and an additional two patients (6%) had a family history of atopy in first-degree relatives. None of the patients had dermographism or chronic idiopathic urticaria. A family history was common. Twelve patients (33%) reported that one or more of their family members had symptoms consistent with AP.

All patients experienced skin discomfort after contact with water at all temperatures, with the exception of one patient who did not experience discomfort with room-temperature water. In two patients the symptoms were less severe in cold water, and in one patient the symptoms were less severe in very hot water. Conversely, three patients stated that symptoms were worse in warm or hot water, and one patient stated that symptoms were worse in cold water. All patients experienced discomfort irrespective of water salinity, except for three patients who did not experience symptoms in cold salt water. Symptoms occurred year around in thirty-four of the patients. In one patient the symptoms occurred only during the summer months, and another patient would often be free of symptoms for months at a time.

The sensation produced by water contact was commonly described as prickling, tingling, burning, stinging, or buzzing to distinguish it from an itching sensation. While bathing, thirteen patients (36%) experienced skin discomfort in an average of 5.4 minutes from first exposure (range, "immediate" to 15 minutes). Seventeen patients (47%) did not experience discomfort while their skin was continually exposed to water. In these patients the discomfort began 2 to 15 minutes after water exposure had ceased. In six patients (17%) no data were available regarding the duration of water contact necessary to produce symptoms. The

duration of discomfort, once produced, ranged from 10 to 120 minutes, with an average duration of 40.6 ± 20.5 minutes. Many of the patients experienced the same type of skin discomfort following skin stimulation unrelated to water exposure, although the discomfort was not as consistently produced by these stimuli as by water contact (Table III). Nineteen patients (53%) sometimes noted symptoms after perspiring, eighteen (50%) after getting in or out of bed, and seventeen (47%) after rapid changes in ambient temperature. Heat could produce the sensation in eleven patients (31%), and cold temperatures could produce it in nine patients (25%). Of the thirty-six patients, seven (19%) noted the irritation with exertion, possibly because of sweating. Seven patients (19%) occasionally experienced skin discomfort after emotional upset, and pressure on the skin could induce the discomfort in six patients (17%).

Among the thirty-two patients for whom data were available, the thighs and legs were affected in thirty-one patients (97%), and symptoms began on the lower extremities in twelve patients (37%) before spreading elsewhere. The trunk was affected in twenty-three patients (72%), and the shoulders or upper extremities in twenty-five (78%). Symptoms were confined to the extremities in eight patients (25%). In most patients, only certain regions of the skin surface seemed to develop symptoms when exposed to water. Localized application of water to these areas would result in discomfort. Areas of skin that did not become symptomatic with whole-body water exposure usually would not respond to localized water application.

With the exception of four patients in whom a transient "blotchy" erythema was occasionally noted during episodes of AP, no patients had consistently visible skin changes. Psychiatric symptoms were common during attacks of AP. Of thirty-six patients, twenty (55%) felt aggressive, irritable, agitated, depressed, or angry during episodes of AP. An additional two patients (6%) experienced occasional headaches, and one of these patients also experienced palpitations and dizziness. There were no other cutaneous abnormalities consistently present in the group of thirty-six patients, and in twenty-one patients (58%), no other cutaneous abnormalities were noted. Tinea pedis, acne vulgaris, localized eczema, and solar elastosis were noted in two patients each, and xerosis, facial telangiectasias, psoriasis, herpes zoster scarring, and vasomotor instability were noted in one patient each. No history of significant medical abnormalities were present in twenty-six patients (72%). Miscellaneous current or past medical problems noted in the remaining ten patients included hay fever in three patients and chronic bronchitis, obstructive jaundice, cholecystitis, colitis, hiatus hernia, obesity, and uric acid stones in one patient each.

Table III. Other stimuli causing pruritus

Stimulus	%
Perspiration	53
Getting in or out of bed	50
Change in ambient temperature	47
Heat	31
Cold	25
Physical exertion	19
Emotional upset	19
Pressure on the skin	17

Treatment with H_1 and/or H_2 antihistamine agents did not result in significant relief of symptoms in any of the thirty-four patients to whom they were given. Of these thirty-four patients, sixteen (47%) reported some diminution of their AP with antihistamine therapy. Fourteen patients, nine men and five women, were treated with ultraviolet light B (UVB) (290 to 320 nm). Eight of these patients (57%) responded favorably. Six of the nine men (66%) noted significant improvement and an additional one patient (11%) noted partial relief. Only one of the five women (20%), however, noted significant improvement. Suberythemal therapy, given two to three times weekly, was necessary to maintain the beneficial effect of the UVB, since most patients noted a prompt recurrence of symptoms when therapy was decreased in frequency or discontinued. Of twenty-two patients, seven (32%) noted that sun exposure diminished the severity of their symptoms, and four of these were among those responding to UVB therapy. Of the remaining three patients who responded to sun exposure, one did not find UVB treatment to be beneficial, and two had not been given UVB therapy. Conversely, three of the eight

patients who responded to UVB therapy did not find sun exposure to be beneficial. In total, of the twenty-five patients treated with sun and/or UVB therapy, eleven (44%) had a favorable response. Four patients noted that the use of bath oils or emulsifying ointment in the bath diminished the severity of the AP. Two patients found that a very hot bath did not cause discomfort, whereas lower-temperature baths did so. Another patient found that remaining completely immersed in water for greater than 30 minutes would prevent the development of AP. Two patients found that exposure to cold ambient temperatures could relieve the irritation once it had started, and one patient noted that heat (i.e., sitting near a heater or fire) relieved the discomfort.

DISCUSSION

The term "aquagenic pruritus" was coined by Shelley[2] in 1970 to describe what was probably the first reported case of this condition. At that time it was thought that AP was a variant of aquagenic urticaria. In 1981 Greaves et al.[1] reported three cases of aquagenic pruritus and clearly distinguished AP from aquagenic urticaria, as well as from other conditions causing skin discomfort in association with water exposure.

AP is characterized by the development of intense, sometimes incapacitating skin discomfort following contact with water. In many of the cases, the discomfort is described as a prickling, tingling, or burning sensation. Many of the patients found the severity of their AP almost intolerable. Some could not tolerate a bath or shower and resorted to regional sponge bathing only when necessary. In more than half of the patients, the discomfort was associated with feelings of marked anger, irritability, or depression. To prevent unnecessary interpersonal conflict, these patients often isolated themselves from other family members after bathing or bathed only when no one else was at home. To compound the distress these patients experienced, many of them had been labeled "neurotic" when they sought medical advice for their complaint from physicians who were unaware of the existence of this clinical entity.

The age of onset of AP in our series of patients varied greatly, ranging from 10 to 78 years of age, with the average age of onset being 32.7 years. The average duration of symptoms prior to diagnosis was 9.7 years (range, 5 months to 30 years), perhaps reflecting the fact that this condition has only recently been characterized. The ratio of males to females was about equal. Of thirty-six patients, thirty-five experienced the discomfort irrespective of the water temperature and thirty-three irrespective of water salinity. The discomfort lasted between 10 and 120 minutes. During a bath, some experienced discomfort while in the water, whereas others developed the skin irritation only after emerging from the water. The onset of discomfort after water exposure has ceased has been previously reported both in aquagenic pruritus[2] and in the water-induced skin discomfort associated with PRV.[3] The legs and thighs were involved in almost all patients, and symptoms began on the lower extremities in approximately one third of the cases. Three fourths of the patients also experienced the discomfort on the trunk and/or upper extremities.

Changes in temperature could also elicit skin discomfort similar to that of AP in many of the patients, although not as consistently as water exposure. Approximately half of the patients sometimes experienced the skin discomfort with changes in ambient temperature or when getting into or out of bed, and 25% sometimes experienced the discomfort during exposure to cold air temperatures. It is interesting to note that the development of discomfort with skin cooling is also a common feature in PRV patients who experience water-induced skin discomfort. Since seventeen patients (47%) did not experience skin discomfort from a bath until after emerging from the water, it might be argued that skin cooling, and not water contact, was responsible for eliciting the discomfort in at least some of these patients. However, of these seventeen patients, only four were among those who noted discomfort during exposure to cold weather, and only ten were among those who noted the discomfort after getting into or out of bed. Thus it is unlikely that skin cooling per se can account for the development of AP in most of the patients studied. Moreover, 31% of the patients sometimes experienced the discomfort during exposure to warm air temperatures.

On the basis of available data, AP is not associated with other cutaneous diseases. Of the thirty-

six patients, only seven (19%) had a personal or family history of atopy, a prevalence similar to that expected in the general population, and none of the patients had dermatographic symptoms. AP also does not appear to be a marker for any systemic abnormalities. Of thirty-six patients, thirty-two were free of significant systemic disease at the time of evaluation.

The symptoms of AP bear a remarkable resemblance to the water-induced pruritus experienced by many patients with PRV. Up to 50% of untreated patients with this disorder experience a generalized, often severe, prickling skin discomfort that develops within minutes of water contact and lasts for 15 to 60 minutes.[3] In many of these patients the pruritus comes on after hot baths or showers,[3,4] but in some patients the symptoms can develop with exposure to either hot or cold water.[4] The pruritus appears to be somewhat temperature dependent, since many patients can diminish the severity of the symptoms if they prevent their skin from cooling after a hot bath or shower. As with AP, some patients also note pruritus while getting into a cold bed[3,4] or during exposure to cold weather.[3] Some patients also find the severity of the skin discomfort nearly intolerable and resort to regional sponge bathing or avoidance of bathing with water altogether.[4,5] All patients presenting with findings consistent with AP should be evaluated periodically for the presence of PRV. We also recommend that the term "aquagenic pruritus" be reserved for patients in whom PRV has been excluded.

The results of therapy for AP have been unrewarding. Although Greaves et al[1] reported that two of their three patients noted significant relief with H_1 antihistamines, we have not found this to be the case in the majority of patients. Of thirty-four patients treated with H_1 and/or H_2 antihistamine agents, none noted complete abolition of the skin discomfort, and only sixteen patients (47%) noted partial relief of symptoms. Four patients noted that the use of bath oil could diminish the severity of their AP, a fact that has been previously reported.[2] The response to UVB therapy was more encouraging, especially for the male patients. Of fourteen patients, eight (57%) experienced significant relief with UVB therapy, although suberythemal therapy, given two or three times weekly, was necessary to maintain the beneficial effect. Sun exposure was less effective in controlling AP, since only seven (32%) of twenty-two patients responded favorably.

The pathogenesis of AP remains unclear. Greaves et al[1] studied blood histamine levels in their three patients before and after water challenge. Two of the patients exhibited abnormal elevations of their levels of blood histamine prior to water exposure, and all three patients showed increases in blood histamine levels after water challenge. In addition, they found that although the total number of mast cells in their patients' skin did not differ significantly from that in normal skin, a significantly increased degree of mast cell degranulation was present prior to water challenge, and the degree of mast cell degranulation increased further after water exposure. They postulated that these baseline elevations in blood histamine levels and mast cell degranulation could have resulted from normal sweating. Despite the rise in blood histamine levels with water contact, it is unlikely that histamine release alone is responsible for the discomfort of AP. First, although histamine release into the skin does induce pruritus, many of the patients with AP complain of a sensation distinctly different from itching. Second, antihistamine agents do not alleviate the skin discomfort in most patients. Greaves et al[1] also applied hyoscine, an acetylcholine antagonist, to the skin of two patients with AP prior to water challenge. Following water exposure, the treated skin remained asymptomatic but the surrounding, untreated skin developed pruritus. This result indicates that acetylcholine release in the skin may play a role in the development of AP. Lotti et al[6,*] recently described patients with AP in whom increased cutaneous fibrinolytic activity (CFA) was present both before and after water challenge. Disappearance of the fibrinolytic activity in the skin specimens with the application of epsilon-aminocaproic acid suggested that the increased fibrinolytic activity was due to plasminogen activators and not to other proteases. Increased CFA had been previously reported in experimental wheals produced by the intradermal injection of acetylcholine

*Lotti T, Steinman HK, Greaves MW, et al: Increased cutaneous fibrinolytic activity in aquagenic pruritus. (Submitted for publication.)

Table IV. Differential diagnosis of water-induced skin irritation

Aquagenic pruritus
Aquagenic urticaria
Cholinergic urticaria
Cold urticaria
Heat urticaria
PRV
Symptomatic dermatographism

and histamine.* The absence of visible skin changes in AP might be explained by persistent low levels of histamine release in the skin, which could be induced by normal sweating, causing a chronic state of tolerance to develop, or by the slow, continuous release of histamine so that threshold concentrations sufficient to cause visible changes were not achieved. One proposed mechanism for the induction of AP is that contact with water results in the percutaneous absorption of a substance through or from the stratum corneum that then directly or indirectly elicits the skin discomfort. Alternatively, as an explanation of why other stimuli such as temperature change can also induce discomfort, water or other stimuli might induce a structural change in the skin. Either the absorbed substance or the physical alteration in the stratum corneum could then cause the release of acetylcholine from cutaneous nerve endings, which in turn could bring about the release of histamine and other mediators from mast cells. The raised levels of acetylcholine and histamine could account for the increase in CFA.

AP must be distinguished from other conditions that can present as skin discomfort in response to water contact. These conditions include aquagenic urticaria, cholinergic urticaria, cold urticaria, heat urticaria, symptomatic dermatographism, and PRV (Table IV). With the exception of PRV, which is excluded on the basis of hematologic tests, the other conditions causing water-related skin discomfort manifest observable skin lesions, which help to distinguish them from AP.

*Ryan TJ: Microvascular injury. Maj Probl Dermatol **7**:49, 1976.

REFERENCES

1. Greaves MW, Black AK, Eady RAJ, Coutts A: Aquagenic pruritus. Br Med J **282**:2007-2010, 1981.
2. Shelley WB: Questions and answers. JAMA **212**:1385, 1970.
3. Fjellner B, Hagermark O: Pruritus in polycythemia vera: Treatment with aspirin and possibility of platelet involvement. Acta Derm Venereol (Stockh) **59**:505-512, 1979.
4. Chanarin I, Szur L: Relief of intractable pruritus in polycythemia rubra vera with cholestyramine. Br J Hematol **29**:669-670, 1975.
5. Gilbert HS, Warner RRP, Wasserman LR: A study of histamine in myeloproliferative disease. Blood **28**:795-806, 1966.
6. Lotti T, Cappugi P, Lattari P, Panconesi E: Increased cutaneous fibrinolytic activity in a case of aquagenic pruritus. Int J Dermatol **23**:61-63, 1984.